AKELOS™

CONFIDENTIAL INVESTOR PRESENTATION

A non-opioid analgesic designed to stay out of the brain.

AKE-1018 — a first-in-class, orally bioavailable, peripherally restricted HCN1 inverse agonist for chronic neuropathic pain.

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LEGAL NOTICE

Note regarding forward-looking statements

Some of the information in this deck contains forward-looking statements within the meaning of the federal securities laws, typically identified by terms such as “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “potential,” “predicts,” or “should.”[1]

THESE STATEMENTS INCLUDE, AMONG OTHERS, THOSE RELATED TO

- The results of research and development activities
- Uncertainties relating to preclinical and clinical testing
- The cost, timing and outcome of the regulatory development and approval process
- Our budgets, expenditures and financing plans
- Our need for substantial additional funds
- Patent and intellectual property matters
- Our dependence on third parties, including contract research and contract clinical trial organizations
- Market opportunity and competition

You should be aware that our business is subject to risks and uncertainties, including the foregoing, that could cause actual results to differ materially from those contained in the forward-looking statements. Readers are cautioned not to place undue reliance on forward-looking statements, which speak only as of the date thereof. We expressly disclaim any obligation to release publicly any updates or revisions to any forward-looking statements contained herein.[1]

This deck also contains projections and forecasts prepared by Akelos for internal use, based on assumptions about conditions and courses of action that management believes are reasonably possible but not necessarily probable. Some of the conditions and courses of action in management’s assumptions inevitably will not materialize, and unanticipated events may occur. Actual results will vary from the projections, and the variations may be material.[1] An investment in the shares is speculative and involves a high degree of risk.[2]

1. Akelos Inc., “Note Regarding Forward-Looking Statements,” Investor Deck, May 5, 2025 (p. 2); Akelos Inc., Private Placement Memorandum (“PPM”), “Cautionary Note Regarding Forward-Looking Statements.” 2. Akelos PPM, “Terms of the Offering — Risk Factors,” p. 5.

INVESTMENT SUMMARY

A validated target, a de-risked lead, and a two-year line of sight to IND

$14M
OFFERING SIZE, COMMON STOCK AT $2.75 PER SHARE[1]

$11.7M
NON-DILUTIVE FUNDING INTO THE TECHNOLOGY TO DATE[2]

24 mo
CANDIDATE SELECTION THROUGH IND SUBMISSION[3]

20M+
US ADULTS LIVING WITH NEUROPATHIC PAIN[4]

WHY NOW

- **The target is human-relevant.** HCN1 mRNA is present in 94.4% of human DRG neurons versus 44.0% for HCN2 — the reverse of the mouse.[5]
- **The mechanism is peripherally restricted by design.** AKE-1018 was designed not to cross the blood–brain barrier; confirmed in silico and in vivo.[6]
- **The in vivo package is published.** Efficacy and a clean 10× safety margin in a rat spared nerve injury model, in *British Journal of Anaesthesia* (2023).[6]
- **The competitive lane is open.** NaV1.7/1.8 programs have repeatedly failed for lack of efficacy in chronic pain.[7]

WHAT THE ROUND BUYS

Lead optimization → development candidate	**12 months**
IND-enabling studies (GLP tox, safety pharm, CMC)	**12 months**
Total program cost to first-in-human	**$13.5M**
Patents issued or allowed	**US · CN · JP · AU**
Exclusive license	**Cornell / Weill Cornell**

At the end of this stage the Company plans and prepares for first-in-human trials, for which it will seek additional funding. Management views this as a potential exit point, in particular for in-licensing by large pharmaceutical partners.[3]

1. Akelos PPM, "Terms of the Offering," p. 5. 2. Akelos, "Experienced Team and Track Record of Success," One-Pager, May 5, 2025. 3. Akelos PPM, "Go Forward Opportunity" and Table 2, pp. 19–20. 4. Akelos PPM, Executive Summary, p. 3. 5. Shiers et al., *Pain*, 2020, as presented in Akelos Investor Deck, May 5, 2025 (p. 89). 6. Tibbs et al., *British Journal of Anaesthesia* 131(4):745–763, 2023. 7. Akelos Investor Deck, May 5, 2025 (p. 19).

THE PROBLEM · 01

Neuropathic pain is common, expensive, and largely untreated

Chronic pain — pain persisting more than three months — is the most common reason people seek medical attention.[1] Neuropathic pain is the subset driven by aberrant activity in the peripheral and/or central nervous system, and it accounts for roughly 18% of chronic pain patients.[2]

116M

US ADULTS LIVING WITH CHRONIC PAIN[1]

20M+

US ADULTS WITH NEUROPATHIC PAIN[1]

$90B

ANNUAL US COST ASSOCIATED WITH NEUROPATHIC PAIN[1]

$500B

ANNUAL US COST OF CHRONIC PAIN, INCL. LOST WORK[1,2]

WHERE IT COMES FROM

- Diabetic neuropathy
- Chemotherapy-induced peripheral neuropathy
- Post-herpetic neuralgia
- Trigeminal neuralgia

Neuropathic pain is also commonly associated with peripheral nerve injury and neurologic disorders such as stroke and multiple sclerosis.[1]

The global picture

Estimates of neuropathic pain prevalence worldwide range from 1.5% to 8% of the population — between 100 million and 560 million people.[2]

Evidence suggests 40–70% of people with chronic pain do not receive proper medical treatment and are at risk of either over- or under-treatment.[3]

1. Akelos PPM, Executive Summary, p. 3, citing NIH Fact Sheet on Pain Management and Gaskin & Richard, *J Pain* 13(8):715–24, 2012. 2. Akelos PPM, "Clinical Overview — Problem Statement," p. 6. 3. Akelos PPM, p. 8, citing Reuben D. et al., *Ann Intern Med* 162(4):295–300, 2015.

