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Private Placement Memorandum

Common Stock

Up to Offering: $14,000,000
Purchase Price: $2.75 per share
Minimum Investment: 5,000 shares for $13,750

The shares offered hereby have not been registered under the Securities Act of 1933, as amended (the "Act") and are being offered and sold to accredited investors in reliance upon the exemption from the registration requirements of the Act provided by Rule 506(c) of Regulation D. Such shares may not be transferred, sold, offered for sale, pledged or hypothecated unless a registration statement under the Securities Act is in effect with respect to the shares or there is an available exemption from such registration.

The shares have not been approved or disapproved by the Securities and Exchange Commission (the "SEC") or any state securities commission nor has the SEC or any state securities commission passed upon the accuracy or adequacy of this Private Placement Memorandum. Any representation to the contrary is a criminal offense.

Akelos may also retain and compensate placement agents in connection with the Offering and may pay sales commissions of up to 9% cash and 9% options.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some of the information in this Private Placement Memorandum contains forward-looking statements within the meaning of the federal securities laws. Forward-looking statements typically are identified by the use of terms such as "anticipates," "believes," "can," "continue," "could," "estimates," "expects," "intends," "may," "plans," "potential," "predicts," "should," or the negative of these terms, although some forward-looking statements are expressed differently.

These statements include, among others, those related to:

- the results of research and development activities;
- uncertainties relating to preclinical and clinical testing;
- 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 organizations; and
- 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 or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances on which any such statement is based.

This Private Placement Memorandum also contains projections and forecasts that have been prepared by us for internal use and are based on assumptions about conditions and courses of action that management believes are reasonably possible, but not necessarily probable. Projections or forecasts compiled on the basis of a set of different conditions and courses of action could differ substantially from those included herein. Readers of these projections and forecasts should be aware that some of the conditions and courses of action in management's assumptions inevitably will not materialize and unanticipated events and circumstances may occur. Therefore, the actual results achieved during the projections or forecasts period will vary from the projections and forecasts, and the variations may be material.

Prospective investors are urged to carefully review the section herein entitled "Risk Factors."

Executive Summary

Akelos Inc. ("Akelos," the "Company," "we" or "us") is a research-based biotechnology company founded to address the opioid epidemic by developing non-opioid drugs specifically for the treatment of neuropathic pain and potentially other CNS disorders. The Company was established in 2018 to develop and commercialize proprietary therapeutic technologies developed by Cornell University and Columbia University. Over the last several months, Akelos has formed a team of consultants and advisors with industry expertise in legal, regulatory, medical, scientific, and financial affairs and has entered into a collaborative partnership with scientists from Weill Cornell Medicine to further develop these compounds.

The Company holds an exclusive license from Cornell to a patent family claiming novel pharmaceutical compounds and their use as painkillers. The patent was filed in the US, Europe, Japan, China, Canada and Australia and is issued or allowed in the US, China, Japan and Australia and we expect allowances everywhere we filed.

Critically, 2,6-DTBP has already been tested *in vitro* and *in vivo*, and the parent pharmacophore shows a compelling and differentiated efficacy profile in animals. The first-generation NCE, RU51-nb2 (subsequently renamed AKE-1018), has two important properties: it potently inhibits HCN1 function (comparable to the parent pharmacophore), and the overall molecule behaves as predicted *in silico* molecular dynamic modeling. Data supporting the overall approach was published in the *Journal of Pharmacology and Experimental Therapeutics* in both 2005 and 2013. New data were also published in 2019 in *Biochemical Pharmacology*. As recently demonstrated by Drs. Gareth Tibbs, Dianna Willis, and Peter Goldstein in their recently published article in the *British Journal of Anaesthesia* (Tibbs et al. 2023), our lead molecule, AKE-1018, provided safe and effective pain relief following peripheral nerve injury. In rats, pain relief was observed within 24 hours of the first oral dose, and once daily dosing over the next seven days provided additional pain relief. AKE-1018 had an **excellent safety profile**: at 10x an effective dose, there were **no adverse cardiovascular effects** (no change in heart rate or blood pressure)**, no adverse motor effects** (no change in muscle strength or coordination), and **no evidence of either sedation or abuse potential**. The *in vivo* effects correlate with *in vitro* inhibition of the HCN1 ion channel. Critically, AKE-1018 was designed to not cross the blood-brain barrier; this was confirmed in both *in silico* molecular modeling and *in vivo* pharmacodynamic studies, highlighting a peripheral mechanism of action.

Importantly, Akelos believes that its drug candidates represent a "platform technology," and that the underlying molecular structure can be modified not only to provide targeted pain relief in a tissue-specific manner, but to treat a broad array of diseases.

The Company is seeking to raise up to $14 million pursuant to the Offering to fund the pre-clinical drug development (2 years) of its patented therapeutic technologies targeting the HCN1 neuron pathway for the treatment of neuropathic pain. Already, the National Institutes of Health (NIH) has awarded Weill Cornell and Burke Neurological Institute faculty members of Akelos' Scientific Advisory Board a $1.7 million NIH HEAL Initiative grant to support the development of HCN1-selective therapeutics for the treatment of neuropathic pain. Most recently, Akelos Inc. was awarded a $3.69 million Phase I/II Fast-Track Small Business Technology Transfer (STTR) grant from the National Institute of Neurological Disorders and Stroke (NINDS). The grant period concluded in January 2026.

Akelos continues to evaluate its proprietary series of HCN1 inverse agonists, including lead compound AKE-1018, for formal Development including IND Enablement. The latest data indicates that AKE-1018 and the chemical series possess favorable drug-like properties.

Pain is the most common reason for people to seek medical attention.[1] Chronic pain is defined as pain that persists for over three months. Such pain greatly impairs an individual's quality of life, is widely prevalent, and has significant economic costs. In the United States (US) alone, at least 116 million adults suffer from chronic pain. The financial costs of the treatment of chronic pain are estimated near half a trillion dollars per year due to missed work and the cost of medical care[2]. Neuropathic pain (chronic pain associated with aberrant activity in the central and/or peripheral nervous system) impacts over 20 million adults in the US alone, with associated costs exceeding $90 billion/year.[3] Neuropathic pain is commonly associated with diabetes, treatment with antineoplastics for cancer, peripheral nerve injury, and neurologic disorders such as stroke and multiple sclerosis.

Globally, neuropathic pain therapeutics are valued at $7.7 billion.[4] The market is projected to expand at a CAGR of 5.6% and reach US$13.3 billion by the end of 2032.[4]

The treatment of neuropathic pain is currently dominated by generic opioids, antidepressants, and anticonvulsants (or a combination thereof) despite the limited efficacy and marked adverse side-effect profile of these drugs.[5] Notably, opioids display limited effectiveness in treating neuropathic pain, and less than 35% of patients derive meaningful benefit from other therapeutic approaches.[6] Indeed, opioid pain relievers (OPRs) are considered "third-line" therapy for the treatment of neuropathic pain

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[11] National Institutes of Health Fact Sheet on Pain Management (Accessed 10/30/2018)

[2] Gaskin, D.J. and P. Richard. The economic costs of pain in the United States. J Pain, 2012. 13(8): 715-24.

[3] Allied Market Research, Neuropathic Pain Market By Drug class (Antidepressants, Anticonvulsant, Opioids, Capsaicin, Others), By Indication (Diabetic Neuropathy, Spinal Stenosis, Chemotherapy-Induced Peripheral Neuropathy, Others), By Distribution channel (Hospital Pharmacies, Drugs Stores and Retail Pharmacies, Online Pharmacies): Global Opportunity Analysis and Industry Forecast, 2022-2032. Accessed 1-8-2024.

[4] Sascha R, Alles A, Smith PA. Etiology and Pharmacology of Neuropathic Pain. *Pharmacological Reviews*. 2018;70(2):315-347.

National Institutes of Health Fact Sheet on Pain Management (Accessed 10/30/2018)

[2] Gaskin, D.J. and P. Richard. The economic costs of pain in the United States. J Pain, 2012. 13(8): 715-24.

and, despite limited efficacy and a suboptimal risk-benefit profile, are prescribed for nearly 20% of patients with polyneuropathy.[5,6]

This practice has contributed to an "opioid epidemic" not just in the United States, where it has been cited as a causal factor in more than 39,147 deaths in 2024 alone. 73.4% of drug overdose deaths in 2024 involved at least one opioid. (SUDORS Dashboard: Fatal Drug Overdose Data | Overdose Prevention | CDC). The virulence of the opioid epidemic, coupled with the size of the neuropathic pain market and lack of safe, effective treatment options creates a compelling opportunity for investment in this area.

Terms of the Offering

Securities Offered:	Shares of common stock, par value $.0001 (the "Shares").
Offering Size:	Up to $14,000,000 (the "Offering").
Purchase Price:	$2.75 per share.
Minimum Investment:	5,000 Shares for $13,750, subject to the Company's right to accept smaller amounts at its sole discretion.
Use of Proceeds:	Proceeds of the Offering will be used for research and development and working capital.
Offering Period:	The Offering will continue until the earlier of: (i) the sale of the Maximum Offering or (ii) 11:59 p.m. Eastern time on December 31, 2026, unless extended by the Company for up to an additional six months (the "Termination Date").
Method of Subscription:	If, after carefully reading this Private Placement Memorandum, obtaining any other information made available to you and being fully satisfied with the results of pre-investment due diligence activities, you would like to purchase Shares, you will be required to complete and deliver the Subscription Agreement, including the investor questionnaire, and deliver payment of the purchase price for the Shares subscribed for in the manner set forth in the Subscription Agreement under "How to Subscribe."
Investor Qualifications:	The Offering is being made pursuant to Rule 506(c) of the Act and only "accredited investors" as such term is defined in the Act, may participate in the Offering.
Placement Agents:	We may retain placement agents in connection with the Offering. We may pay sales commissions to such parties in an aggregate amount not to exceed 9% of the gross proceeds from the Offering.
Capitalization:	Prior to the Offering, there were approximately 31,503,967 shares of Common Stock outstanding, as well as options and warrants to acquire 2,539,865 shares. Cornell University currently holds 5% of the outstanding Common Stock and will continue to hold a 5% interest through the issuance of additional shares by the Company until such time, if ever, as the Company raises an aggregate of $7,000,000 (inclusive of funds raised in the Offering). An aggregate of 5,090,909 shares will be issued in the event the maximum Offering is completed.
Risk Factors:	An investment in the Shares is speculative, involves a high degree of risk, and should be considered only by investors that can bear the economic risks of their investment for an indefinite period of time and that can afford to sustain a total loss of investment. See "Risk Factors" included herein.

PROBLEM STATEMENT

Chronic pain is the most common reason for people to seek medical attention and one of the most prevalent causes of pain in adults.[1] Chronic pain is defined as pain that persists for over three months; such pain greatly impairs an individual's quality of life, is widely prevalent, and has significant economic cost. In the United States alone, at least 116 million adults suffer from chronic pain; the associated costs exceed US$500 billion/year.[2,3] Neuropathic pain (chronic pain associated with aberrant activity in the central and/or peripheral nervous system) accounts for ~18% of patients with chronic pain.

The exact prevalence of neuropathic pain within the global population is unknown, but most studies put estimates at between 1.5% and 8%, equating to between 100 million and 560 million people worldwide; in the United States, up to 21 million people suffer from neuropathic pain.[6]

Common types of neuropathic pain include:

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

The treatment of neuropathic pain commonly involves the prescription of generic opioids, antidepressants, and/or anticonvulsants, despite the limited efficacy and marked adverse side-effect profile of these drugs.[7] In particular, opioids display limited effectiveness in treating neuropathic pain, and less than 35% of patients derive meaningful benefit from other therapeutic approaches.[7] Despite limited efficacy, opioid pain relievers (OPRs) are still prescribed for chronic pain. In 2024, 125.7 million prescriptions were written for OPRs. There is a wide variation of opioid prescription rates across states, and studies suggest that regional variation in use of prescription opioids cannot be explained by the underlying health status of the population. There are substantial risks involved with such therapy, including physical dependence, addiction, and fatal poisoning - as many as one in four patients receiving long-term opioid therapy in a primary care setting struggles with opioid addiction.[8]

As noted on a nearly daily basis, we are in the midst of an "opioid epidemic," and the problem is global. The bitter irony is that neuropathic pain is often refractory to this, and other, treatments. The poor risk-benefit ratio associated with OPRs prompted the FDA to demand the addition of "Black Box" warning labels to package inserts highlighting these risks and the Center for Drug Evaluation &

Research to recommend that hydrocodone-containing OPRs be reclassified to a different and more restrictive schedule. Thus, there is a critical need (and market opportunity) for new safe and effective non-opioid anti-hyperalgesics.

The various manifestations of neuropathic pain are notoriously resistant to the actions of nonsteroidal anti-inflammatory drugs and opioids.[3] In stark contrast to the profound effectiveness of opioids in relieving *acute* nociceptive pain (as seen in the immediate post-operative period, for example), there is no similar panacea for the treatment of neuropathic pain. Any pain that is opioid-resistant is likely neuropathic.[8]

As noted above, neuropathic pain is a global problem with limited effective pharmacologic treatment options. **Table 1** lists drugs commonly utilized for the clinical management of neuropathic pain.[8]

Table 1[8]

Drugs currently used in the clinical management of neuropathic pain

Drug	Target	Status
Gabapentinoids (pregabalin, gabapentin)	$\alpha 2\delta$–1 auxiliary subunit of voltage-gated Ca^{2+} channels	First-line treatment (Finnerup et al., 2015)
Tricyclic antidepressants (amitriptyline)	Noradrenaline/Serotonin uptake systems	First-line treatment (Finnerup et al., 2015)
Noradrenaline/Serotonin uptake inhibitors (duloxetine)	Noradrenaline/Serotonin uptake systems	First-line treatment (Finnerup et al., 2015)
Tramadol	Opioid receptors and noradrenaline/serotonin uptake systems	Second-line treatment (Moulin et al., 2014)
Controlled release opioids	Opioid receptors	Second-line treatment (Moulin et al., 2014)
Cannabinoids	CB1 and CB2 receptors	Third-line treatment (Moulin et al., 2014)
Botulinum toxin	Neurotransmitter release	Fourth-line treatment (Moulin et al., 2014)
Methadone	Opioid and NMDA receptors	Fourth-line treatment (Moulin et al., 2014)
Lamotrigine	Voltage-gated Na^+ channels; L-, P-, and N-type Ca^{2+} channels	Fourth-line treatment (Moulin et al., 2014)
Lacosamide	Slow inactivation of voltage-gated Na^+ channels	Fourth-line treatment (Moulin et al., 2014)
Tapentadol	μ-Opioid receptors and noradrenaline uptake system	Fourth-line treatment (Moulin et al., 2014)
Carbemazepine	Voltage-gated Na^+ channels and $GABA_A$ receptors	Use primarily restricted to trigeminal neuralgia (Demant et al., 2014)
Ziconotide (synthetic ω-conotoxin MVIIA)	N-type voltage-gated Ca^{2+} channels	Administered intrathecally when other treatments fail (McGivern, 2007)
Ketamine	NMDA receptors	Sometimes used clinically (Niesters et al., 2014; Maher et al., 2017)
Lidocaine patch	Voltage-gated Na^+ channels	In clinical use (Finnerup et al., 2015)
Capsaicin patch	TRPV1 channels	In clinical use (Dworkin et al., 2007)

