No Pain, No Gain: Navigating the Clinical and Commercial Realities for Non-Opioids

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The FDA approval of Journavx is a breakthrough achievement, but the journey to meaningfully reduce opioid use is only just beginning

The Dawn of a New Era with Non-Opioids

- The opioid epidemic has fueled significant ongoing efforts to develop safer, non-opioid analgesics
- Journavx, a selective voltage-gated sodium channel blocker that targets Nav1.8 is the first novel non-opioid to receive FDA approval in more than 20 years, a major breakthrough for the field
- As we enter the post approval era, we explore six frontiers that will dictate the future of the Nav class and the non-opioid market:

Nav1.7 vs. Nav1.8: Why did a Nav1.8 asset reach FDA approval first?

Efficacy Ceiling: Can Navs ever match opioids' "holy grail" efficacy?

Next generation Navs: What strategies are being adopted with the selective Nav inhibitors to improve on Journavx?

Pain types for Navs: What are the appropriate pain subtypes for Navs? Could Navs ever make the leap from treating acute to chronic pain?

Beyond Navs: What promising targets could follow Navs? Which non-opioid classes are nearing FDA approval?

Reimbursement landscape: What hurdles from the Journavx launch could inform future non-opioid market access strategies?

Nav Class Overview

- **Definition:** Voltage-gated sodium channels (Nav) that open or close in response to stimuli, allowing sodium ions to trigger action potentials in nociceptors (pain sensing neurons)
- **Subtypes:** There are nine Nav isoforms (1.1-1.9) expressed in neuronal, cardiac, or skeletal tissues
- **Nav1.7-1.9** These isoforms are preferentially expressed peripherally. Inhibitors specific to these channels could provide an analgesic effect while minimizing addiction risk and cognitive impairment (sedation, dizziness) associated with centrally-acting analgesics

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Source: **Xie, Yet al.** (2026). *International Journal of Molecular Sciences*, *27*(3), 1180; **Banh et al.**, (2026). *CNS drugs*, *40*(2), 165-180; **Chen et al.**, (2025). Sodium channels as a new target for pain treatment. *Frontiers in pharmacology*, *16*, 1573254.

Journavx approval highlights the technical advantages for Nav1.8 over Nav1.7: autonomic regulation, redundancy management, and engine-like action potential

Key Question

Why did Nav1.8 assets reach FDA first?

Nav1.7 vs. Nav1.8

	Nav1.7 (e.g., PF-05089771)	Nav1.8 (e.g., Journavx)	Implications
Genetic Validation	**Loss-of-function mutations of SCN9A are strongly** linked to inherited conditions e.g., congenital pain insensitivity	**SCN10A mutations are less studied,** but gain-of-function mutations are linked to small fiber neuropathy	**Target Rationale** More robust genetic evidence drove initial R&D interest in Nav1.7
Autonomic Regulation	**Widespread:** High expression in the baroreceptor reflex and brainstem	**Restricted:** Primarily localized to peripheral nociceptors	**Safety Benefit** Nav1.8 has lower risk for autonomic side effects (e.g., hypotension)
Redundancy Management*	**High autonomic toxicity** risk increases risk of redundancy*	**More favorable safety** allows maximal drug occupancy	**Efficacy Benefit** Nav1.8 has a higher efficacy ceiling due to more optimal drug occupancy/redundancy management and plays a key role in action potentials that drive pain intensity and chronic pain
	**Redundancy is when a Nav channel fires pain signal while another isoform is blocked*		
Role in Actional Potentials	**"The Trigger":** Nav1.7 amplifies stimuli that trigger pain signaling	**"The Engine"**: Nav1.8 drives the depolarizing phase and firing frequency	

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In head-to-head trials, Journavx (Nav1.8) more closely matched the efficacy of its active comparator (including opioids) than PF-05089771 (Nav1.7) in acute pain

Nav1.7 vs. Nav1.8 in Acute Post-Surgical Pain

Key Question

Can Navs ever match opioids' "holy grail" efficacy?

Journavx has yet to consistently match or outperform opioid efficacy

	PF-05089771 (Pfizer)	Journavx (suzetrigine) (Vertex)
Indication(s)	• Moderate-to-severe acute pain	• Moderate-to-severe acute pain
MoA (RoA)	• Nav1.7 inhibitor (oral)	• Nav1.8 inhibitor (oral)

Trial Design	• Phase 2 head-to-head trial (PF-05089771 vs. placebo vs. ibuprofen)
	• Pain after dental surgery (n=235)
	• A single dose administered post-operatively
		• Two pivotal head-to-head trials (Journavx vs. placebo vs. hydrocodone bitartrate/acetaminophen (HD/APAP))
		  - Pain after abdominoplasty (n=1,118)
		  - Pain after bunionectomy (n=1,073)
		• Journavx (2x/day), HD/APAP (4x/day)

