Long-term, Durable Seizure Frequency Reduction in Children with CDKL5 Deficiency Disorder (CDD) Treated with Ganaxolone

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BACKGROUND

The *CDKL5* gene located on the X chromosome provides instructions for making a protein that is important for normal brain development and function. Mutation of the cyclin-dependent kinase-like 5 *(CDKL5)* gene results in decreased levels of the active CDKL5 protein and lead to early-onset treatment-refractory seizures, gross motor impairment, and neurodevelopmental delay[1].

LACK OF LONG-TERM AED DURABILITY IN CDD

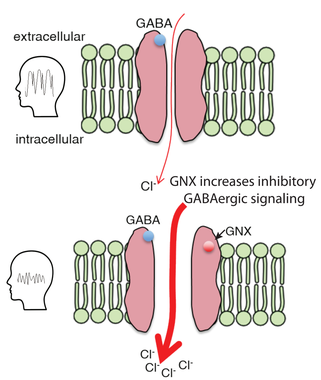
Currently there are no approved drugs indicated for CDKL5 Deficiency Disorder (CDD). Existing antiepileptic drugs (AEDs) and ketogenic diet have demonstrated limited efficacy related to seizure burden and any benefits are typically short-lived. Müller et al. reported seizure response rates at 12-months that were one-third of the noted response rate at 3-months on a stable regimen of various AEDs signifying lack of long-term efficacy[2]. There is a significant need for new antiepileptic drugs that reduce seizure frequency with safe and durable action. Here we report for the first time long-term data in a cohort of subjects on ganaxolone (GNX) that continued into the open-label extension portion of the study.

INVESTIGATIONAL GANAXOLONE

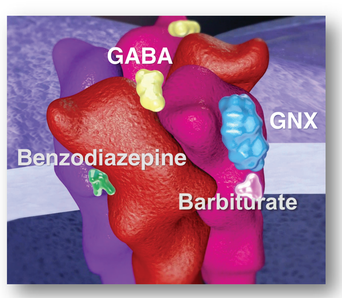
GNX (3α-hydroxy-3β-methyl-5α-pregnan-20-one;) is a positive allosteric modulator of the $GABA_A$ receptor. Although a synthetic analog of the endogenous progesterone metabolite, Allopregnanolone, GNX lacks both nuclear progesterone receptor activity and hormonal effects with chronic dosing. GNX binds to the $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates. Unlike benzodiazepines, GNX activates synaptic and extrasynaptic $GABA_A$ receptors and it does not induce tolerance.

Figure 1: GNX is a neurosteroid that targets the $GABA_A$ receptor

Ganaxolone is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$-R



Ganaxolone targets unique binding sites that are not susceptible to tolerance build up



PHASE 2A STUDY DESIGN

An open-label Phase 2a study was conducted in children with CDD.

Study Objective

- To explore safety, tolerability and potential efficacy of GNX as adjunctive therapy for uncontrolled seizures in children with CDD

Primary Efficacy Endpoint

- % change in 28-day seizure frequency at 26 weeks relative to baseline

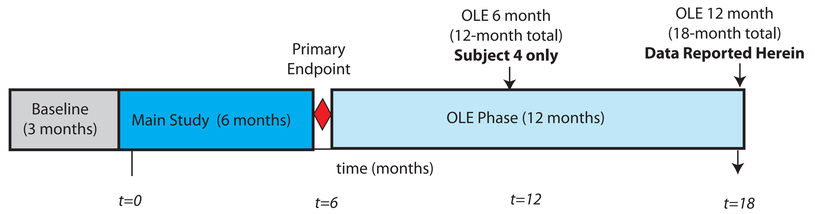
Key Inclusion / Exclusion Criteria

- Subjects between 2 and 18 years of age
- Confirmed *CDKL5* gene mutation
- ≥ 4 unique seizures per 28-day period during baseline

Study Duration

- Subjects that responded to GNX (n=4, seizure frequency reduction > 35 %) were enrolled in the open-label extension (OLE) phase for up to 1-year.