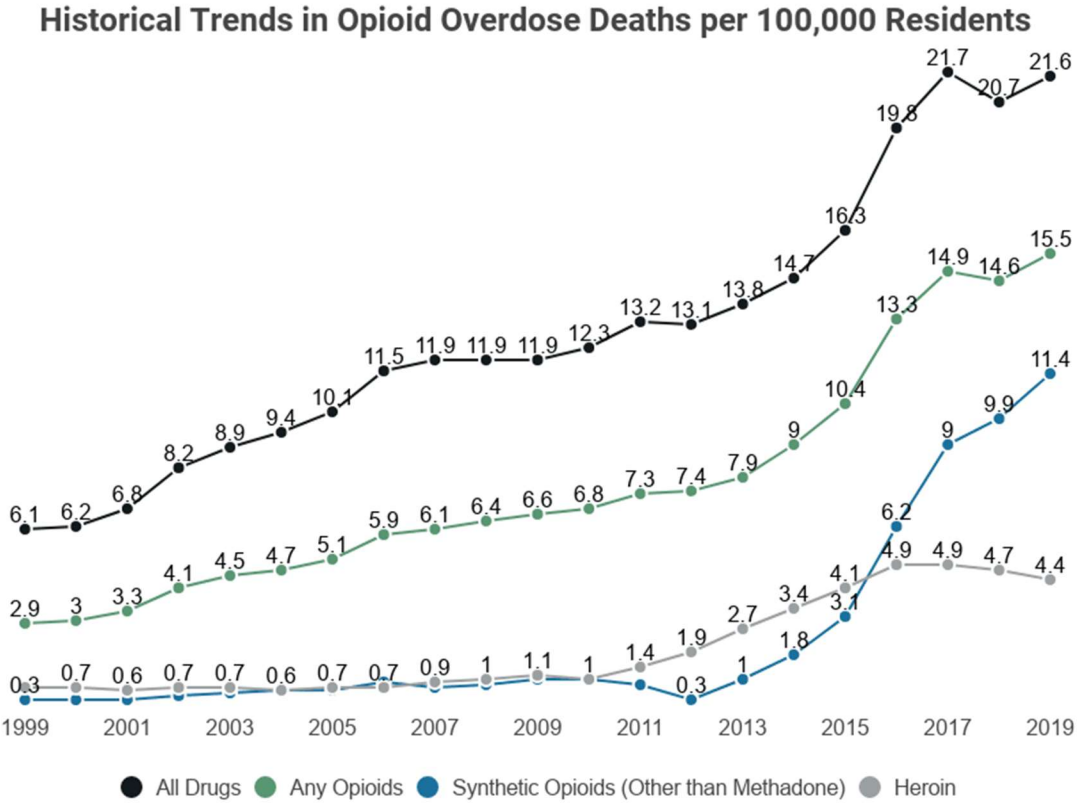
Today, an estimated 22.1% of adults with chronic pain had used a prescription opioid in the past 3 months. Of that number, as many as one in four patients receiving long-term opioid therapy in a primary care setting struggles with opioid addiction. (CDC Fact Sheet). Over 1.6 million have an opioid-use disorder according to the US Department of Health and Human Services (2019), and nearly 75% of drug overdose deaths in 2020 involved an opioid .(Opioid Facts and Statistics | HHS.gov)[4]

[3] Yekkirala AS, Roberson DP, Bean BP, and Woolf CJ. Breaking barriers to novel analgesic drug development. *Nat Rev Drug Discov* 2017. 16:545–564.

[4]Spencer, Merianne R.;Miniño, Arialdi M.;Warner, Margaret.: Drug Overdose Deaths in the United States, 2001–2021. National Center for Health Statistics (U.S.); NCHS data brief ; no. 457 - Published Date : 12/22/2022

Financial costs of the treatment of chronic pain are estimated at half a trillion dollars per year due to missed work and the cost of medical care. Evidence suggests that 40 to 70% of people with chronic pain do not receive proper medical treatment and are at risk for either over- or under-treatment.[5]

The impact on the United States has been cited as a nationwide epidemic, kill more than 136 Americans every day.[8] The national opioid overdose death rate increased 255.74% between 2000 and 2019. Recent efforts to combat the opioid crisis have resulted in a modest flattening of the growth curb, yet the problem is still far from resolved.[9]



Source: drugabusestatistics.org/drug-overdose-deaths/

In 2022 the Biden Administration awarded $1.5 billion to address the opioid crisis and support individuals in recovery. This represents a commitment to identifying solutions for Americans in the form of administrative and financial support to address this problem. Drug manufacturers have seen significant changes in the pain market in recent years, most notably policies from Pharmacy Benefit Managers including Express Scripts limiting the number and strength of opioid drugs prescribed to

[5] Reuben D, et al. National Institutes of Health Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain. *Ann Intern Med.* 2015;162(4):295-300.
[7] Cavalli et al. Int J Immunopathol Pharmacol. 2019
[8] CDC Opioid Fact Sheet, Accessed 1-8-24
[9] https://drugabusestatistics.org/drug-overdose-deaths/

first-time users. The United States has highlighted its commitment to finding a solution, through recent announcements that the NIH will increase funding for the discovery of new drug targets that can be used to develop pain treatments (small molecules, biologics, or devices) that have minimal side effects and little to no abuse/addiction liability. These are the characteristics of the molecules under development at Akelos.

SOLUTION: AKELOS + CORNELL LICENSED TECHNOLOGY

Led by Dr. Steven R. Fox, Akelos is a research-based biotechnology company based in New York City, established through a collaborative partnership with scientists from Weill Cornell Medicine ("WCM").

Akelos is focused on developing novel, non-opiate, anti-hyperalgesic drugs for the treatment of neuropathic pain, a major unmet medical need in today's world. Neuropathic pain may be associated with disease-states (such as diabetes) as well as events secondary to treatment (such as chemotherapy). Current therapies and medications, including opiates, do not adequately treat the often debilitating pain associated with these conditions; consequently, the development of novel drugs in this therapeutic space represents a significant opportunity to address a pressing global health issue.

The company has exclusively licensed patent applications for many compounds developed by Peter Goldstein, M.D., and his colleagues at WCM, that target the HCN1 ion channel, an important and, for the most part, overlooked novel target for the treatment of neuropathic pain.

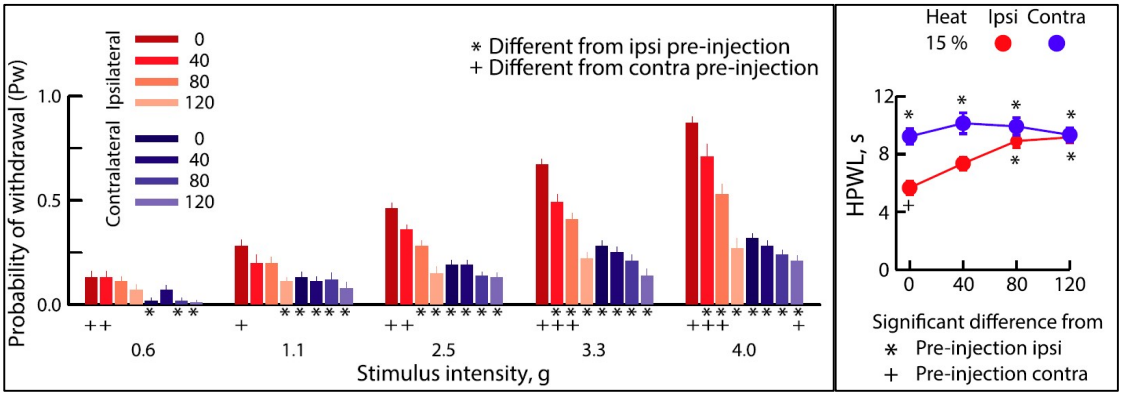
A wide body of research has established that primary sensory neurons play a pivotal role in establishing and maintaining neuropathic pain. When sensory neurons are injured, HCN1 ion channel expression and activity is enhanced, leading to increased membrane excitability in sensory neurons, and a resultant increase in pain. Akelos' patent-pending compounds appear to break this pain cycle by selectively and potently inhibiting HCN1 channel activity, thereby limiting the sensory experience of pain. Specifically, Akelos' compounds act as negative allosteric modifiers of HCN1 function. These compounds can be modified to alter potency, thereby creating new generations of pain-treatment new chemical entities ("NCEs").

To-date, extensive *in vitro* and *in vivo* preclinical studies of Akelos' compounds have demonstrated a compelling and attractive safety (preliminarily) and efficacy profile. We discuss progress to date with our compounds in the section that follows.

PROGRESS TO DATE

FIGURE 1.

A **B**

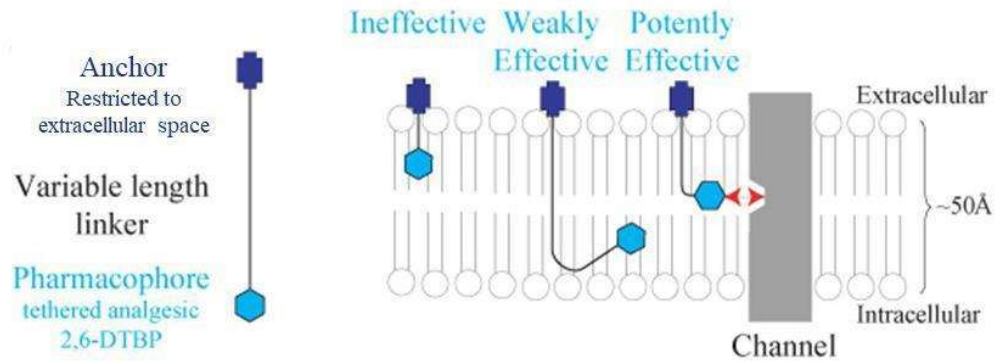


A) Cumulative doses of the active pharmacophore 2,6-di-tert-butylphenol (2,6-DTBP) potently and selectively reduced sensitivity to mechanical stimulation in the paw ipsilateral to injury (red bars), without impairing normal sensation in the paw opposite (blue bars) to the side of nerve injury (as measured by probability of withdrawal)

B) Cumulative doses of 2,6-DTBP potently and selectively reduced sensitivity to thermal stimulation in the paw ipsilateral to injury (red line), while normal sensation in the paw opposite (blue line) to the side of nerve injury is unaffected (as measured by time to respond). Data from Tibbs *et al. J Pharm Exp Ther* 2013.

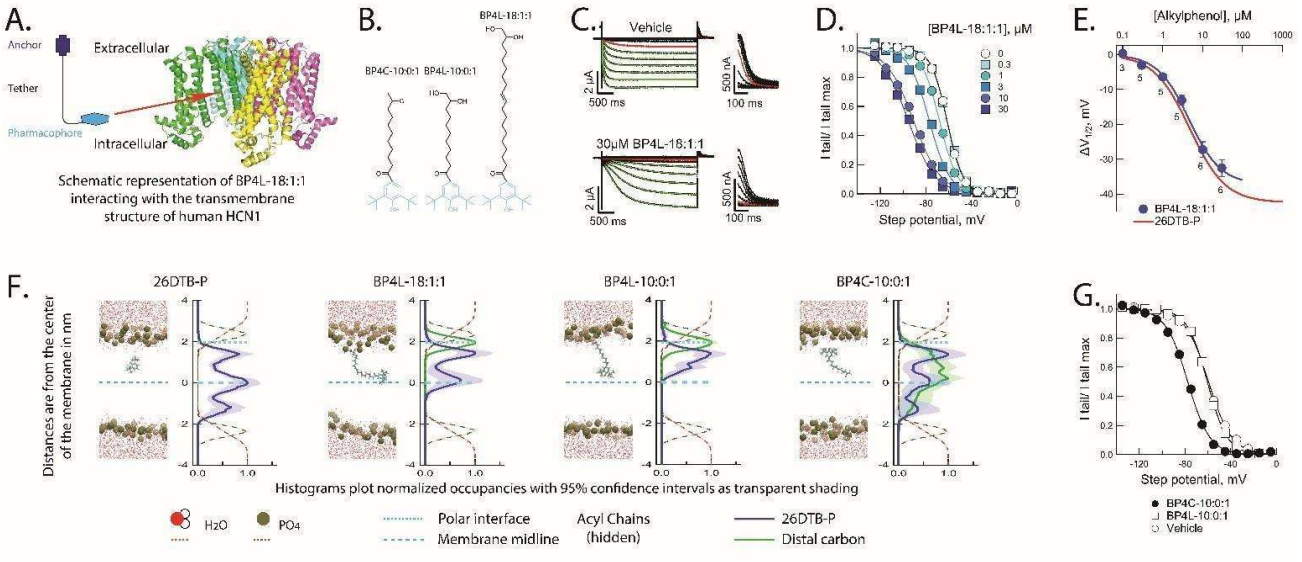
That compound, (2,6-DTBP), is the active pharmacophore backbone of Akelos' licensed patent-pending NCEs. Specifically, the proposed NCEs incorporate 2,6-DTBP as the active pharmacophore, which in turn is connected to a hydrophilic, membrane impermeant, "anchor" by means of an inert hydrocarbon "linker." The basic schema is shown in **Figure 2**. It is worth noting that, in theory, the anchor can be an antibody that targets an extracellular epitope of *any* membrane protein, including HCN1, thereby conferring tissue specificity in addition to membrane protein (*i.e.*, "target") selectivity.

FIGURE 2.



The first-generation NCE, RU51-nb2 has two important properties. In the first instance, it potently inhibited HCN1 function (comparable to the parent pharmacophore) (**Figure 3**).

FIGURE 3. Anchor-tethered 26DTB-P functions according to its design principles and is a potent HCN1 inverse agonist.



A) Schematic representation of BP4L-18:1:1 coupling to the membrane-embedded elements of human HCN1.

B) Structures of short- and medium-length NCEs.

C) Exemplar activation (left) and deactivation (right) current traces from Xenopus oocytes expressing HCN1 demonstrating profound inhibition by the medium length anchor-tethered molecule, BP4L-18:1:1.

D) HCN1 inhibition is concentration dependent.

E) BP4L-18:1:1 is equi-effective as the parent pharmacophore, 26DTB-P.

F) Molecular dynamics simulations. In all cases the ligand was presented in, and entered the membrane from, the external (upper) aqueous compartment. Histograms are each from 12 independent simulations.

G) Consistent with the molecular dynamics, the unanchored molecule (BP4C-10:0:1) is an effective HCN1 inhibitor indicating the channel is agnostic as to the presence of a tether; attachment of an anchor (generating BP4L-10:0:1) renders the short tether molecule ineffective (indicating the ability of the pharmacophore to reach deep into the membrane is critical to inverse agonist function). Data in this figure from Tibbs *et al. Br J Anaesth* 2023.

In the second, the overall molecules behaved as predicted; *in silico* molecular dynamic modeling indicates that the RU51nb2 anchors itself to the inner aspect of the cell membrane, allowing the hydrocarbon linker and the 2,6-DTBP pharmacophore full access to the lipid intramembranous lipid bilayer (**Figure 3F**).

In each of the four pairs of panels, the left-hand graphic is a still image from a 200 ns high-resolution molecular dynamics simulation and the right is a normalized density distribution depicting the occupancy of simulation cube with respect to the membrane midline. For the lipid headgroups and 26DTB-P pharmacophore, the densities were determined following the phosphate group and the entirety of the disubstituted phenol ring, respectively. The behavior of the tether-anchor complex was determined by following the distal terminal carbon. In each density plot, the midline of the membrane was established with respect to the distance between the phosphate peaks while the dotted line representing the polar interface was assigned on the basis of the location of maximal occupancy of the diol anchor in RU51nb2 (=AKE-1018).

