Ganaxolone in CDKL5 Deficiency Disorder: Open-label Phase 2a Results and Ongoing Pivotal Phase 3 Study Design

MARINUS PHARMACEUTICALS

BACKGROUND

CDKL5 is a protein whose gene is located on the X chromosome. The *CDKL5* gene 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 active protein and lead to early-onset treatment-refractory seizures, gross motor impairment, sleep disturbances, and neurodevelopmental delay[1].

Unmet Medical Need

Early drug-resistant epilepsy, usually starting in the first months of life, tends to be the most common feature of CDKL5 deficiency. Seizures are generally highly polymorphic and many different seizure types can also occur in the same patient, changing with time. Complex partial seizures, infantile spasms, myoclonic, generalized tonic-clonic, and tonic seizures have all been reported. Very often, patients treated with antiepileptic drugs (AEDs) experience a brief seizure-free honeymoon period, which, unfortunately, is followed by relapses.[2]

Efficacy of multiple AEDs and ketogenic diet in patients with the CDKL5 mutation is very low. The poor short and long-term response to standard and unapproved AEDs and ketogenic diet are summarized in Table 1.

Responder Rate of AEDs after 3, 6, and 12 months(>50% reduction in seizures in the last 4 weeks compared to 4 weeks baseline period) Adapted from Müller A. *et al.*[3]

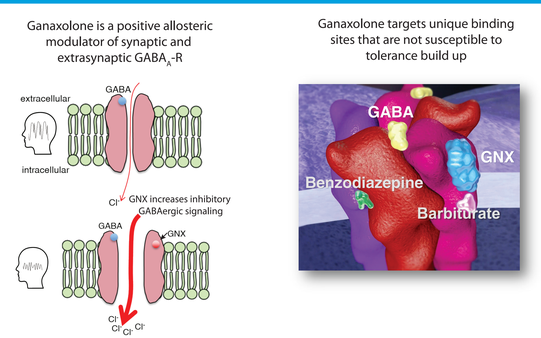
AED	N	Responder rate after 3 months	Responder rate after 6 months	Responder rate after 12 months
VPA	34	7 (21%)	6 (18%)+	3 (9%)
LEV	31	5 (16%)	4 (13%)	0
TPM	31	5 (16%)	1 (3%)	1 (3%)
Steroids/ACTH	26	5 (19%)	0	0
PB	26	2 (8%)	2 (8%)	2 (8%)
VGB	25	8 (32%)	2 (8%)	1 (4%)
LTG	23	5 (22%)	2 (9%)	2 (9%)
CLB	17	4 (24%)	1 (6%)	0
RUF	13	1 (8%)	0	0
CBZ	15	2 (13%)	1 (7%)	1 (7%)
OXC	14	1 (7%)	1 (7%)	1 (7%)
ZNS	11	2 (18%)	1 (9%)	0
PHT	10	1 (10%)	1 (10%)	1 (10%)
ESM	8	0	0	0
CLN	6	2 (33%)	1 (17%)	1 (17%)
BR	5	1 (20%)	1 (20%)	1 (20%)
MSX	3	0	0	0
FBM	3	3 (100%)	2 (6%)	1 (33%)
LCM	3	0	0	0
STP	3	0	0	0
PRM	1	0	0	0
Ketogenic diet	12	2 (17%)	2 (17%)	1 (8%)

LEV: levitiracetam; VPA: valproic acid; TPM: Topiramate; PB: phenobarbital; VGB: vigabatrin; LTG: lamotrigine; CLB: clobazam; RUF: rufinamide; CBZ: carbamazepine; STM: sultiame; ZNS: zonisamide; PHT: phenytoin; ESM: ethosuximide; CLN: clonazepam; BR: bromide; MSX: mesuximide; FBM: felbamate: LCM: lacosamide; STP: stiripentol; PRM: primidone

Investigational Ganaxolone

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one; GNX) 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 activates synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates; it does not induce tolerance. GNX has anticonvulsant activity with an acceptable safety and tolerability profile in doses of 900 to 1,800 mg/day in adults and children.

