CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215904Orig1s000

SUMMARY REVIEW

Summary Review

Date	March 18, 2022
From	Philip H. Sheridan, MD Nick Kozauer, MD Billy Dunn, MD
Subject	Summary Review
NDA#	NDA 215904
Applicant	Marinus Pharmaceuticals
Date of Submission	July 20, 2021
PDUFA Goal Date	March 20, 2022
Proprietary Name	Ztalmy
Established or Proper Name	Ganaxolone
Dosage Form(s)	Oral suspension (50 mg/ml)
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD) in patients 2 years of age and older
Applicant Proposed Dosing Regimen(s)	Patients 28 kg or less: Weight-based dosing of 63 mg/kg/day administered in three divided doses of 21 mg/kg (with a maximum daily maintenance dose of (b) (6) mg), following a 3-week titration. Patients weight greater than 28 kg: 1800 mg/day administered in three divided doses of 600 mg, following a 3-week titration.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD) in patients 2 years of age and older
Recommended Dosing Regimen(s) (if applicable)	Patients 28 kg or less: Weight-based dosing of 63 mg/kg/day administered in three divided doses of 21 mg/kg (with a maximum daily maintenance dose of (b) (6) mg), following a 3-week titration. Patients weight greater than 28 kg: 1800 mg/day administered in three divided doses of 600 mg, following a 3-week titration.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene cause CDKL5 deficiency disorder (CDD), which is characterized by early-onset seizures with severe encephalopathy. The overall incidence of CDD is reported to be approximately 1 per 42,000 live births (with reported cases increasing as genetic testing becomes more common). Despite an understanding of the underlying genetic etiology, the pathogenesis of CDD remains unclear.

The clinical severity of CDD is variable, although most children experience treatment-resistant seizures and severe neurodevelopmental impairment. Patients may experience one or more of several different seizure types, including tonic-clonic, atonic, clonic, tonic, myoclonic, absence, and focal seizures, as well as infantile spasms (IS). Three stages of seizures in the course of CDD have been described, including: Stage I, early onset epilepsy (with an onset at 1 to 10 weeks of age); Stage II, epileptic encephalopathy with IS and hypsarrhythmia; and Stage III, refractory tonic seizures with myoclonia.

Patients with CDD generally respond poorly to currently approved drugs for the treatment of various seizure types. There are no approved treatments specifically for seizures associated with CDD.

Ganaxolone (referred to as GNX in this summary review) is a synthetic neuroactive steroid. The exact mechanism of action for GNX is unknown; however, GNX acts as a selective positive allosteric modulator of both synaptic and extrasynaptic gamma-aminobutyric acid type A ($GABA_A$) receptors located in the central nervous system (CNS), which are known to have inhibitory effects on neurotransmission.

The application provides data from Study 1042-CDD-3001 (Study 3001); a global, 17-week, randomized, double-blind, placebo-controlled, add-on trial conducted in patients with CDD 2-21 years of age. One hundred and one patients were randomized in a 1:1 ratio to either a single dose-level of orally-administered GNX (dosed 3 times/day) or placebo. Doses were based on a mg/kg/day basis in patients weighing 28 kg or less, and on a mg/day basis in patients weighing greater than 28 kg (with a maximum daily dose of 1800 mg in all patients). The primary efficacy

evaluation for Study 3001 was based on the difference between treatment arms in the median 28-day frequency of major motor seizures (defined as bilateral tonic-clonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic seizures) from a 6-week baseline phase through the 17-week double-blind phase. Patients receiving GNX demonstrated a highly statistically significant and clinically meaningful 27.1% greater reduction in major motor seizures compared with placebo (p=0.0036). The strength of this finding was supported by several conservative sensitivity analyses. Consistent effects were also observed across all subgroups based on age, sex, and geographical region (with the largest treatment effect observed in US patients). In the context of the rare nature of CDD, the trial was not powered for the analyses of the secondary endpoints; however, analyses of responder definitions based on quartiles of treatment response and clinician and parent/caregiver-rated global impression of change scores consistently favored GNX numerically. The findings from Study 3001 establish the efficacy of GNX for the treatment of seizures associated with CDD in patients 2 years of age and older.

