CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215904Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	215904
Priority or Standard	Priority
Received Date(s)	7/20/2021
PDUFA Goal Date	3/20/2022
Division/Office	DN 2
Reviewer Name(s)	Steven Dinsmore, DO
Review Completion Date	2/15/2022
Established/Proper Name	Ganaxolone
(Proposed) Trade Name	ZTALMY
Applicant	Marinus Pharmaceuticals
Dosage Form(s)	Suspension for oral administration
Applicant Proposed Dosing Regimen(s)	(b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD).
Recommendation on Regulatory Action	Approval for the indication of the treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD), in patients 2 years of age and older.
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD).

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3 Glossary

3001	Study 1042-CDD-3001
0900	Study 1042-0900
0600	Study 0700
0603	Study 0603
0700	Study 0700
AC	advisory committee
AE	adverse event
AED	antiepilepsy drug
Allo-S	Allopregnanolone Sulfate Level
AR	adverse reaction
AESI	Adverse Events of Special Interest
ASM	anti-seizure medication
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDD	CDKL5 deficiency disorder
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CGI-I	Clinical Global Impression – Improvement scale
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DB	Double blind
DILI	Drug-induced Liver Injury
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GNX	ganaxolone
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IS	Infantile Spasms
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OL	Open Label
OPQ	Office of Pharmaceutical Quality
OORR	Out of Reference Range
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POS	partial onset seizures
PP	per protocol
PPD	postpartum depression
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
TTO	time to onset

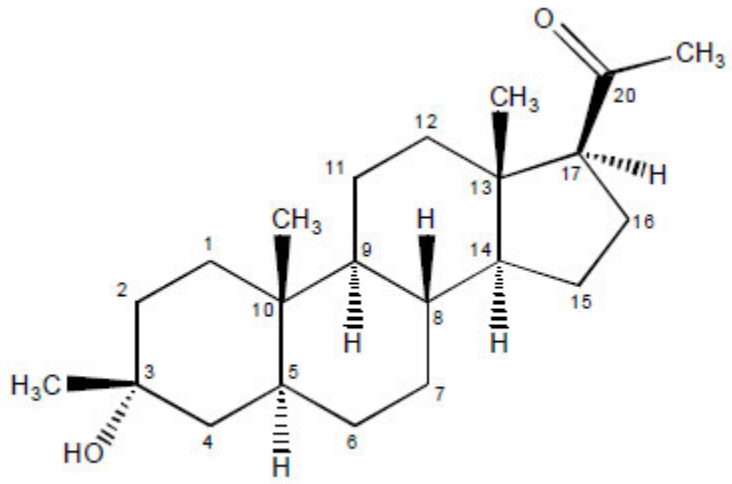
1. Executive Summary

1.1. Product Introduction

1.1.1. Description

Ganaxolone (GNX) is a member of a novel class of neuroactive steroids called epalons, which specifically modulate the GABAA receptors in the central nervous system. Ganaxolone is a synthetic analog of the endogenous neurosteroid allopregnanolone, the metabolite of progesterone. Due to the 3β-methyl substituent in its chemical structure, which prevents its metabolism and oxidation at the 3α-hydroxy moiety, GNX does not have hormonal activity and does not undergo back-conversion, avoiding the side effects, biotransformation, and tolerance associated with allopregnanolone.

Figure 1 GNX Chemical Structure



Ganaxolone

Molecular Weight: 332.53
Formula: $C_{22}H_{36}O_2$

1.1.2. Summary

Ganaxolone is the first of a new class of drugs, the epalons. Compared to currently available ASMs, GNX has a distinctive mechanism of action and provides both phasic and tonic inhibitions by activating synaptic and extrasynaptic GABAA receptors at sites distinct from those bound by benzodiazepines and barbiturates. In preclinical studies, GNX demonstrated antiseizure activity over a wide range of animal models suggesting a potentially broad therapeutic utility; like many

other GABA-enhancers; however, it could exacerbate absence seizures[1].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of the effectiveness of ganaxolone for the treatment of seizures associated with Cyclin-dependent Kinase-like 5 Deficiency Disorder (CDD).

Efficacy of GNX for the treatment of seizures associated with CDD disorder is supported by a single study, 3001 where the result of the primary endpoint was robust. The secondary endpoints of Study 3001 were not powered to achieve statistical significance, but the results are in alignment with a treatment benefit for CDD. The proportion of patients with a greater than or equal to 50% reduction from baseline seizure frequency numerically favored the GNX treatment arm although this result was not statistically significant. Other secondary endpoints examined for alignment with a treatment benefit included a CGI-I (Parent/Caregiver) score and CGI-I (Clinician) score. The result of the CGI-I (Parent/Caregiver) scores numerically favored the GNX group. The result of the CGI-I (Clinician) identified that larger proportions of clinicians caring for GNX treated patients (39.6%) rated the response to treatment as "minimally improved" compared to clinicians caring for patients in the PBO treatment (27.1% minimally improved),

There is also durability of treatment effect identified as patients on GNX treatment arm of study 3001 continued into open label treatment. When the trendlines plotting the percent change from baseline seizure frequency out to 34 weeks were analyzed, it was seen that 35 of 42 patients (83%) had a trendline consistent with sustained or improving seizure control compared to baseline frequency.

Although the influence of intrinsic baseline levels of Allopregnanolone-sulfate (Allo-S) on effectiveness was a concern early in development of GNX, the Applicant's analysis of GNX efficacy across the low, mid and high range of baseline Allo-S levels does not identify a relationship between baseline the Allo-S level and efficacy of GNX treatment.

The observed improvement in change from baseline seizure frequency of the 7 patients with a CDD diagnosis in the open label study 0900 adds support for evidence of effectiveness. In this study there was a numerical reduction in seizure frequency from baseline observed at 3 months and 6 months of treatment.

(b) (4)

In addition to the prespecified outcome result of Study 3001, there was consistent GNX

[1] S. Lattanzi, A. Riva, and P. Striano, "Ganaxolone Treatment for Epilepsy Patients: From Pharmacology to Place in Therapy," *Expert Review of Neurotherapeutics* (2021), https://dx.doi.org/10.1080/14737175.2021.1904895.

treatment benefit identified across differing epileptic disorders and domains of outcome measurement. This totality of evidence supports the conclusion of GNX efficacy for treatment of treatment of seizures associated with CDD Deficiency Disorder.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Cyclin-dependent Kinase-like 5 deficiency disorder (CDD) is a rare but severe condition with seizure frequency and intensity that is refractory to current therapy as well as severe cognitive and motor developmental delays. CDD is linked to the X chromosome and affects the female gender four times more often than males.

Efficacy in this submission is based on a single double blind randomized placebo controlled pivotal study (Study 3001) comparing GNX to PBO during the 17-week combined titration plus maintenance phase. The endpoint was the change from baseline in 28-day seizure frequency analyzed using the Wilcoxon Rank-Sum test. The primary analysis used all available data, even if they were collected after the patient stopped taking study medication, regardless of whether the subject took rescue medication. The result of the primary endpoint was robust and the secondary endpoints all numerically favored ganaxolone. An observation from pivotal Study 3001 that was not in alignment with GNX efficacy for CDD treatment was a small excess of GNX patients over placebo (PBO)- treated patients who had high frequency rescue medication treatment.

Support of GNX efficacy also includes the observation of a durable effect on seizure reduction in the majority of patients on GNX in the double-blind phase of Study 3001 who continued to open-label week 34 of GNX treatment. Additional supporting observations of efficacy include the finding of seizure frequency reduction over baseline at both 13 and 26 weeks in the seven patient CDD subset enrolled in open-label Study 0900. (b) (4)

There was a potential drug-induced liver injury (DILI) -related death identified in the safety dataset of Study 0900. This event was evaluated and adjudicated by the DILI team that noted “we do not agree that the primary cause of death was liver failure based on near normal INR and albumin when the subject transitioned to comfort care. Indeed, cholestasis of sepsis is a more likely explanation of her persistent jaundice”, see Hepatic Failure Case Section 8.5.1. The potential for cholestatic liver injury was further evaluated in two partial onset seizure studies in adults. The double-blind interval of Study 0600 was examined to provide additional comparison to PBO while the double-blind to open label extension component of Study 603 was examined to allow assessment of a longer exposure duration, median 308 days. This analysis did not identify evidence of a pattern in hepatic associated chemistry parameters consistent with cholestatic liver injury, see Section 13.4, ALP Screening. The safety profile is favorable with reversible CNS adverse reactions of “somnolence”, “dizziness”, and “gait disturbance” that may be monitored. A REMS is not required, and labeling will provide adequate management of safety.