Figure 2: Timeline of open-label study of GNX in subjects with CDD.



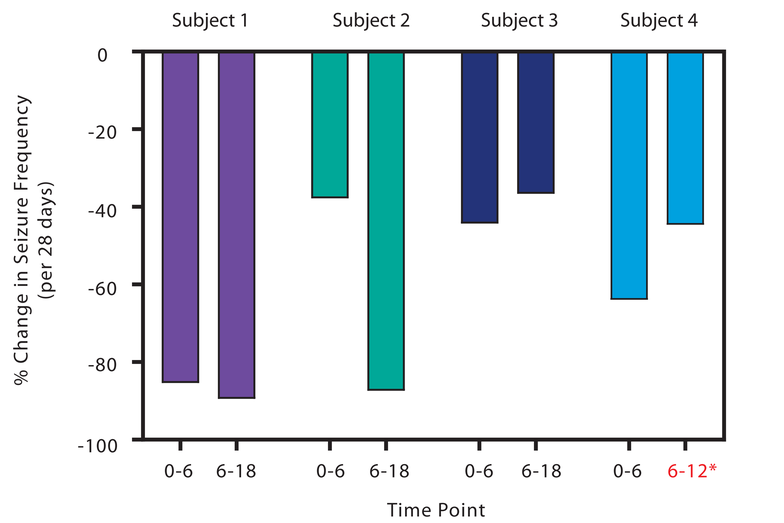
RESULTS

7 patients were enrolled at three sites (2 in U.S. and 1 in Italy). Subject #1-4 entered the OLE phase

Patient	Age (years)	Gender	Baseline Seizure Rate (/28 days)	Concomitant AEDs (Baseline)
1	7.7	F	310.0	carbamazepine
2	11.4	F	115.7	valproic acid
3	8.6	F	103.4	clonazepam, valproic acid, clobazam
4	3.2	F	104.7	-
5	2.6	F	33.7	carbamazepine
6	16.5	F	103.3	carbamazepine
7	3.0	M	669.3	clobazam, rufinamide

Four subjects were included in the OLE phase with a -54.1% (median) change in seizure frequency at the 6-month primary endpoint. To date, median seizure frequency for these subjects improved to -66.0%. One subject continued to experience a robust and durable seizure reduction (85-90%) and another subject dramatically improved from 6-months to 18-months (38% to 87% reduction). Two subjects noted mild increases in seizure frequency at 12 or 18-months relative to 6-months, yet both remain improved from baseline and demonstrate clinically meaningful seizure reductions (-37 to -45%) at or beyond 12 months.

Figure 3: Percentage change in Seizure Frequency



Percent change in seizure frequency in four subjects that were included in the OLE phase. 0-6 refers to % Δ seizure frequency from 0-6 months on GNX relative to baseline (main study). 6-18 refers to % Δ seizure frequency from 6-18 months in the OLE phase on GNX relative to baseline (OLE phase). Note: Subject 4 only has 6-month OLE data (12-month total) at the time of abstract submission.

CONCLUSION

CDD is a recently recognized distinct clinical entity with significant unmet medical need. New drugs that effectively reduce seizures with durable action and that are well-tolerated are highly needed. GNX has demonstrated preliminary evidence of sustained, long-term efficacy in a small cohort of subjects. These findings are medically important since the durability of existing AEDs in this patient population is severely limited. Based on these encouraging data, the first global randomized, controlled pivotal study with GNX in children with CDD has been initiated to further investigate the drug's effect.

REFERENCES

1. Mangatt M, Wong K, Anderson B, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. *Orphanet J Rare Dis.* 2016;11(1). doi:10.1186/s13023-016-0418-y
2. Müller A, Helbig I, Jansen C, et al. Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. Eur J Paediatr Neurol. 2016;20(1):147-151. doi:10.1016/j.ejpn.2015.09.001