The risks associated with GNX are acceptable to support approval. The most common treatment-related adverse reactions were related to somnolence and sedation, occurring in 44% of GNX-treated patients in Study 3001, versus 24% in placebo. Other commonly reported adverse reactions from Study 3001 included pyrexia (occurring in 18% of GNX-treated patients versus 8% in placebo), salivary hypersecretion (occurring in 6% of GNX-treated patients versus 2% in placebo), and seasonal allergies (reported in 6% of GNX-treated patients versus 0% in placebo). No imbalances in deaths or in the incidence of serious adverse reactions between GNX-treated patients and placebo were observed. Labeling will include a WARNING AND PRECAUTIONS section describing the risk of somnolence and sedation. Labeling with also include the standard WARNINGS AND PRECAUTIONS sections related to the risk of suicidal behavior and ideation and treatment withdrawal common to all drugs approved for the treatment of seizures.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene cause CDKL5 deficiency disorder (CDD), which is characterized by early-onset seizures with severe encephalopathy. • The overall incidence of CDD is reported to be approximately 1 per 42,000 live births (with reported cases increasing as genetic testing becomes more common). • The clinical severity of CDD is variable, although most children experience treatment-resistant seizures and severe neurodevelopmental impairment. Patients may experience one or more of several different seizure types, including tonic-clonic, atonic, clonic, tonic, myoclonic, absence, and focal seizures as well as infantile spasms (IS). Three stages of seizures in the course of CDD have been described, including: Stage I, early onset epilepsy (with an onset at 1 to 10 weeks of age); Stage II, epileptic encephalopathy with IS and hypsarrhythmia; and Stage III, refractory tonic seizures with myoclonia. • Less than 10% of patients with CDD experience only several seizures a month, about 12% only have several episodes weekly, and up to 80% experience daily seizures.	CDD is a rare and serious genetic developmental epileptic encephalopathy.
Current Treatment Options	• There are no FDA-approved treatments for the seizures associated with CDD. • Patients with CDD generally respond poorly to the currently approved drugs for the treatment of various seizure types.	There are no approved treatments for the seizures associated with CDD.
Benefit	• The application provides data from Study 1042-CDD-3001 (Study 3001); a global, 17-week, randomized, double-blind, placebo-controlled, add-on trial conducted in patients with CDD 2-21 years of age. One hundred and one patients were randomized in a 1:1 ratio to either a single dose-level of orally-administered GNX (dosed 3 times/day) or placebo. Doses were based on a mg/kg/day basis in patients weighing 28 kg or less, and on a	The findings from Study 3001 establish the efficacy of GNX for the treatment of seizures associated with CDD in patients 2 years of age and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mg/day basis in patients weighing greater than 28 kg (with a maximum daily dose of 1800 mg in all patients). The primary efficacy evaluation for Study 3001 was based on the difference between treatment arms in the median 28-day frequency of major motor seizures (defined as bilateral tonic-clonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic seizures) from a 6-week baseline phase through the 17-week double-blind phase. • Patients receiving GNX demonstrated a highly statistically significant and clinically meaningful 27.1% greater reduction in major motor seizures compared with placebo (p=0.0036). • The strength of the result of the primary efficacy analysis was supported by several conservative sensitivity analyses. Consistent effects were also observed across all subgroups based on age, sex, and geographical region (with the largest treatment effect observed in US patients). • The trial was not powered for the analyses of the secondary endpoints; however, analyses of responder definitions based on quartiles of treatment response and clinician and parent/caregiver-rated global impression of change scores consistently favored GNX numerically.	
Risk and Risk Management	• The most common treatment-related adverse reactions were related to somnolence and sedation, occurring in 44% of GNX-treated patients in Study 3001, versus 24% in placebo. • Other commonly reported adverse reactions from Study 3001 included pyrexia (occurring in 18% of GNX-treated patients versus 8% in placebo), salivary hypersecretion (occurring in 6% of GNX-treated patients versus 2% in placebo), and seasonal allergies (reported in 6% of GNX-treated patients versus 0% in placebo). • No imbalances in deaths or in the incidence of serious adverse reactions between GNX-treated patients and placebo were observed.	The risks associated with GNX are acceptable to support approval. Labeling will include a WARNING AND PRECAUTIONS section describing the risk of somnolence and sedation. Labeling with also include the standard WARNINGS AND PRECAUTIONS sections related to the risk of suicidal behavior and ideation and treatment withdrawal common to all drugs approved for the treatment of seizures.

2. Background

This application contains data intended to support the safety and effectiveness of ganaxolone (abbreviated as "GNX" in this summary review) for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. GNX is a new molecular entity (NME) that has not been approved for any indication and has not previously been the subject of any marketing application. There are no FDA-approved treatments for seizures associated with CDD.

Mutations in the CDKL5 gene cause a disorder characterized by early-onset seizures with severe encephalopathy, previously considered a variant of Rett syndrome. CDKL5 is an X-linked gene that encodes a phosphorylated protein with protein kinase activity. With an overall incidence of 1 per 42,000 live births, CDD represents one of the most common genetic causes of epilepsy in children (with reported cases increasing as genetic testing becomes more common). Despite an understanding of the underlying genetic etiology, the pathogenesis of CDD remains unclear.

The clinical severity of CDD is variable, although most children experience treatment-resistant seizures and severe neurodevelopmental impairment. Patients may experience one or more of several different seizure types, including tonic-clonic, atonic, clonic, tonic, myoclonic, absence, and focal seizures, as well as infantile spasms (IS). Three stages of seizures in the course of CDD have been described, including: Stage I, early onset epilepsy (with an onset at 1 to 10 weeks of age); Stage II, epileptic encephalopathy with IS and hypsarrhythmia; and Stage III, refractory tonic seizures with myoclonia.

The pharmacologic management of CDD has focused on mitigating seizure burden using a variety of nonspecific therapies, and patients are often refractory to these agents.

GNX is a synthetic neuroactive steroid. The exact mechanism of action for GNX is unknown; however, GNX acts as a selective positive allosteric modulator of both synaptic and extrasynaptic gamma-aminobutyric acid type A ($GABA_A$) receptors located in the central nervous system (CNS), which are known to have inhibitory effects on neurotransmission.

The applicant has provided data from a single adequate and well-controlled clinical trial (Study 3001) as the primary basis of support of the effectiveness of GNX for the treatment of seizures associated with CDD; an approach determined to be acceptable in form at a March 11, 2021, pre-New Drug Application (pre-NDA) meeting. The application also contains supportive open-label safety data obtained in patients with CDD. Additionally, GNX has been studied in several other epilepsy and non-epilepsy indications. The impact of the efficacy and safety findings from these development programs will be discussed in this review.

GNX received orphan drug designation on June 28, 2017, for "treatment of cyclin-dependent kinase-like 5 gene-related early-onset infantile epileptic encephalopathy."

The detailed regulatory history of the GNX development program is provided in Dr. Steven Dinsmore's clinical review.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Refer to the OPQ review for details of the product quality assessment.

The OPQ review describes GNX as a synthetic analog of the endogenous neurosteroid allopregnanolone (USAN: brexanolone). Brexanolone was approved on March 19, 2019, under the tradename Zulresso, for the treatment of postpartum depression in adults; however, because GNX differs from allopregnanolone by the presence of a methyl group at the 3β position, ganaxolone is considered an NME.

GNX is a cherry-flavored, immediate release, nonsterile oral suspension containing 50 mg/mL GNX. The OPQ review finds that all excipients are present in the drug product at lower levels then currently approved drug products per the Inactive Ingredient Database (IID), with the exception of polyvinyl alcohol which was present in the formulation evaluated in the nonclinical toxicity studies.

The microbial quality of the active pharmaceutical ingredient (API) and of the drug product were found to be adequate. The long-term stability data provided in the application were found to support a 24-month shelf-life when stored at controlled room temperature and an in-use period of (b) (4) days from container-closure system opening. Manufacturing facilities for this product were found to be acceptable.

The OPQ review determined that there is a need for extractable/leachable data to confirm that the container closure system does not adversely impact the drug product, as a formal study under long-term storage was not performed. However, the OPQ review concludes that given the seriousness of the indication and the fact that the risk to product quality due to leachables is presumed to be low, these data can be obtained through the conduct of a postmarketing commitment (PMC).

OPQ recommends approval.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for this application was Dr. Ed Fisher, with Dr. Lois Freed performing the secondary review. The following are the main findings from the nonclinical review of this application:

- GNX was active in several traditional rodent seizure models (e.g., chemically-induced convulsions and corneal kindling).