Overall, the totality of evidence, including the pivotal study endpoint, durability of benefit, the antiseizure biologic effect in adult POS treatment, demonstrate benefit of GNX with a favorable safety profile where the primary safety issues are monitorable and reversible and no serious outlier safety signals were identified. The availability of GNX for treatment of seizures in patients with CDKL5 deficiency syndrome, will be a significant advance to address a notable unmet medical need in this rare disease population where current treatment is empirically guided and only off label treatment for seizures is available.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CDD is a rare disease • The "typical" individual with CDD, defined by having a pathogenic gene variant that impairs CDKL5 function, is characterized by onset of treatment-resistant epilepsy and severe cognitive and motor developmental delays CDD which is linked to the X chromosome and which affects the females four times more often than males. • Most children experience treatment-resistant seizures and severe neurodevelopmental impairment. Patients may experience 1 or more of several different seizure types, including tonic-clonic, atonic, clonic, tonic, myoclonic, absence, and focal seizures as well as infantile spasms. • In less than 10% of patients there are only several seizures a month; about 12% have several episodes weekly and up to 80% have seizures every day.	CDD is a rare disease characterized by refractory epilepsy.
Current Treatment Options	• There is no FDA approved treatment for CDD • No specific anti-seizure medication (ASM)was associated with improved seizure control for CDD. The four most frequently prescribed ASMs were broad spectrum, prescribed in over 50% of individuals. The most frequently prescribed medications (prescribed in more than 50% of individuals) were levetiracetam (n = 136), topiramate (n = 107), clobazam (n = 100), and phenobarbital (n = 89).	There is an unmet medical need for CDD treatment. Currently there are no approved therapies, and treatment is empirically based.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Treatment for neurologic features of CDD is currently symptom-based and empiric rather than CDD specific.	
Benefit	• A single pivotal trial and a broad totality of evidence supports the conclusion of GNX efficacy for treatment of treatment of seizures associated with CDD • The benefit was obtained in a disease known to be refractory to antiepilepsy drug treatment • Patients entering the study, before starting GNX, had continued seizures while on their established background treatment.	Availability of a specific treatment for the seizures associated with CDD will be an important advance for providers and patients who currently rely on empirically driven unapproved treatment options.
Risk and Risk Management	• The primary adverse reactions seen in GNX treatment are central nervous adverse effects including "somnolence", "dizziness", and "gait disturbance". Although there was a high frequency of "somnolence" serious adverse events were rare. • Proposed labeling: The safety data do not indicate need for a special risk evaluation and mitigation strategy (REMS). "Somnolence" and "Sedation" are included in Section 5 of proposed labeling. • The safety data do not indicate a need for a special risk evaluation and mitigation strategy (REMS). "Somnolence", "Sedation" (b) (4) are included in Section 5 of proposed labeling.	Somnolence, and the related term sedation are effects of central nervous system depression seen frequently in treatment with antiseizure medication. These adverse reactions are reversible upon discontinuation of treatment. This adverse reaction may be monitored.

1.4. Patient Experience Data- N/A

2. Therapeutic Context

2.1. [4]Analysis of Condition

The applicant provides an overview of the condition as part of the summary of clinical efficacy and reports that the CDKL5 gene is located on the short arm of the X chromosome and encodes a serine-threonine kinase essential for neuronal maturation and development. Mutations of the CDKL5 gene cause a disorder characterized by early onset seizures with severe encephalopathy, previously considered a variant of Rett syndrome due to the presence of common clinical features. The identification of the unique genetic locus led to recognition of a distinct clinical entity, CDD. With an overall incidence of 1 per 42,000 live births, mutations in CDKL5 are currently one of the most common genetic causes of epilepsy in children. Despite this strong genetic link, the pathogenesis of CDD remains unclear. Presently, there is no cure, and the limited treatment options available have focused on mitigating seizure burden using a variety of nonspecific anticonvulsants.[2] It was not until January 2020 that CDD was officially awarded an ICD10 code (G40.42) by the World Health Organization, a landmark in the recognition of CDD as a distinct clinical disorder. Currently, the LouLou Foundation, a private nonprofit foundation to promote understanding of and therapy for CDD, is aware of over 1200 documented cases worldwide (LouLou Foundation, 2020)[3]

Severity of CDD is variable, although most children experience treatment-resistant seizures and severe neurodevelopmental impairment. Patients may experience 1 or more of several different seizure types, including tonic-clonic, atonic, clonic, tonic, myoclonic, absence, and focal seizures as well as infantile spams (IS). Three stages of seizures in the course of CDD have been proposed: Stage I, early onset epilepsy (onset 1 to 10 weeks); Stage II, epileptic encephalopathy with IS and hypsarrhythmia; Stage III, tonic seizures with myoclonia and variable level of control with ASMs. Frequent myoclonic jerks are a key component of the epileptic manifestations at this later stage. Some patients show a peculiar seizure pattern with prolonged generalized tonic-clonic events lasting 2 to 4 minutes gradually transitioning to repetitive, distal myoclonic jerks. In the last several years, the number of subjects reported with CDKL5 early-onset epileptic encephalopathy has grown as genetic testing for the disorder becomes more common. Children with CDD may also be diagnosed with Lennox Gastaut syndrome (LGS) or with West syndrome based on seizure semiology.

[2] Barbara Terzic et al., "Temporal Manipulation of Cdkl5 Reveals Essential Postdevelopmental Functions and Reversible Cdkl5 Deficiency Disorder–Related Deficits," *The Journal of Clinical Investigation* 131, no. 20 (10/15/2021), https://dx.doi.org/10.1172/JCI143655.

[3] Loulou Foundation is a private non-profit UK foundation dedicated to advancing research into the understanding and development of therapeutics for CDKL5 deficiency disorder. https://www.louloufoundation.org/

2.2. Analysis of Current Treatment Options

There is no FDA approved treatment for CDD. In a study where data was collected both retrospectively and prospectively through the dedicated Centers of Excellence as part of a clinic-based research study, it was concluded that treatment for neurologic features of CDD is currently symptom-based and empiric rather than CDD specific while epilepsy in this population is highly refractory, and no specific ASM was associated with improved seizure control. The four most frequently prescribed anti-seizure medications were broad spectrum, prescribed in over 50% of individuals. The most frequently prescribed medications (prescribed in more than 50% of individuals) were levetiracetam (n = 136), topiramate (n = 107), clobazam (n = 100), and phenobarbital (n = 89).

Sixty-one individuals (n = 61 of 168, 36%), out of the total number of individuals with ASM data, were treated with cannabis derivatives, including FDA-approved cannabidiol (off label Epidiolex- a product not approved for CDD), and non-FDA-approved cannabis derivatives. This was predominantly in combination with other epilepsy treatments. Of 86 individuals for whom Epidiolex was differentiated from non-FDA-approved cannabis derivatives, 19 reported using Epidiolex (22%) and 18 reported using non-FDA-approved cannabis derivatives.[4]

[4] H. E. Olson et al., "Current Neurologic Treatment and Emerging Therapies in Cdkl5 Deficiency Disorder," *Journal of Neurodevelopmental Disorders* 13, no. 1 (Dec 2021), https://dx.doi.org/10.1186/s11689-021-09384-z.

Table 1 Current ASM Treatment Options for CDD

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
No FDA approved treatments						
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Keppra (levetiracetam)	indicated for the treatment of partial-onset seizures in patients 1 month of age and older	1999	Oral: weight-based dosing in patients less than 16 years of age, twice daily. Twice daily for patient age 16 years and older	CDD: 14% had 2 week response, 5% had 3 month response, 9% had seizure worsening. *	Source: Keppra PI Section 5: Warnings & Precautions: • Behavior Abnormalities and Psychotic Symptoms • Suicidal Behavior and Ideation • Somnolence and Fatigue • Anaphylaxis and Angioedema • Serious Dermatological Reactions • Coordination Difficulties • Hematologic Abnormalities • Increase in Blood Pressure Section 6.1: Clinical Trials 2 most frequent Adverse Reactions- Adults: Asthenia & Somnolence Pediatric Patients, 4 Years to <16 Years: Headache & Nasopharyngitis	
Topamax (topiramate)	Epilepsy: <u>initial monotherapy</u> for the treatment of partial-onset or primary generalized tonic-clonic seizures in	1996	Oral: Monotherapy-<u>Pediatric Patients 2 to 9 Years of Age;</u> weigh based dosing twice	CDD: 26% had 2 week response, 13% had 3 month response, 5% had seizure worsening.*	Source: Topamax PI Section 5: Warnings & Precautions • Acute Myopia and Secondary Angle Closure Glaucoma• Visual Field Defects • Oligohidrosis and Hyperthermia	

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
	patients 2 years of age and older; adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox Gastaut syndrome in patients 2 years of age and older.		daily. Adults and Pediatric Patients 10 Years of Age and Older; twice daily		• Metabolic Acidosis • Suicidal Behavior and Ideation • Cognitive/Neuropsychiatric Adverse Reactions • Serious Skin Reactions • Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) • Kidney Stones • Hypothermia with Concomitant Valproic Acid (VPA) Use Section 6.1: Clinical Trials Monotherapy Epilepsy- Adults 16 Years of Age and Older: adverse reactions causing discontinuation were difficulty with memory, fatigue, asthenia, insomnia, somnolence, and paresthesia Pediatric Patients 6 to 15 Years of Age: adverse reactions resulting in discontinuation were difficulty with concentration/attention, fever, flushing, and confusion	