Primary Efficacy Endpoint	**Total Pain Relief over 0–6 hours (TOTPAR6)** *Ibuprofen* 14 *PF-0508977* 7 *Placebo* 4 *p-value: n.s. against placebo or ibuprofen*	**Pain reduction (Numeric Pain Rating Scale) 48 hours post treatment** *Abdominoplasty* *Journavx* 118 *HD/APAP* 118 *Placebo* 70 p<0.0001 vs. placebo *Bunionectomy* *HD/APAP* 120 *Journavx* 100 *Placebo* 70.6 p=0.002 vs. placebo
Safety	• Non-addictive • Nausea, vomiting, dizziness, headache	• Non-addictive • Itching, muscle spasms, increased creatine phosphokinase, rash

Source: Journavx package insert, Clinical trials.gov

With efficacy established for Nav1.8 in acute pain, future clinical development of Navs is largely focusing on chronic pain

Nav Inhibitors Pipeline (Marketed and Clinical Pipeline Assets for Pain in the U.S.) (n=10)

Key Question

What are the appropriate pain subtypes for Navs? Could Navs ever make the leap from treating acute to chronic pain?

Identifying the most appropriate pain type for Navs remains a challenge, as different pain subtypes respond to Nav inhibitors differently

Legend

FEPS = Familial Infantile Episodic Limb Pain
IsFN = Idiopathic Small Fiber Neuropathy
EM = Erythromelagia

Nav1.7
Nav1.8
Multiple (Nav1.7-1.9)

Oral
Injectable

Phase I

ANP-230
FEPS
AlphaNavi Pharma

CC-8464
FEPS/IsFN
Pelthos

STC-004
Not specified
Eli Lilly/SiteOne

iN1011-N17
Chronic osteoarthritis
iN Therapeutics

Kindolor
Chronic Pain
Lohocla Research Corp

Phase II

OLP-1002
Chronic osteoarthritis
OliPass

ST-503
Small Fiber Neuropathy
Sangamo Therapeutics

LTG-001
Post-Operative Pain
Latigo Bio

Phase IIb

Halneuron (tetrodotoxin)
Chemotherapy Induced Pain
Dogwood Therapeutics
**also in development for general cancer pain*

Approved

Journavx (suzetrigine)
Mod-Severe Acute pain
Vertex Pharmaceuticals
**also in development for peripheral diabetic neuropathy*

Source: Pharmaprojects; Company Websites

Next-generation single- and multi-subtype Nav inhibitors employ novel approaches to potentially address the limitations seen with Journavx

Strategies to Improve Navs

Key Question

What strategies are being adopted with the selective Nav inhibitors to improve on Journavx?

Select strategies for single subtype Nav inhibitors

PK/Dosing (LTG-001)	• LG-001, a Nav1.8 inhibitor is targeting a 1.5-hour onset and once daily dosing • Journavx offers onset of effect at 4 hrs and twice daily dosing
Binding residency time (STC-004)	• By increasing residency time at Nav1.8, STC-004 could provide a continuous blockade required for chronic pain
Antisense oligonucleotide (OLP-1002)	• By silencing Nav1.7 on a genetic level, OLP-1002 aims for near-perfect selectivity and improved response duration

Select strategies for multi-subtype Nav inhibitors

Functional redundancy (ANP-230)	• ANP-230 inhibits Nav1.7-1.9 • Goal is to reach complete suppression of pain signaling
Additional NMDA targeting (Kindolor)	• By targeting Nav1.7, 1.8, and NMDA receptors, the goal of Kindolor is to prevent the development of chronic pain
Pan Nav blockade (Halneuron)	• Blocks Nav1.1–1.7 and is targeting chemotherapy pain • It aims for longer-lasting pain relief in chemo-induced pain