- In a CNS safety pharmacology study in rat, GNX produced dose-dependent sedation as a function of time.

- GNX did not inhibit the hERG channel at a concentration of 10 μM and there were no alterations in blood pressure, heart rate, or qualitative or quantitative ECG parameters in a cardiovascular safety pharmacology study in conscious telemetered beagle dogs up to the highest dose tested (15 mg/kg).

- A non-conjugated major human metabolite, M2, demonstrated no functional activity at the $GABA_A$ receptor and was negative for mutagenicity in the Ames test; however, it produced a positive response in an in vitro chromosomal aberration test. Further nonclinical assessment of this metabolite will be required postmarketing.

- The M47 human metabolite, a sulfate conjugate, is present in plasma at a similar range as M2 and also requires further postmarketing evaluation as literature reports suggest that sulfate conjugates of neuroactive steroids may have pharmacologic activity.

- Refer to Dr. Fisher's review for a detailed discussion of the findings from the toxicity studies conducted with GNX in rat and dog. The main findings in the 6-month study in rat were related to sedation. These findings were present at all doses in both sexes, but lessened with the duration of the study. Dose-dependent sedation-related effects were also observed in the 12-month study in dog. Dose-related increases in heart rate were also noted in this study, but without any adverse ECG findings. Sedation was also present in a juvenile toxicity study in rat.

- GNX was negative for genotoxicity in both in vitro and in vivo assays.

- In an acute neurotoxicity study in neonatal rats, dose-related increases in neuronal necrosis were observed at all doses in both sexes. These findings were similar to a positive control; however, there were no adverse behavioral abnormalities observed in the juvenile toxicity studies in rat. These results will be described in labeling.

Drs. Fisher and Freed recommend approval of this application.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Ramakrishna Samala and Dr. Dawei Li (clinical pharmacology reviewers), Dr. Gopichand Gottipati (clinical pharmacology team lead), Dr. Michael Bewernitz (pharmacometrics reviewer), and Dr. Atul Bhattaram (pharmacometrics team lead).

Table 1 summarizes the conclusions of the OCP review with respect to the pharmacologic and clinical pharmacokinetic (PK) properties of GNX.

Table 1: Summary of OCP Review Findings

Mechanism of Action	GNX is a selective positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors in the CNS.
Formulation	The to-be-marketed 50 mg/mL oral suspension formulation is identical to the clinical trial formulation.
Metabolism	GNX undergoes metabolism by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6. Multiple metabolites (M60b, M18, M73, M62, M43, and M47) were identified from mass-balance and lactation studies. The exposures of two non-conjugated metabolites, M60b and M18, exceeded the exposures of GNX. M60b did not show drug-interaction liabilities, but such liabilities were not assessed for M18 because of its low abundance and the challenges involved with synthesizing and testing it as an isolated compound; however, OCP states that it is not considered to pose any significant drug-interaction liability. Other metabolites were reported to be conjugated and/or minor metabolites and therefore not expected to be active (with the possible exception of the M47 sulfate conjugate discussed in Section 4 of this review).
Absorption	GNX demonstrated a T_{max} of 2-3 hours following oral administration. When administered with high-fat meal, GNX C_{max} and $AUC_{0\text{-}inf}$ increased by 3-fold and 2-fold, respectively. GNX was administered with food in the clinical efficacy study; therefore, the impact of a reduction in GNX exposures in the fasted state on efficacy is unknown. The OCP review recommends that GNX be administered with food.
Distribution	GNX is highly-plasma protein bound (99% at 500 ng/mL).
Excretion	The terminal half-life for GNX at steady-state is 7.8 to 10.1 hours. GNX and its metabolites are excreted in feces and urine. Following a single oral dose of 300 mg [^{14}C]-GNX to healthy male subjects, 55% of the total radioactivity was recovered in feces (2% as unchanged GNX) and 18% of the total radioactivity dose was recovered in urine (undetected as unchanged GNX).

Dosing Recommendations

The OCP review notes that the dosage in patients with CDD is based on a body weight cut-off (28 kg) and requires an initial titration period (at weekly intervals). Dosing is weight-based in patients weighing 28 kg or less, with a maximum daily dose of 63 mg/kg. In patients weighing more than 28 kg, fixed-doses are to be administered and the maximum daily dose is 1800 mg. Dosing in all patients is divided three times daily. The following tables, reproduced from the OCP review, summarize the recommended GNX dosing.

Table 2: Recommended Dosing Schedule for Patients Weighing 28 kg or Less

Dosage	Total Daily Dosage	Days
6 mg/kg three times daily	18 mg/kg/day	1 to 7
11 mg/kg three times daily	33 mg/kg/day	8 to 14
16 mg/kg three times daily	48 mg/kg/day	15 to 21
21 mg/kg three times daily	63 mg/kg/day	22 to ongoing

Table 3: Recommended Dosing Schedule for Patients Weighing More Than 28 kg

Dosage	Total daily dosage	Days
150 mg three times daily	450 mg	1 to 7
300 mg three times daily	900 mg	8 to 14
450 mg three times daily	1350 mg	15 to 21
600 mg three times daily	1800 mg	22 to ongoing

Drug-Drug Interactions

Based on a dedicated PK study with itraconazole, a strong CYP3A4 inhibitor, OCP concluded that a dosage adjustment for GNX is not needed in the setting of strong, moderate, or weak CYP3A4 inhibitors.

The OCP review states that the concomitant administration of rifampin (a potent CYP3A4 inducer) with GNX decreased the GNX AUC by 68% and the C_{max} by 57%. Therefore, OCP concludes that when concomitant use with strong or moderate CYP3A4 inducers cannot be avoided, the GNX dosage may need to be increased, but should not exceed the maximum recommended daily dosage.

With regard to the effect of GNX on the PK of other drugs, OCP concluded that no dosage adjustment is needed for CYP3A4 substrates when concomitantly administered with GNX. OCP also concluded that a clinically significant interaction between GNX and oral contraceptives is unlikely at clinically relevant concentrations.

Renal Impairment
The impact of renal impairment on the PK of GNX is being evaluated in an ongoing study; however, the OCP review states that because renal excretion is a minor pathway in the elimination of GNX, renal impairment is unlikely to result in clinically significant GNX exposures. The final clinical study report (CSR) for the renal impairment study will be required as a postmarketing requirement (PMR).