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



Phase 2a Study Design

- A 26-week (main study) 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
- Secondary Efficacy Endpoints
  - % change of seizure-free days per 28-days
  - Clinical Global Impression of Improvement – Clinician
  - Clinical Global Impression of Improvement – Parent/Caregiver
- 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

RESULTS

7 patients were enrolled at three sites (2 in U.S. and 1 in Italy)

Efficacy Results

Five of 7 subjects saw an improvement in seizure frequency at the end of the 26-week main study (median seizure reduction of -44.4%) (Figure 2).

Median 77% increase in seizure-free days (data not shown).

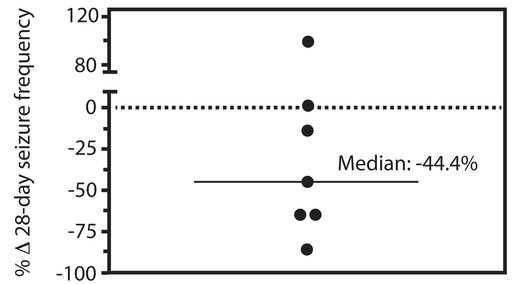
Table 2: CDD subject demographics and baseline characteristics

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

Patients experienced a median "minimally improved" rating on the Clinical Global Impression of Improvement scale (clinician rated) and it correlated with primary efficacy endpoint outcome (Figure 3).

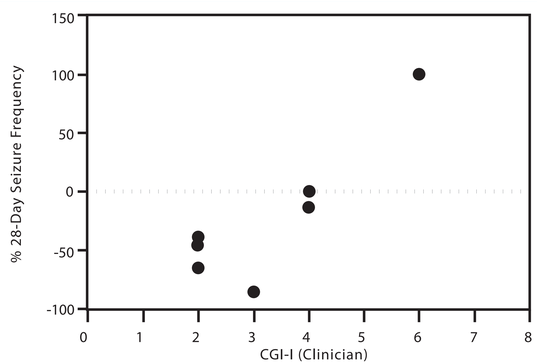
Patients experienced a median "much improved" rating on the Clinical Global Impression of Improvement scale (parent/caregiver rated) (data not shown).

Figure 2: Primary Efficacy Endpoint Results.

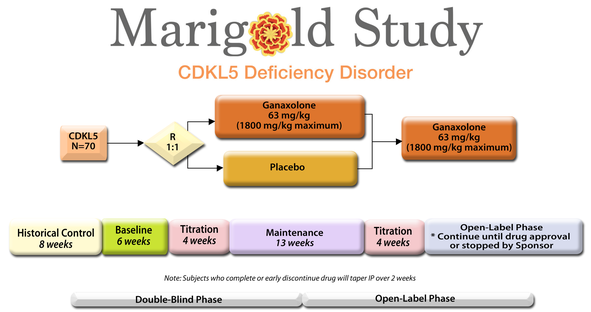


Excludes 6 days of data from one subject deemed unreliable by the PI

Figure 3: Correlation between Clinical Global Impression of Improvement (Clinician rated) and % change in 28-day seizure frequency.



1 very much improved 2: much improved 3: minimally improved
4: no change 5: minimally worse 6: much worse 7: very much worse



The Marigold Study - Phase 3 Pivotal Study - Currently Enrolling

- Double-blind, placebo-controlled, randomized 1:1
- N=70
- Ages 2-21
- Confirmed disease-related *CDKL5* gene variant
- ≥16 major motor or drop seizures per month
- Up to 4 concomitant AEDs
- ~43 global sites – US, Europe, others
- Oral ganaxolone – suspension or capsule
- Primary Endpoint: % reduction in seizures
- Non-Seizure Secondary outcome measures:
- Behavioral/neuropsychiatric changes correlated with domains of attention & sleep

www.themarigoldstudy.com

PHASE 2A STUDY CONCLUSIONS

- GNX demonstrated a robust seizure reduction in most patients with CDD.
- A meaningful improvement was noted on the Clinical Global Impression of Improvement scales, both clinician and parent/caregiver administered.
- GNX was generally safe and well-tolerated.
- These durable efficacy data motivated the design and initiation of the first ever Phase 3, pivotal study in CDD (The Marigold Study)

REFERENCES

1. Mangatt, M. et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. *Orphanet J. Rare Dis. 11*, (2016).
2. Kilstrup-Nielsen, C. et al. What we know and would like to know about CDKL5 and its involvement in epileptic encephalopathy. *Neural Plasticity 2012*, (2012).
3. Müller, A. 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.* 20, 147–151 (2016).