Of note, this model does not incorporate the HCN1 protein itself; that modeling is now feasible given the recent publication of the cryo-electron microscopic HCN1 structure by the MacKinnon group at Rockefeller University in 2017.[6]

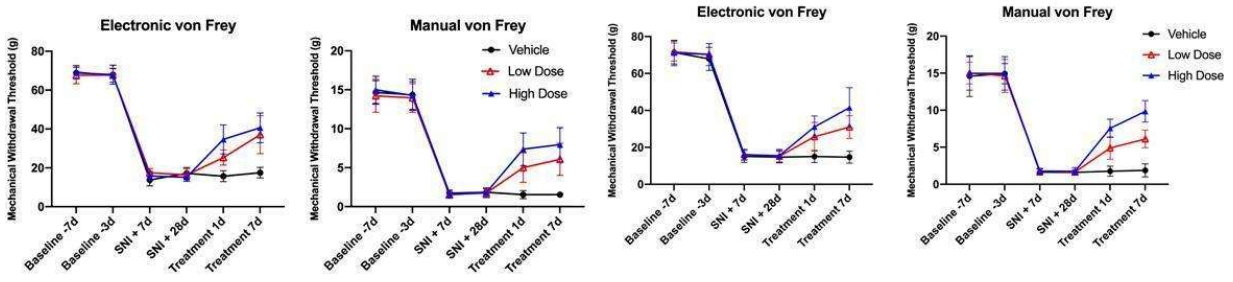
Recently published data in *Biochemical Pharmacology* (2019) described how H-bond propensity, ring saturation and adduct geometry differentially determined efficacy and potency (based on *in vitro* electrophysiology and kinetic modeling).[7]

In October 2019, the National Institutes of Health (NIH) awarded Weill Cornell and Burke Neurological Institute faculty members of Akelos' Scientific Advisory Board a two-year $1.7 million grant through the NIH's Helping to End Addiction Long-term Initiative (HEAL) HEAL Initiative to support the development of HCN1-selective therapeutics for the treatment of neuropathic pain. In September 2022, Akelos was awarded a Phase I/II Fast Track Small Business Technology Transfer (STTR) award from the NIH, the goal of which is to identify a high-potency HCN1-selective molecule to replace the existing pharmacophore (2,6-DTBP) which is currently present in AKE-1018. According to well-accepted industry standards, there is ample reason to optimize the current pharmacophore. Increasing potency should: **1.** minimize total dosing requirements; **2:** minimize risk of adverse side effects due to off-target interactions; **3.** improve dosing interval as a function of potency vs clearance.

Critical work during the award period demonstrated that RU51nb2 (aka, AKE-1018) rapidly relieved mechanical hyperalgesia (**Figure 4**) and thermal allodynia (to both heat and cold) (**Figure 5**) in an adult rat spared nerve injury model of neuropathic pain. The antihyperalgesic effects were dose-dependent and occurred within 24 hours of a single dose of drug (enteral administration), and there was continued improvement with daily dosing over a seven-day time frame. Importantly, the effects were nearly identical in both male and female rats. Additional safety studies demonstrated that at a 10-fold higher dose than that which produced pain relief, there were no adverse effects on cardiovascular function (no change in either heart rate or blood pressure; **Figure 6**) or motor function (no evidence of impaired muscle strength/coordination or sedation; **Figure 7**), nor was there any evidence of abuse potential (**Figure 8**).

[6] Lee CH, MacKinnon R. Structures of the Human HCN1 Hyperpolarization-Activated Channel. Cell. 2017;168(1):111-120.

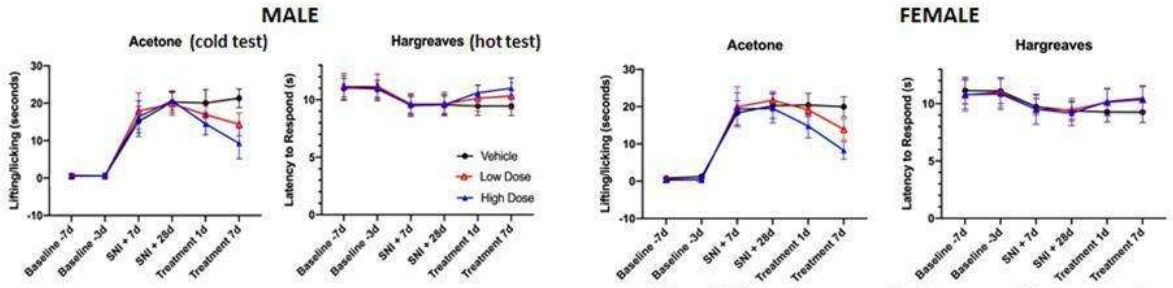
[7] Alkylphenol inverse agonists of HCN1 gating: H-bond propensity, ring saturation and adduct geometry differentially determine efficacy and potency. Biochem Pharmacol. 2019 Feb 12. pii: S0006-2952(19)30051-6. doi: 10.1016/j.bcp.2019.02.013. [Epub ahead of print]



Timepoint	Comparison	Electronic von Frey	Manual von Frey
	ANOVA	F(10, 165) = 25.97	F(10, 165) = 16.25
Treatment, 1 day	Vehicle vs. Low Dose	p < 0.0001	p = 0.0001
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001
	Low Dose vs. High Dose	p = 0.0037	p = 0.0221
Treatment, 7 day	Vehicle vs. Low Dose	p < 0.0001	p < 0.0001
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001
	Low Dose vs. High Dose	NS; p=0.6001	NS; p = 0.0962

Timepoint	Comparison	Electronic von Frey	Manual von Frey
	ANOVA	F(10, 165) = 13.58	F(10, 165) = 19.74
Treatment, 1 day	Vehicle vs. Low Dose	p = 0.0014	p < 0.0001
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001
	Low Dose vs. High Dose	NS; p = 0.1645	p = 0.0003
Treatment, 7 day	Vehicle vs. Low Dose	p < 0.0001	p < 0.0001
	Vehicle vs. High Dose	p < 0.0001	p < 0.0001
	Low Dose vs. High Dose	p = 0.0244	p < 0.0001

FIGURE 4. RU51nb2 (= BP4L-18:1:1 = AKE-1018) relieves nerve-injury induced mechanical hyperalgesia in a dose-dependent manner. Sciatic spared nerve injury (SNI) produces profound mechanical hyperalgesia that is stable over time in male and female rats. "d" denotes time (days) relative to surgery. Treatment is either for 1 or 7 days as indicated. In both instances, BP4L-1:1:1 relieves the neuropathic response. N = 12 animals (male) per group; total # groups, 3. Low dose 0.58 mmole/kg; high dose 1.74 mmole/kg. Data are presented as mean ± SD. Data from Tibbs *et al.* Br J Anaesth 2023.

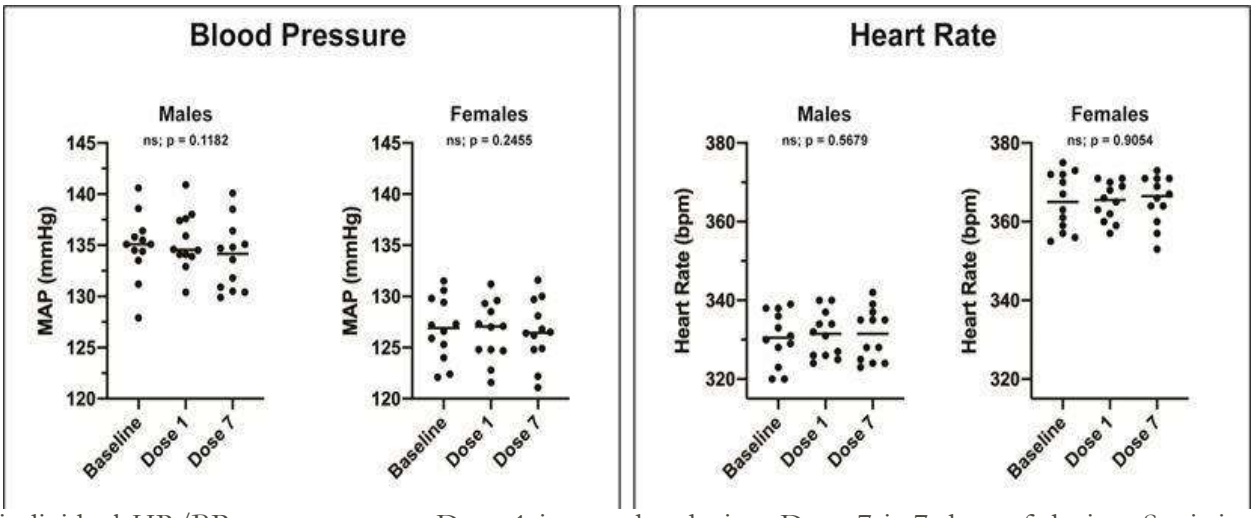


Timepoint	Comparison	Acetone	Hargreaves
	ANOVA	F(10, 165) = 10.69	F(10, 165) = 11.42
Treatment, 1 day	Vehicle vs. Low Dose	NS; p = 0.0502	NS; p = 0.2466
	Vehicle vs. High Dose	p = 0.0010	p = 0.0038
	Low Dose vs. High Dose	NS; p = 0.0751	NS; p = 0.4391
Treatment, 7 day	Vehicle vs. Low Dose	p < 0.0001	NS; p = 0.1111
	Vehicle vs. High Dose	p < 0.0001	p = 0.0008
	Low Dose vs. High Dose	p = 0.0071	NS; p = 0.2666

Timepoint	Comparison	Acetone	Hargreaves
	ANOVA	F(10, 165) = 11.72	F(10, 165) = 10.47
Treatment, 1 day	Vehicle vs. Low Dose	NS; p = 0.4224	NS; p = 0.1428
	Vehicle vs. High Dose	p = 0.0006	NS; p = 0.1036
	Low Dose vs. High Dose	p = 0.0014	NS; p = 0.9895
Treatment, 7 day	Vehicle vs. Low Dose	p < 0.0001	p = 0.0435
	Vehicle vs. High Dose	p < 0.0001	p = 0.0200
	Low Dose vs. High Dose	p < 0.0001	NS; p = 0.9609

Figure 5. RU51nb2 (= BP4L-18:1:1 = AKE-1018) relieves nerve injury-induced thermal hypersensitivity in a dose-dependent manner. Sciatic spared nerve injury (SNI) produces profound thermal hypersensitivity to both the sensation of cold (Acetone) and heat (Hargreaves) in male and female rats that is stable over time. "d" denotes time (days) relative to surgery. Treatment is either for 1 or 7 days as indicated. In both instances, BP4L-1:1:1 relieves the neuropathic response. N = 12 animals per group; total # groups, 3. Low dose 0.58 mmole/kg; high dose 1.74 mmole/kg. Data are presented as mean ± SD. Data from Tibbs et al. *Br J Anaesth* 2023.

Figure 6. RU51nb2 (= BP4L-18:1:1 = AKE-1018) lacks cardiovascular effects. Measurements obtained 1 hr after dosing. 24 animals total (12 male; 12 female). Data for each animal is from 20



individual HR/BP measurements. Dose 1 is one day dosing; Dose 7 is 7 days of dosing. Statistics: repeated measures ANOVA. Data from Tibbs et al. *Br J Anaesth* 2023.

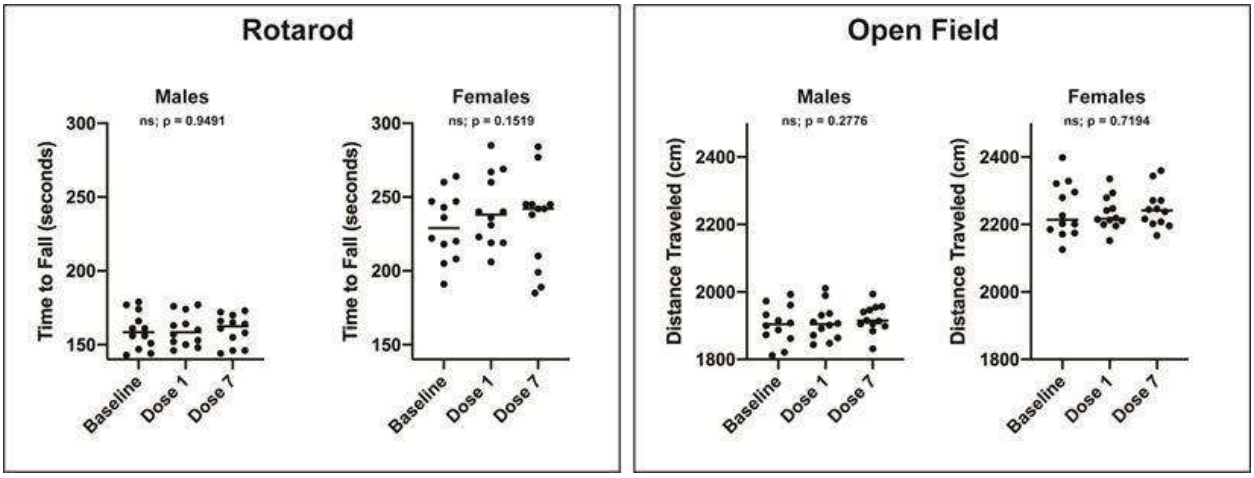


Figure 7. RU51nb2 (= BP4L-18:1:1 = AKE-1018) has no effect on motor behavior. Measurements were taken 1 hour after dosing. 24 animals total (12 male; 12 female). Data for each animal is from 10 replicates using the Ugo Basile Rat Rotarod ramping from 5 – 80 rpm. Motor activity was measured using the Stoelting any-box automated tracking system. Total activity was measured over 20 minutes. Data from Tibbs et al. *Br J Anaesth* 2023.

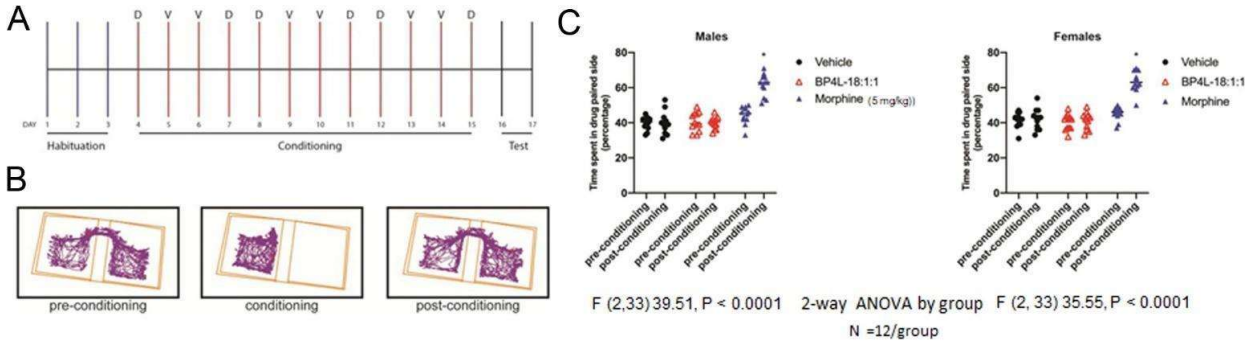


Figure 8. RU51nb2 (= BP4L-18:1:1 = AKE-1018) at 10×-low antihyperalgesic dose does not result in conditioned place preference. (**A**) Dosing and testing paradigm. Dosing commences after 3 days of habituation to the testing platform using the schema shown. Testing occurs on days 16 and testing. D = drug administration, V = Vehicle. (**B**) Example of a single animal trail map. (**C**) BP4L-18:1:1 at 10×-low antihyperalgesic dose (i.e., 5.8 mmol/kg) does not result in conditioned place preference. In contrast, morphine (5 mg/kg) administered as an active comparator clearly results in place preference. Data from Tibbs et al. *Br J Anaesth* 2023.