Hepatic Impairment
The OCP review notes that that the impact of hepatic impairment on the PK of GNX is being evaluated in an ongoing study. Since GNX undergoes clearance via the hepatic route, hepatic impairment can increase GNX exposures. OCP recommends that patients with impaired hepatic function be monitored for the incidence of adverse reactions and indicates that the GNX dosage may need to be reduced if such reactions occur. The final CSR for the hepatic impairment study will be required as a PMR.

Thorough QT Study
The OCP review indicates that the data submitted with this application are not adequate to characterize the risk of QTc prolongation associated with the oral administration of GNX; therefore, the QT-Interdisciplinary Review Team (QT-IRT) recommends that the applicant conduct a thorough-QT (TQT) trial to evaluate the effect of GNX on the QTc interval. This study will be required as a PMR.

Other Specific Populations
The OCP review states that age, sex, and race are not expected to have clinically-relevant effects on GNX exposure after body weight is accounted for.

OCP recommends approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Steven Dinsmore was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer and Dr. John Lawrence was the biometrics team lead.

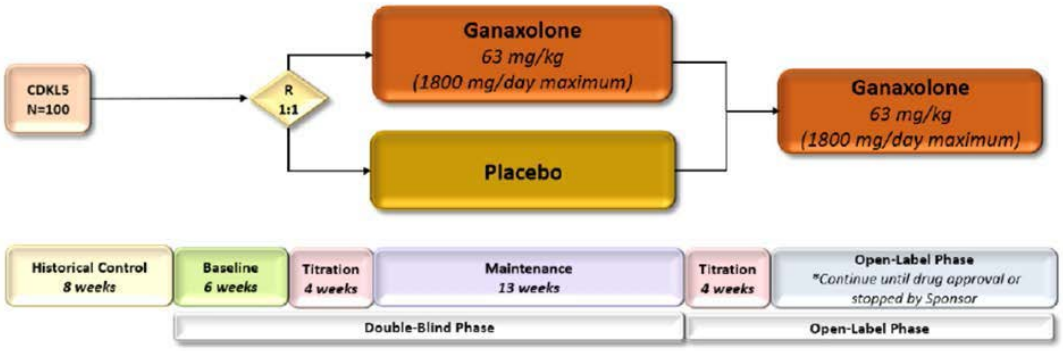
Study 1042-CDD-3001 (Study 3001)

Study 3001 was a global, double-blind, randomized, placebo-controlled, parallel-arm trial designed to evaluate the safety and effectiveness of GNX for the treatment of seizures

associated with CDD in patients 2 years of age and older. The double-blind phase of the trial consisted of a 6-week prospective baseline period, a 4-week titration period, and a 13-week maintenance period. The double-blind phase was preceded by an 8-week screening period to assess eligibility for enrollment based on the frequency of major motor seizures (defined as bilateral tonic-clonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic seizures). Approximately 100 patients with CDD 2-21 years of age were to be randomized in a 1:1 ratio to receive either GNX or placebo in addition to their standard seizure treatment(s). After participation in the double-blind phase of the trial, patients were offered enrollment into a long-term open-label extension phase.

Figure 1, reproduced from the biometrics review, depicts the trial design for Study 3001:

Figure 1: Study 3001: Trial Design



Patients eligible for enrollment into Study 3001 were required to have molecular confirmation of a pathogenic or likely pathogenic mutation in the CDKL5 gene, seizures inadequately controlled by at least 2 previous treatment regimens, and a minimum of 16 major motor seizures per 28 days during each month of the 2-month period prior to screening.

Please refer to refer to Section 5 of this review for a tabular presentation of the GNX titration and maintenance dosing schedule, which is the dosing schedule that wasused in Study 3001. As stated in that summary, dosing was based on a mg/kg/day basis for patients weighing 28 kg or less and on a mg/day basis for patients weighing greater than 28 kg. Doses were administered three times per day. The maximum permitted maintenance dosing for any patient was 1800 mg/day.

The primary efficacy endpoint was the percentage change from baseline in the 28-day frequency of major motor seizures (defined as per the enrollment criteria described above) during the 17-week double-blind treatment phase (i.e., the titration plus maintenance periods). This endpoint was analyzed using the Wilcoxon rank-sum test using all available data regardless of whether a patient took rescue medication. Please refer to Dr. Ling's review for additional details of this analysis.

The protocol also specified the following two secondary endpoints that were hierarchically-controlled for Type I error:

- The percentage of patients with a 50% or greater reduction from baseline in the 28-day frequency of major motor seizures (analyzed using Fisher's Exact test)

- The Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17-week double-blind treatment phase (analyzed using ordinal logistic regression)

Dr. Ling notes that the neither the protocol or statistical analysis plan (SAP) specified whether the CGI-I endpoint referred to the clinician- or caregiver-rated versions of the scale, and indicates that both results were reported in the CSR.

All efficacy analyses were conducted using the modified intention-to-treat (mITT) population, defined as all randomized subjects who received at least one dose of study drug.

Results
101 patients were enrolled and randomized (N=50 for GNX; N=51 for placebo). Baseline and demographic characteristics were balanced between the two treatment arms. The majority of enrolled patients were female (79.2%; consistent with the demographics of CDD), 92% were White, and the median age at baseline was 7.3 years (range 2-19 years). Most (96%) patients were receiving between 1-4 concomitant drugs for the treatment of seizures at baseline, with the most common such drugs being valproate (42%), levetiracetam (32%), clobazam (29%), and vigabatrin (24%).

Primary Efficacy Analysis
Table 4, reproduced based on Dr. Ling's review, presents the results of the primary efficacy analysis for Study 3001.

Table 4: Change from Bassline in 28-Day Major Motor Seizure Frequency

	Placebo	**GNX**
Baseline		
N	51	49
Median	49.2	54.0
Q1,Q3	18.7, 120.0	31.3, 147.3
Double-blind phase		
N	51	50
Median	55.5	45.0
Q1,Q3	21.6, 124.7	23.5, 106.3
Percent change from baseline		
N	51	49
Median	-6.9	-30.7
Q1,Q3	-24.1, 39.7	-49.5, -1.9
Hodges-Lehman estimate of location shift (95% CI)		-27.1 (-47.9, -9.5)
Wilcoxon test p-value		0.0036

The 27.1% greater reduction in the 28-day frequency of major motor seizures observed in the GNX-treated patients compared to placebo was both highly statistically significant and clinically meaningful. Dr. Ling conducted a sensitivity analysis of the primary efficacy endpoint using an analysis of covariance (ANCOVA) which also demonstrated a highly statistically significant 35.2% seizure reduction for the GNX treatment arm relative to placebo (p-value = 0.0084), supporting the results of the primary efficacy analysis. Dr. Ling further notes that the amount of missing data in Study 3001 was small, and that a worst-case analysis of the impact of these data on the results of the primary efficacy analysis supported the strength of that finding.