The default treatment is a drug class that doesn't work well here — and kills

Opioid pain relievers are considered third-line therapy for neuropathic pain and carry a suboptimal risk–benefit profile, yet they are prescribed for nearly 20% of patients with polyneuropathy.[1]

39,147
US DEATHS IN 2024 IN WHICH OPIOIDS WERE CITED AS A CAUSAL FACTOR[1]

73.4%
OF US DRUG OVERDOSE DEATHS IN 2024 INVOLVED AT LEAST ONE OPIOID[2]

125.7M
OPIOID PAIN RELIEVER PRESCRIPTIONS WRITTEN IN THE US IN 2024[3]

1 in 4
PATIENTS ON LONG-TERM OPIOID THERAPY IN PRIMARY CARE STRUGGLE WITH ADDICTION[3]

- Opioids display limited effectiveness in treating neuropathic pain, and fewer than 35% of patients derive meaningful benefit from other therapeutic approaches.[3]
- The national opioid overdose death rate increased 255.74% between 2000 and 2019; recent efforts have flattened the curve modestly, but the problem is far from resolved.[4]
- The poor risk–benefit ratio prompted the FDA to require "black box" warning labels on package inserts highlighting these risks.[3]

Capital is already moving against the problem

In 2022 the Biden Administration awarded $1.5 billion to address the opioid crisis and support individuals in recovery. Pharmacy benefit managers, including Express Scripts, have moved to limit the number and strength of opioid drugs prescribed.[5]

The virulence of the opioid epidemic, coupled with the size of the neuropathic pain market and the lack of safe, effective treatment options, creates a compelling opportunity for investment in this area.[2]

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1. Akelos PPM, Executive Summary, p. 3. 2. Akelos PPM, p. 4, citing CDC SUDORS Fatal Drug Overdose Data Dashboard. 3. Akelos PPM, "Clinical Overview — Problem Statement," p. 6, citing Reuben D. et al., *Ann Intern Med*, 2015. 4. Akelos PPM, p. 8, citing drugabusestatistics.org. 5. Akelos PPM, p. 8.

Every incumbent class is a compromise

Treatment is dominated by generic opioids, antidepressants and anticonvulsants — or a combination — despite limited efficacy and a marked adverse side-effect profile.[1]

CLASS	REPRESENTATIVE AGENTS	THE COMPROMISE
Gabapentinoids	Gabapentin; pregabalin (Lyrica®)	Researchers have found limited efficacy for neuropathic pain despite widespread use — gabapentin exceeds $1.5B in global sales and Lyrica® exceeded $3.6B at peak.[2] Burdened by CNS side effects and generic erosion.[3]
Antidepressants	Duloxetine (Cymbalta®, Lilly)	Resulted in minimal pain reduction in patients with chemotherapy-induced peripheral neuropathy.[2]
Opioids	Tramadol; morphine	One of the most common treatments for neuropathic pain despite lack of efficacy, leading to potential misuse and addiction (~30%).[2]
Topicals	Lidocaine; capsaicin	Limited to localized relief, with minimal efficacy for systemic neuropathic pain.[3]
Anticonvulsants / steroids	Various generics	Anticonvulsants remain the largest drug-class segment of the market, but fewer than 35% of patients derive meaningful benefit from non-opioid approaches.[1,4]

The clinical consequence

Patients cycle through ineffective options, often forced to choose between inadequate pain relief and debilitating side effects.[3]

The commercial consequence

Payers are aggressively seeking non-opioid alternatives to reduce long-term healthcare costs and the liabilities associated with addiction, and the FDA and EMA are actively fast-tracking non-opioid analgesics through expedited pathways.[3]

1. Akelos PPM, Executive Summary, p. 3, and "Clinical Overview," p. 6. 2. Akelos One-Pager, May 5, 2025, citing Goodman & Brett, *JAMA Intern Med*, 2019 and Smith et al., *JAMA*, 2013. 3. Artane Partners, "Project Aqua" Pre-NDA Teaser (V.3), "Market Gap & Urgency," p. 3. 4. Akelos PPM, "Competition / market segmentation," p. 24.

CIPN is the entry point: severe, growing, and with no approved therapy

Chemotherapy-induced peripheral neuropathy is the most prevalent neurological complication of oral or intravenous chemotherapy.[1]

- CIPN is a progressive, enduring and often irreversible condition featuring pain, numbness, tingling and sensitivity to cold in the hands and feet, sometimes progressing to the arms and legs.[2]
- 30% of all patients receiving chemotherapy — and 93% of those receiving platins — develop CIPN.[2]
- Although symptoms may improve after the causative chemotherapy stops, approximately 30–40% of patients face chronicity of symptoms.[1]
- Patients often deem CIPN so unbearable that they are willing to discontinue cancer treatment despite the potential for decreased survival.[2]
- Rising global cancer incidence is driving more chemotherapy use; the WHO estimates new cancer cases will rise by 70% over the next two decades.[3]

$1.66B → $1.78B

GLOBAL CIPN TREATMENT MARKET, 2024 → 2025 · CAGR 7.1%[1]

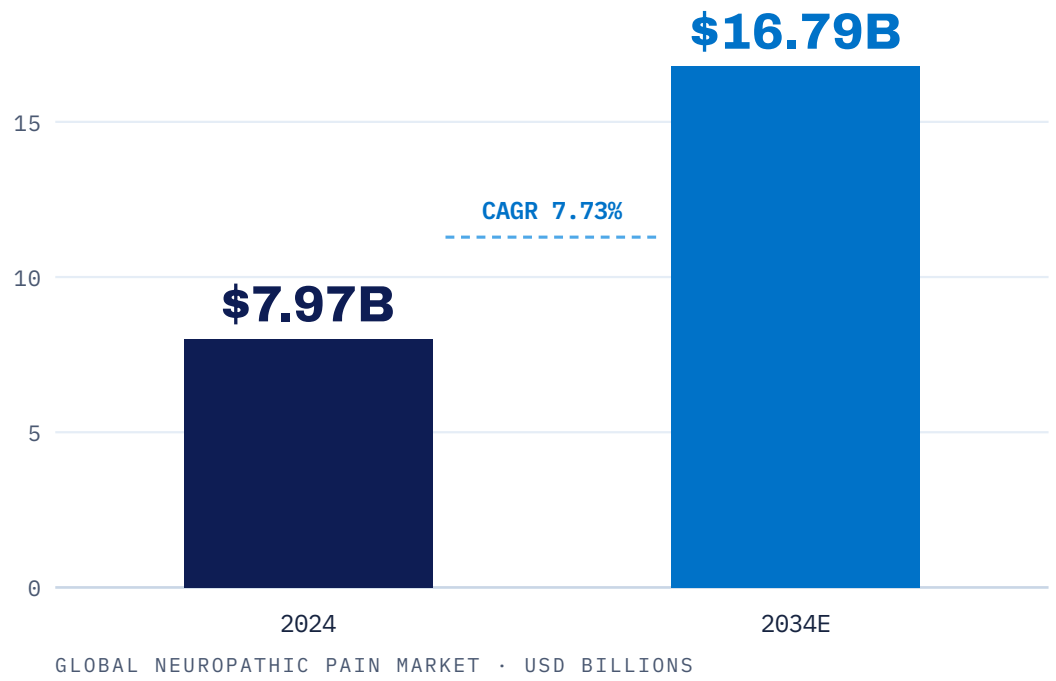
Why it is the right first indication

CIPN is the leading segment of the neuropathic pain market and, per the Company's positioning analysis, represents a market with no approved therapies — offering a rapid regulatory path and immediate addressability upon approval.[1,3]