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
Onfi (clobazam)		2011	Oral: ONFI should be administered in divided doses twice daily (the 5 mg dose can be administered as a single daily dose).	CDD: 48% had 2 week response, 36% had 3 month response, 16% had seizure worsening.*		
phenobarbital	Anticonvulsant–For the treatment of generalized and partial seizures	identified as an antiepileptic drug in 1912	Oral: 60 to 120mg/day	CDD: 37% had 2 week response, 9% had 3 month response, 3% had seizure worsening.*	Source Dailymed[5] CNS depression- sedation, hyperactivity in children. Respiratory/Circulatory–Respiratory depression, apnea, circulatory collapse. Allergic reaction- including urticaria, angioedema, and similar conditions. Hypersensitivity reactions in this category include localized swelling, particularly of the eyelids, cheeks or lips, and erythematous dermatitis. Rarely, exfoliative dermatitis (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) Other Reported Reactions (less than 1/100): Headache, injection site reactions, hypersensitivity reactions (angioedema, skin rashes, exfoliative dermatitis), fever, liver damage, megaloblastic anemia following chronic	This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA

[5] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e34926f-e5e5-41da-836a-c854b00d1a20

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
					phenobarbital use.	
Epidiolex (cannabidiol)	treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older	2018	Oral: twice daily	CDD: 29% had 2 week response, 21% had 3 month response, 29% had seizure worsening. *	Source: Epidiolex PI Section 5: Warnings & Precautions • Hepatocellular Injury • Somnolence and Sedation • Suicidal Behavior and Ideation • Hypersensitivity Reactions • Withdrawal of Antiepileptic Drugs Section 6.1: Clinical Trials Experience The most frequent cause of discontinuations was transaminase elevation. Discontinuation for transaminase elevation occurred at an incidence of 1.3% in patients taking EPIDIOLEX 10 mg/kg/day, 5.9% in patients taking EPIDIOLEX 20 mg/kg/day, and 0.4% in patients on placebo. Somnolence, sedation, and lethargy led to discontinuation in 3% of patients taking EPIDIOLEX 20 mg/kg/day compared to 0% of patients taking EPIDIOLEX 10 mg/kg/day or on placebo.	

*H. E. Olson et al., "Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder," Journal of Neurodevelopmental Disorders 13, no. 1 (Dec 2021), 40, https://doi.org/10.1186/s11689-021-09384-z, <Go to ISI>://WOS:000696540900001 https://jneurodevdisorders.biomedcentral.com/track/pdf/10.1186/s11689-021-09384-z.pdf.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

GNX, a new molecular entity has not been approved for marketing in the US or any other country or withdrawn or suspended from marketing in any country.

GNX was originally patented by Glaxo Laboratories in 1976. In 1993, CoCensys Pharmaceuticals commenced a clinical development program focusing on migraine and infantile spasms. In 1999, CoCensys and its pipeline, including GNX, were acquired by Purdue Pharmaceuticals, which did not pursue further development of GNX. Marinus licensed GNX in 2005 and commenced a clinical development program in 2006.

3.2. Summary of Presubmission/Submission Regulatory Activity

An Orphan Drug Application was submitted on 23 February 2017, and the designation was subsequently received on 28 June 2017 for "treatment of cyclin-dependent kinase-like 5 gene-related early-onset infantile epileptic encephalopathy."

QT Study: On 11 August 2020, agreement was received by the FDA, via email, that the results of the TQTc study could be submitted post- submission. If the TQTc data are unavailable during the review of the NDA, FDA agreed that the TQTc study would become a post-marketing requirement. This study is currently on-going.

Type C meeting 1/8/21

The specific objectives of this meeting are to:

- Obtain FDA agreement that the proposed study as designed could serve as the single efficacy registration study to support the approval of GNX for this indication

- Obtain FDA agreement that the data from subjects with CDD in the recently completed double-blind portion of this Phase 3 Study, with supportive data from the open-label extension of Study 1042-CDD-3001 and the open-label Study 1042-0900, provides an adequate basis for filing and review of the NDA to support approval of GNX in the proposed indication as a treatment for CDD.

These items were restated in the Pre-NDA meeting of 3/11/21 where the Division stated that:

“As stated in our Type C meeting response of 8 January 2021, the presentation of efficacy and safety data in your briefing document appears adequate for the filing of an NDA for review. The

adequacy of these data to support approval of ganaxolone for the proposed indication will be a matter of NDA review."

Mid Cycle Communication 12/10/21

SIGNIFICANT ISSUES

A possible signal for Drug-Induced Liver Injury (DILI) is under review (i.e., the evaluation of the etiology of cholestatic liver disease in Patient (b) (6) [Study 1042-0900]). See also the October 27, 2021, Clinical Information Request, below.

3.3. Foreign Regulatory Actions and Marketing History

GNX has not been approved for marketing in the US or any other country or withdrawn or suspended from marketing in any country

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

4.1.1. Duplicate eDiary entries

There was a late identification of duplicate seizure diary entries resulting from a data transfer error that included data in the 01 September 2020 data snapshot and original CSR . This affected less than 2% of the over 73,000 total diary entries This issue does not raise a major concern on the study integrity as the error was discovered and corrected prior to the database lock. This issue has been considered by the statistical reviewer, see Efficacy Results

4.1.2. eDiary Proxy Data

Proxy Data Entry

When the sponsor submitted requested eDiary information they mentioned that there was the potential for proxy data entry by study staff. The source used to support proxy data entry were provided except for 6 data entries and the process of proxy data entry was documented, the statistical reviewer does not consider it a major concern. See "Statistical Review and Evaluation"[6].

[6] NDA 215904 Xiang Ling, PhD. STATISTICAL REVIEW AND EVALUATION DB1

4.2. Product Quality – Drug Substance, Drug Product Manufacturing, Microbiology Integrated Review.

From DARRTS, REV-QUALITY-25 (Integrated Quality Review), Executive Summary:

The OPQ review team recommends that NDA 215904 for ZTALMY (ganaxolone)oral suspension be APPROVED subject to the post-marketing commitment (PMC) below.

Description: Provide extractable/leachable results to confirm that the container closure system does not adversely impact the drug product per Study Protocol MRP-01-01.

Milestones:

Submission of the interim extractables report, April 20, 2022
Submission of the interim leachable / extractable correlation report, June 29, 2022
Submission of the final PMC report with 6 months leachable data as a Changes Being Effected (CBE-0) supplement, March 31, 2023

The above PMC is necessary as the drug product is an aqueous oral suspension intended for chronic use. Although the applicant indicates that no leachables were found in a simulated leachable study, a formal study under long-term storage conditions was not done. Allowing the study to be performed post-marketing is justified as GNX is intended to treat a serious seizure disorder that is resistant to current antiepileptic drugs. The product will be administered orally, and components of the container closure system comply with regulatory requirements to food packaging. Additionally, results from the applicant's simulated leachable study support a conclusion that the risk to product quality due to leachables is low. Thus, the potential benefit to patients outweighs any potential risk due to product quality

4.3. Clinical Microbiology

See Section 4.2

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical Review is pending at the time of this writing

4.5. Clinical Pharmacology

The Clinical Pharmacology review concluded that GNX must be taken with food[7]. Additional labeling recommendations include drug-drug interaction entries. Four Post-Marketing Requirements are recommended including:

[7]NDA 215904, OCP Review Team, Office of Clinical Pharmacology Integrated Clinical Pharmacology Review.

1. Hepatic Impairment Study
2. Renal Impairment Study
3. Thorough QT (TQT) Study
    a. In an email communication dated 08/11/2020, the Agency agreed with the applicant's plan to submit the clinical study report of the Thorough-QT (TQT) study (1042-TQT-1001 with amendment 2) after filing the NDA. This study is ongoing and once completed, the clinical study report should be submitted.
4. In-vitro DDI study to evaluate DDI potential of M47

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Listing of Clinical Trials

Study Number	abbreviated number	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	study Area	Year	Duration exposure months	Healthy / Patients
1042-GNX.AME-1001	1001		A Phase 1, OL study of the absorption, metabolism, and excretion of [14C]-GNX following a single oral dose in healthy male subjects	Single oral dose 300 mg GNX	GNX 300 mg, radiolabeled	0	8		single oral dose ADME, radiolabeled-male			Healthy lactating female subjects
CA042-9402.01	9402.01		OL, single-dose study of the absorption, metabolism, and elimination of GNX following a high-fat meal	300mg	[14C] GNX with (b) (4) PO	0	6		single dose, metabolism-elimination following high fat			Healthy Subjects
CA042-9404.01	9404.01		OL, single-dose study of the absorption, metabolism, and elimination of GNX following a high-fat meal	300mg	dispersion in yogurt PO	0	6		single dose, metabolism-elimination following high fat			Healthy Subjects
CA042-9405.01	9405.01		OL, single-dose crossover study comparing the bioavailability of 2 formulations of GNX following a high-fat meal	600mg	GNX-β-CD suspension in yogurt or (b) (4) ®, PO	0	6		single dose, food effect, 2 formulations, high fat			Healthy Subjects
CA042-9302.01	9302.01		OL, single-dose, crossover study to compare the PK of 3 formulations of GNX following a high-fat meal	300mg	GNX-β-CD, GNX- (b) (4) or GNX (b) (4) suspension, PO	0	6		single dose, food effect following high fat , single dose			Healthy Subjects
CA042-9301.01	9301.01		OL, rising, single-dose study of the safety, tolerance and PK of GNX following a high-fat meal	50, 150, 300, 450, 600 mg	GNX- (b) (4) suspension	0	15		single dose, food effect following high fat , dose range			Healthy Subjects
CA042-9401.01	9401.01		OL, single-dose, comparison of the effect of food on the PK of GNX following a 10-hour fast, a	300mg	neat drug PO	0	12		single dose, food effect			Healthy Subjects