For Study 3001, patients/caregivers/legally authorized representatives (LARs) entered seizure data into an electronic diary (eDiary). The eDiary permitted the retroactive entry and/or editing of seizure entries within a 7-day window; however, there was also a process for entries outside of that window by proxy. Following an Office of Scientific Investigations (OSI) request, the applicant clarified that a total of 2695 seizures for 38 patients at 22 sites were entered by proxy (approximately 4% of all seizures). Dr. Ling evaluated the impact of these data on the findings from Study 3001 using a sensitivity analysis based on a dataset flagging these proxy data. This sensitivity analysis indicated that the efficacy outcome for Study 3001 was not affected, yielding a p-value of 0.0034.

Secondary Efficacy Analyses

Given the rare prevalence of CDD, it is important to note that Study 3001 was only powered to detect a statistically significant treatment effect on the analysis of the primary efficacy endpoint, an endpoint that is independently clinically meaningful.

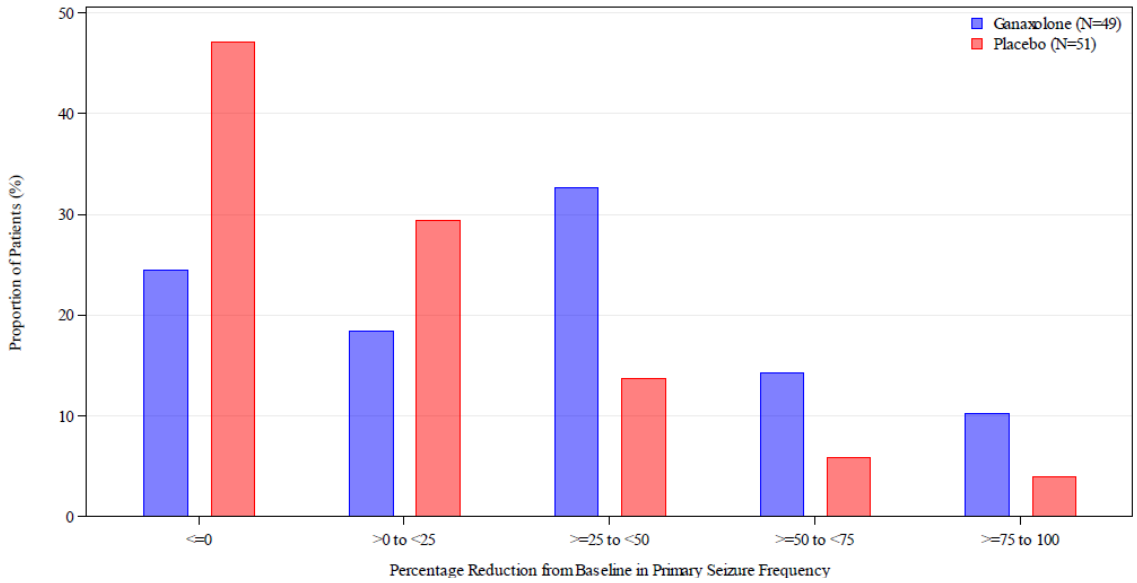
Table 5, based on Dr. Ling's review, presents the results of the analysis of the treatment difference in the percentage of patients with at least a 50% reduction in the frequency of major motor seizures from baseline.

Table 5: Percentage of Patients With at Least a 50% Reduction from Baseline in Major Motor Seizures

	Placebo	GNX
Response rate, N	51	48
n (%)	5 (9.8)	12 (24.5)
Difference (95% CI)		14.7 (-4.7, 33.8)
Fisher's Exact test p-value		0.0643

Figure 2, reproduced from the CSR and verified by Dr. Ling, descriptively presents the percentage reductions from baseline in the 28-day frequency of major motor seizures based on quartiles.

Figure 1: Proportion of Patients by Category of Percent Reduction in 28-Day Seizure Frequency



Drs. Ling and Dinsmore both comment on the consistent numerical trends favoring GNX in the analyses of the various responder categories, including the greater percentage of placebo-treated patients who were either unchanged or worse, in the context of the pre-specified analysis of the 50% responder cut-off that approached statistical significance. The only bin that favored placebo over GNX was greater than 0% to less than 25%; however, as a much greater total percentage of GNX-treated patients than placebo-treated patienst was included in the bins representing greater treatment effect sizes, it is not surprising that there would be a greater proportion of placebo-treated patients in the bin with the smallest positive treatment effect. In addition, this bin likely patients whose responses are particularly influenced by the natural variability in responses, independent of drug effect. The overall distribution of patients in these responder groups is supportive of and consistent with the effectiveness of GNX.

Table 6, based on Dr. Ling's review, presents the results of the analyses of the CGI-I as rated by the parent/caregiver and clinician, respectively.

Table 6: Summary of CGI-I Results

Variable	Placebo	GNX
CGI-I (Parent/Caregiver), N	48	48
Very Much Improved, n (%)	1 (2.1)	0
Much Improved, n (%)	7 (14.6)	13 (27.1)
Minimally Improved, n (%)	13 (27.1)	17 (35.4)
No Change, n (%)	22 (45.8)	14 (29.2)
Minimally Worse, n (%)	4 (8.3)	2 (4.2)
Much Worse, n (%)	1 (2.1)	2 (4.2)
Very Much Worse, n (%)	0	0
Odds Ratio (95% CI)		1.87 (0.89, 3.91)
Logistic Regression p-value	9	0.0971
CGI-I (Clinician), N	48	48
Very Much Improved, n (%)	0	0
Much Improved, n (%)	7 (14.6)	7 (14.6)
Minimally Improved, n (%)	13 (27.1)	19 (39.6)
No Change, n (%)	19 (39.6)	16 (33.3)
Minimally Worse, n (%)	9 (18.8)	2 (4.2)
Much Worse, n (%)	0	3 (6.3)
Very Much Worse, n (%)	0	1 (2.1)
Odds Ratio (95% CI)		1.41 (0.68, 2.94)
Logistic Regression p-value		0.3518

As discussed earlier, the SAP did not clearly specify which version of the CGI-I was to be the second hierarchically-tested secondary efficacy endpoint; however, results of both analyses would be considered nominal, regardless, given the lack of statistical significance of the first secondary efficacy endpoint (i.e., 50% responders).