Recent work indicates that selective inhibition of HCN1 channel function may be a viable strategy for relieving CIPN.[4]

1. Akelos Investor Deck, May 5, 2025 (p. 18), citing PMC8236465 and healthcareresearchreports.com. 2. Akelos One-Pager, May 5, 2025, citing Wolf et al., *Eur J Cancer* 2008; Hall et al., *BMC Fam Pract* 2008; Freynhagen & Bennett, *BMJ* 2009; von Hehn et al., *Neuron* 2012; Colvin, *Pain* 2019. 3. Artane Partners, "Project Aqua" Pre-NDA Teaser (V.3), "Market Opportunity," p. 7. 4. Akelos PPM, p. 24.

A market that roughly doubles over the next decade



GLOBAL NEUROPATHIC PAIN MARKET · USD BILLIONS

- The global neuropathic pain market was valued at **$7.97B in 2024** and is expected to reach approximately **$16.79B by 2034**, a CAGR of 7.73%.[1]
- A second published estimate puts global neuropathic pain therapeutics at **$7.7B** and projects **$13.3B by 2032** at a 5.6% CAGR.[2]
- By indication, diabetic neuropathy holds the highest value share at **46.7%**; CIPN accounts for an estimated **42.4%** of revenue.[3]
- Growth drivers include rising incidence of diabetes and cancer, new treatment options, and growth in the number of pain management centers.[3]

Serviceable focus

The Company's obtainable market is deliberately and exclusively focused on chronic neuropathic pain — avoiding the saturated acute pain market crowded with generics, NSAIDs and short-acting opioids, where differentiation is difficult and pricing power is low.[4]

1. Precedence Research, "Neuropathic Pain Market," as cited in Akelos Investor Deck, May 5, 2025 (p. 18) and Akelos PPM, References — Market Projections. 2. Allied Market Research 2023, as cited in Akelos PPM, Executive Summary, p. 3, and Artane Partners "Project Aqua" Teaser, p. 7. 3. Akelos PPM, p. 24. 4. Artane Partners, "Project Aqua" Pre-NDA Teaser (V.3), "Market Opportunity," p. 7.

THE SCIENCE · 01

Injured sensory neurons turn HCN1 up. Akelos turns it back down.

Analgesia without anesthesia — a peripheral mechanism that reduces neuronal excitability at the site of injury rather than blunting the brain.[1]

Neuronal injury
Nerve damage, chemotherapy, diabetes, surgery

→

HCN1 upregulated
Channel expression and function are enhanced

→

Hyperexcitability
Aberrant firing in primary sensory neurons → pain

→

AKE-1018 selectively inhibits HCN1
A molecule nearly identical in structure to a known, safe existing anesthetic — optimized to selectively and potently inhibit HCN1 and limit the experience of pain.

Disease-linked, not just present

HCN1 channel expression and function are upregulated in CIPN, peripheral nerve injury and diabetic neuropathy.[1]

A causal chemotherapy link

Oxaliplatin increased HCN1 mRNA expression, driving chemotherapy-induced hypersensitivity.[1]

Structurally validated

The binding site for propofol (2,6-diisopropylphenol) on human HCN1 has been identified and published in *Nature*, reinforcing the proposed mechanism.[2]

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1. Akelos One-Pager, May 5, 2025, "Akelos' Novel Mechanism of Action" and "Proprietary Assets Targeting HCN1 Pathways." 2. Kim E.D., Wu X., Lee S. et al., "Propofol rescues voltage-dependent gating of HCN1 channel epilepsy mutants," *Nature* 632:451–459 (2024), as cited in Akelos PPM, p. 17.

HCN1 is the obvious target in humans — and the species difference matters

Despite compelling mouse data linking HCN2 to the initiation of neuropathic pain, there is a strong rationale for developing alkylphenol-derived HCN1-selective therapeutics for the treatment of neuropathic pain in humans.[1]

- HCN1 is present in human dorsal root ganglia at the gene and mRNA level.[1]
- HCN1 mRNA is present in a far larger proportion of human DRG neurons than HCN2 — **94.4% vs 44.0%** — in contrast to mice, where the two are seen with roughly equal frequency (71.5% and 70.9%).[1]
- HCN1 appears to be the predominant functional HCN isoform in human sensory neurons, with relative mRNA expression HCN1 > HCN2 >> HCN3 > HCN4.[1]
- **HCN1 protein is absent from human heart.**[1]
- HCN1-selective inhibitors do not produce bradycardia.[1]
- 2,6-di-isopropylphenol inhibits HCN1 homomers and HCN1+HCN2 heteromers with equal efficacy — both of which are likely present in human DRG neurons.[1,2]
- Of the three identified HCN1-selective channel-modulating chemical series, the Akelos version is the only one known to block both HCN1 and HCN1/HCN2 heteromers.[1]

CHANNEL	% OF TOTAL NEURONAL POP.	% NOCICEPTORS
HCN1	**94.4**	**73.9**
NaV1.7	96	69
NaV1.8	71	71

mRNA EXPRESSION FOR EACH TARGET IN HUMAN DRG. NOCICEPTORS DEFINED AS CGRP- AND/OR P2X3R-POSITIVE. SHIERS ET AL., *PAIN* 2020.[2]

In the authors' words

Shiers and colleagues note that these marked species differences may have important implications for the role of different HCN isoforms in pain states between mouse models and human patients.[1]

1. Akelos Investor Deck, May 5, 2025, "HCN1 is the Obvious Target" (p. 89) and "Why Targeting HCN1 Matters" (p. 75), citing Ray et al. 2018; Shiers et al. 2020; North et al. 2018; Young et al. 2014; Stillitano et al. 2008; McClure et al. 2011; Resta et al. 2018; Chen et al. 2005; Joyce et al. 2019; Kim et al. *Nature* 2024. 2. Akelos, "NaV1.7 / 1.8 vs HCN1" target comparison memo, citing Shiers et al., *Pain*, 2020.

