LADDER Database

RTI INTERNATIONAL

RESEARCH REPORT

Published March 2024

Efficacy, safety, and tolerability of soticlestat as adjunctive therapy for the treatment of seizures in patients with Dup15q syndrome or CDKL5 deficiency disorder in an open-label signal-finding phase II study (ARCADE)

Principal Investigator: Ronald Thibert, DO, MSPH – Massachusetts General Hospital for Children

WHAT WAS THE RESEARCH ABOUT?

Dup15q syndrome is a rare neurodevelopmental disorder associated with epileptic encephalopathy, or treatment-resistant epilepsy that starts in early childhood and results in reduced or worsening cognitive and behavioral functioning. Many individuals with dup15q syndrome experience a high rate of seizures, but medications are not effective at controlling or reducing the occurrence of seizures. There are currently no approved treatment options, but this study (called ARCADE) presented the efficacy, safety, and tolerability of a medication for the treatment of seizures in patients with either dup15q syndrome or cyclin dependent kinase-like 5 deficiency disorder (CDD). This report will focus on findings for the eight patients in the study who had dup15q syndrome.

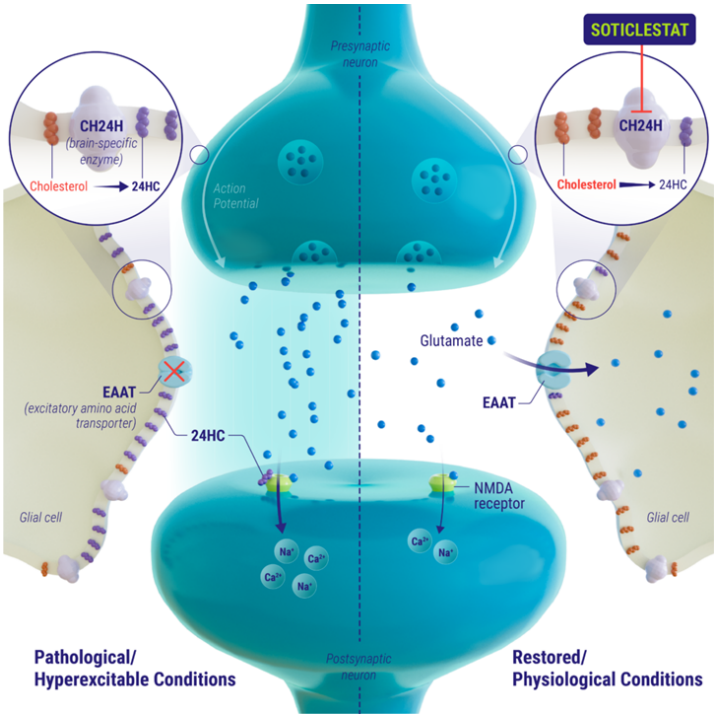
WHO WAS IN THE STUDY?

Patients were five males and three females with dup15q syndrome. Information regarding patient subtype was not provided. Patients ranged from 9 to 27 years of age (mean age = 15.4 years). All patients were White and not Hispanic or Latino. On average, these patients took 3.25 antiseizure medications (ASMs) at baseline (range: 1-5). Mean motor seizure frequency at baseline was 132.3 per 28 days (range: 35-224). Motor seizures included hemiclonic, focal with motor signs, focal to bilateral tonic-clonic convulsion, generalized tonic-clonic convulsion, tonic, atonic, bilateral clonic, infantile spasms, epileptic spasms, and convulsive status (>30 minutes). The most common ASMs used by these patients were rufinamide (50%), lamotrigine (50%), clobazam (37.5%), and levetiracetam (37.5%).

WHAT DID THE RESEARCH TEAM DO?

ARCADE was a phase II, open-label pilot study of a medication called soticlestat. Phase II trials examine the effectiveness of a drug, and because the study was open label, both patients and physicians were aware of the treatment being provided (i.e., there was no blinding). Soticlestat is thought to work by reducing glutamatergic signaling and attenuating neural hyperexcitation associated with epilepsy disorders.

After a 4–6-week baseline period, patients started a 20-week treatment period which involved 8 weeks of dose-optimization, followed by 12 weeks of a maintenance period. During dose optimization, patients gradually received a higher dose of soticlestat until the appropriate maximum dose was found. During this time, patients were monitored for safety and tolerability of the drug. **The primary efficacy endpoint was percentage of change from baseline in motor seizure frequency per 28 days during the 12-week maintenance period.**



STUDY PARTICIPANTS

8 participants (5 males, 3 females)

3.25

Antiseizure medications on average (range: 1-5)

9-27 years

Mean of 15.4 years of age

The secondary endpoints were:

1. the percentage change from baseline in **motor seizure frequency** during the full 20-week treatment period
2. the percentage change from baseline in **all seizure frequency** during the maintenance (12 week) and full treatment (20 week) periods
3. the proportion of patients who were considered **treatment responders** (defined as experiencing a reduction in motor seizure frequency from baseline of ≥25%, ≥50%, ≥75%, or 100% during the maintenance and full treatment periods
4. **global functioning** as rated by both clinicians and caregivers using the Clinical Global Impression of Change (CGI-C) and the Caregiver Global Impression of Change (Care GI-C) scales, respectively
5. change from baseline in a chemical called **24S-hydroxycholesterol (24HC)**; 24HC is found in the brain and can be measured in plasma (the liquid portion of blood), and is considered a biomarker for soticlestat activity in the brain