Both Drs. Ling and Dinsmore observe that numerically greater proportions of GNX-treated patients were rated as improved compared to placebo. Similarly, numerically fewer GNX-treated patients who were rated as unchanged or worse.

Subgroup Analyses
Dr. Ling conducted subgroup analyses for the primary efficacy endpoint based on age, sex, and geographical region. These results all consistently favored GNX, an important consideration in the context of a single efficacy trial. Notably, US patients treated with GNX had a 34.2% reduction in the 28-day frequency in major motor seizures compared to placebo, versus a 19.7% in the same analysis for non-US patients. These findings support the robustness of the results of the primary efficacy analysis.

Open-Label Extension Data
Dr. Dinsmore conducted an exploratory analysis of the percent change in the frequency of major motor seizures from the double-blind baseline period in Study 3001 through Weeks 21 and 34 of the open-label extension phase. Dr. Dinsmore generated trendlines that extended across these periods where a positive slope indicated an increasing frequency of seizures, and a negative slope indicated a sustained or continued improvement in seizure frequency. Please

see Dr. Dinsmore's review for the details of this analysis; however, Dr. Dinsmore found that 35 of the 42 patients (83%) included in this analysis had results that were consistent with sustained or improving seizure control compared to baseline. Although there are limitations to the interpretability of such an assessment, it is reassuring that these findings are also consistent with the results of the prespecified efficacy analyses in Study 3001.

Other GNX Development Programs in Epilepsy

(b) (4)

Efficacy Conclusions

This application contains controlled data from Study 3001, which are intended to support the effectiveness of GNX for the treatment of seizures associated with CDD in patients 2 years of age and older. The result of the primary efficacy analysis, the change from baseline in the 28-day frequency of major motor seizures, was highly clinically meaningful in favor of GNX (a 27% greater reduction compared to placebo) and also highly statistically significant (p=0.0036). The clinical importance of this degree of seizure reduction is clear; particularly in a patient population known to respond poorly to currently approved drugs for the treatment of seizures. The results of this analysis remained robust in the setting of several conservative sensitivity analyses conducted by Dr. Ling. Additionally, these results were consistent across all subgroups based on age, sex, and geographical region (with the strongest results observed in US patients).

The results of the analyses of the hierarchically-ordered secondary endpoints in Study 3001 did not reach statistical significance; however, they all consistently favored GNX. Critically, as Dr. Ling observes, in a very rare patient population, Study 3001 was not powered to demonstrate statistically significant results beyond the analysis of the primary efficacy endpoint. This approach is consistent with the discussion at a December 19, 2017, Type C Guidance meeting with the applicant where the Agency stated that "the single primary endpoint will determine if the trial indicates efficacy or not." Ultimately, there were no results from the analyses of these secondary endpoints that contradicted the primary efficacy analysis. Dr. Dinsmore's exploratory analyses of the efficacy data from the open-label extension phase of Study 3001 were also consistent with the sustained efficacy of GNX in this population.

Although not necessary to support an approval, a further consideration in support of GNX for the proposed indication is that the GABAergic system is an established target in the treatment of epilepsy; therefore, GNX has a mechanistically plausible basis for an expectation of clinical efficacy. (b) (4)

Particularly in the context of a very rare and serious disease with no approved treatments, the strength of the findings from Study 3001 provide substantial evidence of the effectiveness of GNX for the treatment of seizures associated with CDD in patients 2 years of age and older.

8. Clinical - Safety

Dr. Steven Dinsmore conducted the clinical safety review of this application.

The application contains safety data in patients with CDD from the placebo-controlled efficacy and safety study (Study 3001; including its open-label extension phase) and an open-label proof-of-concept study that also enrolled 7 patients with CDD (out of 31 total patients enrolled) (Study 0900).

The double-blind phase of Study 3001 was examined by Dr. Dinsmore to compare the safety of the GNX treatment arm to placebo. He then performed a review of the pooled open-label safety data from the open-label extension phase of Study 3001 and the 7 CDD patients enrolled in Study 0900.

This application also provides supportive safety data from the GNX development programs for other indications including POS, postpartum depression, post-traumatic stress disorder (PTSD), and IS. Dr. Dinsmore conducted a review of these additional data, as appropriate, to supplement his analyses of the safety data obtained in patients with CDD. As part of this approach, Dr. Dinsmore performed a comprehensive analysis of the safety data from a Phase 3 trial in POS and a Phase 2 trial in PTSD, representing 471 adult patients, as these legacy datasets were most amendable to such a review.

Exposure in Patients with CDD

There were 102 patients with CDD who were exposed to at least a single dose of GNX, including 83 with exposure to GNX for at least 6 months, and 50 who were exposed for at least 12 months. Fourteen patients weighing more than 28 kg had a modal dose of 1800 mg/day while the 62 patients weighing 28 kg or less had a modal dose of 63 mg/kg/day.

In the context of a rare disease such as CDD, these exposures are adequate to allow for a clinical safety review of the application; particularly considering the additional supportive safety data from the development of GNX for other related indications, as discussed above.

Deaths

In Study 3001, the following single death was reported.

- [redacted] (Subject [redacted]) randomized to GNX in the double-blind phase was receiving 33 mg/kg/day GNX. On Day 381 during the open-label extension phase, [redacted] experienced severe meningococcal sepsis and died on Day 382. The investigator assessed the death as unlikely to be related to study drug. Dr. Dinsmore agrees that this death is unlikely to be related to GNX because of the lack of mechanistic plausibility and temporal relationship to treatment.

In Study 0900, the following single death was reported.