PATENT OVERVIEW

Research by Weill Cornell Medicine scientists has resulted in intellectual property covering novel compounds and methods of treating pain using these compounds. This IP consists of a patent family, filed in the US, Europe, Japan, China, Canada, and Australia, all derived from PCT International Patent Application, PCT/US2019/038493, filed on June 27, 2019. Patents have been issued or allowed in the US, China, Japan and Australia and we expect allowances everywhere we filed. The claims cover Akelos' lead compound, AKL1018, other related compounds, and their use to treat pain.

FOCUS OF PRECLINICAL RESEARCH

The Goldstein & Willis labs conducted pivotal *in vitro* structural and mechanistic studies into alkylphenol-mediated inhibition of HCN1 channels and their potential as antihyperalgesics. Recent work has led to the following published peer-reviewed articles:

1. Joyce RL, Beyer NP, Vasilopoulos G, Woll KA, Hall AC, Eckenhoff RG, Barman DN, Warren JD, Tibbs, GR & Goldstein PA. 2019. Alkylphenol inverse agonists of HCN1 gating: H-bond propensity, ring saturation and adduct geometry differentially determine efficacy and potency. *Biochem Pharmacol* 2019.163:493-508.

2. Tibbs GR, Uprety R, Warren JD, Beyer NP, Joyce RL, Ferrer MA, Mellado W, Wong VSC, Goldberg DC, Cohen MW, Costa CJ, Li Z, Zhang G, Dephoure NE, Barman DN, Sun D, Ingólfsson HI, Sauve AA, Willis DE, Goldstein PA (2023) An anchor-tether 'hindered' HCN1 inhibitor is antihyperalgesic in a rat spared nerve injury neuropathic pain model. *Br J Anaesth* 131:745-763. 10.1016/j.bja.2023.06.067

3. Joyce RL, Tibbs GR, Warren JD, Costa CJ, Aromolaran K, Sanford RL, Andersen OS, Li Z, Zhang G, Willis DE, Goldstein PA (2023) Probucol is anti-hyperalgesic in a mouse peripheral nerve injury model of neuropathic pain. *Neurobiol Pain* 14:100141. 10.1016/j.ynpai.2023.100141

4. Kim, E.D., Wu, X., Lee, S. et al. Propofol rescues voltage-dependent gating of HCN1 channel epilepsy mutants. *Nature* 632, 451–459 (2024). 10.1038/s41586-024-07743-z

Research teams from Weill Cornell Medicine, the University of Miami, and Linköping University in Sweden reported identifying the binding site for the alkylphenol general anesthetic 2,6-diisopropylphenol (also known as propofol) on the human HCN1 (hHCN1) ion channel. These findings reinforce the proposed mechanism of action and support ongoing efforts to identify next-generation pharmacophores.[8]

In a recently published article in Cell Chemical Biology, researchers also demonstrated that selective HCN1 inhibition does not affect the electrophysiological properties of human induced pluripotent stem cell-derived atrial-like cardiomyocytes. This observation aligns with data showing that HCN2 and HCN4 are the primary isoforms expressed in human cardiac tissues.[9]

Tibbs *et al*. 2023 describes the current work on RU51nb2 (= AKE-1018) and Joyce *et al*. 2023 describes the antihyperalgesics effects of the clinically utilized antihyperlipidemic agent, probucol (which is a dimerized congener of 2,6-DTBP).[10]

As demonstrated by Drs. Gareth Tibbs, Dianna Willis, and Peter Goldstein in their recently published article in the British Journal of Anaesthesia (Tibbs et al. 2023), our lead molecule, AKE-1018, provided safe and effective pain relief following peripheral nerve injury (Figures 4-5). In rats, pain relief was observed within 24 hours of the first oral dose, and once daily dosing over the next seven days provided significant additional pain relief. AKE-1018 had an excellent safety profile: at 10x an effective dose, there were no adverse cardiovascular effects (no change in heart rate or blood pressure; Figure 6), no adverse motor effects (no change in muscle strength or coordination), and no evidence of either sedation or abuse potential (Figures 7-8). The in vivo effects correlated with in vitro inhibition of the HCN1 ion channel. Critically, AKE-1018 was designed to not cross the blood-brain barrier; this was confirmed in both in silico molecular modeling and in vivo pharmacodynamic studies, highlighting a peripheral mechanism of action.

In 2019, Akelos acquired a Sophion QPatch II 48-channel automated patch clamp system, which will greatly improve efficiency and facilitate *in vitro* identification of enhanced pharmacophores.

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[8] Kim, E.D., Wu, X., Lee, S. et al. Propofol rescues voltage-dependent gating of HCN1 channel epilepsy mutants. Nature 632, 451–459 (2024). https://doi.org/10.1038/s41586-024-07743-z

[9] Harde E, Hierl M,Weber M, et al. Selective and brain-penetrant HCN1 inhibitors reveal links between synaptic integration, cortical function, and working memory, Cell Chemical Biology 3, 577-592 (2024). https://doi.org/10.1016/j.chembiol.2023.11.004

[10] Tibbs et al. An anchor-tether 'hindered' HCN1 inhibitor is antihyperalgesic in a rat spared nerve injury neuropathic pain model. British Journal of Anaesthesia, VOLUME 131, ISSUE 4, P745-763, 2023.

The Willis lab was an established research team with expertise in cell biology, protein synthesis, and axonal transport. They focused on changes in the axonal localization and availability of mRNAs encoding ion channel proteins and neuropeptides that have been implicated in chronic pain, with a particular emphasis on the signaling mechanisms and RNA binding proteins that drive axonal localization. These studies are fundamental to understanding how aberrant axonal translation may lead to maladaptive plasticity as is evident in neuropathic pain and neuropathy. While Dr. Willis is pursuing multiple research projects centered on maladaptive plasticity, she has also performed the required in vivo studies evaluating the anti-hyperalgesic efficacy of our compounds.

PHYSIOCHEMICAL, ADME AND PHARMACOLOGICAL ASSAYS

Akelos continues to evaluate its proprietary series of HCN1 inverse agonists, including lead compound AKE-1018, for formal Development including IND Enablement. The latest data indicates that AKE-1018 and the chemical series possess favorable drug-like properties.

AKE-1018 was evaluated in a series of physiochemical, ADME and pharmacological assays. The data is summarized below:

Solubility:

AKE-1018 exhibits very good solubility in pharmaceutically-acceptable GRAS oils such as peanut oil (which was used in preclinical animal efficacy studies). AKE-1018 also displays very good solubility in aqueous vehicles containing appropriate solubilizing agents such as ethanol, polyethylene glycol (PEG) and a common cyclodextrin; all are pharmaceutically-acceptable diluents. As expected due to its chemical structure and high lipophilicity, AKE-1018 has low solubility at physiologic pH in the absence of added diluents.

#	Approach	Medium	Solubility, Mean (n=3) ± SD	Solubility, Mean (n=3) ± SD
1	Kinetic	Phosphate buffered saline (pH 7.4)	-	-
2		Simulated gastric fluid	17.61 ± 3.09 µg/mL	34.12 ± 6.00 µMol
3		Simulated intestinal fluid	-	-
4		80% EtOH in water	51.93* ± 1.12 µg/mL	100.62* ± 2.16 µMol
5		20% hydroxypropyl-β-cyclodextrin in water	48.25 ± 0.45 µg/mL	93.49 ± 0.88 µMol
6		80% PEG 400 in water	50.24* ± 0.64 µg/mL	97.34* ± 1.24 µMol
7		20% PEG 400 / 20% Cremaphor EL / water	51.35* ± 0.36 µg/mL	99.50* ± 0.69 µMol
8	Thermodynamic	Sesame oil	31.40* ± 0.81 mg/mL	60.75* ± 1.57 mMol
9		Peanut oil	31.52* ± 1.72 mg/mL	60.99* ± 3.32 mMol

* - The upper solubility limit was reached. The actual solubility is **likely higher than reported**.

Microsomal stability:

AKE-1018 displays exceptional stability upon incubation with human liver microsomes. The calculated intrinsic clearance indicates a half-life of greater than 10 h, suggesting QD testing may be adequate in humans. This stability may be due, in part, to high protein binding.

Compound I.D.	Client Compound I.D.	Test Concentration	Incubation (minutes)	% Compound Remaining (% remaining) 1st	2nd	Mean	Half-Life (minutes) 1st	2nd	Mean	Clint (µl/min/mg)
Intrinsic clearance (liver microsomes- human)										
100078078-1	AKE-1018	1.0E-07 M	0	100.00	100.00	100.00	732.6	627.9	680.2	10.2
100078078-1	AKE-1018	1.0E-07 M	15	98.53	111.94	105.24				
100078078-1	AKE-1018	1.0E-07 M	30	102.74	100.67	101.71				
100078078-1	AKE-1018	1.0E-07 M	45	103.49	103.47	103.48				
100078078-1	AKE-1018	1.0E-07 M	60	90.89	95.75	93.32				

Note: Unit of Clint is µL/min/mg for microsomes, S9 and UGT assays; µL/min/pmol for CYP assays; µL/min/Million cells for hepatocyte assays

In a second study aimed at evaluating microsomal stability across species, AKE-1018 similarly showed exceptional robustness (T1/2 >> 1h).

*Compound stability in **mouse** liver microsomes*

Compound	*Time, min*	*% remaining (n=2)*	*Negative control (% remaining)*
AKE-1018	0	100.0	100.0
	15	98.1	ND
	30	96.4	ND
	45	96.7	ND
	60	**95.2**	**99.8**
Verapamil	0	100.0	100.0
	15	57.0	ND
	30	41.8	ND
	45	35.4	ND
	60	**28.6**	**93.8**

*Compound stability in **rat** liver microsomes*

Compound	*Time, min*	*% remaining (n=2)*	*Negative control (% remaining)*
AKE-1018	0	100.0	100.0
	15	96.4	ND
	30	98.0	ND
	45	99.1	ND
	60	**104.6**	**95.6**
Verapamil	0	100.0	100.0
	15	82.9	ND
	30	70.5	ND
	45	58.2	ND
	60	**46.0**	**100.5**

*Compound stability in **human** liver microsomes*

Compound	*Time, min*	*% remaining (n=2)*	*Negative control (% remaining)*
AKE-1018	0	100.0	100.0
	15	96.7	ND
	30	94.2	ND
	45	99.2	ND
	60	**91.6**	**97.5**
Verapamil	0	100.0	100.0
	15	88.8	ND
	30	79.6	ND
	45	68.4	ND
	60	**59.0**	**97.6**

Protein Binding:

AKE-1018 is very highly protein bound.

PPB data obtained for tested compound and control samples in mouse plasma

Test compound	Peak area (response) for plasma compartment	Peak area (response) for buffer compartment	Unbound, %	Bound, %	Protein binding (%)	PPB classifi-cation
AKE-1018	1.00	ND	0.00	100.00	**100**	High
	1.38	ND	0.00	100.00		
Propanolol (positive control)	2.75	0.43	15.49	84.51	86	High
	2.80	0.38	13.46	86.54		
Fluconazol (negative control)	1.15	0.89	77.54	22.46	20	Low
	1.19	0.97	81.58	18.42		

PPB data obtained for tested compound and control samples in rat plasma

Test compound	Peak area (response) for plasma compartment	Peak area (response) for buffer compartment	Unbound, %	Bound, %	Protein binding (%)	PPB classifi-cation
AKE-1018	0.77	ND	0.00	100.00	**100**	High
	0.73	ND	0.00	100.00		
Propanolol (positive control)	2.94	0.34	11.64	88.36	89	High
	2.90	0.30	10.47	89.53		
Fluconazol (negative control)	1.00	0.81	80.79	19.21	22	Low
	1.07	0.81	75.80	24.20		

PPB data obtained for tested compound and control samples in human plasma

Test compound	Peak area (response) for plasma compartment	Peak area (response) for buffer compartment	Unbound, %	Bound, %	Protein binding (%)	PPB classifi-cation
AKE-1018	0.68	ND	0.00	100.00	**100**	High
	0.67	ND	0.00	100.00		
Propanolol (positive control)	2.65	0.45	16.96	83.04	84	High
	2.70	0.41	15.08	84.92		
Fluconazol (negative control)	1.11	0.78	70.00	30.00	30	Low
	1.10	0.76	69.19	30.81		

Despite high protein binding, AKE-1018 achieves good plasma exposures upon oral dosing and exhibits efficacy in a rodent model of neuropathic pain, indicating adequate free drug engages the pharmacological target.

Permeability:

AKE-1018 exhibits low but appreciate permeability in the standard Caco2 cell line assay. There is no efflux (A->B/B->A ratio) observed. This data is supportive of the appreciable plasma exposure levels observed in rats orally dosed with AKE-1018 and may reflect good oral bioavailability.

Compound I.D.	Client Compound I.D.	Test Concentration	Permeability (10^{-6} cm/s)			Percent Recovery(%)		
			1st	2nd	Mean	1st	2nd	Mean
A-B permeability (Caco-2, pH 6.5/7.4)								
100078078-1	AKE-1018	1.0E-05 M	0.12	0.02	0.1	38	43	41
B-A permeability (Caco-2, pH 6.5/7.4)								
100078078-1	AKE-1018	1.0E-05 M	0.04	0.01	0.0	35	37	36

hERG Channel inhibition:

AKE-1018 does not inhibit the cardiac ion channel hERG at all concentrations tested:

CiPA hERG Assay Data Table

Compound ID	Client Compound ID	Batch Number	Concentration (μM)	% inhibition		
				n1	n2	mean
US034-0030073-1	AKE-1018	OSPT-3389	0.1	4.19	7.45	5.82
US034-0030073-1	AKE-1018	OSPT-3389	0.3	4.56	6.27	5.41
US034-0030073-1	AKE-1018	OSPT-3389	1	3.08	0.27	1.67
US034-0030073-1	AKE-1018	OSPT-3389	3	7.66	7.70	7.68
US034-0030073-1	AKE-1018	OSPT-3389	10	7.19	3.30	5.24
US034-0030073-1	AKE-1018	OSPT-3389	30	12.84	12.69	12.76
Time-Matched Vehicle Control	0.33% DMSO Addition 1			5.69	5.63	5.66

CYP Inhibition:

AKE-1018 did not appreciably inhibit any of the five major isoforms tested: CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4 (both the midazolam and testosterone binding sites), across the concentration range.