Sodium channels have been tried for two decades. The record is poor.

NAV-TARGETING AGENTS — A LONG HISTORY OF FAILURES[1]

DRUG (SPONSOR)	TARGET	OUTCOME
AZD3161 (AstraZeneca)	NaV1.7	Evaluated for pain relief. Failed due to a lack of efficacy.
Raxatrigine (GSK)	NaV1.7	Trigeminal neuralgia & neuropathic pain. Failed due to a lack of efficacy.
PF-05089771 (Pfizer)	NaV1.7	Selective inhibitor evaluated for DPN. Failed due to a lack of efficacy.
Funapide (Teva/Xenon)	NaV1.7	Postherpetic neuralgia and osteoarthritis. Failed due to a lack of efficacy.
DSP-2230 (Sumitomo Dainippon)	NaV1.7/1.8	Dual blocker for neuropathic pain. Failed due to a lack of efficacy.
VX-150 (Vertex)	NaV1.8	Early NaV1.8 inhibitor. Failed due to a lack of efficacy.
PF-01247324 (Pfizer)	NaV1.8	NaV1.8 inhibitor for pain treatment. Failed due to a lack of efficacy.
A-803467 (Abbott)	NaV1.8	Preclinical blocker with promising data. Failed on safety and efficacy concerns.
Suzetrigine (Vertex)	NaV1.8	Studied in acute (surgical) and chronic pain. Failed to outperform placebo in chronic pain.

REASON TO BELIEVE IN HCN TARGETING

Ivabradine (Amgen / Servier)

A pan-HCN (1,2,3,4) blocker approved for heart failure. Studied in pain, it demonstrated a dose-dependent relationship with pain scores — but led to bradycardia, which is expected with pan-HCN agents.[1]

The read-through

Human proof that HCN blockade moves pain scores, with the liability traced to the isoforms Akelos does not target. HCN1 protein is absent from human atrial and ventricular tissue, and HCN1-selective inhibitors do not produce bradycardia.[2]

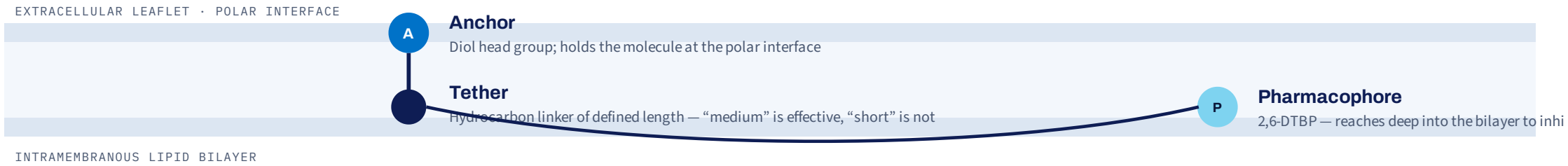
Reported analysis showed a reduction of 0.126 ± 0.01 (SEM) NRS points per milligram of ivabradine, with the two participants with painful diabetic neuropathy responding particularly well.[3]

1. Akelos Investor Deck, May 5, 2025, “Target engagement: HCN1 Versus NaV1.7 & NaV1.8” (p. 19), citing Bernard Healey et al. 2021. 2. Akelos Investor Deck, May 5, 2025, “Why Targeting HCN1 Matters” (p. 75). 3. Akelos, “NaV1.7 / 1.8 vs HCN1” target comparison memo (quoted analysis of ivabradine dose–response).

THE ASSET · 01

AKE-1018: an anchor-tethered pharmacophore that behaves exactly as modelled

The lead new chemical entity — originally RU51-nb2 — potently inhibits HCN1 function, comparable to the parent pharmacophore 2,6-DTBP, and the whole molecule behaves as predicted in *in silico* molecular dynamic modelling.[1]



Design principle confirmed

The unanchored molecule is an effective HCN1 inhibitor, indicating the channel is agnostic to the presence of a tether. Attaching an anchor to a *short* tether renders the molecule ineffective — establishing that the pharmacophore’s ability to reach deep into the membrane is critical to inverse agonist function.[1]

Anchor-tether strategy

The strategy optimizes access of the pharmacophore to its binding site, achieving high effector-site concentration.[2]

Screening infrastructure in place

In 2019 Akelos acquired a Sophion QPatch II 48-channel automated patch clamp system, improving efficiency and facilitating *in vitro* identification of enhanced pharmacophores.[3]

1. Akelos PPM, Figure 3 and accompanying text, pp. 12–13; data from Tibbs et al., *Br J Anaesth* 2023. 2. Akelos One-Pager, May 5, 2025. 3. Akelos PPM, p. 17.

Published efficacy: oral dosing, rapid onset, both sexes

Drs. Gareth Tibbs, Dianna Willis and Peter Goldstein reported that AKE-1018 provided safe and effective pain relief following peripheral nerve injury, in the *British Journal of Anaesthesia*.[1]

< 24 h

TO ANTIHYPERALGESIC EFFECT AFTER A SINGLE ENTERAL DOSE[2]

7 days

CONTINUED IMPROVEMENT WITH ONCE-DAILY DOSING[2]

M = F

EFFECTS WERE NEARLY IDENTICAL IN MALE AND FEMALE RATS[2]

Oral

ORALLY BIOAVAILABLE; ENTERAL ADMINISTRATION IN THE PUBLISHED MODEL[2,3]

MODEL AND READOUTS

- Adult rat **spared nerve injury** model of neuropathic pain.[2]
- Rapidly relieved **mechanical hyperalgesia**.[2]
- Rapidly relieved **thermal allodynia** to both heat and cold.[2]
- Antihyperalgesic effects were **dose-dependent**.[2]
- The *in vivo* effects correlated with *in vitro* inhibition of the HCN1 ion channel.[1]

STATISTICAL RESULT

Efficacy was statistically significant as measured by reductions in the time and probability of animal subject response to mechanical and thermal stimulation following nerve injury.[3]

Related human-adjacent evidence

Joyce et al. 2023 describes the antihyperalgesic effects of probucol — a clinically used antihyperlipidemic agent that is a dimerized congener of 2,6-DTBP.[4]

1. Akelos PPM, Executive Summary, p. 2, and p. 17, citing Tibbs et al., "An anchor-tether 'hindered' HCN1 inhibitor is antihyperalgesic in a rat spared nerve injury neuropathic pain model," *British Journal of Anaesthesia* 131(4):745–763, 2023. 2. Akelos PPM, p. 13 (award-period results, Figures 4–5). 3. Akelos One-Pager, May 5, 2025; Akelos Investor Deck, May 5, 2025 (p. 51). 4. Akelos PPM, p. 17, citing Joyce et al. 2023.