- [redacted] (Subject [redacted]) with Lennox-Gastaut syndrome (LGS) was receiving 54 mg/kg/day GNX. At birth, [redacted] experienced necrotizing enterocolitis resulting in short bowel syndrome. The patient had additional co-morbidities of hepatic dysfunction, hypotonia (all extremities), left eye ptosis, and urinary incontinence. Dr. Dinsmore's review contains an extensive discussion of this case. On Day 157, the patient was hospitalized due to reported hepatic failure. [redacted] took [redacted] last dose of study drug on Day 159 and was withdrawn from the study on Day 160. Between Days 160 and 355, the patient was hospitalized several times for various medical reasons including hepatic failure, jaundice, hyperbilirubinemia, and liver enlargement. On Day 355, the patient died with a diagnosis of hepatic failure. The investigator assessed this diagnosis as unlikely to be related to study drug.

  The Office of New Drugs (OND) drug-induced liver injury (DILI) team was consulted regarding this case. Their consultation concluded that hepatic failure was unlikely to be the primary cause of death based on the near normal INR and albumin when the patient transitioned to comfort care. They further indicated that cholestasis of sepsis is a more likely explanation of her persistent jaundice. In addition to reviewing the hepatic safety data obtained from CDD patients, both Dr. Dinsmore and the DILI team also evaluated the risk of DILI in the adult clinical trial data (both adverse reaction and laboratory data) submitted with this application from adults with POS. These analyses did not identify any evidence of DILI with GNX.

Two additional deaths were reported during Study 0501 (an open-label extension phase of a study in IS)

- [redacted] (Subject [redacted]) was receiving between 36 and 45 mg/kg/day of GNX. The patient had co-morbidities including cortical dysplasia, microcephaly, and lobar holoprosencephaly in addition to IS. On Day 85, [redacted] experienced severe aspiration during a tube feeding and died of asphyxia the same day. The investigator assessed the death as unlikely to be related to study drug. Dr. Dinsmore agrees that this death is unlikely to be related to GNX.

- [redacted] (Subject [redacted]) was receiving greater than 54 mg/kg/day of GNX. The patient had co-morbidities including microcephaly and lobar

holoprosencephaly in addition to IS. The patient had (b) (6) last dose of study medication on Day 262. On Day 263, (b) (6) died due to respiratory failure. The investigator assessed the death as not related to study drug. In the context of the course and severity of the patient's underlying medical conditions, Dr. Dinsmore agrees that this death is unlikely to be related to GNX.

Dr. Dinsmore reports that there were no other deaths reported in the pediatric epilepsy trials conducted with GNX. The only death that occurred in the adult trials was in a POS patient (b) (6). Several additional deaths were reported in ongoing adult trials in refractory status epilepticus; however, these deaths were consistent with the severity of the underlying condition and not found to be drug-related.

Serious Adverse Events (SAEs)

Dr. Dinsmore reports that there were 16 SAEs during the double-blind treatment phase of Study 3001 from 11 (10.1%) patients, including 6 (10.5%) patients in the GNX treatment arm and 5 (9.8%) in the placebo arm. Dr. Dinsmore concludes there was no difference in the nature and incidence of SAEs between treatment arms in the double-blind phase of Study 3001.

In the pooled open-label data from Studies 3001 and 0900 (comprising a total of 101 patients), there were 55 SAEs from among 23 (22.7%) patients. Dr. Dinsmore's analysis of the SAEs that occurred with a plausible temporal relationship to GNX treatment (defined as less than 56 days from treatment onset) identified 14 events from among 9 patients. Five preferred terms (PTs) contributed to these events, including, seizure (5 cases), dehydration (3 cases), aspiration (2 cases), and one case each of unresponsiveness to stimuli and upper respiratory tract infection. From among these 14 events, he finds that only 2 that have a possible causal relationship to GNX treatment (one event each of aspiration and unresponsiveness to stimuli). Dr. Dinsmore concludes that these events may be related to the potential of GNX to cause sedation. The risk for somnolence and sedation, which were common adverse reactions associated with GNX in Study 3001, will be prominently presented as a WARNINGS AND PRECAUTIONS section in labeling.

Dr. Dinsmore concludes that the SAE data from the additional trials contained in this application were consistent with the data obtained from patients with CDD.

Discontinuations Due to Adverse Events:

There were 6 patient discontinuations during the double-blind phase of Study 3001: 5 due to adverse events (AEs) and 1 due to withdrawal by subject. Four of the 5 patients who discontinued treatment due to an AE were in the placebo arm, while only 1 (due to seizure) was in the GNX arm. During the open-label extension phase of Study 3001, there were 6 patients who discontinued treatment due to an AE between Days 142 and 239. Dr. Dinsmore notes that the lack of a clear temporal relationship to treatment in these cases reduces the likelihood that these discontinuations were due to treatment with GNX.

Two of the 7 patients with CDD enrolled in Study 0900 discontinued treatment, although not due to an AE(s) (one patient discontinued due to lack of efficacy and another withdrew consent).

Adverse Events of Special Interest

Reproductive system and breast disorders

Reproductive system and breast disorders were identified as a theoretical safety concern given that GNX is a synthetic neurosteroid. Dr. Dinsmore comments that only a single AE falling under this system organ class (SOC) was identified in the double-blind phase of Study 3001; a (b) (6) male patient with spontaneous penile erection. Dr. Dinsmore further reports that only 4 patients (3.6%) with CDD represented in the open-label treatment data had events falling under this SOC (e.g., menorrhagia, polymenorrhea, and oligomenorrhea); an incidence that is too small to discern any clear drug-related signal beyond the expected background rate. Dr. Dinsmore similarly did not find any associated signal of AEs in this SOC in the adult data from POS patients contained in this application.

Effects on Growth and Development

Dr. Dinsmore comments that the ability to perform a range of developmental milestones that were evaluated in Study 3001 was similar in both GNX-treated patients and placebo. He also notes that there were no apparent drug-related effects on other measures of growth and deployment that were evaluated in that trial.

Treatment-Emergent Adverse Events (TEAEs)

Table 7, reproduced from the information contained in Dr. Dinsmore's review, summarizes the most common TEAEs that occurred in Study 3001.

Table 7: Treatment-Emergent Adverse Reactions: Study 3001

Adverse Reactions	**GNX** (N=50) %	**Placebo** (N=51) %
Somnolence	38	20
Pyrexia	18	8
Upper respiratory tract infection	10	6
Sedation	6	4
Salivary hypersecretion	6	2
Seasonal allergy	6	0
Bronchitis	4	0
Influenza	4	2
Gait disturbance	4	2
Nasal congestion	4	2

The term somnolence also includes the terms lethargy and hypersomnia

Dr. Dinsmore concludes that this pattern of TEAEs is largely consistent with that observed with many drugs approved for the treatment of seizures. As Table 3 indicates, somnolence is clearly the most commonly observed TEAE with GNX treatment. As discussed earlier in this summary review, product labeling will contain a WARNINGS AND PRECAUTIONS section

related to the risk of somnolence and sedation.