CYP1A2 (Phenacetin)						
Compound ID	Conc (μM)	Conc (Log)	Area Ratio	Relative Activity (% of NC)	% Inhibition	IC50 (μM)
α-Napthoflavone (PC)	3.00	0.477	4.52E-03	13.9%	86.1%	
	0.00		3.26E-02	100%	0.00%	
AKE-1018	100	2.000	3.17E-02	97.2%	2.76%	> 100
	33.3	1.522	3.18E-02	97.5%	2.45%	
	11.1	1.045	3.20E-02	98.2%	1.84%	
	3.70	0.568	3.24E-02	99.4%	0.61%	
	1.23	0.090	3.23E-02	99.1%	0.92%	
	0.412	-0.385	3.25E-02	99.7%	0.31%	
	0.137	-0.863	3.24E-02	99.4%	0.61%	
	0.00		3.26E-02	100%	0.00%	

CYP2C9 (Tolbutamide)						
Compound ID	Conc		Area Ratio	Relative Activity (% of NC)	% Inhibition	IC50 (μM)
	(μM)	(Log)				
Sulfaphenazole (PC)	20.0	1.301	3.93E-04	9.63%	90.4%	
	0.00		4.08E-03	100%	0.00%	
AKE-1018	100	2.000	1.65E-03	40.4%	59.6%	75.9
	33.3	1.522	3.10E-03	76.0%	24.0%	
	11.1	1.045	3.91E-03	95.8%	4.17%	
	3.70	0.568	4.05E-03	99.3%	0.74%	
	1.23	0.090	4.06E-03	99.5%	0.49%	
	0.412	-0.385	4.07E-03	99.8%	0.25%	
	0.137	-0.863	4.07E-03	99.8%	0.25%	
	0.00		4.08E-03	100%	0.00%	

CYP2C19 (S-Mephenytoin)						
Compound ID	Conc		Area Ratio	Relative Activity (% of NC)	% Inhibition	IC50 (μM)
	(μM)	(Log)				
Nootkatone (PC)	20.0	1.301	2.66E-04	18.5%	81.5%	
	0.00		1.44E-03	100%	0.00%	
AKE-1018	100	2.000	1.16E-03	80.6%	19.44%	> 100
	33.3	1.522	1.32E-03	91.7%	8.33%	
	11.1	1.045	1.38E-03	95.8%	4.17%	
	3.70	0.568	1.41E-03	97.9%	2.08%	
	1.23	0.090	1.43E-03	99.3%	0.69%	
	0.412	-0.385	1.42E-03	98.6%	1.39%	
	0.137	-0.863	1.43E-03	99.3%	0.69%	
	0.00		1.44E-03	100%	0.00%	

CYP2D6 (Dextromethorphan)						
Compound ID	Conc		Area Ratio	Relative Activity (% of NC)	% Inhibition	IC50 (μM)
	(μM)	(Log)				
Quinidine (PC)	3.00	0.477	1.29E-02	8.38%	91.6%	
	0.00		1.54E-01	100%	0.00%	
AKE-1018	100	2.000	1.47E-01	95.5%	4.55%	> 100
	33.3	1.522	1.48E-01	96.1%	3.90%	
	11.1	1.045	1.50E-01	97.4%	2.60%	
	3.70	0.568	1.51E-01	98.1%	1.95%	
	1.23	0.090	1.53E-01	99.4%	0.65%	
	0.412	-0.385	1.52E-01	98.7%	1.30%	
	0.137	-0.863	1.53E-01	99.4%	0.65%	
	0.00		1.54E-01	100%	0.00%	

CYP3A4 (Midazolam)						
Compound ID	Conc		Area Ratio	Relative Activity (% of NC)	% Inhibition	IC50 (µM)
	(µM)	(Log)				
Ketoconazole (PC)	5.00	0.699	1.59E-03	0.73%	99.3%	
	0.00		2.17E-01	100%	0.00%	
AKE-1018	100	2.000	2.12E-01	97.7%	2.30%	> 100
	33.3	1.522	2.13E-01	98.2%	1.84%	
	11.1	1.045	2.13E-01	98.2%	1.84%	
	3.70	0.568	2.14E-01	98.6%	1.38%	
	1.23	0.090	2.15E-01	99.1%	0.92%	
	0.412	-0.385	2.14E-01	98.6%	1.38%	
	0.137	-0.863	2.16E-01	99.5%	0.46%	
	0.00		2.17E-01	100%	0.00%	

CYP3A4 (Testosterone)						
Compound ID	Conc		Area Ratio	Relative Activity (% of NC)	% Inhibition	IC50 (µM)
	(µM)	(Log)				
Ketoconazole (PC)	1.00	0.000	2.66E-03	8.50%	91.5%	
	0.00		3.13E-02	100%	0.00%	
AKE-1018	100	2.000	1.43E-02	45.7%	54.3%	81.7
	33.3	1.522	2.19E-02	70.0%	30.0%	
	11.1	1.045	2.76E-02	88.2%	11.8%	
	3.70	0.568	3.09E-02	98.7%	1.28%	
	1.23	0.090	3.11E-02	99.4%	0.64%	
	0.412	-0.385	3.12E-02	99.7%	0.32%	
	0.137	-0.863	3.12E-02	99.7%	0.32%	
	0.00		3.13E-02	100%	0.00%	

Summary:

The data (QC reports available) are consistent with rodent pharmacokinetic and efficacy studies that demonstrated substantial plasma exposures and the reversal of mechanical allodynia and thermal hyperalgesia in a neuropathic pain model (rat Spared Nerve Injury).

AKE-1018 possesses favorable drug-like properties and should continue to be vetted as a possible Development Candidate for IND Enablement. In parallel, more potent analogs with lower protein binding should be pursued.

FUTURE AKELOS DEVELOPMENT EFFORTS WILL FOCUS ON CLINICAL STUDIES ENABLING FDA REGULATORY SUBMISSION

Akelos team is undertaking the Offering to fund the pre-clinical drug development of its patent-pending therapeutic technologies targeting the HCN1 neuron pathway for the treatment of neuropathic pain.

Akelos will use the proceeds from the Offering to progress and de-risk several elements of its drug overall drug development effort:

(1) NCE refinement: WCM's work has already identified a lead compound which appears to have selectivity for HCN1 channels, and which has anti-hyperalgesic properties and has generated other lead compounds which appear to also have selectivity for HCN1 channels, and we intend to create NCEs which are HCN1 selective and are restricted to peripheral compartments without blood-brain barrier penetration. Utilizing to-be-chosen lead compounds, we will create NCEs which have been shown to bind both *in vitro* and *in vivo* to HCN1 channels. Once created, we will expeditiously move forward in phase 1B/2A studies, aiming to establish safety and efficacy for the treatment of chemotherapy-induced neuropathic pain.

(2) Team development: To retain a best-in-class executive team consisting of an Operations/Business Development Director, as well as other key strategic hires that augment Akelos' clinical development capabilities.

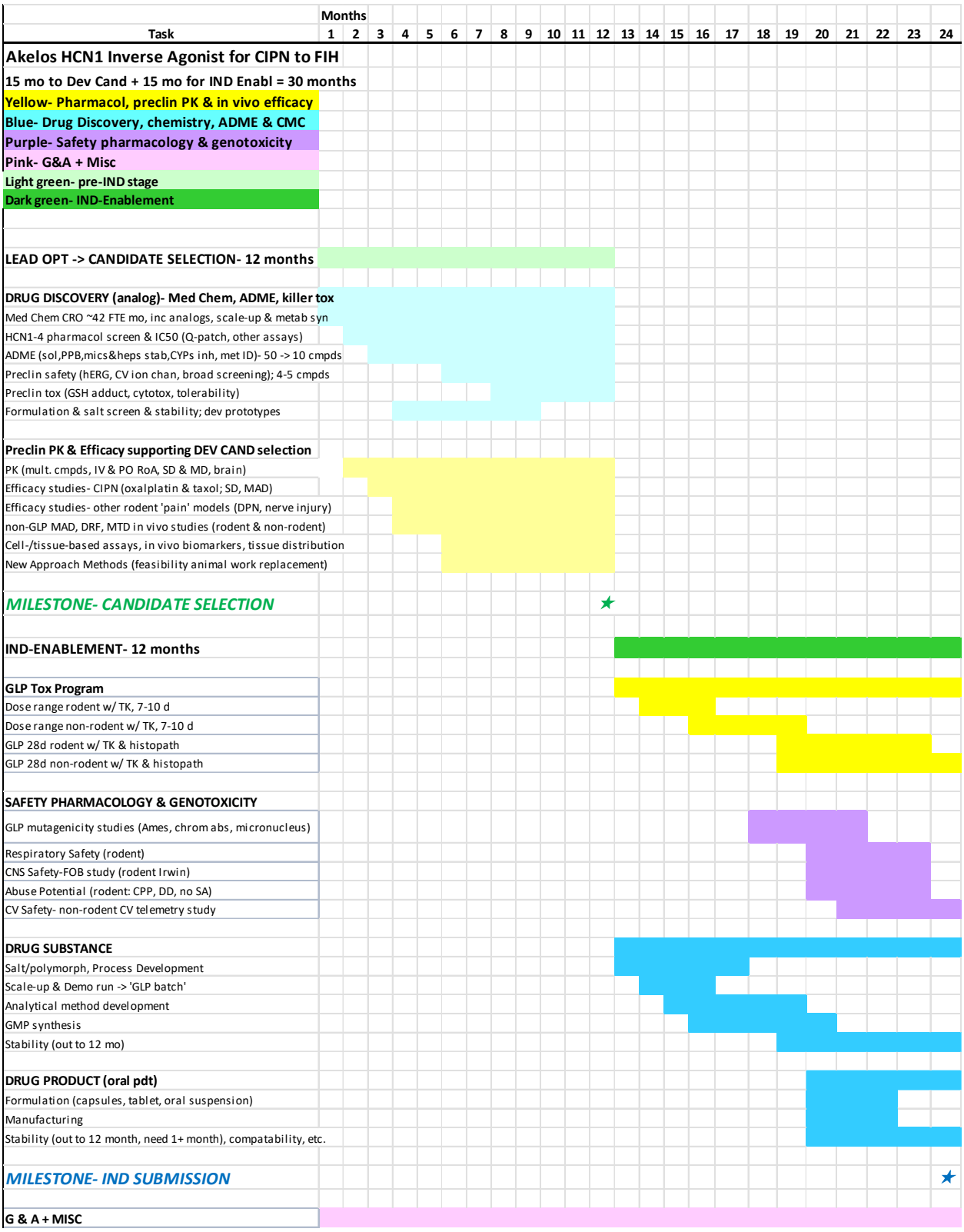
(3) Pre-clinical trials: Partnering with WCM as well as 3rd party CROs, we plan to execute pre-clinical and Phase 1 clinical trials to establish the pharmacokinetic and other toxicity profiles for clinical development. We will follow a comprehensive drug development process through pre-clinical and clinical phases as outlined (See Table 2).

Once chemical lead NCEs are identified, we will aggressively pursue regulatory pathways, focused on either post-chemotherapy induced neuropathy, painful peripheral diabetic neuropathy, and/or post-herpetic neuropathic pain.

Importantly, we believe we will need approximately $14 million to fund Akelos' operations through to IND submission, focusing initially on moving from lead compounds to NCEs, which are expected to be the lead drug candidates in our planned clinical trials.

At the end of this stage, we will plan and prepare for First-in-Human (FIH) trials, for which we will seek additional funding. Crucially, this will be a potential exit point, at which time we can evaluate the opportunity, in particular for in-licensing by Big Pharma.

Table 2 - Preclinical and Clinical Drug Development Timeline



BUDGET AND FUNDING

Our aim is to identify and develop one or more chemical compounds that have the potential to be therapeutic products and that are protected by strong intellectual property. Aiming for the developed compounds to be seen by third parties as robust clinical candidates worthy of in-licensing or subsequent acquisition. The project will be broken into several stages with associated milestones and exit points, and our funding is planned accordingly (see Table 3).

Table 3 - Preclinical and Clinical Drug Development Financials

	TOTAL Cost		Task
	$13,503,000		**Akelos HCN1 Inverse Agonist for CIPN to FIH**
			12 mo to Dev Cand + 12 mo for IND Enabl = 24 months
	$2,690,000		**Yellow- Pharmacol, preclin PK & in vivo efficacy**
	$5,305,000		**Blue- Drug Discovery, chemistry, ADME & CMC**
	$550,000		**Purple- Safety pharmacology & genotoxicity**
	$4,958,000		**Pink- G&A + Misc**
			Light green- pre-IND stage
			Dark green- IND-Enablement
Party	**Cost**		
ALK+CROs	**$2,680,000**		**LEAD OPT -> CANDIDATE SELECTION- 12 months**
Akelos	**$1,030,000**	**total**	**DRUG DISCOVERY (analog)- Med Chem, ADME, killer tox**
Med Chem	$450,000		Med Chem CRO ~42 FTE mo, inc analogs, scale-up & metab syn
Pharmacol	$150,000		HCN1-4 pharmacol screen & IC50 (Q-patch, other assays)
ADME	$200,000		ADME (sol,PPB,mics&heps stab,CYPs inh, met ID)- 50 -> 10 cmpds
Safety	$80,000		Preclin safety (hERG, CV ion chan, broad screening); 4-5 cmpds
Safety	$75,000		Preclin tox (GSH adduct, cytotox, tolerability)
CMC	$75,000		Formulation & salt screen & stability; dev prototypes
Akelos	**$1,650,000**	**total**	**Preclin PK & Efficacy supporting DEV CAND selection**
PK	$300,000		PK (mult. cmpds, IV & PO RoA, SD & MD, brain)
in vivo efficacy	$400,000		Efficacy studies- CIPN (oxalplatin & taxol; SD, MAD)
in vivo efficacy	$250,000		Efficacy studies- other rodent 'pain' models (DPN, nerve injury)
Tox	$200,000		non-GLP MAD, DRF, MTD in vivo studies (rodent & non-rodent)
PK & tox	$150,000		Cell-/tissue-based assays, in vivo biomarkers, tissue distribution
NAM	$100,000		New Approach Methods (feasibility animal work replacement)
			MILESTONE- CANDIDATE SELECTION

ALK+CROs	**$5,865,000**		**IND-ENABLEMENT- 12 months**
Akelos	**$1,040,000**	**total**	**GLP Tox Program**
Tox	$50,000		Dose range rodent w/ TK, 7-10 d
Tox	$90,000		Dose range non-rodent w/ TK, 7-10 d
Tox	$300,000		GLP 28d rodent w/ TK & histopath
Tox	$600,000		GLP 28d non-rodent w/ TK & histopath
Akelos	**$550,000**	**total**	**SAFETY PHARMACOLOGY & GENOTOXICITY**
Safety	$200,000		GLP mutagenicity studies (Ames, chrom abs, micronucleus)
Safety	$50,000		Respiratory Safety (rodent)
Safety	$50,000		CNS Safety-FOB study (rodent Irwin)
Safety	$125,000		Abuse Potential (rodent: CPP, DD, no SA)
Safety	$125,000		CV Safety- non-rodent CV telemetry study
Akelos	**$3,275,000**	**total**	**DRUG SUBSTANCE**
CMC	$250,000		Salt/polymorph, Process Development
CMC	$300,000		Scale-up & Demo run -> 'GLP batch'
CMC	$125,000		Analytical method development
CMC	$2,500,000		GMP synthesis
CMC	$100,000		Stability (out to 12 mo)
Akelos	**$1,000,000**	**total**	**DRUG PRODUCT (oral pdt)**
Clin	$350,000		Formulation (capsules, tablet, oral suspension)
Clin	$500,000		Manufacturing
Clin	$150,000		Stability (out to 12 month, need 1+ month), compatability, etc.
			MILESTONE- IND SUBMISSION
Akelos	**$4,958,000**		**G & A + MISC**
Akelos	$720,000		CEO Fox ($30K/month x 24 months; full-time)
Akelos	$600,000		CSO Dax ($25K/month x 24 months; full time)
Akelos	$480,000		CBO tbd ($20K/month x 24 months; full time)
Akelos	$168,000		Office admin ($7K/month x 24 months; full time)
consultant	$100,000		CMC consultant for IND Enablement
consultant	$120,000		PK & Toxicology consultant for pre-IND & IND Enablement
consultant	$200,000		Acting CMO for pre-IND, IND Enable + Phase 1
Akelos	**$2,570,000**		**MISC (24 months)**
Akelos	$1,200,000		Cornell license fee

Akelos	$70,000	D&O insurance ($10K/yrs1-2 + $50K FIH)
Akelos	$300,000	Travel
Akelos	$150,000	Consumables ($5K/month)
Akelos	$100,000	Software (inc chem modeling)
Akelos	$750,000	IP (attorney fees, new patent filings & patent fees)

Acceleration to Milestones:

The team is pursuing or considering multiple strategies by which to accelerate the achievement of the mission-critical milestones.