Clean at ten times the effective dose

At a 10-fold higher dose than that which produced pain relief, no adverse effects were observed across cardiovascular, motor, sedation or abuse-liability assessments.[1]

NO CV EFFECT

Cardiovascular

No change in heart rate or blood pressure.[1]

NO MOTOR EFFECT

Motor function

No evidence of impaired muscle strength or coordination.[1]

NON-SEDATING

Sedation

No evidence of sedation; no change in activity.[1,2]

NO ABUSE SIGNAL

Abuse potential

No evidence of abuse potential — a hallmark liability of opioids.[1,2]

Why the cardiac result follows from the biology

HCN2 and HCN4 are the primary isoforms expressed in human cardiac tissues, and HCN1 protein is absent from human heart. Consistent with this, researchers demonstrated in *Cell Chemical Biology* that selective HCN1 inhibition does not affect the electrophysiological properties of human iPSC-derived atrial-like cardiomyocytes.[3]

PRECEDENT FOR THE CHANNEL FAMILY

HCN channels as therapeutic targets have already been exploited for the treatment of heart failure by Servier Laboratories (Procoralan®) and Amgen (Corlanor®, under license to Servier) — so there is ample evidence that inhibition of HCN channels with a non-specific HCN channel blocker is well tolerated in humans. There is strong support for the development of novel selective HCN blockers as anticonvulsants, anesthetic adjuncts, and most importantly, antihyperalgesics.[4]

1. Akelos PPM, p. 13 (Figures 6–8) and Executive Summary, p. 2, reporting results published in Tibbs et al., *Br J Anaesth*, 2023. 2. Akelos Investor Deck, May 5, 2025, "The Lead NCE — AKE-1018" (p. 51). 3. Akelos PPM, p. 17, citing Harde E., Hierl M., Weber M. et al., *Cell Chemical Biology* 3:577–592 (2024). 4. Akelos PPM, "Competition," p. 24, citing Postea O. & Biel M., *Nat Rev Drug Discov* 10:903–14, 2011.

Designed not to enter the brain — and confirmed twice

AKE-1018 was designed *not* to cross the blood–brain barrier. This was confirmed in both *in silico* molecular modelling and *in vivo* pharmacodynamic studies, highlighting a peripheral mechanism of action.[1]

Excluded from the CNS as designed

Listed among the defining properties of the lead NCE alongside oral bioavailability, potent HCN1 inhibition, and effective membrane anchoring *in silico*.[2]

Analgesia without anesthesia

The molecule is nearly identical in structure to a known, safe existing anesthetic, but optimized to selectively and potently inhibit HCN1 and limit the experience of pain.[3]

WHAT PERIPHERAL RESTRICTION BUYS

- Avoids the CNS side-effect burden — lethargy, dizziness, cognitive impairment — that limits gabapentinoids.[4]
- Addresses the root cause of neuropathic pain signals without the liabilities of the current standards of care.[4]
- Supports the observed absence of sedation and abuse potential at 10× the efficacious dose.[1]

Note on modelling

The published molecular dynamics model does not incorporate the HCN1 protein itself; that modelling is now feasible given publication of the cryo-EM HCN1 structure by the MacKinnon group at Rockefeller University in 2017.[5]

1. Akelos PPM, Executive Summary, p. 2, and p. 17. 2. Akelos Investor Deck, May 5, 2025, “The Lead NCE — AKE-1018” (p. 51). 3. Akelos One-Pager, May 5, 2025. 4. Artane Partners, “Project Aqua” Pre-NDA Teaser (V.3), pp. 3, 5. 5. Akelos PPM, p. 13, citing Lee C.H. & MacKinnon R., *Cell* 168(1):111–120, 2017.

POSITIONING

Competitors are treating a different problem, or treating this one bluntly

Unlike peers focused on acute pain or broader mechanisms, Akelos is positioned with a first-in-class, NIH-funded HCN1 program directly addressing the critical unmet need of chronic neuropathic pain.[1]

PROGRAM	MECHANISM	STAGE	FOCUS	POSITIONING
Akelos — AKE-1018	**HCN1 blocker, peripherally restricted**	**Preclinical / IND-enabling**	**Chronic neuropathic pain (initially CIPN)**	**First-in-class approach directly addressing chronic neuropathic pain, where no effective non-opioid exists. Peripherally restricted design aims to deliver potent analgesia without CNS side effects. Supported by NIH Fast-Track funding.[1]**
Vertex — suzetrigine	NaV1.8 inhibitor	FDA approved	Acute pain (post-surgical, musculoskeletal)	An advance in acute pain, but limited to short-term indications. Does not address chronic neuropathic pain.[1]
Pfizer — Lyrica® (pregabalin)	Calcium channel α2δ ligand	Marketed	Broad chronic pain, fibromyalgia, epilepsy	Blockbuster non-opioid, but limited by CNS side effects (dizziness, somnolence, dependence risk) and loss of exclusivity.[1]
Novaremed — MP-101	Neuromodulator (NMDA pathway)	Phase 2	CIPN, diabetic neuropathy	Active in CIPN. Akelos' HCN1 program offers a mechanistically distinct, peripherally restricted approach, potentially reducing CNS risks.[1]
Algiax — AP-325	$GABA_A$ modulator	Phase 2a	Neuropathic pain	Demonstrated proof-of-concept in neuropathic pain. Akelos is differentiated by a novel ion-channel mechanism, with potential for broader efficacy and a safer long-term profile.[1]
Grünenthal — QUTENZA®	High-concentration capsaicin (topical)	Approved / Phase III	PHN, diabetic peripheral neuropathy	Approved for peripheral neuropathic pain in Europe and, in the US, for PHN and DPN of the feet; a Phase III trial targets post-surgical neuropathic pain.[2]

1. Artane Partners, "Project Aqua" Pre-NDA Teaser (V.3), "Competitive Landscape — Non-Opioid Pain Therapeutics," pp. 5–6. 2. Akelos PPM, "Competition," p. 27.