Dr. Dinsmore's review of the TEAE data from the additional trials contained in this application did not reveal any unique signals that were not present in the data obtained from patients with CDD.

Laboratory Findings
There were no clinically significant differences in chemistry, hematology, or urinalysis findings between the GNX and placebo arms in Study 3001.

The findings from Dr. Dinsmore's review of the laboratory data from the additional trials contained in this application were consistent with the results of his analysis of data obtained from patients with CDD.

As discussed previously in regard to the LGS patient who died with a preliminary diagnosis of hepatic failure, there was no evidence of any laboratory abnormalities suggestive of a liver toxicity signal for GNX in the data submitted with this application.

Vital Signs
There were no clinically significant differences in blood pressure, heart rate, respiratory rate, or body temperature between the GNX and placebo arms in Study 3001.

The findings from Dr. Dinsmore's review of the vital sign data from the additional trials contained in this application were consistent with the results of his analysis of data obtained from patients with CDD.

Electrocardiograms (ECGs)
There were no clinically significant differences in ECG parameters between the GNX and placebo arms in Study 3001. As discussed in Section 4 of this review, a TQT study will be required as a PMR.

Overdosage
There were no reports of GNX overdose in the clinical development programs discussed in this application.

Safety Conclusions
The overall safety profile of GNX is consistent with that of many products approved for the treatment of seizures and supports the approval of GNX for the treatment of seizures associated with CDD in patients 2 years of age and older. Product labeling will include a WARNINGS AND PRECAUTIONS section describing the risks of somnolence and sedation. Standard WARNINGS AND PRECAUTIONS sections from drugs approved for the treatment of seizures, including for suicidal ideation and behavior and the risks of rapid treatment withdrawal, will also be included in labeling.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of GNX is acceptable for the intended population, the clinical trial design is acceptable, and the efficacy findings were clear.

10. Pediatrics

The clinical efficacy trial was conducted in a CDD patient population two years of age and older. Pediatric Research Equity Act (PREA) requirements were not triggered for this orphan indication.

11. Other Relevant Regulatory Issues

Clinical
No Good Clinical Practice (GCP) issues were identified in Dr. Dinsmore's clinical review.

Dr. Dinsmore concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the OSI reviewer for this application and Dr. Phillip Kronstein the OSI team lead. One foreign (France) and two domestic clinical research sites were investigated. OSI concludes that despite some protocol deviations at the French site, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication.

Please see the discussion of the issue of proxy eDiary entry for Study 3001 in Section 7 of this review.

Controlled Substance Staff (CSS)
Dr. Katherine Bonson was the CSS reviewer for this application. CSS concludes that the nonclinical and clinical abuse-related data submitted in this application demonstrate that GNX has abuse potential and should be recommended for Schedule V of the Controlled Substance Act (CSA). Of note, the applicant had proposed that GNX be placed in Schedule IV of the CSA. Please refer to the CSS review for a detailed discussion of the basis for their conclusion. CSS will convey this recommendation to the Drug Enforcement Agency (DEA), which will make a final determination regarding scheduling.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Justine Kalonia was the primary DMEPA reviewer for this application, and Dr. Stephanie DeGraw was the acting team lead. DMEPA indicates that the final agreed-upon prescribing information (PI), instructions for use (IFU), medication guide (MG), and carton and container labeling are acceptable.

Dr. Chad Morris reviewed the proposed proprietary name, Ztalmy, and concluded that this name is acceptable.

12. Labeling

Please refer to the final negotiated product labeling. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategy (REMS)
The Division of Risk Management (DRM) has determined that a REMS is not necessary for GNX.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following studies are recommended as PMRs:

4218-1 A 26-week carcinogenicity study of ganaxolone in the CB6F1-Tg rasH2 transgenic mouse.

Draft Protocol Submission:	01/2023
Final Protocol Submission:	03/2023
Study Completion:	11/2023
Final Report Submission:	02/2024

4218-2 A 104-week carcinogenicity study of ganaxolone in rat.

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023
Study Completion:	07/2025
Final Report Submission:	10/2025

4218-3 A 2-year carcinogenicity study of the major human unconjugated plasma metabolite, M2, in rat.

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023
Study Completion:	07/2025
Final Report Submission:	10/2025

4218-4 A juvenile animal toxicology study of the major human unconjugated plasma metabolite, M2, in rat.

Draft Protocol Submission:	01/2023
Final Protocol Submission:	06/2023
Study Completion:	10/2023
Final Report Submission:	02/2024

4218-5 A central nervous system (CNS) distribution study of the major human plasma metabolite, M47 (sulfate-conjugated ganaxolone), in rat.

Draft Protocol Submission:	05/2023
Final Protocol Submission:	06/2023
Study Completion:	09/2023
Final Report Submission:	11/2023

4218-6 An in vitro assessment of the the drug interaction potential of the M47 metabolite as a perpetrator for major drug metabolizing enzymes and transporters, in accordance with "In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry."

Draft Protocol Submission:	05/2023
Final Protocol Submission:	06/2023
Study Completion:	09/2023
Final Report Submission:	11/2023

4218-7 A clinical pharmacokinetic trial to determine an appropriate dose of ganaxolone to minimize toxicity in patients with varying degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Final Report Submission:	12/2022

4218-8 A clinical pharmacokinetic trial to determine an appropriate dose of ganaxolone to minimize toxicity in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Final Report Submission:	05/2022

4218-9 A Thorough QT trial to evaluate the effect of ganaxolone on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, and its Questions and Answers (R3)."

Final Report Submission: 12/2022

The following study is recommended as a PMC:

4218-10 Provide extractable/leachable results to confirm that the container closure system does not adversely impact the drug product.

Interim Reports: 04/2022 (extractables report)
06/2022 (leachable extractable correlation report)

Final Report Submission: 03/2023

14. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
03/18/2022 01:07:57 PM

NICHOLAS A KOZAUER
03/18/2022 01:09:46 PM

WILLIAM H Dunn
03/18/2022 01:18:19 PM