1. Aggressive profiling of Lead AKE-1018 will be undertaken to determine if this NCE can become the Development Candidate worthy of IND-Enablement. If AKE-1018 demonstrates acceptable potency and activity in preclinical Chemotherapy-Induced Peripheral Neuropathy (CIPN) models, AKE-1018 may enter IND Enablement up to 3 months sooner than forecasted for a yet-to-be-named Advanced Lead.

2. It may be possible to accelerate approval to human dosing by placing clinical trials in Australia which may shorten development time by 3 months.

3. A first-in-class non-opioid therapeutic to treat neuropathic pain may be suitable for First-Track designation (preclinically) or Breakthrough designations (clinically) which will accelerate overall development (e.g., to NDA submission).

TRADEMARK

On July 23, 2019, the United States Patent and Trademark Office ("USPTO") registered the Company's trademark AKELOS, in International Class 42, for, inter alia, medical research. On December 28, 2024, the USPTO accepted the Company's Section 8 declaration of use and Section 15 declaration of incontestability regarding the AKELOS trademark. On January 6, 2026, Akelos received Notices of Allowance from the United States Patent and Trademark Office (USPTO) for its trademark applications for AKELES and AKELESS.

MARKET

Neuropathic pain is a complex, chronic pain condition that is accompanied by tissue and nerve fiber damage or injury. Globally, neuropathic pain therapeutics are estimated to generate roughly **US$8.1–**

8.6 billion annually as of 2025. The market is projected to expand at approximately **7–8% annually**, with global revenue expected to reach roughly **US$15–17 billion by the early-to-mid 2030s**.

Rising occurrence of diabetes and cancer, new treatment options to treat neuropathic pain, growth in the number of pain management centers, and increasing demand for neuropathic pain treatment are major factors driving revenue growth of the global neuropathic pain market currently. Other factors driving market growth include rapid product launches for the treatment of neuropathic pain, a growing awareness among patients for the treatment of neuropathic pain, and an increasing demand for generic drugs.[6]

Pharmaceutical companies are focusing on developing new and improved drugs to fulfil unmet needs of patients suffering from neuropathic pain. However, challenges such as severe side effects of opioids and steroids and rising costs of branded drugs are likely to restrain the growth of the global neuropathic pain market in the next eight years.[6]

The global neuropathic pain market is segmented on the basis of drug class, indication, and distribution channel. On the basis of drug class, the market has been segmented into Tricyclic Antidepressant, Anticonvulsant, Local Anesthetic, Opioid, Steroid, and Other. The Anticonvulsants drug class segment is expected to remain the largest segment in the global neuropathic pain market, registering a CAGR of 6.4% in terms of value over the forecast period. The profile of this drug class, with less side effects, is expected to contribute to its growing popularity. The Anticonvulsants segment is projected to reach a market valuation of US$3.3 billion by the end of 2024. The Tricyclic Antidepressant segment is also likely to emerge as the most preferred drug class type for both patients and physicians globally over the forecast period.[6]

On the basis of indication, the market has been segmented into Diabetic Neuropathy, Chemotherapy-Induced Peripheral Neuropathy (CIPN), and Others. The highest market share is held by the Diabetic Neuropathy segment, followed by the CIPN segment. The Diabetic Neuropathy segment is estimated to account for the highest value share of 46.7% of the global neuropathic pain market. This is drawing increased investments to the market, thereby driving its growth.[6] The CIPN segment is estimated to account for 42.4% revenue share in the global neuropathic pain market.[6] Recent work indicates that selective inhibition of HCN1 channel function may be a viable strategy for relieving CIPN.[6]

COMPETITION

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 anti-convulsants, anesthetic adjuncts, and most importantly, anti-hyperalgesics.[11]

In the pain space, HCN1-selective blockers have been collectively developed by the Romanelli (Department of Neuroscience, Psychology, Drug Research and Child Health, Section of Pharmaceutical and Nutraceutical Sciences, University of Florence, Florence, Italy) and Cerbai (Department of Neuroscience, Psychology, Drug Research and Child Health - NEUROFARBA - Pharmacology and Toxicology Section, University of Florence, Florence, Italy) groups.[12,13] The lead compound in this series, MEL57A, has recently been shown to relieve oxaliplatin-induced neuropathic pain.[14] MEL57A is structurally distinct from the alkylphenol-based HCN1-selective molecules under development by Akelos, and has a different mechanism of action (direct pore blockade vs. gating inhibition), which we believe will offer greater opportunities for next-generation drug synthesis. With regards to platform, MEL57A lacks the "anchor-tether" construct adopted by Akelos, which has broader implications with regards to future avenues of drug development.

Previously, Pfizer Neusentis (Cambridge, UK) demonstrated considerable interest in understanding HCN channel contribution to sensory transduction with research efforts focusing on pain management, regenerative medicine, and disorders linked to ion channels.[15,16] Following Pfizer's merger with Allergen, however, Pfizer announced on 3 December 2015 that it was closing Neusentis and "[reducing] its investment in pain as a dedicated early research and development area," thereby removing a leading competitor from this space. Gareth Young, Ph.D., who had been a leading figure in the Neusentis efforts, is now Associate Director, GlaxoSmithKline US; at present, the main focus of research efforts at GSK are HIV/infectious diseases, respiratory illnesses, oncology, immune-inflammation, and vaccine development.

The Julius lab at UCSF has published data demonstrating that $Na_V1.1$ may play a role in nociception as it relates to pain arising in the gastrointestinal tract.[17] The extent to which it participates in

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[11] Postea O, Biel M. Exploring HCN channels as novel drug targets. *Nat Rev Drug Discov* 2011;10:903-14.
[12] Melchiorre M, Del Lungo M, Guandalini L, et al. Design, synthesis, and preliminary biological evaluation of new isoform-selective f-current blockers. *J Med Chem* 2010;53:6773-7.
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[17] Osteen JD, Herzig V, Gilchrist J, et al. Selective spider toxins reveal a role for the NaV1.1 channel in mechanical pain. *Nature* 2016;534:494-9.
20 Pipeline | R&D | Grünenthal (grunenthal.com)
21 Vertex Announces Positive Results From the VX-548 Phase 3 Program for the Treatment of Moderate-to-Severe Acute Pain
22. Grünenthal and Averitas Pharma announce completion of recruitment for Phase III clinical trial with QUTENZA® in post-surgical neuropathic pain

neuropathic pain following peripheral nerve injury per se is less clear as the thermal and mechanical pain assays used by those authors measured pain following intraplanar injection of Hm1A; this is not the same as direct nerve injury. Further, there is no evidence to date to suggest that $Na_V1.1$ participates in chemotherapy-induced painful neuropathy (CIPN) or painful diabetic peripheral neuropathy (PDPN). Consequently, there is no direct competition with respect to developing HCN1-selective antagonists for these conditions.

Astraea Therapeutics (Mountain View, CA) is a discovery-stage biopharmaceutical company, focused on the discovery and preclinical development of small-molecule therapeutics for the treatment of drug addiction and central nervous system disorders. Their pipeline consists of lead optimization programs for discovering drug candidates against major molecular targets important for the treatment of CNS disorders, particularly drug addiction and pain. Working in conjunction with research groups from Wake Forest School of Medicine (Winston-Salem, NC) and Wakayama Medical University (Wakayama, Japan), Astraea scientists recently published work describing a new bi-functional ligand that is an agonist at both μ opioid and nociceptin/orphanin FQ peptide (NOP) receptors. This compound, AT-121, produced potent acute analgesic effects without inducing opioid-associated hyperalgesia or short-term physical dependence in rhesus monkeys; while it attenuated capsaicin-induced thermal allodynia, it is unknown whether AT-21 effectively relieves other forms of neuropathic pain. A notable limitation of the ligand was the gradual onset of tolerance to the antinociceptive effects of AT-121, suggesting a restricted role for this compound in treating chronic pain. Publication: Ding et al. A bifunctional nociceptin and mu opioid receptor agonist is analgesic without opioid side effects in nonhuman primates. *Sci. Transl. Med.* 10, eaar3483 (2018).

Large pharmaceutical companies are vying for an increased part of the pain market. (See Table 4)

Table 4 - Pharmaceutical Companies in the Pain Space

Source: Precedence Research, 2025

Source: Mordor Intelligence, 2025

A number of pharmaceutical companies have begun research collaborations or acquired technology to develop non-opioid painkillers. Companies including Merck, Purdue, and Roche have entered into agreements pursuant to which they have committed to invest in excess of $250 million, subject to the achievement by the recipients of development and/or regulatory milestones.

Grünenthal, the self-proclaimed global leader in pain management has a multi-faceted pipeline in the area. Their foundational product, Qutenza™ is a patch containing prescription-strength capsaicin. In Europe, it is approved for the treatment of peripheral neuropathic pain. In the US, it is approved for the treatment of neuropathic pain associated with post-herpetic neuralgia, and in 2020 it also received approval for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet in adults.[20] The Company's Phase III trial AV001 aims to evaluate QUTENZA® in post-surgical neuropathic pain (PSNP).[22]

Vertex Pharmaceuticals' VX-548 is in Phase III development for VX-548 in Acute ~~and~~ Neuropathic Pain. VX-548 is an oral, selective NaV1.8 inhibitor that is highly selective for NaV1.8 relative to other NaV channels. NaV1.8 is a voltage-gated sodium channel that plays a critical role in pain signaling in the peripheral nervous system. NaV1.8 is a genetically validated target for the treatment of pain, and Vertex has previously demonstrated positive proof-of-concept results and a well-tolerated profile with VX-548 in two Phase 2 studies of acute pain following abdominoplasty and bunionectomy surgeries and in a Phase 2 study in painful diabetic peripheral neuropathy, a type of peripheral neuropathic pain. Vertex's approach is to selectively inhibit NaV1.8 using small molecules with the objective of creating a new class of medicines that have the potential to provide superior relief of acute pain without the limitations of opioids, including their addictive potential. VX-548 is the most recent molecule to enter clinical development from Vertex's portfolio of NaV1.8 inhibitors.[21]

REGULATORY PATHWAY

The process of drug development in the U.S. is extremely lengthy and costly. Any product candidate we may successfully develop must be approved by the FDA through the New Drug Application ("NDA") process before it can be legally marketed in the U.S. The FDA process can take up to 10 years or more and up to approximately $100 million.

The data required to support an NDA is generated in two distinct development stages: nonclinical and clinical. For new chemical entities, the nonclinical development stage generally involves synthesizing the active component, developing the formulation, and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology, and drug metabolism studies in the laboratory, which support subsequent clinical testing. These nonclinical tests include laboratory

evaluation of product chemistry, formulation, stability, and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the nonclinical tests must comply with federal regulations, including the FDA's Good Laboratory Practice regulations ("GLPs"). The sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of an Investigational New Drug ("IND") application. An IND is a request for authorization from the FDA to administer an investigational drug product to humans and must become effective before human clinical trials may begin. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials, including concerns that human research subjects will be exposed to unreasonable health risks, and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance.

We will need to raise substantial funds to complete the requirements for submission of an IND, which we expect to take approximately two years, and even then, there can be no assurance that an IND submission will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board ("IRB") at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

Clinical trials are generally conducted in three sequential phases that may overlap, known as Phase 1, Phase 2 and Phase 3 clinical trials. Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug. Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits and provide a

preliminary evaluation of efficacy. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks. Phase 3 clinical trials generally involve large numbers of patients at multiple sites (from several hundred to several thousand subjects) and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for physician labeling. Phase 3 clinical trials may include comparisons with placebo and/or comparator treatments.

The results of the nonclinical studies and clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the drug and proposed labeling, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use. After the FDA evaluates an NDA, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete, and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, nonclinical studies, or manufacturing. If a Complete Response Letter is issued, the applicant may resubmit the NDA addressing all of the deficiencies identified in the letter, withdraw the application, or request an opportunity for a hearing. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings, or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing or clinical trials and surveillance to monitor the effects of approved products.

INVESTMENT EXIT

In light of the extremely lengthy, costly, and uncertain development and regulatory approval process required to bring a drug from compound to commercial drug, we believe that the most likely exit path will be via acquisition by a large, established pharmaceutical company. However, there can be no assurance that Akelos will ever be sold, what the terms of a possible sale might be or when, if ever, investors in the Offering will have the opportunity to exit their investment in the Company.

An investment in our company is highly speculative and involves a high degree of risk. Before you invest you should carefully consider the risks and uncertainties described below as well as the other information contained in this Private Placement Memorandum and the other subscription materials. If any of the following risks actually occur, our business and prospects could be materially adversely impacted and the value of our stock could go down. This means you could lose all or a part of your investment. You are strongly advised to review this Private Placement Memorandum and the other subscription materials relating to the Offering, and to consult with your legal and financial advisors before investing in the Offering.

Limited Operating History.

We are a pre-clinical development stage biopharmaceutical company and since inception our operations have been limited to organizational activities and the negotiation and entry into the license agreement and collaboration agreement. These operations provide a limited basis for prospective investors to assess our ability to complete development of any products and the advisability of investing in our securities. Our prospects need to be considered in light of the uncertainties, risks, expenses and difficulties frequently encountered by companies in their early stages of operations. There can be no assurance that we will be able to implement our business plan, continue to fund our operations or successfully develop any products,

Losses and Need for Additional Financing

The pharmaceutical development and regulatory process is extremely expensive and lengthy. We expect to incur significant and increasing losses from operations for the foreseeable future and will require substantial funds for product research and development activities, including the costs of preclinical and clinical trials and payment of our obligations to our licensor, as well as for the regulatory approval process and potential commercialization of any product we may successfully develop. Because of the risks and uncertainties associated with pharmaceutical product development, we are unable to predict the extent of any future losses, whether we will ever generate significant revenues or if we will ever achieve or sustain profitability. We will seek to finance future cash needs through equity offerings or corporate collaboration and licensing arrangements. To the extent that we raise additional capital by issuing equity or equity-linked securities (including convertible debt), the share ownership of existing stockholders will be diluted. In addition, pursuant to our license agreement, we have agreed to issue the licensor shares of common stock representing five percent of our outstanding capital stock on a fully-diluted basis until such time as we have raised, on a cumulative basis, $7,000,000 in financing proceeds, which obligation will further dilute investors in our company.

We currently have no commitments or agreements relating to any of these types of transactions and we cannot be certain that any significant funding will be available on acceptable terms, if at all. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate our research and development programs or curtail or cease our operations. We believe these conditions raise substantial doubt about our ability to continue as a going concern.

Early Stage of Products

Our product candidates are in the early stages of the development process and will require substantial further capital expenditures, development, testing, and regulatory clearances prior to

commercialization. Initial activities conducted on our behalf will test our lead compound in experiments in neuropathic animal models aimed at determining whether such compound can form the basis of an Investigational New Drug ("IND") application. There can be no assurance that these efforts will be successful. Our ability to successfully develop any product candidates is also subject to the risks of failure and delay inherent in the development of new pharmaceutical products, including: delays or adverse outcomes during product development, clinical testing, or manufacturing; unplanned expenditures in product development, clinical testing, or manufacturing; failure to receive regulatory approvals; emergence of superior or equivalent products; inability to manufacture on our own, or through any others, product candidates on a commercial scale; and failure to achieve market acceptance. The development and regulatory approval process takes several years and it is not likely that any of such products, even if successfully developed and ultimately approved by the United States Food and Drug Administration ("FDA") or any comparable foreign regulatory authority, would be commercially available for at least eight to 10 years or more. Of the large number of drugs in development, only a small percentage successfully completes the regulatory approval process and is commercialized. Accordingly, even if we are able to obtain the requisite financing to fund our development programs, we cannot assure you that our product candidates will be successfully developed or commercialized. Our failure to develop, manufacture or receive regulatory approval for or successfully commercialize any of our product candidates, could result in the failure of our business and a loss of all of your investment in our company.