Study Number	abbreviated number	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	study Area	Year	Duration exposure months	Healthy / Patients
			high- carbohydrate meal, or a high-fat meal									
1042-0700	700	PTSD	POC, 6 Week DB randomized study followed by 6 wk OL RX in adults	400 - 1200mg/day	GNX 200mg capsules BID	53	59		PTSD	2011	3	Patient
1042-PPD-2002	2002	Post partum depression	DB, PBO controlled multiple dose escalation study to evaluate safety PK and efficacy	IV infusion over 60 hours (IV injection 2-12 mg/h; IV bolus 12 mg) IV injection 20 mg/h for 6 hours / 900mg/day	GNX injection / GNX oral Capsule	45	46		PPD	2017	1	Patient
1042-PPD-2003	2003	Post partum depression	Double-blind, PBO-controlled multicenter study to evaluate safety, tolerability, and efficacy of GNX in women with PPD	675 - 1350mg/day	GNX oral capsules at HS or TID	0	84		PPD	2018		Patient
CA042-9501.01	9501.01		A rising dose tolerability and pharmacokinetic crossover study of ganaxolone in young, healthy, male and female volunteers 8m, 9f	300 or 900mg	GNX-β-CD suspension in (b) (4) PO	0	17		PK tolerability			Healthy Subjects
1042-0500	500	infantile spasms	DB, PBO controlled add on, dose escalation, incomplete crossover study to evaluate the safety, tolerability and antiepileptic activity of GNX in IS	3mg/kg to 18mg/kg TID	GNX oral suspension	19	38		Pediatric Epilepsy	2007	0.5	Patient
1042-0501	501	infantile spasms	OL extension of 1042-0500- up to 2 years	3mg/kg to 18mg/kg TID	GNX oral suspension	0	54		**Pediatric Epilepsy**	**2007**	**24**	Patient
1042-0800	800	Fragile X syndrome	POC DB, crossover trial of GNX and PBO	9mg/kg/day up to 36 mg/kg/day to	GNX oral suspension (50mg/ml) TID	30	29		Pediatric Epilepsy	2012	1.3	Patient

Study Number	abbreviated number	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	study Area	Year	Duration exposure months	Healthy / Patients
				max 1800mg/day								
1042-0900	900	PCDH19 & rare genetic	A Phase 2A, OL, proof-of-concept study of GNX in children with PCDH19 female pediatric epilepsy and other rare genetic epilepsies	oral, 900 - 1800mg/day	GNX oral suspension (50 mg/mL), TID or GNX 200mg or 225mg Capsules BID	0	30 (CDD-7)		**Pediatric Epilepsy**	**2015**	**43**	Patient
1042-CDD-3001 (OL)	3001	CDD	A Phase 3, long-term OL phase of study 1042-CDD-3001	GNX oral ,≤ 1800 mg/day, (dosing bases on mg/kg and mg/kg/day)	GNX oral suspension (50 mg/mL)			88	**Pediatric Epilepsy**	**2018**	**17.5**	Patient
1042-CDD-3001	3001	CDD	A Phase 3, double-blind, randomized, PBO-controlled trial of adjunctive GNX treatment in children and young adults with CDD which consists of a 6-week prospective baseline period to collect seizure data, followed by a 17-week double-blind treatment phase, which is then followed by a long-term OL phase	GNX oral ,≤ 1800 mg/day, (dosing bases on mg/kg and mg/kg/day)	GNX oral suspension (50 mg/mL)	51	50		Pediatric Epilepsy	2018	4.25	Patient
CA042-9408.01	9408.01	Refractory partial or generalized seizures	OL, 17-week, flexible escalating dose add on study of the safety , optimal dose and potential efficacy o f GNX (same population)	variable escalating dose to max total of 36mg/kg	GNX beta cyclodextrin suspension	0		45	**Pediatric Epilepsy**	**1996**	**48**	Patient
CA042-9408.01	9408.01	Refractory partial or generalized seizures	OL, 2 month flexible escalating dose add on study of safety tolerability, dose range and efficacy in pediatric or adolescent patients with refractory	variable escalating dose to max total of 36mg/kg	GNX beta cyclodextrin suspension			15	**Pediatric Epilepsy**	**1995**	**24**	Patient

Study Number	abbreviated number	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	study Area	Year	Duration exposure months	Healthy / Patients
			partial or generalized seizures									
1042-C14GNX-lac-1001	1001		A Phase 1, OL study of the excretion of [14C]-GNX into breast milk following a single oral dose in healthy, lactating female subjects	Single oral dose 300 mg GNX	GNX 300 mg, radiolabeled and nonradiolabeled powder	0	5		lactation study-excretion-radiolabeled			Healthy lactating female subjects
CA042-9403.01	9403.01	Healthy subjects	Double-blind, PBO-controlled, single- and 14-day multiple-dose study of the safety, tolerability, and PK of GNX administered following a high fat meal (males)	50, 200, or 500mg QD	GNX-β-CD in yogurt	5	12		Food effect study			Healthy Subjects
CA042-9407.01	9407.01		DB, PBO controlled, rising, single dose study of the safety tolerability and PK of GNX after High fat meal (males)	900, 1200, 1500 mg (15 mg/mL), or 1500 mg (30 mg/mL)	GNX-β-CD complex suspension in (b) (4)	8	16		Food effect study			Healthy Subjects
CA042-9505.01	9505.01		Double-blind, randomized, PBO-controlled, 14-day multiple-dose study of the safety, tolerability, and PK of GNX administered following a high-fat meal	250,500, or 750 mg TID	GNX-β-CD suspension in (b) (4) , PO	12	30		Food effect study			Healthy Subjects
1042-0400	400		Double-blind, single-dose, randomized, PBO-controlled, crossover study of the safety, tolerability, relative bioavailability, and PK of GNX suspension in fasted and fed subjects	200 mg fasted, 400 mg fasted, 400 mg following 50% fat meal	GNX oral suspension (50 mg/mL)	2	6		Food effect study			Healthy Subjects
1042-DDI-1001	1001		A Phase 1 study to assess the effects of itraconazole and rifampin on the PK of GNX in healthy adult subjects	200-600 mg	GNX oral suspension (50 mg/mL)	0	32		DDI			Healthy adult subjects

Study Number	abbreviated number	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	study Area	Year	Duration exposure months	Healthy / Patients
1042-0600	600	Uncontrolled POS	DB, randomized PBO controlled, add on, safety, tolerability, PK, efficacy	200mg to 500mg TID	GNX oral suspension (50mg/ml)	49	98		Adult Epilepsy	2007	3	Patient
1042-0601	601	Uncontrolled POS	OL extension of 1042-0600 up to 2 years	200mg to 500mg TID	GNX oral suspension (50mg/ml)	0	124		**Adult Epilepsy**	**2007**	**24**	Patient
1042-0602	602	Uncontrolled POS	OL extension for patients deriving benefit from 1042-0601	200mg to 500mg TID	GNX oral suspension (50mg/ml)	0	11		**Adult Epilepsy**	**2009**	**24**	Patient
1042-0603	603	Uncontrolled POS- DB	Phase 3, double-blind, randomized, PBO-controlled, add-on, safety, tolerability, PK, and efficacy study of GNX in adults with uncontrolled partial-onset seizures followed by long-term OL treatment	Cohort 1: 1200 mg/day, Cohort 2: 1800 mg/day	GNX capsules (200 mg & 225 mg capsules for Cohort 1 and 225 mg capsules for Cohort 2) dosed BID	Cohort 1: 22, Cohort 2 180	Cohort 1: 24, Cohort 2: 179		Adult Epilepsy	2013	2	Patient
1042-0604	604	drug resistant POS	Second year OL extension study of GNX in subjects with Drug resistant POS	GNX oral 900-1800mg/day	GNX 225mg capsules BID	0	26		**Adult Epilepsy**	**2015**	**17**	Patient
1042-SE-2001	2001	Status epilepticus	P2 CB, Randomized, PBO controlled study to evaluate the safety, tolerability, efficacy and PK of adjunctive IV GNX in patients ≥12 years with SE	GNX IV ≤713 mg/day	GNX IV solution 3mg/ml	0	17		Adult Epilepsy	2018	0.16	Patient
1042-HAP-1001	1001		A randomized, double-blind, PBO- and active-controlled crossover study to evaluate the abuse potential of oral GNX in recreational CNS depressant users	400-2000 mg	GNX oral suspension (50 mg/mL)	0	54		abuse potential study			recreational CNS depressant users
1042-0603	603	OL						331		**2013**	**19**	Patient

5.2. Review Strategy

The strategy for review of efficacy follows the discussion sequency seen in Conclusions on the Substantial Evidence of Effectiveness while the Safety review strategy is provided in Section 8.1, Safety Review Approach.