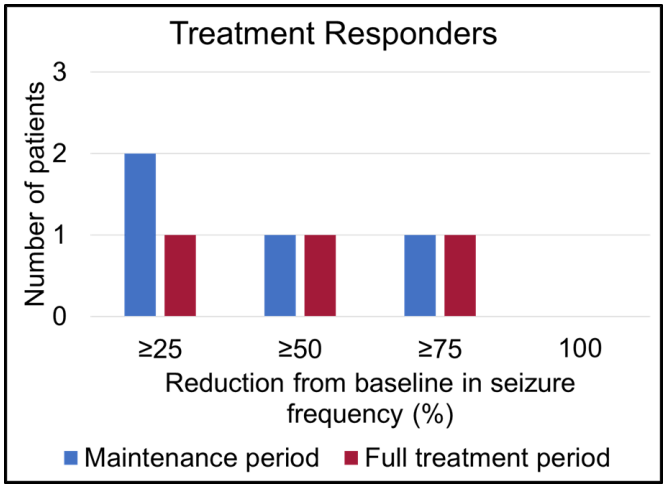
WHAT DID THE RESEARCH TEAM LEARN?

Seizure Frequency

Patients had an increase from baseline in motor seizure frequency during the maintenance and full 20-week treatment periods. However, they also showed an overall decrease decrease in all seizures (both motor and non-motor seizures) over those periods.

Treatment responders

During the 12-week maintenance period, one patient (12.5%) experienced a reduction in motor seizure frequency from baseline of ≥75%, one patient (12.5%) experienced a reduction of ≥50%, and two patients (25.0%) experienced reductions of ≥25%. During the 20-week treatment period, one patient (12.5%) experienced a reduction in motor seizure frequency from baseline of ≥75%, one patient (12.5%) experienced a reduction of ≥50%, and one patient (12.5%) experienced a reduction of ≥25%.

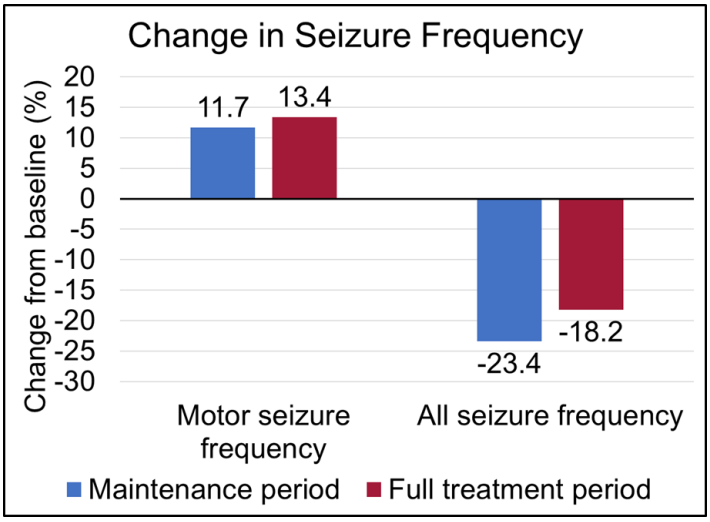


Global Functioning

At the last visit, of the eight patients with Dup15q syndrome, 50% reported improvement in CGI-C score and 50% reported improvement in Care GI-C score relative to baseline.

Plasma 24HC Levels

The median decrease from baseline in plasma 24HC levels was 73.3% after two weeks of treatment. These levels remained fairly stable throughout the rest of the study.



Adverse Events

Seven patients (87.5%) reported mild or moderate treatment-emergent adverse events, the most common of which were fatigue, seizures, and lethargy. No serious events were reported.

WHAT DOES THIS MEAN FOR FAMILIES?

Overall, these results were inconclusive regarding the efficacy of soticlestat for the treatment of seizures in individuals with dup15q syndrome. Although there was a reduction in all seizure frequency, there was also an increase in motor seizure frequency, likely due to the older age of individuals in the study.

Importantly, there were only eight patients with dup15q syndrome in this study. Two patients were classified as treatment responders, showing a reduction from baseline in motor seizure frequency. Additional studies with a larger number of patients and placebo controls are needed to better understand whether this drug could be beneficial for individuals with dup15q syndrome.

Full article by Dr. Demarest and colleagues:

Read here

Demarest S, Jeste S, Agarwal N, Arkilo D, Asgharnejad M, Hsiao S, Thibert R. Efficacy, safety, and tolerability of soticlestat as adjunctive therapy for the treatment of seizures in patients with Dup15q syndrome or CDKL5 deficiency disorder in an open-label signal-finding phase II study (ARCADE). Epilepsy Behav. 2023 May;142:109173. doi: 10.1016/j.yebeh.2023.109173. Epub 2023 Apr 1. PMID: 37011526.