Extensive Regulation

The clinical development, manufacturing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA in the United States and by comparable authorities in foreign markets. In the United States, we will not be permitted to market our product candidates until we receive approval of an NDA or comparable filing from the FDA. The process of obtaining FDA approval is expensive, takes many years and can vary substantially based upon the type, complexity and novelty of the products involved. We will be required to demonstrate through well-controlled clinical trials that our product candidates are safe and effective with a favorable benefit-risk profile for use in their target indications before we can seek regulatory approvals for their commercial sale. Our product candidates have only been tested in a pre-clinical setting and we have not filed an IND for any product candidates. Success in pre-clinical studies or early clinical trials does not mean that later clinical trials will be successful, as product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through initial clinical testing. We also may need to conduct additional clinical trials that are not currently anticipated. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results.

If we are able to advance our product candidates to the clinical stage, the clinical trials will need to be conducted in accordance with current good clinical practice standards governing the design, safety monitoring, quality assurance and ethical considerations associated with clinical studies. Clinical trials are subject to oversight by the FDA, other foreign governmental agencies and IRBs at the study sites where the clinical trials are conducted. In addition, clinical trials must be conducted with product candidates produced in accordance with applicable current good manufacturing practices, which are the FDA's regulations governing the design, monitoring and control of manufacturing processes and facilities. Clinical trials may be suspended by the FDA, other foreign governmental agencies, or us for various reasons, including:

- deficiencies in the conduct of the clinical trials, including failure to conduct the clinical trial in accordance with regulatory requirements or clinical protocols;
- deficiencies in the clinical trial operations or trial sites;
- the product candidate may have unforeseen adverse side effects;
- deficiencies in the trial design necessary to demonstrate efficacy;
- fatalities or other adverse events arising during a clinical trial due to medical problems that may not be related to clinical trial treatments;
- the product candidate may not appear to be more effective than current therapies; or
- the quality or stability of the product candidate may fall below acceptable standards.

The FDA has substantial discretion in the pharmaceutical approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, only a small percentage of drugs under development result in the submission of an NDA to the FDA and even fewer are approved for commercialization.

Our obligation to comply with extensive government regulations, including new regulations that may be adopted in the future, will require us to raise substantial funds, which may not be available to us on acceptable terms or at all.

License and Collaboration Agreements

Our compounds under development, including the related intellectual property rights, were licensed from Cornell University. Under the terms of our license agreement, (the "License Agreement"), the licensor generally has the right to terminate such agreement in the event of a material breach by us. Our license requires us to make annual maintenance fees and milestone payments, achieve diligence objectives and meet expenditure requirements prior to commercialization of any product. We are also required to pay all patent costs associated with the licensed products. Our ability to satisfy these obligations depends on our ability to obtain financing, as well the efforts of third parties, including the licensor. We have also entered into a collaboration agreement ("Collaboration Agreement") with Cornell University to support research on behalf of its Joan & Sanford I. Weill Medical College, in the laboratory of Dr. Goldstein. Both agreements require Cornell to comply with reporting and other obligations mandated for entities that receive funding from the U.S. government. If there is any conflict, dispute, disagreement or issue of non-performance between us and our licensing and/or collaboration partner regarding our rights or respective obligations under the license agreement or collaboration agreement, including any conflict, dispute or disagreement arising from our failure to satisfy payment obligations under such agreements, our ability to develop and commercialize the affected product candidate may be adversely affected. Any loss of our rights under these agreements could delay or completely terminate our product development efforts for our product candidates.

Loan Repayment

Pursuant to the License Agreement and Collaboration Agreement, we owe Cornell University and Burke Neurological Institute, contracted by Cornell University to provide laboratory and research services, $1.2 million (the "Research Loan"). In the event that Akelos fails to generate significant revenue or files for bankruptcy, such Research Loan will take precedence and you may not receive returns from the revenue generated, or may not receive any or all of their capital commitment. Your

investment will rank below the Research Loan with respect to any distributions, payouts, return of capital or right to the assets, tangible and intangible, of Akelos.

Intellectual Property

Our future success will depend to a significant extent on our ability to obtain and keep patent protection for our products and technologies on an international basis, enforce our intellectual property rights to prevent others from using our inventions, and operate without infringing on the patents or proprietary rights of others. We cannot assure you that any patent applications that we have licensed or may license in the future pursuant to the collaboration agreement, or any other such agreement we may enter into will issue as patents or that any patent rights we obtain will adequately protect our product candidates or afford any competitive advantages. We also cannot assure you that such patent rights will not be challenged or circumvented by third parties. In addition, disputes may arise as to ownership of intellectual property rights arising from developments under our collaboration agreement. Further, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before a potential product can be commercialized, any related patent may expire or remain in existence for only a short period following commercialization, reducing or eliminating any advantage afforded by the patent. If we sue others for infringing our patents, a court may determine that such patents are invalid or unenforceable. Even if the validity of our patent rights is upheld by a court or administrative agency, a court may not prevent the alleged infringement of our patent rights on the grounds that such activity is not covered by our patent claims. In addition, third parties may sue us for infringing their patents. In the event of a successful claim of infringement against us, we may be required to pay substantial damages, stop certain research and development efforts or obtain licenses from third parties, which may not be available on acceptable terms, if at all. We may also be unsuccessful in efforts to protect our trade secrets, know-how and other proprietary information.

Competition

We operate in the highly competitive pharmaceutical market and will face competition from many different sources, including commercial pharmaceutical and biotechnology enterprises, academic institutions, government agencies, and private and public research institutions. Many of such potential competitors have significantly greater financial, product development, manufacturing and marketing resources than us. Large pharmaceutical companies have extensive experience in clinical testing and obtaining regulatory approval for drugs. In addition, many universities and private and public research institutes are active in pain management research, some in direct competition with us. We also may compete with these organizations to recruit scientists and clinical development personnel. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. New developments, including the development of other biological and pharmaceutical technologies and methods of treating disease, occur in the pharmaceutical and life sciences industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. We will also face competition from these third parties in recruiting and retaining qualified personnel, establishing clinical trial sites and patient registration for clinical trials and in identifying and in-licensing new product candidates.

Reliance on Third Parties.

We do not have the ability to conduct our preclinical testing or clinical trials ourselves. We are relying on our collaboration partner to conduct the initial studies to support an IND filing. We intend to use contract research organizations ("CROs") to conduct any clinical trials we may be able to initiate and

will rely upon such CROs, as well as medical institutions, clinical investigators and consultants, to conduct our trials in accordance with applicable government regulations and other guidelines. Our future CROs, investigators and other third parties will play a significant role in the conduct of these trials and the subsequent collection and analysis of data from the clinical trials. There is no guarantee that any CROs, investigators and other third parties upon which we rely for administration and conduct of our clinical trials will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fail to meet expected deadlines, fail to adhere to our clinical protocols or otherwise perform in a substandard manner, our clinical trials may be extended, delayed or terminated. If any of our clinical trial sites terminate for any reason, we may experience the loss of follow-up information on patients enrolled in our ongoing clinical trials unless we are able to transfer the care of those patients to another qualified clinical trial site. In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, the integrity of the data generated at the applicable clinical trial site may be jeopardized.

We will completely depend on third parties to supply product for our preclinical and clinical studies. Our product development programs would be adversely affected by a significant interruption in our ability to receive such materials. Furthermore, our third-party suppliers will be required to maintain compliance with cGMPs and will be subject to inspections by the FDA or comparable regulatory authorities in other jurisdictions to confirm such compliance. In the event that the FDA or such other authorities determine that our third-party suppliers have not complied with cGMP, clinical trials could be terminated or subjected to a clinical hold until such time as we are able to obtain appropriate replacement material. Any delay, interruption or other issues that arise in the manufacture, packaging, or storage of our products as a result of a failure of the facilities or operations of our third-party suppliers to pass any regulatory agency inspection could significantly impair our ability to develop and commercialize our products.

Product Liability or Indemnification Claims

We will face an inherent risk of product liability exposure related to the testing of our product candidates in the event we are able to initiate human clinical trials, and claims could be brought against us if use or misuse of one of our product candidates causes, or merely appears to have caused, personal injury or death. While we have and intend to maintain product liability insurance relating to our clinical trials, our coverage may not be sufficient to cover claims that may be made against us and we may be unable to maintain such insurance. Any claims against us, regardless of their merit, could severely harm our financial condition, strain our management and other resources or destroy the prospects for commercialization of the product which is the subject of any such claim. We are unable to predict if we will be able to obtain or maintain product liability insurance for any products that may be approved for marketing. Additionally, we have entered into various agreements where we indemnify third parties for certain claims relating to the testing and use of our product candidates. These indemnification obligations may require us to pay significant sums of money for claims that are covered by these indemnifications.

Retention of Personnel; Advisors

We are dependent on the continued service of Dr. Steven Fox, our President and founder and currently our sole employee. Our success will depend on our ability to attract and retain highly qualified management and clinical development personnel. At such time, if ever, as we have the

resources to hire such personnel, we will face the highly competitive market for the services of qualified personnel in the pharmaceutical industry. We expect to rely, for the foreseeable future, in substantial part on independent organizations, advisors and consultants to provide certain services, including substantially all aspects of product research, regulatory approval and clinical management. There can be no assurance that the services of independent organizations, advisors and consultants will be available to us on a timely basis when needed. If we fail to attract and retain required personnel or are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement our business plan. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any reason, our business prospects may be materially harmed.

We have established an informal advisory board and scientific advisory board comprised of individuals with expertise in areas we believe are important to implementing our business strategy. However, our advisors are employed by other parties and have responsibilities and time commitments unrelated to Akelos and there can be no assurance as to the level of effort or input we can expect from such individuals.

No Market for Our Securities; Exit Strategy

There is no public market for our any of our securities and there can be no assurance that any liquid trading market for our securities will ever exist. We have no plans or arrangements with respect to an initial public offering ("IPO") of our securities and there can be no assurance that an IPO will ever occur. While we believe a more likely exit for our 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 that such an opportunity would be available to us in the next few years, if at all. Prospective investors should be prepared to hold the shares and bear the economic risk of an investment in our company for an indefinite period of time.

Arbitrary Determination of Offering Price

The Offering price of the Shares was determined by our founder and does not necessarily bear any relationship to our book value, assets, financial condition, or other established criteria of value.

Restrictions on Transfer; No Dividends

The Shares to be sold in the Offering were not qualified or registered for offer or sale under the securities laws of any country or jurisdiction. Such shares are "restricted securities" as such term is defined in Rule 144 of the Act and they may not be sold or otherwise transferred except in compliance with applicable securities laws. We have never paid and do not expect to pay dividends on our Common Stock for the foreseeable future.

Best Efforts Offering; No Minimum

The Offering is being made on a "best efforts" basis and there is no minimum amount of proceeds required to close. There can be no assurance that any significant number of Shares will be sold or that we will receive substantial proceeds from the Offering. Investors will bear the risk of our inability to raise sufficient funds from the Offering to meet our financial obligations to our licensor or otherwise finance our operations for any significant period of time.

Control by Management

Even if we can complete the maximum offering and issue an aggregate of 5,090,909 Shares, Steven Fox, the Founder and Chief Executive Officer of Akelos, will continue to hold a majority of the outstanding common stock of the Company and will be able to control our affairs and operations, including the expenditure of funds, the composition of the board of directors and the terms of any future financings, which may include the authorization and issuance of preferred stock or debt having dividend preferences, liquidation preferences, approval, voting or other rights senior to the investors in the Offering.

Other business activities of the management team

Members of the management team engage in other business activities and may establish and manage other business ventures in the future. Members of the management team are not required to devote any portion of their business time and attention to the affairs of the Company.

Advisory Board; Scientific Advisory Board

Members of the advisory boards do not owe a fiduciary duty to the Company. There is no guarantee that advisors will not have any interest, financial or otherwise, direct or indirect, or engage in any business or transaction of any nature, which is in conflict with the business of the Company.

Personal Investment by the management team and other affiliates

Members of the management team and their affiliates may invest in the Company for their own personal accounts. Personal investments may be used to replace Subscribers who are unable to meet the suitability or accreditation requirements to invest in the Company.

BIOGRAPHIES

Dr. Steven R. Fox, President and Chief Executive Officer

Dr. Fox is a Doctor of Dental Surgery, an accomplished and successful business entrepreneur, and is internationally recognized for overseeing and developing 17 patents in cosmetic dentistry. Dr. Fox has overseen all facets of management including financing, research and development, staffing, accounting, operations and marketing, and financial public relations. He has served on the faculty of leading universities including Harvard University and New York University, and also served as an officer for Harvard University. In addition, Dr. Fox has appeared many times on national television programs such as CNN, Fox News and CNBC; has been featured in numerous top business publications, such as The Wall Street Journal and Forbes Magazine; received the Medal of Freedom from the Republican Members of the United States Senate; and was also the recipient of the Ernst & Young Entrepreneur of the Year award. Dr. Fox currently runs a dental practice for Implant, General & Cosmetic Dentistry, and also serves as Chairman of The Rebel Group, which advises entrepreneurs, start-ups, and investors on all matters relating to investing and capital raises. Dr. Steven Fox received his Bachelor of Arts degree from University of Rochester, with honors in science, and his Doctor of Dental Surgery degree from New York University.

Robert Benson, Ph.D., Intellectual Property Advisor

Dr. Benson is a seasoned technology transfer professional with over 20 years of experience in licensing and intellectual property. Before becoming a Principal of South Shaker Associates LLC, he spent nearly a decade as Director of Business Development for the Office of Technology Development at Harvard University. Dr. Benson also spent 13 years as a Supervisory Licensing Specialist in the Office of Technology transfer at the National Institute of Health. He has wide experience with licensing and intellectual property matters and a broad understanding of molecular sciences, including material sciences, chemistry, and biotechnology. Dr. Benson is a patent agent and worked as a patent examiner at the USPTO in the medicinal chemistry and biotechnology areas. He has a Ph.D. in chemical physics from New York University.

Peter Barton Hutt, FDA Counsel

Peter Barton Hutt is a Senior Counsel in the Washington, DC law firm of Covington & Burling, specializing in Food and Drug Law. He began his law practice with the firm in 1960 and, except for his four years in the government, has continued at the firm ever since. From 1971 to 1975 he was Chief Counsel for the Food and Drug Administration, and since then, has been the leading figure in Food and Drug Law. Beginning in 1994, he taught Food and Drug Law each Winter Term at Harvard

Law School. Mr. Hutt is the co-author of four editions of Food and Drug Law: Cases and Materials (Foundation Press) and has published more than 175 book chapters and articles on Food and Drug Law and on health policy. He has represented the national trade associations for food, prescription drug, nonprescription drug, dietary supplement, and cosmetic industries. Mr. Hutt was named by the Washingtonian magazine as one of Washington's 50 best lawyers (out of more than 40,000) and as one of Washington's 100 most influential people; by the National Law Journal as one of the 40 best health care lawyers in the United States; and by Global Counsel as the best FDA regulatory specialist in Washington, DC. He was elected a lifetime member of the National Academy of Medicine in 1971, the year that it was established.