6. Review of Relevant Individual Trials Used to Support Efficacy

Study 1042-CDD-3001 is the primary clinical study to support the use of GNX for the treatment of CDD. Study 1042-0900 provides supportive efficacy data for this application.

6.1. 1042-CDD-3001:

A Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone Treatment in Children and Young Adults with Cyclin dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) Followed by Long-term Open-label Treatment

6.1.1. Study Design

Overview and Objective

The primary objective of this study is to assess the efficacy of GNX compared with PBO as adjunctive therapy for treatment of primary seizures in children and young adults with genetically confirmed CDD at the end of the 17-week double-blind phase. This was a multicenter conducted globally, with 36 participating sites.

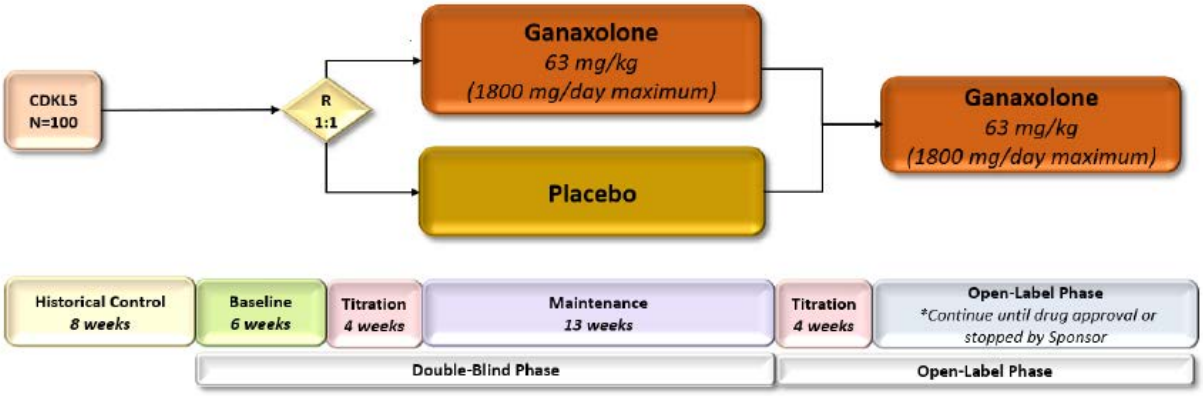
Trial Design

This is a global, double-blind, randomized, PBO-controlled trial of adjunctive GNX treatment in children and young adults with CDD. The trial consists of a 6-week prospective baseline period to collect seizure data, followed by a 17-week double-blind treatment phase, which is then followed by a long-term open-label phase, see Figure 2.

Participants were required to complete a daily seizure calendar noting seizure type and frequency in an eDiary calendar to determine GNX's effect on seizures. In rare cases when an eDiary completion was not feasible, a paper seizure calendar could be used to log in daily seizure type and frequency.

A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained.

Figure 2 1042-CDD-3001 Study Design



Key Inclusion Criteria

1. Molecular confirmation of a pathogenic or likely pathogenic CDKL5 variant, early onset, difficult to control seizures, and neurodevelopmental impairment are required.
2. Male or female subjects aged 2 through 21 years, inclusive.
3. Subject/parent or LAR willing to give written informed consent/assent, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.
4. Failure to control seizures despite appropriate trial of 2 or more ASMs at therapeutic doses
5. Have at least 16 seizures of primary seizure types: bilateral tonic (sustained motor activity greater than or equal to 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic per 28 days in each 1-month period in the 2-month period prior to screening.
6. Subject must be approved to participate by sponsor and/or designee (i.e., Epilepsy Consortium) after review of medical history, genetic testing, seizure classification, and historical seizure calendars.
7. Participants should be on a stable regimen of 0-4 anti-seizure medications (including moderate or strong inducer or inhibitor ASMs, e.g., carbamazepine, phenytoin, etc.) for greater than or equal to 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the double-blind phase. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet did not count towards this limit but were required to be unchanged for 3 months prior to screening.
8. Parent/caregiver is able and willing to maintain an accurate and complete daily electronic seizure calendar for the duration of the study.
9. Able and willing to take investigational product with food 3 times daily. Ganaxolone must be administered with food.
10. Sexually active female of childbearing potential must be using a medically acceptable method of birth control and have a negative quantitative serum β-human chorionic

growth hormone (β-HCG) test collected at the initial screening visit.

Key Exclusion Criteria

1. Previous exposure to GNX
2. West Syndrome with hypsarrhythmia pattern on EEG or seizures predominantly of Infantile Spasm (IS) type; if EEG pattern/seizure type is uncertain, study inclusion should be reviewed and determined by the sponsor/sponsor delegate.
3. Concurrent use of ACTH, prednisone or other glucocorticoid was not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. Moderate or strong inducer or inhibitor AEDs were allowed (e.g., carbamazepine, phenytoin, etc.).
4. Subjects on ACTH, prednisone, or other systemically (non-inhaled) administered steroids should have been off the product greater than 28 days prior to screening. Concomitant PRN topical or intranasal steroids for dermatologic reactions and allergic rhinitis were allowed and did not warrant exclusion from the study.
5. Subjects with a positive result on THC or CBD test (via urine or plasma drug screen) at the screening visit, and a positive result on THC or CBD test (via plasma) at the baseline visit without prescription for Epidiolex (may go by another n
6. ame in countries outside the United States) in epilepsy were excluded from the study. Concomitant Epidiolex (CBD) use was allowed in the double-blind phase provided the subject had been on a stable dose for at least 1 month prior to screening and was expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. THC and/or CBD were allowed in the open-label phase.
7. Changes in ASMs within the last month prior to screening. All ASMs must have been stable in dose for at least 1 month prior to screening unless otherwise noted.
8. Had an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain imaging (MRI).
   Had any disease or condition (medical or surgical; other than CDD) at screening that might have compromised the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, or hepatic systems; or other conditions that might have interfered with the absorption, distribution, metabolism, or excretion of GNX or would have placed the subject at increased risk.
9. An AST (SGOT) or ALT (SGPT) greater than 3 x ULN at study entry. If AST or ALT increased greater than 3 x upper limit of normal (ULN) during the study, subject was followed with weekly laboratory repeat testing and continued in study if levels were trending down. Subject was discontinued if levels did not decline to less than 3 x ULN.
10. Total bilirubin levels greater than ULN at study entry. In cases of documented, stable medical condition (e.g., Gilbert's Syndrome) resulting in levels of total bilirubin greater than ULN, the medical monitor determined if a protocol exception could be made. If total bilirubin increased to 1.5 x ULN or more during study, the subject was discontinued.
11. Subjects with significant renal insufficiency, eGFR < 30 mL/min (calculated using the Cockcroft-Gault formula.
12. Had active suicidal plan/intent or had active suicidal thoughts in the past 6 months or a

suicide attempt in the past 3 years.

Sample Size

There were 101 patients randomized with 95 (94.1%) of patients completing the 17 week double blind phase of the study.

Dosing

Subjects received either GNX or PBO, prescribed in increments of 15 mg/kg/day up to 63 mg/kg/day (maximum 1800 mg/day) as an oral suspension. Subjects weighing less than or equal to 28 kg were dosed on an mg/kg basis, and subjects weighing greater than 28 kg were dosed by mg/day. The dosing regimens during the initial 28-day taper for subjects weighing less than or equal to 28 kg and subjects weighing greater than 28 kg are shown in Table 3 and Table 4, respectively.

Table 3 Oral Suspension (50 mg/mL) Dosing for Subjects Weighing ≤ 28 kg

Dose	Total mg/kg/day	Days
6 mg/kg TID	18	1 - 7
11 mg/kg TID	33	8 - 14
16 mg/kg TID	48	15 - 21
21 mg/kg TID	63	22 - 28

Table 4 Oral Suspension (50 mg/mL) Dosing for Subjects Weighing > 28 kg

Dose	mL per Dose	Total mg/kg/day	Days
150 mg TID	3	450	1 - 7
300 mg TID	6	900	8 - 14
450 mg TID	9	1350	15 - 21
600 mg TID	12	1800	22 - 28

After the initial 28-day taper, dosing was maintained at 21 mg/kg TID (63 mg/kg/day) for the remaining 13 weeks of the double-blind phase of the study and the open-label phase of the study.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency through the end of the 17-week, double-blind treatment phase relative to the 6-week prospective baseline period. The primary seizure types include bilateral tonic (sustained motor activity greater than or equal to 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures or focal to bilateral tonic-clonic.

Key Secondary Efficacy Endpoints

- Number (%) of subjects with a greater than or equal to 50% reduction from baseline in primary seizure frequency.
- Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17-week DB treatment phase.

Additional Secondary Efficacy Endpoints

Seizure Control

- Change baseline in the percentage of seizure-free days during the 17-week DB treatment phase, based on the primary seizure types
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID)

Behavioral/Neuropsychiatric

- Caregiver Global Impression of Change in Attention (CGICA) score
- CGI-C in parent/caregiver identified behavioral target- potential domains include sociability, communication, irritability, and hyperactivity

Statistical Analysis Plan

The baseline, post-baseline, and arithmetic and percent changes from baseline in 28-day seizure frequency will be summarized using descriptive statistics. The difference between the treatment groups in the percent changes will be tested for statistical significance. Since the percent differences are anticipated to display skewness and/or outliers, the test will be performed using the Wilcoxon Rank-Sum statistic using a 2-sided significance level of 0.05.