Source: Pharmaprojects; Company Websites

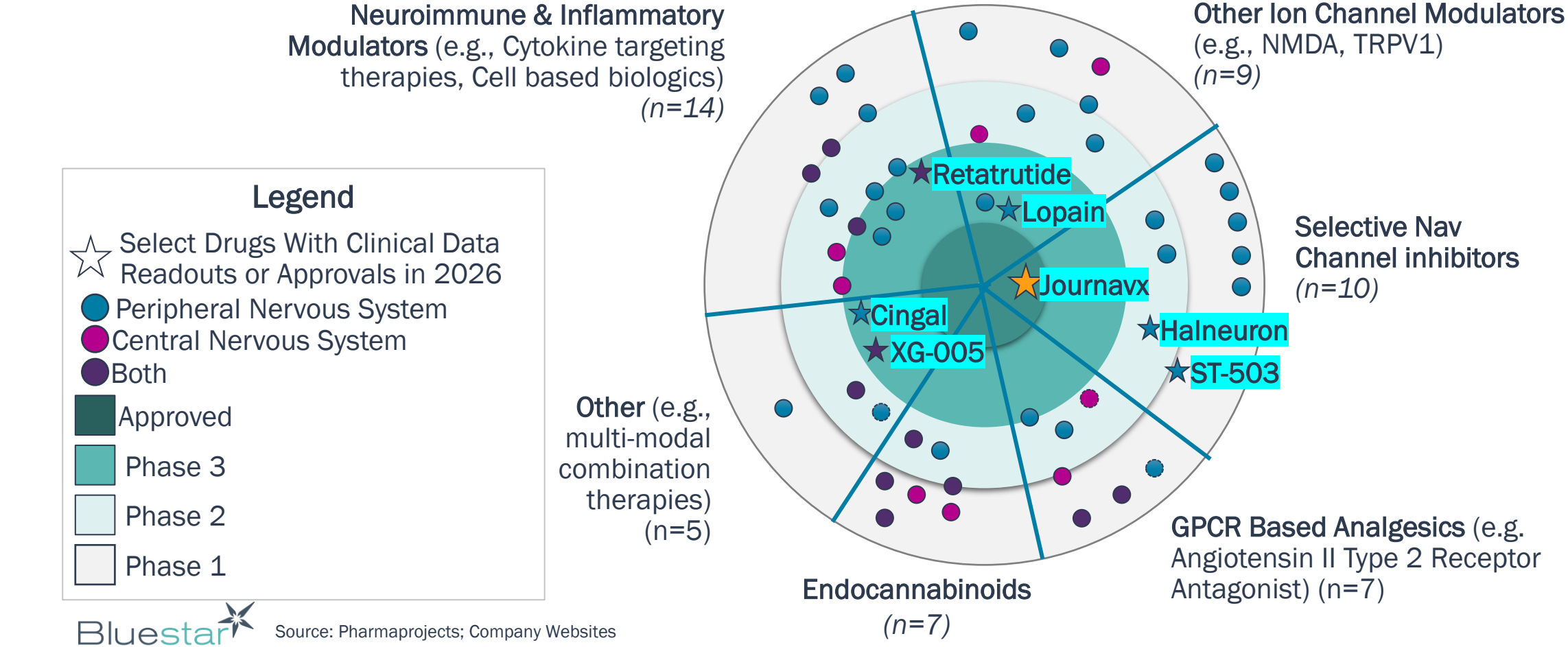
The non-opioid landscape extends well beyond Nav channels to include diverse mechanisms such as GPCRs, endocannabinoids, and neuroimmune modulators

Non-Opioids Pipeline in the U.S. (n=52)

Key Question

What promising targets could follow Navs? Which non-opioid classes are nearing FDA approval?

Assets with readouts in 2026 are either targeting chronic pain indications or exploring novel mechanisms



Source: Pharmaprojects; Company Websites

Journavx's premium pricing, tiered access, and evidence generation strategy may provide a roadmap for reimbursement and market entry for future non-opioids

Commercial Outlook for Journavx and Other Non-Opioids

Key Questions

What commercial and reimbursement hurdles from the Journavx launch could inform future market access strategies for other non-opioids?

Journavx U.S. Eight-months Launch Performance

- **$60M Revenue** ($27M in Q4 2025 alone; revenue missed forecast expectations of $33M)
- **420K patients treated** (550K prescriptions written by 35K HCPs)
- **~200M lives covered** (coverage in 21 states to date; Journavx is on 100+ healthcare systems and 950 hospital formularies)
- **Cost: ~$31/day** (NSAIDs/opioids cost <$2/day)

Key Challenges	Select Strategies
Premium Price Justification Journavx's lack of superior efficacy over NSAIDs/opioids in head-to-head trials makes its price unjustifiable especially as a first line therapy	**Real World Evidence** Vertex's conducted Phase IV to ease payer restrictions. Journavx led to a 90.9% opioid-free recovery (vs. the 10% with NSAIDs only)
High Tier Placement/ Non-Preferred Brand Status Higher costs and non-superiority data relegate Journavx to non-preferred status, forcing mandatory step edits through generic NSAIDs and/or opioids	**Health Economics and Outcomes Research** Vertex cites ICER's $30K cost burden associated with each opioid use disorder (OUD) case; ~85K patients will develop an OUD annually

Source: Vertex Q4 Earnings Press Release and Transcript (Feb 2026); Manalac, T (2025, February 24) BioSpace; Pretorius, R. (2025, March 17) Syenza News; Bell, J. (2025, November 4), BioPharma Dive; Dunleavy, K. (2025, November 4) Bell, J. (2025, March 6) BioPharma Dive; Abbreviations: NSAIDs, Non-steroidal anti-inflammatory drugs; ICER = Icer Cost Effectiveness Analysis

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