BEYOND THE LEAD

Swap the anchor and the same chemistry becomes a delivery platform

The lead candidate is architected with two chemical prongs: an anchor (non-active component) and a payload (the active pain-relief API).[1]

The insight

The anchor is non-selective — but it can be replaced with a targeting system or a monoclonal antibody that potentially targets the molecule to specific tissues in the body. Next-generation development will focus on producing mAB-anchored therapeutics.[1]

Already in the plan

Second-generation use of an HCN1-selective antibody as the anchor further enhances tissue targeting.[2]

Why it is disruptive

It creates a platform asset with potential for unique patented therapies across multiple diseases, may allow drug delivery to be localized to specific tissues, and unlocks broad-based pain therapeutics with improved safety profiles — not limited to neuropathic pain.[1]

PROGRAM 1

AKE-1018

PERIPHERALLY RESTRICTED HCN1 INVERSE AGONIST FOR CHRONIC NEUROPATHIC PAIN

$14M

SOUGHT[3]

PROGRAM 2

AKE-XG

NEXT-GENERATION ANTIBODY-ANCHORED PLATFORM PROGRAM

$1.5M

SOUGHT[3]

THERE IS NO GUARANTEE THAT AKELOS INC.'S OBJECTIVES WILL BE REALIZED.[1]

AKELOS

1. Akelos Investor Deck, May 5, 2025, "Disruptive Future Platform Potential Beyond Neuropathic Pain" (p. 70). 2. Akelos One-Pager, May 5, 2025. 3. Akelos Investor Deck, May 5, 2025, "Vision for the Future – Disruptive Therapeutics" (p. 67); Akelos Speed Pitch Deck, January 17, 2025 (p. 6).

One patent family, filed in six jurisdictions, already granted in four

ROOT APPLICATION

PCT/US2019/039493

"Substituted Alkylphenols as HCN1 Antagonists," filed June 27, 2019. All patents in the family derive from this application.[1]

- Patents claiming Akelos' lead compound, related compounds, and methods of treating pain have been **issued or allowed in the US, China, Japan and Australia**.[1]
- The family was filed in the **US, Europe, Japan, China, Canada and Australia**; allowances are expected in Europe and Canada.[1,2]
- The Company holds an **exclusive license from Cornell** to a patent family claiming novel pharmaceutical compounds and their use as painkillers.[2]
- A comprehensive IP strategy is intended to capture new inventions in real time.[1]

JURISDICTION STATUS

JURISDICTION	STATUS
United States	**Issued or allowed**
China	**Issued or allowed**
Japan	**Issued or allowed**
Australia	**Issued or allowed**
Europe	Filed — allowance expected
Canada	Filed — allowance expected

License obligations to note

The license requires annual maintenance fees and milestone payments, achievement of diligence objectives, and expenditure requirements prior to commercialization; Akelos also pays all patent costs associated with the licensed products.[3] Cornell holds 5% of outstanding common stock and will continue to hold 5% through the issuance of additional shares until the Company raises an aggregate of $7,000,000.[4]

1. Akelos Investor Deck, May 5, 2025, "Intellectual Property" (p. 56); Akelos One-Pager, May 5, 2025. 2. Akelos PPM, Executive Summary, p. 2. 3. Akelos PPM, "License and Collaboration Agreements," p. 32. 4. Akelos PPM, "Terms of the Offering — Capitalization," p. 5.

ASSETS · VALIDATION

$11.7 million of non-dilutive capital and a peer-reviewed record

Third parties — the NIH among them — have already funded and scrutinised this programme.[1]

FUNDING INTO THE TECHNOLOGY TO DATE

Prior academic research funding, Goldstein Lab	**$8.0M**
NIH HEAL Initiative grant to the Weill Cornell / Burke team (Oct 2019, two-year)	**$1.7M**
NINDS Phase I/II Fast-Track STTR awarded to Akelos	**$3.69M**
Total non-dilutive funding in the technology	**$11.7M**

The 2019 HEAL award supported development of HCN1-selective therapeutics for neuropathic pain. The STTR award, made in September 2022, has the goal of identifying a high-potency HCN1-selective molecule to replace the existing 2,6-DTBP pharmacophore currently present in AKE-1018; the grant period concluded in January 2026.[2]

SELECTED PEER-REVIEWED RECORD

Tibbs et al., *British Journal of Anaesthesia*, 2023

An anchor-tether “hindered” HCN1 inhibitor is antihyperalgesic in a rat spared nerve injury neuropathic pain model. 131(4):745–763.[3]

Kim, Wu, Lee et al., *Nature*, 2024

Propofol rescues voltage-dependent gating of HCN1 channel epilepsy mutants. 632:451–459 — identifying the propofol binding site on human HCN1.[4]

***Biochemical Pharmacology*, 2019**

Alkylphenol inverse agonists of HCN1 gating: H-bond propensity, ring saturation and adduct geometry differentially determine efficacy and potency.[5]

***J. Pharmacology & Experimental Therapeutics*, 2005 & 2013**

Data supporting the overall approach.[6]

1. Akelos One-Pager, May 5, 2025; Artane Partners “Project Aqua” Teaser (V.3), p. 10. 2. Akelos PPM, p. 13, and Executive Summary, p. 3; Akelos Investor Deck, May 5, 2025 (p. 61). 3. Akelos PPM, references, p. 47. 4. Akelos PPM, p. 17. 5. Akelos PPM, p. 13. 6. Akelos PPM, Executive Summary, p. 2.