Three sensitivity analyses of the primary efficacy endpoint will be performed (1) To examine the primary outcome measure when a subject stops recording measurements permanently prior to the end of the 17-week DB phase using the imputation approach outlined in the Statistical Analysis Plan, (2) to explore the possibility that subjects who stop recording seizure counts tend to have higher counts than other subjects, and (3) To examine the effect of GNX compared to PBO among subjects with low Allo-S levels.

All efficacy analyses will be conducted in the ITT population. A supportive analysis of the primary and secondary efficacy endpoints also will be conducted in the PP population.

The estimand that is most clinically relevant as well as estimable in a manner that protects the integrity of randomization is the outcome measure (e.g., the percent change in 28-day seizure frequency), where ALL randomized subjects would be included in this analysis throughout the study period. Hence, all available data will be used, even if they were collected after the subject stopped taking study medication, regardless of whether the subject took rescue medication.

For the analyses of seizures, the baseline phase consists of 6 weeks before the first day of

treatment and the DB phase starts the day following the first day of DB treatment until the final visit for subjects who do not enter the OLE and up to the day before the first dose of OLE treatment for those who do. The first day of treatment is not in either phase since the seizures could occur both before and after the first treatment.

Tests of significance between the 2 treatment groups will be performed for the primary endpoint with a 2-sided significance level of 0.05.

Protocol Amendments

There were two protocol versions following the original protocol 1042-CDD-3001. The changes up to final Protocol Amendment 2.0 of 5/26/21 did not change the primary efficacy assessment.

6.1.2. Study Results

Compliance with Good Clinical Practices

At all times, the clinical monitor ensured they were performing remote monitoring/target source data reviews in accordance with applicable national laws and regulations and/or temporary national emergency measures and regulations and GCP.

Financial Disclosure

No conflicts of interest identified, see Section 13.2 Financial Disclosure

Patient Disposition

Subject disposition is summarized in Table 5. Of 101 subjects randomized, 95 (94.1%) completed the 17-week double-blind phase; 6 (5.9%) subjects discontinued from the study. Discontinuations from study were due to adverse effects (AEs) (1 [2.0%] subject in the GNX group, 4 [7.8%] subjects in the PBO group) and withdrawal by subject or parent/legally appointed representative (LAR) (1 [2.0%] subject in the GNX group). Additionally, 1 subject in the GNX group discontinued study drug due to an AE but continued in the study until the end of the double-blind phase (Table 14.1.1). At time of database lock for the primary clinical study report (CSR), 89 subjects continued in the open-label phase.

Table 5 Subject Disposition and Reason for Study Discontinuation (17-week Double-blind Phase)[8]

	Placebo n (%)	Ganaxolone n (%)	Total n (%)
Category			
Subjects screened			114

[8] Applicant Clinical Study Report: 1042-CDD-3001, Table 4, page 31

Not randomized[a]			13 (11.4)
Screen failures[a]			13 (11.4)
Non-screen failures[a]			0
Randomized[a]	51	50	101 (88.6)
Safety/ITT Population[b,c]	51 (100)	50 (100)	101 (100)
PP Population[b,d]	48 (94.1)	48 (96.0)	96 (95.0)
Subjects who Completed 17-week DB Phase[e]	47 (92.2)	48 (96.0)	95 (94.1)
Subjects who Completed 17-week DB Phase but Stopped Taking Study Drug Before the Ende	0	3 (6.0)	3 (3.0)
Reason for Discontinuation			
Adverse event	4 (7.8)	1 (2.0)	5 (5.0)
Lost to follow-up	0	0	0
Lack of efficacy	0	0	0
Physician decision	0	0	0
Withdrawal by subject or parent/LAR	0	1 (2.0)	1 (1.0)
Protocol violation/protocol deviation	0	0	0
Death	0	0	0
Sponsor decision	0	0	0
Other	0	0	0

ITT = Intent-to-Treat; PP = Per Protocol; DB = double-blind; LAR = Legally Authorized Representative.
[a] Percentages are based on screened subjects.
[b] Percentages are based on randomized subjects.
[c] The safety and intention-to-treat populations include all randomized subjects who received at least 1 dose of study drug
[d] The per protocol (PP) population includes ITT subjects who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and had no major protocol violations.
[e] Percentages are based on safety population.

Reviewer Comment: The ds.xpt dataset was examined to check Applicant's Table 4. The analysis using the ds dataset did not allow assessment of the cause of discontinuation. However, the numbers of patients who were screened, randomized and completed as well as the number of patients who discontinued in each treatment arm was confirmed.

Protocol Violations/Deviations

No subjects were discontinued due to a protocol deviation. Protocol deviations occurred in the following categories: procedures/tests, ICF issues, laboratory, visit schedule, inclusion/exclusion, study drug, and concomitant medications.

Table 6 Summary of Protocol Deviations (17-Week Double-Blind Phase, Safety Population), Pre Treatment Interval (Applicant Study 1042-CDD-3001,Table 14.1.8.1)

Category	Placebo (N=51)		Ganaxolone (N=50)		Total (N=101)	
	n	%	n	%	n	%
Pre-treatment	42	(82.4)	41	(82.0)	83	(82.2)
Procedures / Tests	29	(56.9)	28	(56.0)	57	(56.4)
ICF Issues	7	(13.7)	10	(20.0)	17	(16.8)
Laboratory	7	(13.7)	6	(12.0)	13	(12.9)
Visit Schedule	5	(9.8)	8	(16.0)	13	(12.9)
Inclusion / Exclusion	4	(7.8)	6	(12.0)	10	(9.9)
Procedures/Test	3	(5.9)	5	(10.0)	8	(7.9)
Study Drug	1	(2.0)	3	(6.0)	4	(4.0)
CCMEDS	1	(2.0)		0	1	(1.0)
Other	1	(2.0)		0	1	(1.0)

Table 7 Summary of Protocol Deviations (17-Week Double-Blind Phase, Safety Population), DB Period, on Treatment (Applicant Study 1042-CDD-3001,Table 14.1.8.1)

Category	Placebo (N=51)		Ganaxolone (N=50)		Total (N=101)	
	N	%	N	%	N	%
On-treatment (DB)	45	(88.2)	46	(92.0)	91	(90.1)
Procedures / Tests	29	(56.9)	26	(52.0)	55	(54.5)
Visit Schedule	18	(35.3)	16	(32.0)	34	(33.7)

Category	Placebo (N=51)		Ganaxolone (N=50)		Total (N=101)	
	N	%	N	%	N	%
Laboratory	12	(23.5)	14	(28.0)	26	(25.7)
Study Drug	12	(23.5)	7	(14.0)	19	(18.8)
Procedures/Test	5	(9.8)	7	(14.0)	12	(11.9)
Other	4	(7.8)	4	(8.0)	8	(7.9)
ICF Issues	5	(9.8)	2	(4.0)	7	(6.9)
CCMEDS	1	(2.0)	2	(4.0)	3	(3.0)

Reviewer Comment: Examination of the categories of protocol deviation that occurred during the double-blind treatment period reveal the distribution of deviations between treatment arms is generally balanced. There is no evidence of a structural bias in deviations toward the GNX or PBO arm.

Tables of Demographic Characteristics for Study 1042-CDD-3001

Demographic characteristics are presented for subjects in the safety population Table 8 through Table 14.[9]

Table 8 Patient Population by Treatment

Actual Treatment for Period 01	Count	% of Total
GNX	50	49.5%
Placebo	51	50.5%
All	101	100.0%

Table 9 Patient Population by Age

		Actual Treatment for Period 01		
		GNX	Placebo	All
Age	N	50	51	101
	Mean	6.78	7.73	7.26
	Std Dev	4.70	4.38	4.55
	Min	2	2	2
	Quantiles25	3	4	3
	Median	5	7	6
	Quantiles75	10	11	11
	Max	19	19	19

Table 10 Patient Population by Age Group

	Actual Treatment for Period 01					
	GNX		Placebo			
Age Group	Count	Column %	Count	Column %	Count	% of Total
0< Age <=2	6	12.0%	5	9.8%	11	10.89%
2 < Age <=5	23	46.0%	16	31.4%	39	38.61%
5< Age <=10	10	20.0%	16	31.4%	26	25.74%
10< Age	11	22.0%	14	27.5%	25	24.75%
All	50	100.0%	51	100.0%	101	100.00%

Table 11 Patient Population by Sex (*CDD is linked to the X chromosome and affects the female gender four times more often than men)*[10]

	Actual Treatment for Period 01					
	GNX		Placebo			
Sex	Count	Column %	Count	Column %	Count	% of Total
F	39	78.0%	41	80.4%	80	79.21%
M	11	22.0%	10	19.6%	21	20.79%

[9] Demographics Tables Created using JMP Clinical "Demographics Distribution" Report, derived from Study 1042-CDD-3001 Safety Set.

