



KNOPP
NEUROSCIENCES

Frequently Asked Questions: KNS-760704 for ALS

What is KNS-760704?

KNS-760704 (dexpramipexole) is a drug candidate for the treatment of ALS. Its full chemical name is (6R)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazole-diamine dihydrochloride monohydrate, though the compound is also referred to in the scientific literature as R-(+) pramipexole, RPPX, or SND919CL2x. As suggested by the name, “dexpramipexole,” KNS-760704 is the R-(+) enantiomer (or mirror-image structure) of pramipexole, a prescription drug approved for the treatment of Parkinson’s disease and restless legs syndrome under the trade names Mirapex® and Sifrol®. A critical structural difference between pramipexole and KNS-760704 conveys very different pharmacologic properties. Pramipexole is effective in Parkinson’s disease, in which dopamine levels are reduced, because it potently stimulates dopamine receptors. Because of its high potency, pramipexole must be administered in very small doses. By contrast, KNS-760704 does not potently stimulate dopamine receptors, and has the potential to be safely dosed at much higher levels that may enable it to protect nerve cells. KNS-760704 was first identified as a potential treatment for ALS by James Bennett, M.D., Ph.D., formerly of the University of Virginia. NOTE: KNS-760704 and pramipexole are very different drugs. Pramipexole should only be taken as indicated and prescribed.

What is Knopp Neurosciences?

Knopp is an emerging life sciences company in Pittsburgh, PA, USA, committed to developing novel treatments for ALS and other neurodegenerative disorders. Our highest priority is demonstrating whether our lead compound, KNS-760704, is safe and effective as a treatment for ALS and, if so, to bring the medicine to the market as quickly as possible. Knopp is led by experienced pharmaceutical executives, neuroscientists, and entrepreneurs committed to addressing unmet medical needs. The company’s name honors the late Walter Knopp, a Pittsburgh entrepreneur and ALS patient whose visionary gift to the University of Pittsburgh supported the discovery of potential ALS biomarkers licensed by Knopp.

How does KNS-760704 work?

Although the exact mechanism of action of KNS-760704 remains under investigation, the compound has been shown in laboratory studies to protect neurons under stress. Knopp’s scientists hypothesize that it does so by increasing the efficiency of mitochondria, the parts of a cell that create energy for neurons and others cell types, especially under conditions of stress. Since ALS imposes significant stresses on mitochondria in motor neurons, the clinical research rationale for this program is that KNS-760704 may have the potential to help maintain energy production in stressed mitochondria within motor neuron cells. Links to scientific publications concerning KNS-760704 are provided at www.knoppneurosciences.com in the RESEARCH: PUBLICATIONS section.

What is the development status of KNS-760704?

Knopp has completed preclinical studies and Phase 1 and Phase 2 clinical trials that support the advancement of KNS-760704 into Phase 3 trials. KNS-760704 was safe and well-tolerated in three Phase 1 studies in healthy volunteers who received the drug as single doses or as multiple doses for up to 4.5 days, and in one Phase 2 study involving 102 ALS subjects treated for up to nine months. In the Phase 2 study,



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encouraging clinical trends on motor function and survival were also seen. However, the preliminary clinical potential of KNS-760704 must be further tested in large, well-controlled Phase 3 studies, which are expected to be initiated in the first half of 2011.

How does Orphan Drug designation help?

KNS-760704 has been granted Orphan Drug designation for the treatment of ALS in both the U.S. and Europe. An orphan disease is one with low prevalence (defined by the FDA as existing in less than one in 200,000 people in the U.S. and by the European Commission as existing in fewer than five of 10,000 people). Orphan designation is granted to programs demonstrating promise for the diagnosis and/or treatment of a rare disease. This designation provides regulatory and financial incentives to facilitate the drug development process, but does not allow a drug candidate to bypass the rigorous regulatory pathways required for approval.

How does Fast Track designation help?

In addition to granting Orphan Drug status to KNS-760704 in ALS, the U.S. FDA has also designated the development program as a Fast Track program. This designation is granted to new drug products intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Fast-track designation effectively identifies KNS-760704 for ALS as a high-priority program and facilitates communications and discussions regarding trial design and other regulatory matters. Fast-track designation doesn't eliminate development steps, but may accelerate the review of study data at the time of submission for approval.

Can I participate in clinical trials?

Knopp expects to begin Phase 3 studies in the first half of 2011 pending review by regulatory authorities in the U.S., Canada, and Europe. When the next trial is ready to begin enrollment, a full list of study sites will be posted at www.clinicaltrials.gov, along with contact information for each site. The study summary will also list eligibility criteria for study participants. The selection of patients for these trials is the responsibility of the Principal Investigator at each participating center in accordance with the research protocol.

Is KNS-760704 available now through an early access program?

As an ALS-focused company, Knopp is deeply focused on the urgent concerns of patients with a fatal and rapidly progressing disease and committed to advancing KNS-60704 toward possible approval with all the speed we can. Despite the apparent promise of KNS-760704, its long-term safety in a large population of ALS patients has not been fully established and the potential risks of the drug have not been adequately identified. This concern is underscored by a number of recent clinical trials in ALS in which experimental therapies actually worsened outcomes for patients, despite earlier hopeful signals. In addition, advancing KNS-760704 to potential approval for all patients requires evaluating it in well-controlled protocols, which by their design have limited enrollment. For exactly these reasons, Knopp is unable to support the use of the compound under any early access program at this time. We recognize these reasons may seem insufficient to a patient or a loved one, but they're essential to fulfilling our obligations and mission of advancing a meaningful treatment for the benefit of all ALS patients as rapidly as possible.

What else can I do?

You can have a real impact. By getting involved with a local chapter of the ALS Association or the Muscular Dystrophy Association, you can help promote awareness and raise money to advance research and support other patients. The ALS support community is a dynamic, inspiring resource for patients and families. We're all in this fight together, and every participant makes a difference reaching far and wide. And please contact Knopp if you have further questions.