THE PLAN · 01

Twenty-four months: candidate selection, then IND enablement

Twelve months to a development candidate, twelve months of IND-enabling work — with defined milestones and exit points, and funding planned accordingly.[1]

MONTH 0 — MONTH 12 — MONTH 24

Pre-IND stage · Lead optimization → candidate selection
Med chem · pharmacology screen & IC50 · ADME · preclinical safety & tox · formulation · PK · in vivo efficacy

IND enablement
GLP tox program · safety pharmacology & genotoxicity · drug substance (incl. GMP synthesis) · drug product

Milestone · Candidate selection
$2,680,000 committed to lead optimization across Akelos and CROs

Milestone · IND submission
$5,865,000 committed to IND enablement

Post-IND: plan and prepare for first-in-human trials, for which additional funding will be sought — a potential exit point, in particular for in-licensing by large pharmaceutical partners.

Regulatory sequencing

A pre-IND meeting is planned for regulatory concurrence with, and guidance on, the clinical program prior to definitive toxicology studies.[2]

Clinical design intent

The Phase 1b study includes an option for adaptive design, to ensure the proper dose and regimen are selected for later-stage clinical studies.[2]

Regulatory reality

An IND becomes effective 30 days after receipt by the FDA unless the agency raises concerns and places the IND on clinical hold within that period.[3]

1. Akelos PPM, “Budget and Funding,” Tables 2 and 3, pp. 20–22. 2. Akelos Investor Deck, May 5, 2025, “Product Development” (p. 65). 3. Akelos PPM, “Regulatory Pathway,” p. 28.

The IND-enabling package, costed line by line

$5,865,000 across four workstreams over twelve months, executed by Akelos with contract research organizations.[1]

GLP TOXICOLOGY PROGRAM	$1,040,000
Dose range, rodent with TK, 7–10 d	$50,000
Dose range, non-rodent with TK, 7–10 d	$90,000
GLP 28-day rodent with TK & histopathology	$300,000
GLP 28-day non-rodent with TK & histopathology	$600,000

SAFETY PHARMACOLOGY & GENOTOXICITY	$550,000
GLP mutagenicity (Ames, chromosome aberration, micronucleus)	$200,000
Respiratory safety (rodent)	$50,000
CNS safety — FOB / Irwin study (rodent)	$50,000
Abuse potential (rodent: CPP, DD, no SA)	$125,000
Cardiovascular safety — non-rodent CV telemetry	$125,000

DRUG SUBSTANCE	$3,275,000
Salt / polymorph, process development	$250,000
Scale-up & demo run → GLP batch	$300,000
Analytical method development	$125,000
GMP synthesis	$2,500,000
Stability (out to 12 months)	$100,000

DRUG PRODUCT (ORAL)	$1,000,000
Formulation (capsules, tablet, oral suspension)	$350,000
Manufacturing	$500,000
Stability, compatibility and related work	$150,000

Also funded pre-candidate: PK across multiple compounds and routes; CIPN efficacy studies (oxaliplatin and taxol); other rodent pain models (DPN, nerve injury); non-GLP MAD, DRF and MTD studies; and $100,000 for New Approach Methods assessing the feasibility of replacing animal work.[1]

1. Akelos PPM, “Budget and Funding,” Table 3, pp. 21–22.

Where the money goes

Total program cost from lead optimization through first-in-human readiness: **$13,503,000** over 24 months.[1]

DRUG DISCOVERY, CHEMISTRY, ADME & CMC
$5.305.000

PHARMACOLOGY, PRECLINICAL PK & EFFICACY
$2.690.000

SAFETY
$550.000

G&A + MISCELLANEOUS
$4.958.000

G&A AND MISCELLANEOUS, ITEMISED

CEO (24 months, full time)	**$720,000**
CSO (24 months, full time)	**$600,000**
CBO — to be hired (24 months, full time)	**$480,000**
Office administration (24 months)	**$168,000**
CMC, PK/toxicology and acting-CMO consultants	**$420,000**
Cornell license fee	**$1,200,000**
Other miscellaneous over 24 months	**$1,370,000**

WHAT THE PROCEEDS ARE FOR

- **NCE refinement.** Create HCN1-selective NCEs restricted to peripheral compartments without blood–brain barrier penetration, shown to bind HCN1 both *in vitro* and *in vivo*.[2]
- **Team development.** Retain a best-in-class executive team including an operations/business development director and key strategic hires that augment clinical development capability.[2]
- **Pre-clinical execution.** Partner with Weill Cornell Medicine and third-party CROs to establish pharmacokinetic and toxicity profiles for clinical development.[2]

Regulatory focus will be on post-chemotherapy-induced neuropathy, painful peripheral diabetic neuropathy, and/or post-herpetic neuropathic pain.[2] Per the offering documents, proceeds will be used for research and development and working capital.[3]

1. Akelos PPM, “Budget and Funding,” Table 3, pp. 21–22. 2. Akelos PPM, “Go Forward Opportunity,” p. 19. 3. Akelos PPM, “Terms of the Offering — Use of Proceeds,” p. 5.

VALUE CREATION

Pain assets repeatedly clear $1 billion — and the market punishes the wrong mechanism

$1B

TOTAL LICENSING DEAL — LILLY / CENTREXION **CNTX-0290**, A SOMATOSTATIN RECEPTOR TYPE 4 (SSTR4) AGONIST[1]

Up to $1B

COMPANY ACQUISITION — LILLY / SITEONE THERAPEUTICS **STC-004**, TARGETING NAV1.8[2]

$285M

VC FUNDING RAISED ACROSS THREE ROUNDS BY **LATIGO BIOTHERAPEUTICS**, AN EARLY-STAGE NAV1.8 DEVELOPER — AT AN ESTIMATED $1.5 BILLION VALUATION[3]

–19.28%

VERTEX SHARE PRICE DECLINE — A MULTIBILLION-DOLLAR MOVE — AFTER **VX-993**, A NAV1.8 INHIBITOR, FAILED PHASE II ENDPOINTS AND THE PROGRAM WAS ABANDONED[4]

The read for Akelos

Capital is flowing into non-opioid pain at billion-dollar scale — and concentrating in a mechanism with a documented record of chronic-pain failures. Akelos offers exposure to the same commercial opportunity through a differentiated, human-relevant target.[1,4,5]

Anticipated exit

Management believes a more likely exit for investors will be through the acquisition of Akelos by a larger pharmaceutical company. There have been no discussions with respect to any potential sale transaction, and it is unlikely such an opportunity would be available in the next few years, if at all. Investors should be prepared to hold the shares for an indefinite period.[6]

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1–4. Akelos Investor Deck, September 3, 2025, "Pain Drugs Repeatedly Exceed $1 Billion in Valuation" (p. 11), citing pharmaphorum; Eli Lilly and Company; AInvest; CB Insights. 5. Akelos Investor Deck, May 5, 2025 (p. 19). 6. Akelos PPM, Risk Factors ("Arbitrary Determination of Offering Price" section context), p. 33 ff.