[10] M. Jakimiec, J. Paprocka, and R. Smigiel, "Cdkl5 Deficiency Disorder-a Complex Epileptic Encephalopathy," *Brain Sciences* 10, no. 2 (Feb 2020), https://dx.doi.org/10.3390/brainsci10020107.

	Actual Treatment for Period 01					
	GNX		Placebo			
Sex	Count	Column %	Count	Column %	Count	% of Total
All	50	100.0%	51	100.0%	101	100.00%

Table 12 Patient Population by Race

	Actual Treatment for Period 01					
	GNX		Placebo			
Race	Count	Column %	Count	Column %	Count	% of Total
ASIAN	2	4.0%	3	5.9%	5	4.95%
WHITE	46	92.0%	47	92.2%	93	92.08%
OTHER	2	4.0%	1	2.0%	3	2.97%
All	50	100.0%	51	100.0%	101	100.00%

Table 13 Patient Population by Ethnicity

	Actual Treatment for Period 01					
	GNX		Placebo			
Ethnicity	Count	Column %	Count	Column %	Count	% of Total
HISPANIC OR LATINO	4	8.0%	6	11.8%	10	9.90%
NOT HISPANIC OR LATINO	44	88.0%	43	84.3%	87	86.14%
NOT REPORTED	1	2.0%	1	2.0%	2	1.98%
UNKNOWN	1	2.0%	0	0.0%	1	0.99%
Missing	0	0.0%	1	2.0%	1	0.99%
All	50	100.0%	51	100.0%	101	100.00%

Table 14 Patient Population by Country and Treatment Arm

	GNX		PBO	
COUNTRY	N Patients	% GNX Patients	N Patients	% PBO Patients
USA	18	36	24	47
ITA	9	18	6	12
RUS	7	14	7	14
POL	5	10	5	10
AUS	4	8	2	4
GBR	4	8	3	6
FRA	3	6	3	6
ISR	0	0	1	2

Reviewer Comment: The age distribution by subgroups 2yr less than Age less than or equal to 5yr (n = 39) and 5yr less than Age less than or equal to 10yr (n= 26) has some imbalance between treatment arm with no greater than an 11.4% difference between arms. This is explained by the small sample size. The overall small study sample size does not provide for a stratification by age subgroup. This difference between treatment arms is not likely to impact the outcome. Examination of distribution by sex does not show an imbalance across treatment arms but there is a notable imbalance between male and female participants. This is due to the

predominance of female patients in the affected population.

Other Baseline Characteristics

Concomitant AEDs during DB Treatment Period

Table 15 Proportion of Patients on 1 or more AEDs by Treatment Arm

Treatment Arm	# Patients	% Patients
GNX	45	90
Placebo	43	84

Table 16 Concomitant AED Frequency by Treatment Arm

	GNX, n= 50		PBO, n= 51	
# AEDs	# Patients	% Patients	# Patients	% Patients
1	13	26	10	20
2	18	36	18	35
3	9	18	13	25
4	5	10	2	4

Table 17 Frequency of Concomitant AEDs by Treatment Arm

GNX			PBO	
Standardized Medication Name	# Patients on AED	% Patients	# Patients on AED	% Patients
VALPROATE SEMISODIUM*	15	30	14	27
LEVETIRACETAM*	12	24	8	16
CLOBAZAM*	10	20	12	24
VIGABATRIN*	8	16	10	20
CLONAZEPAM	6	12	4	8
TOPIRAMATE	6	12	7	14
ZONISAMIDE	6	12	6	12
RUFINAMIDE	5	10	5	10
LAMOTRIGINE†	3	6	6	12
OXCARBAZEPINE†	3	6	0	0
PERAMPANEL	3	6	3	6
PHENOBARBITAL	3	6	3	6
GABAPENTIN	2	4	1	2
MIDAZOLAM HYDROCHLORIDE	2	4	1	2
NITRAZEPAM	2	4	2	4
BRIVARACETAM	1	2	0	0
CANNABIDIOL	1	2	1	2
CARBAMAZEPINE	1	2	1	2
DIAZEPAM	1	2	0	0
ETHOSUXIMIDE	1	2	0	0
FELBAMATE	1	2	3	6
IMMUNOGLOBULINS NOS	1	2	0	0
LACOSAMIDE	1	2	3	6

GNX			PBO	
Standardized Medication Name	**# Patients on AED**	**% Patients**	**# Patients on AED**	**% Patients**
LORAZEPAM	1	2	0	0
PYRIDOXINE	1	2	0	0
PHENYTOIN	0	0	2	4
SULTIAME	0	0	1	2
*Four most frequent AEDs in both GNX and PBO treatment arms †Greater than 2% difference in frequency between arms, LTG > in PBO, OXC > in GNX.				

Reviewer comment: The proportion of patients in each treatment arm on 1 or more AEDs is similar, see Table 15. The distribution of patients by number of concomitant AEDs is similar between treatment arms, see Table 16 . The proportion of patients on individual AEDs was examined. In both the GNX and PBO treatment arms the 4 AEDs with the largest proportion of patients were valproate semisodium, levetiracetam, clobazam, and vigabatrin, see Table 17. From among all remaining ASMs, there were two that had a greater than 2% difference between treatment arms; these were lamotrigine and oxcarbazepine. Lamotrigine had a higher frequency of use in the PBO arm with a 6% frequency in the GNX arm compared to 12% in the PBO arm while oxcarbazepine had a 6% frequency in the GNX arm, and none was used in the PBO arm. Overall, there was no notable difference in the concomitant ASMs between treatment arms.

Treatment Compliance

Treatment compliance is evaluated by examining the days dosed in the adexsum.xpt dataset. The mean, and median days dosed in the GNX treatment arm were 93.7% and 99.2% respectively while the mean and median days dosed in the PBO treatment arm were 93.7 and 100% respectively, see Table 18. There was no difference in study drug dosing by treatment arm.

Table 18 Percent of Days Dosed with Study Drug by Treatment Arm

Treatment Arm	# Patients	Mean % days dosed (AVAL)	Std Dev (AVAL)	Min (AVAL)	Median % days dosed (AVAL)
GNX	50	93.7	14.7	30.3	99.2
Placebo	51	93.7	14.2	33.7	100.0

The frequency of rescue medication use was examined in the cm.xpt dataset. There were 23 (46%) patients in the GNX treatment arm and 20 (39%) patients in the PBO treatment arm that received rescue medication intervention. The mean and median number of rescue medication interventions in the GNX treatment arm were 13.9 and 4 respectively while in the PBO treatment arm the mean and median number of rescue medication interventions were 11.3 and 5 respectively. Overall, there was no notable difference in the proportion of patients that received rescue medications across the treatment arms, see Table 19.

Rescue Medication Treatment

The frequency of rescue medication treatment in individual patients in the GNX and PBO treatment arms is presented in the histogram below, Figure 3. There are several patients in the GNX treatment arm that received higher frequencies of rescue medication than patients in the PBO treatment arm. This trend is examined further by creating group subsets of rescue medication treatment by treatment frequency. Those receiving greater than or equal to 10 instances of rescue medication treatment are examined in comparison to the subset of patients that received fewer than 10 instances of rescue medication treatment, see Table 20 and Table 21. Among patients that received greater than or equal to 10 instances of rescue medication treatment there was an excess of instances in the GNX treatment arm over the PBO treatment arm with 270 instances occurring from among 7 patients in the GNX treatment arm and 166 instances from among 5 patients in the PBO treatment arm. These frequencies are examined by patient age and Allo-s levels. The mean and median age of patients in the GNX treatment arm are 10.7 years and 14 years respectively with mean and median Allo-s levels of 3.0ng/ml and 0.74ng/ml respectively. In the PBO treatment arm the mean and median age were 4.1 years and 5.0 years respectively with a mean and median Allo-s levels of 0.8 and 0.56ng/ml respectively. The increased frequency of rescue medication use in the GNX treatment arm is associated with an older age. The higher mean Allo-s level within the GNX treatment group is likely driven by outlier patients in light of the median value of 0.74ng/ml that is similar to the median value of the PBO group.

Among patients that received less than 10 instances of rescue medication treatment, the proportion of patients in the GNX and PBO treatment arms and mean and median rescue instances were similar, see Table 21. The mean and median age of patients in the treatment arms and mean Allo-S levels were also similar. The median Allo-S level in the PBO treatment arm was approximately twice that in the GNX treatment arm. However, in light of the overall similarity of rescue frequencies in the two arms, interpretation of the difference in Allo-S levels is uncertain.

