Information for the Dravet Community about STK-001 from Stoke Therapeutics
April 2020

Caregivers in the Dravet community recently generated a list of questions about the upcoming clinical trial of STK-001, an exciting new treatment from Stoke Therapeutics. Based on published data and conversations between DSF's Scientific and Medical Advisory Boards, we are able to address many of the community's questions here.

About STK-001

STK-001 is not like traditional daily medications we give to patients. It is not given orally and dispersed throughout the bloodstream and brain. Instead, it targets the specific cells that need it, namely neurons that produce a certain type of sodium channel made from the gene *SCN1A.* Patients with Dravet syndrome have one healthy copy of *SCN1A* and one mutated copy, resulting in about 50% of the sodium channels needed. STK-001 increases the number of healthy sodium channels created from the remaining healthy copy of *Scn1a* to normal levels in animal models. It is administered directly to the fluid surrounding the brain via a lumbar puncture (spinal tap) at an anticipated frequency of 2-3 times per year.

How it Works

STK-001 raises levels of sodium channels to normal by increasing the efficiency of a processing step after the cell reads the gene. When a cell needs a sodium channel, it makes a transcript of *SCN1A* so as not to disturb the original DNA, processes that transcript down to the most efficient instructions possible, then uses that processed transcript (mRNA) to create sodium channels. It is not 100% efficient: Some of the transcripts are lost during processing, and STK-001 works to decrease the number of lost transcripts, increasing processing efficiency. It is not considered gene therapy because it does not bind directly to or alter a cell's DNA.

STK-001 is made of a sequence of nucleotides specific to *SCN1A* and thus only targets cells already expressing *SCN1A.* It does not affect other genes or production of other types of sodium channels in animal models. It is appropriate for all types of *SCN1A* mutations because it focuses on the remaining healthy copy's transcripts, which all patients have.

Potential Therapeutic Value

STK-001 targets the underlying problem caused by the mutation and has the potential to be the first disease-modifying therapy for Dravet syndrome. However, it is not anticipated to be a one-time treatment or a cure. Stoke has generated preclinical data in animals demonstrating proof-of-mechanism and proof-of-concept, and STK-001 has been granted Orphan Drug Designation by the FDA as a potential new treatment for Dravet syndrome.

About the Preclinical (Animal) Data

The most up-to-date summary of research can be found in Stoke's Corporate Presentation (March 2020), here: https://investor.stoketherapeutics.com/static-files/8f62c4b1-8e67-49a7-a9c6-1b60e4843dab

The highlights most relevant to our community include:

Mouse Data

- When given to mice with Dravet syndrome on the 2nd day after birth, 97% of the animals survived to Day 90, compared to only 23% survival in non-treated mice.
    - 80% reduction in spontaneous seizures between Day 22 and 46
    - 76% of treated mice were seizure free, compared to 48% of the non-treated mice.
    - No adverse effects of increasing sodium channels above "normal" levels
- When given to mice with Dravet 14 days after birth, closer to when seizures begin, 65% of the animals survived.
    - Doubling that dose on Day 14 increased survival rate to 85%.
- Both timings of injections (Day 2 and Day 14) resulted in ASO presence and sodium channels at or near normal levels in the brain cells that express *Scn1a* at ~90 days after a single injection.
- No data suggest that STK-001 makes the condition *worse,* considering nearly 2/3 of the animals die without any treatment.

Non-human Primates (NHPs)

- Non-human primate data are on healthy primates, not animals with Dravet syndrome, but show up to a 3-fold increase in sodium channel levels in all parts of the brain that express *Scn1a.*
- No observed adverse events at highest dose tested
- No change in platelet counts or renal/hepatic function
- No adverse histopathology in brain, liver or kidney

These preclinical data are encouraging, but mice are not tiny humans, and healthy non-human primates are not Dravet patients. Safety will be the primary focus as Stoke moves from animals to humans.

About the Monarch Study

The Monarch study is a Phase 1/2a open-label study of children and adolescents ages 2 to 18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives will be to assess the safety and tolerability of STK-001, as well as to characterize how STK-001 interacts with the body's chemistry and other medications. A secondary objective will be to assess the efficacy as an add-on antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency over a 12-week treatment period. Stoke also intends to measure non-seizure aspects of the disease, such as quality of life as secondary endpoints. Stoke plans to enroll approximately 40 patients at 20 sites in the United States. Enrollment and dosing are expected to begin in the second half of 2020.

Eligibility and Enrollment

- Enrollment is expected to open later in 2020. Please speak with your physician if you are interested in participating.
- Patients must have an *SCN1A* variant and Dravet syndrome. Variants in other genes are acceptable, as long as they are not in genes associated with epilepsy or seizures.
- Age 2-18. Adults will be included in future trials for safety data at a minimum.
- A certain minimum number/frequency of countable seizures during a baseline period will be required, similar to other recent trials in Dravet syndrome. Comorbidities alone will not qualify.
- Patients may not be taking sodium channel blockers as daily anti-seizure medications. Emergency treatment with sodium channel blockers is acceptable.
- Patients may not be simultaneously enrolled in another clinical trial during a period of blinded treatment or placebo. Patients enrolled in open label extensions or observational studies may be eligible.
- Patients taking certain pharmaceutical and artisanal formulations of CBD may be included.
- The Monarch Study will only enroll patients in the US. While international participants are not excluded, the frequent visits required may make it impractical. Travel reimbursement will be provided up to a certain distance/dollar amount, which will likely not cover all expenses associated with international travel.
- The study sites have not been announced, but more information will be available through DSF and clinicaltrials.gov as the start date approaches. If you are interested in participating in the study, you should speak with your physician.

Trial Design and Follow-up

- Monarch is an open label study, so all patients enrolled will receive treatment with STK-001. There is no placebo group.
- Monarch is a 7 month study. There is a one month observation period, followed by a single injection and a 6 month follow up period. Patients will then transition to an open label extension for further treatment and monitoring if they meet entry criteria.
- STK-001 is delivered via intrathecal injection (a lumbar puncture). This procedure is used for delivery of a number of medicines and is a well-established route of administration. Because the treatment needs to get to the brain, it is not possible to inject it into the blood via a port

or IV. Most patients will receive a mild sedative and local anesthesia. General anesthesia is not likely to be necessary.

- Physicians will work with patients to maintain the best possible health of participants, including adjusting other medications as necessary throughout the trial.
- Frequent safety tests will be performed. Medication level testing will also be performed.
- After each dose level, an independent safety monitoring committee will evaluate the patients' responses and determine whether STK-001 can be administered at the net highest dose.
- After the first phase of the trial, if successful, patients will require repeated dosing. Most patients will likely require 2-3 doses per year, but more studies need to be done before ongoing treatment protocols are created.

Future Availability

Because Stoke has not tested STK-001 in any humans yet, it is too early to speculate about future availability, timelines for Phase 2 or 3 clinical trials, inclusion of adult patients, availability outside of the US, or cost. If the treatment proves safe (first) and effective (second) in humans, Stoke is committed to expanding access to those who need it as quickly as possible.

If you posed a question that was not answered here or would like a more detailed explanation, please reach out to Nicole (nicole@dravetfoundation.org). If you have specific medical questions, please contact your physician.