THE PEOPLE

Leadership, strategic advisors and scientific advisory board

A Nobel Prize recipient, leading clinical anesthesiologists specializing in pain management, the former Chief Counsel for the FDA, a former US Senator, and senior pharmaceutical executives with experience developing pain drugs.[1]

Steven R. Fox, DDS

PRESIDENT & CHIEF EXECUTIVE OFFICER

20+ years as an entrepreneur; Ernst & Young Entrepreneur of the Year; Medal of Freedom recipient; former CEO of a public oral care company; Chairman, The Rebel Group; former faculty at Harvard University and NYU.[2]

Peter A. Goldstein, MD

SCIENTIFIC CO-FOUNDER · SAB

Principal Investigator, C.V. Starr Laboratory for Molecular Neuropharmacology, Weill Cornell Medical College; 18+ years in the Department of Anesthesiology at Weill Cornell Medical Center.[2]

Gareth Tibbs, PhD

SCIENTIFIC CO-FOUNDER · SAB

A leading authority on HCN channel function with deep domain expertise in the biophysics of HCN channels; B.A. and Ph.D. from University College London.[2]

Cyrus Arman, PhD, MBA

HEAD OF BUSINESS DEVELOPMENT

Corporate, clinical and commercial strategy for Amgen, Nimble Therapeutics and NEUVOGEN; former President and Principal Operating Executive, CytoDyn.[3]

Scott L. Dax, MS, PhD

RESEARCH & DEVELOPMENT CHAMPION

Former Chief Scientific Officer at CerSci Therapeutics; analgesics research team leader at Johnson & Johnson; inventor on 100+ issued patents worldwide.[1]

Peter Hutt, JD

FDA COUNSEL

50+ years as a food and drug law specialist; former Chief Counsel, U.S. Food and Drug Administration; Senior Counsel, Covington & Burling LLP; faculty member, Harvard Law School.[2]

Robert Benson, PhD

INTELLECTUAL PROPERTY ADVISOR

20+ years in licensing and intellectual property; Principal of South Shaker Associates; former department head at Harvard University; former supervisor at the NIH.[2]

Senator Thomas Daschle

STRATEGIC HEALTHCARE ADVISOR

Health Policy and Management Executive Council, Harvard School of Public Health; Council on Governance for Sustainability, World Economic Forum; Federal Advisory Board of Accenture.[3]

Michael Levitt, PhD

ACCLAIMED BIOPHYSICIST · SAB

Robert W. & Vivian K. Cahill Professor in Cancer Research, Stanford School of Medicine; recipient of the 2013 Nobel Prize in Chemistry.[1]

Charles Berde, MD, PhD

PRINCIPAL INVESTIGATOR & KOL · SAB

Sara Page Mayo Chair in Pediatric Pain Medicine and Director of Pain Treatment Services, Boston Children's Hospital; Professor of Anesthesia (Pediatrics), Harvard Medical School.[1]

Dianna Willis, PhD

PROMINENT PAIN RESEARCHER · SAB

Head, Laboratory for Axonal and RNA Biology, and Director of the Center for Pain Research, Burke Neurological Institute; Assistant Professor of Neuroscience, Weill Cornell Medicine.[1]

Darryle D. Schoepp, PhD

STRATEGIC ADVISOR · SAB

30+ years in pharmaceutical research and drug discovery; former SVP and Neuroscience Research Head at Merck; former VP, Neuroscience Delivery Research at Eli Lilly; 200+ publications and 15 US patents.[1]

1. Akelos Investor Deck, September 3, 2025, "Distinguished Scientific Advisory Board" (p. 29); Akelos One-Pager, May 5, 2025. 2. Akelos Investor Deck, May 5, 2025, "Team" (p. 53). 3. Akelos Investor Deck, May 5, 2025, "Strategic Advisors" (p. 54); Akelos PPM, Management biographies, p. 39.

THE ASK

$14,000,000 to take a peripherally restricted HCN1 inhibitor to an IND

TERMS OF THE OFFERING[1]

Securities offered	**Common stock, par $0.0001**
Offering size	**Up to $14,000,000**
Purchase price	**$2.75 per share**
Minimum investment	**5,000 shares · $13,750**
Use of proceeds	**R&D and working capital**
Investor qualification	**Rule 506(c) · accredited only**
Offering period	**Through Dec 31, 2026**
Shares issued at maximum	**5,090,909**

OFFERED ON A BEST-EFFORTS BASIS WITH NO MINIMUM. PRIOR TO THE OFFERING THERE WERE APPROXIMATELY 31,503,967 SHARES OF COMMON STOCK OUTSTANDING, PLUS OPTIONS AND WARRANTS FOR 2,539,865 SHARES. THE OFFERING PERIOD MAY BE EXTENDED BY UP TO SIX MONTHS AT THE COMPANY'S DISCRETION. THE OFFERING PRICE WAS DETERMINED BY THE FOUNDER AND DOES NOT NECESSARILY BEAR ANY RELATIONSHIP TO BOOK VALUE, ASSETS OR FINANCIAL CONDITION.[1,2]

WHAT IT DELIVERS

- Funds pre-clinical drug development and IND-enabling studies for the lead program.[3]
- Builds out R&D and regulatory teams in anticipation of Phase 1 trials.[3]
- Carries the Company through to IND submission — approximately two years.[4]

TO EXPRESS INTEREST

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1. Akelos PPM, "Terms of the Offering," p. 5. 2. Akelos PPM, Risk Factors — "Best Efforts Offering; No Minimum" (p. 36) and "Arbitrary Determination of Offering Price." 3. Akelos Investor Deck, May 5, 2025, "Vision for the Future" (p. 67). 4. Akelos PPM, "Regulatory Pathway," p. 28, and "Go Forward Opportunity," p. 19. 5. Akelos One-Pager, May 5, 2025. — This presentation is not an offer to sell or a solicitation of an offer to buy securities; any offering is made solely by the Private Placement Memorandum.