Senator Thomas Daschle, Strategic Healthcare Advisor

Senator Daschle provides clients with strategic public policy advice on a wide range of international issues. Senator Daschle has participated in the development and debate of almost every major public policy issue of the last three decades. In 1978, he was elected to the U.S. House of Representatives, where he served for eight years. In 1986, he was elected to the U.S. Senate and was chosen as Senate Democratic Leader in 1994. Senator Daschle is one of the longest-serving Senate Democratic leaders in history and served as both Majority and Minority Leader. During his tenure, Senator Daschle navigated the Senate through some of its most historic economic and national security challenges. In 2003, he chronicled some of these experiences in his book, Like No Other Time: The 107th Congress and the Two Years That Changed America Forever. In the 2013 book The U.S. Senate: Fundamentals of American Government, Senator Daschle explored the inner workings of this important part of the legislative branch.

Since leaving the Senate, Senator Daschle has remained an active and learned voice among policymakers. He has distinguished his experience in health care through the publication of "Critical: What We Can Do About the Health Care Crisis" and "Getting It Done: How Obama and Congress Finally Broke the Stalemate to Make Way for Health Care Reform." Senator Daschle has also emerged as a leading thinker on climate change, food security and renewable energy policy. He serves as the chair of the DuPont Advisory Committee on Agriculture Innovation and Productivity as well as the BP Tangguh Independent Advisory Panel.

In 2007, Senator Daschle joined with former Majority Leaders George Mitchell, Bob Dole, and Howard Baker to create the Bipartisan Policy Center, an organization dedicated to finding common ground on some of the pressing public policy challenges of our time. Senator Daschle serves on numerous public and private boards, including the Center for American Progress and the National Democratic Institute for International Affairs. He is a member of the Council on Foreign Relations. He also serves on the Health Policy and Management Executive Council at the Harvard School of Public Health, as well as the Council on Governance for Sustainability at the World Economic Forum and the Federal Advisory Board of Accenture.

Cyrus Arman, PhD, MBA, Head of Business Development

Dr. Arman has over 15 years of experience in corporate, clinical, and commercial strategy for biotechnology companies, including advising C-level management and boards of directors on strategy, transactional opportunities, financing, and risk mitigation. Most recently he served as President and Principal Operating Executive for CytoDyn, Inc. where he was responsible for resetting the corporate strategy, rebuilding the leadership team, securing financing, and executing on development plans. Prior to CytoDyn, Cyrus served as Chief Business Officer for Nimble Therapeutics and was responsible for leading transactions, finance acquisition, and corporate strategy. Prior to Nimble he was the Vice President of Corporate Development and Strategy at NEUVOGEN, Inc., an early-stage immuno-oncology company, where he was responsible for corporate development, business operations, and corporate strategy functions. Prior to NEUVOGEN, he was a director in Amgen's Corporate Strategy unit. Cyrus began his career as a management consultant where he advised clients in completing complex strategic projects involving multi-billion-dollar business development investments and partnerships in both the Biopharma and Diagnostics sectors.

Dr. Arman has an MBA from the University of California Los Angeles, a PhD in Neuroscience and an MS in Biomedical Engineering from the University of Southern California, and a BS in Biopsychology from the University of California San Diego.

ADVISORY BOARD

Eric Horodas, Esq.

Eric Horodas is an accomplished attorney, investor, and hotelier with over 40 years of experience in real estate investing in syndication and over 23 years' experience as a hotel investor and hotel manager. In 1995, Mr. Horodas Formed Greystone hotels to acquire and manage hotel assets. Since that time, he has acquired or developed 12 hotels in California and Oregon, raising an excess of $80 million in equity and $120 million in debt for his hotel company. Mr. Horodas is also a principal of Handro Properties and its affiliated entities with interests and multifaceted investment portfolio including various private equity funds, hedge funds and real estate projects throughout the United States and Europe. Mr. Horodas was a founding partner of the law firm Rubinstein & Perry in 1987 and represented national real estate projects as well as several State Insurance Commissioners in connection with the liquidation and rehabilitation of both workers compensation and life and health insurance companies. Prior to that, Mr. Horodas was a shareholder/partner of the Consolidated Capital Companies, a real estate investment firm. Eric holds a BA from the University of Rochester and a JD from New York University School of Law.

Alan Horowitch, MD

Dr. Horowitch graduated from Boston University School of Medicine in 1980. He completed post graduate years 1 and 2 at Mount Zion Hospital in San Fransisco, then graduated the San Fransisco Orthopedic Training Program in 1987. He did fellowship training in orthopedic trauma surgery at LA County USC Medical Center and fellowship training in orthopedic spine surgery at the Wiltse Spine Fellowship in Long Beach, California.

Dr. Horowitch practiced orthopedic surgery in San Diego, California and Yuma, Arizona for 20 years. He incorporated Advanced Open MRI and Advanced Radiology Healthcare, providers of state-of-the-art radiology services – which was subsequently sold to a hospital organization. As the sole owner of Southwest Desert Management Services, Incorporated he has invested in income properties in Phoenix, Arizona and Durango, Colorado.

Dr. Horowitch maintains residences in San Diego, California and Lisbon, Portugal. He is an avid aviator with 5000 hours logged in over 15 different models of aircraft.

Robert Kutnick, MD

Dr. Robert Kutnick is a widely admired published internist and pulmonologist who has been in private practice medicine for over 40 years delivering exemplary care to a wide range of local, national, and international clients. He was recognized by New York magazine as one of New York's best physicians on numerous occasions. Dr. Kutnick is a member of the Cornell Medical College faculty and lists the Cornell Division of the Columbia Presbyterian Medical Center where he serves as a member of the Pulmonary-Critical Care Department as his primary institution. Dr. Kutnick is a former Director of the Pulmonary Rehabilitation Department at Lenox Hill Hospital where he still holds an affiliation and teaching appointment. Dr. Kutnick's medical training was spent at Montefiore Division of the Albert Einstein College of Medicine where he completed his residency and pulmonary fellowship and at which he held faculty and teaching appointments. Dr. Kutnick graduated Summa Cum Laude from the State University of New York at Buffalo and obtained his medical degree from the Albert Einstein College of Medicine where he was inducted as a member of the Alpha Omega Honor Medical Society.

SCIENTIFIC ADVISORY BOARD

Peter Goldstein, MD, Scientific Co-Founder

Dr. Goldstein is a graduate of Cornell University, and he received his medical degree from the Mt. Sinai School of Medicine of the City University of New York. He completed a one-year internship in the Dept. of Surgery at the Mt. Sinai Hospital in New York, followed by a residency in Anesthesiology at the Columbia-Presbyterian Hospital in New York. Dr. Goldstein received an additional two years of training in the Dept. of Physiology and Biophysics at the College of Physicians and Surgeons of Columbia University as a Post-Doctoral Trainee through the United States Public Health Service. Dr. Goldstein was an Assistant Attending in Anesthesiology at the Columbia Presbyterian Medical Center before joining the Department of Anesthesiology at the Weill Cornell Medical Center in 2000.

Dr. Goldstein is a Principal Investigator in the C.V. Starr Laboratory for Molecular Neuropharmacology in the Department of Anesthesiology at the Weill Cornell Medical College, and his laboratory is primarily interested in ion channel biophysics (with an emphasis on HCN channels); additional research areas include regulation of cellular excitability, synaptic transmission, thalamic physiology, and the molecular and cellular mechanisms contributing to anesthetic-induced unconsciousness. Research efforts have been supported by grants from both private and federal (National Institutes of Health and Department of Defense) organizations. He has authored numerous publications and serves on various state and national committees related to the practice of anesthesiology. His clinical practice focuses on anesthesia for neurosurgery and bariatric procedures.

Charles B. Berde, MD, PhD

Dr. Berde is the Endowed Sara Page Mayo Chair and Senior Associate in Pediatric Pain Medicine in the Department of Anesthesiology, Critical Care and Pain Medicine at Boston Children's Hospital and Professor of Anesthesia (Pediatrics) at Harvard Medical School, Boston, MA.

He completed an MD and PhD (Biophysics) at Stanford University; his Residency in Pediatrics, at Boston Children's Hospital; Residency in Anesthesiology, at Massachusetts General Hospital; and Fellowship in Pediatric Anesthesiology, at Boston Children's Hospital.

Dr. Berde co-founded and for 33 years directed the Pain Treatment Service at Boston Children's Hospital, the first and most clinically active acute and chronic pain management program for children in the world. Dr. Berde's translational research concerns local anesthetic mechanisms and the development of novel prolonged duration local anesthetics that are now in clinical trials. His clinical research concerns clinical pharmacology of analgesics and local anesthetics in children, clinical outcomes of treatment of neuropathic pain and cancer pain in children, and EEG brain dynamics studies in children during general anesthesia. Dr. Berde is the author of over 200 original peer reviewed

articles and over 110 chapters and reviews. He was profiled as one of Time Magazine's "Heroes in Medicine" in 1997. He has received several awards and honors for his pioneering work in pediatric pain relief and anesthesiology, including the 2003 Scientific Achievement Award of the Reflex Sympathetic Dystrophy Syndrome Association, the 2015 International Association for the Study of Pain Special Interest Group in Pediatric Pain Distinguished Career Award, the 2018 Society for Pediatric Anesthesia Myron Yaster Lifetime Achievement Award, and the 2018 American Society for Regional Anesthesia John Bonica Lifetime Achievement award.

Scott L. Dax, MS, Ph.D.

Dr. Dax has over 25 years of experience guiding R&D at large pharma houses and small biotech companies. His leadership roles span chemistry, drug discovery, pharmacology, technology, and intellectual property. He most recently served as Chief Scientific Officer at CerSci Therapeutics, leading the development of a new generation of non-opioid drugs to treat acute post-surgical pain and chronic painful diabetic neuropathy. Dr. Dax's notable work resulted in private equity investments and NIH grants. CerSci Therapeutics was acquired by ACADIA Pharmaceuticals in 2020. Dr. Dax currently consults for life science companies as President of DRx Pharma Consulting & Services. He has also held leadership positions in pharmaceutical and biotechnology companies including Johnson & Johnson, Galleon Pharmaceuticals, and BioMotiv. Dr. Dax is an inventor of over 100 issued patents worldwide and has published over 100 abstracts/publications. He earned his Master and Doctorate degrees in chemistry at the University of Michigan and was an NIH post-doctoral awardee at the University of Wisconsin.

Michael Levitt, Ph.D.

Dr. Levitt is a biophysicist and professor of structural biology at Stanford University, a position he has held since 1987. Levitt received the 2013 Nobel Prize in Chemistry, together with Martin Karplus and Arieh Warshel, for “the development of multiscale models for complex chemical systems.” Dr. Levitt was elected an EMBO Member in 1983, a Fellow of The Royal Society (FRS) in 2001, and a member of the National Academy of Sciences in 2002. He received the DeLano Award for Computational Biosciences in 2014. He was elected an ISCB Fellow by the International Society for Computational Biology in 2015. Dr. Levitt received degrees from King’s College London (BScs) and the University of Cambridge (PhD). His fields include Computational Structural Biology, Structure Determination, and Simulation of Mesoscale Molecular Dynamics. Institutions include Stanford University, Weizmann Institute of Science, Laboratory of Molecular Biology, and University of Cambridge.

Darryle D. Schoepp, Ph.D.

Dr. Schoepp has over thirty years of experience in the discovery and development of innovative Neuroscience therapeutics in the pharmaceutical industry. This includes 20 years at Eli Lilly as a scientist and leader of the Neuroscience department, and 12 years at Merck as the CNS Therapeutic area leader.

As a scientist he has over 200 publications (>19,000 citations of this work) and is an inventor of 15 US patents. He is recognized for having made major contributions in the investigation of the excitatory amino acid neurotransmitter glutamate in disease pathophysiology, pharmacology, and therapeutics. His bench and leadership roles have led to the discovery and introduction into patients of over 20 novel first in class agents for psychiatric and neurological diseases. These include the first AMPA/kainate and metabotropic receptor negative and positive modulators (e.g. tezampanel, talampanel, LY354740, LY341595, eglumetad and pomoglumetad) investigated for migraine, pain, cognition, anxiety disorders and schizophrenia. While at Lilly, he was a co-discoverer of the compound LY246736 (alipimovan/Entereg) a first in class peripherally restricted opioid antagonist for post-operative ileus. Dr. Schoepp' was recipient of the 2002 Pharmacia / ASPET Award for Experimental Therapeutics and 2007 Ray Fuller / ASPET Lecturer in Neurosciences in recognition of translational pharmacology work in the glutamate field.

At Merck his team built a pipeline of innovative first-class agents for Alzheimer's disease, Parkinson's disease, pain/migraine, and schizophrenia. Merck Neuroscience successfully developed and launched the first in class orexin receptor antagonist Suvorexant (Belsomra) for insomnia and created the novel first in class oral CGRP antagonists ubrogepant (Ubrelvy) and atogepant for migraine treatment and prevention (commercialized by Allergan/Abbvie).

Dr. Schoepp received his bachelor's degree in Pharmacy from North Dakota State University and his doctoral degree in Pharmacology and Toxicology from West Virginia University.

Gareth R. Tibbs, Ph.D., Scientific Co-Founder

Gareth R. Tibbs Ph.D. is a former Research Associate in the Department of Anesthesiology at Weill Cornell Medicine. Dr. Tibbs received his undergraduate degree in Biochemistry from University College, London and his Ph.D. from the same department in 1986. Following a post-doctoral fellowship in the Biochemistry Departments of Imperial College, London, and Dundee University in Scotland, where he examined fundamental mechanisms governing neurotransmitter release, Dr. Tibbs joined Professor Steven A. Siegelbaum's research group in the Center for Neurobiology and Behavior at Columbia University. With Professor Siegelbaum and colleagues, Dr. Tibbs examined the structural basis for activation and conduction in cyclic nucleotide-regulated ion channels and was the first to identify the gene encoding the HCN1 pacemaker channel, which is now implicated as a key driver of

the hyperexcitability in sensory neurons associated with peripheral neuropathic pain. Following the identification of the *Hcn1* gene, Dr. Tibbs conducted pivotal studies on the structure-function relationship of HCN channels and has identified key regulatory aspects of that relationship. His work has been published in leading scientific journals, including, among others: *Cell*, *Neuron*, and *Nature*. Beginning in 2009, Dr. Tibbs has worked with Professor Peter A. Goldstein in the Department of Anesthesiology at Weill Cornell Medicine, examining the structural determinants that underlie the selective inhibition of HCN1 channels by non-anesthetic alkylphenols, with the long-term aim of developing novel, non-opiate-based therapeutics for the treatment of neuropathic pain.

Dianna E. Willis, Ph.D.

Dianna E. Willis, Ph.D., is the former head of the Laboratory for Axonal and RNA Biology, Director of the Center for Pain Research, and Associate Director at the Burke Neurological Institute, an Assistant Professor of Neuroscience at Weill Cornell Medicine, and Director of the Burke-Blythedale Program in Pediatric Clinic Neuroscience. Dr. Willis received her undergraduate degree in Biology from the University of Pittsburgh in 1994, and her Ph.D. in Molecular Biology and Genetics from the University of Delaware in 2002. Her postdoctoral training at Nemours Biomedical Research at the Alfred I. duPont Hospital for Children from 2002 – 2007 focused on the newly emerging understanding of local translation in neuronal axons. After completing a visiting scientist position in the Department of Molecular and Cellular Neurobiology at Vrije Universiteit in the Netherlands in 2007, she returned to Nemours as an Assistant Research Scientist in the Center for Translational Neurobiology. In 2010, Dr. Willis was recruited to be the Director of the Center for Pain Research at the Burke Neurological Institute. Her research has focused on understanding how aberrant axonal translation may lead to maladaptive plasticity as is evident in neuropathic pain and neuropathy. In 2016, she was named Associate Director of the Burke Neurological Institute, and in 2018, Dr. Willis became Director of the Burke-Blythedale Program in Pediatric Clinical Neuroscience.

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