Table 19 Rescue Incidents by Treatment Arm, Mean, SD, Median

Treatment Arm	# Patients with Rescue Entry	% of Patients with Rescue Requirement	Mean (# Rescue Incidents)	Std Dev (# Rescue Incidents)	Median (# Rescue Incidents)	
GNX	23	46	13.9	22	4	
Placebo	20	39	11.3	19	5	

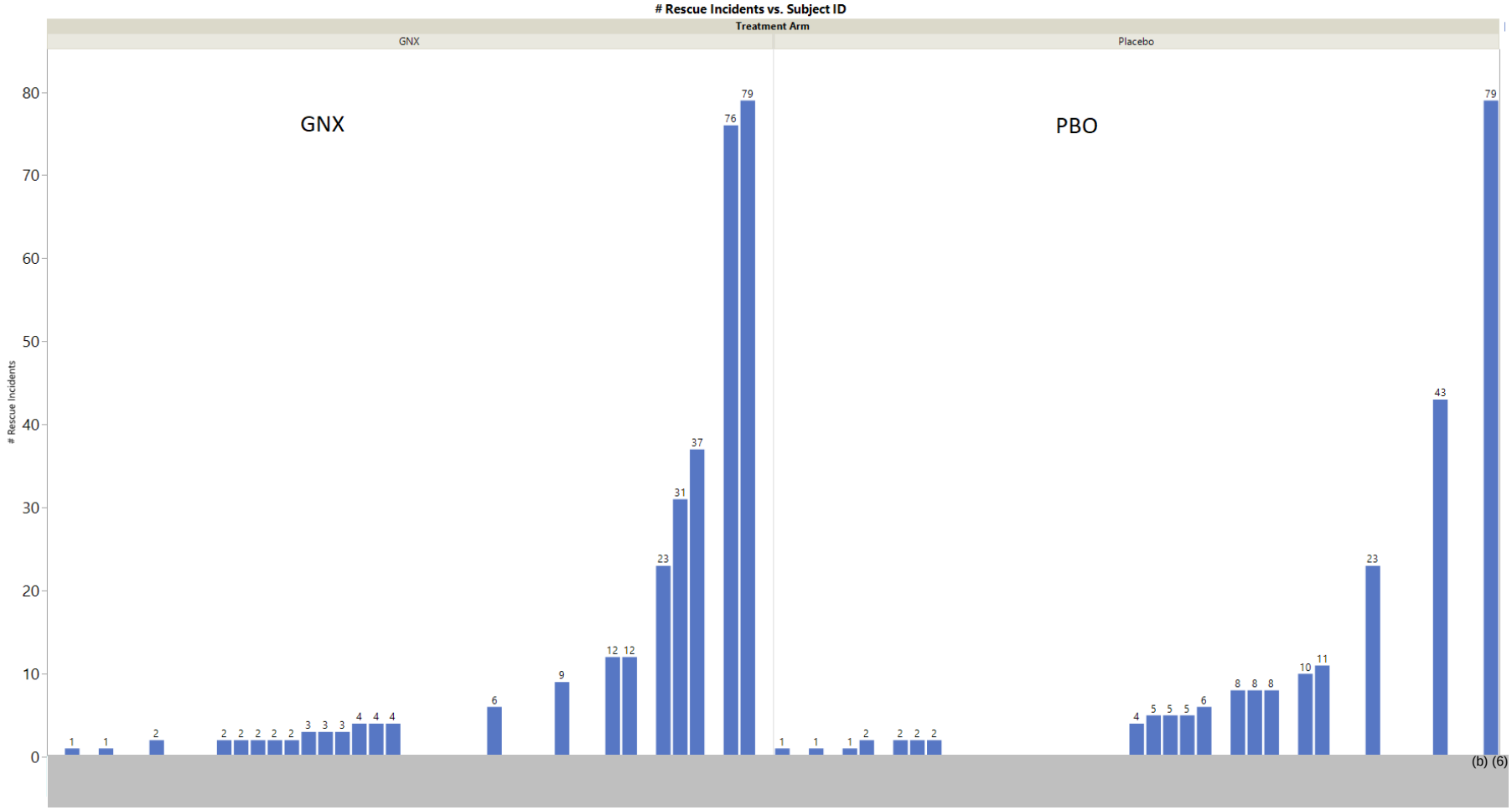
Table 20 Patients with ≥10 instances of Rescue Medication Treatment by Age and Allo-s Level

≥10	# Patients	% patients	Mean Rescue instances	Median Rescue Instances	Rescue Instances	Mean (AGE)	Median (AGE)	Mean (ALLO) ng/ml	Median (ALLO) ng/ml
GNX	7	14	38.6	31	270	10.7	14	3.0	0.74
PBO	5	9.8	33.2	23	166	4.1	5	0.8	0.56

Table 21 Patients with < 10 instances of Rescue Medication Treatment by Age and Allo-s Level

< 10	# Patients	% Patients	Mean Rescue instances	Median Rescue Instances	Rescue Instances	Mean (AGE)	Median (AGE)	Mean (ALLO) ng/ml	Median (ALLO) ng/ml
GNX	16	32	3.1	2.5	50	6.6	5	1.7	1.12
PBO	15	29.4	4.0	4.0	60	7.6	7	2.6	2.04

Figure 3 Study 3001 Frequency of Rescue Incidents by Patient ID and Treatment Arm



Reviewer Comment: An observation from pivotal Study 3001 not in alignment with GNX efficacy for CDD treatment was an excess of GNX patients over PBO treated patients who had high frequency rescue medication treatment. In those patients with ≥ 10 instances of rescue medication treatment, there were 7 in the GNX treatment arm and 5 in the PBO arm with 270 and 166 total instances of rescue treatment respectively. Among those with less than 10 instances of rescue treatment in the GNX and PBO treatment arms, there were 16 patients with 50 instances of rescue treatment and 15 patients with 60 instances of rescue treatment in the GNX and PBO arms respectively. From among the high frequency rescue group in the GNX treatment arm, there were two patients with very high frequency rescue, one each with 76 and 79 instances. If there was one less outlier, the overall use of high frequency and total rescue use would be near evenly divided between GNX and PBO arms. The small difference between arms in number of patients that had entries of rescue medication use, including the high frequency use subset, is likely due to chance but is also divergent from expectations of the expected GNX treatment benefit.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the percentage change from baseline in 28-day major motor seizure frequency during the 17-week double-blind treatment phase. At the end of the 17-week double-blind phase, there was a statistically significant difference in the median percent change from baseline in seizure frequency (-30.7% for subjects in the GNX group, -6.9% for subjects in the PBO group, Wilcoxon Test p = 0.0036) between treatment groups, see Table 22.

Table 22 Study 3001, DB Treatment Interval, Summary of 28 Day Major Motor Seizure Frequency, Percent Change from Baseline†

Study 3001, 17-week Double-blind Phase, ITT Population, Percent Change from Baseline		
	PBO (n=51)	GNX (n=49)
Mean (SD)	64.62 (272.43)	-13.99 (64.53)
Median (95% Distribution-Free CI)	**-6.90 (-16.47, 15.34)**	**-30.66 (-35.94, -11.98)**
Q1, Q3	-24.13, 39.66	-49.50, -1.85
Min, Max	-89.7, 1796.9	-96.2, 215.4
Hodges-Lehmann Estimate of Location Shift (95% CI)[a]	-27.08 (-47.92, -9.55)	
Wilcoxon Test p-value	**0.0036**	

[a] An estimate of how far the responses in the GNX group are shifted from the PBO group.
† Shaded cells confirmed by statistical reviewer, taken from STATISTICAL REVIEW AND EVALUATION, Table 3, page 10.

The statistical reviewer noted that an interim analysis was performed for 52 subjects who completed the 17-week double blind phase of Study 3001 where the p value for the primary endpoint was found to be 0.003. This did not cross the O'Brien-Fleming boundary and the study continued to conduct the final analysis.

There was a late identification of duplicate seizure diary entries resulting from a data transfer

error that included data in the 01 September 2020 data snapshot and original CSR . This affected less than 2% of the over 73,000 total diary entries. The duplicate records were excluded in the updated data snapshot on 19 May 2021 data. The removal of these duplicate records resulted in minor differences between analysis results based on the 2 data snapshots. The previously reported analysis using the 01 September 2020 snapshot showed a similar effect size and p value, where the seizure reduction from baseline was 32.2% for GNX and 4.0% for PBO, with a p-value of 0.002.

The statistical reviewer also performed a sensitivity analysis of the 28-day seizure frequency for handling study dropouts. The amount of missing data was small. The statistical reviewer conducted a worst-case type of analysis in which the worst observed data (largest percent change from baseline) was used for subjects in the GNX group who dropped out during the treatment phase. The statistical significance of the GNX treatment effect on seizure frequency was still maintained (p-value=0.0158).

Gender, Race, Age, and Geographic Region

The statistical reviewer examined subgroup analyses for the primary endpoint and noted that subgroups of race were not included as majority of the subjects were White and the number of subjects of other races was limited.

There appeared to have a treatment effect on seizure frequency favoring GNX across the subgroups of age, gender, and geographical regions, see Table 23.

Table 23 Summary of Percent Change in Seizure Frequency by Demographics Subgroups

	Placebo		Ganaxolone		Ganaxolone vs. Placebo	
	N	Median % change	N	Median % change	Treatment difference	95% CI
Age						
<7 years	22	-9.0%	29	-30.7%	-27.0%	(-63.2, 4.4)
>=7 years	29	-1.5%	20	-30.1%	-31.1%	(-56.2, -9.4)
Gender						
Male	10	7.4%	11	-32.0%	-42.1%	(-95.2, -8.4)
Female	41	-10.2%	38	-27.5%	-22.2%	(-48.4, -1.4)
Geographical Region						
USA	24	2.2%	17	-32.0%	-34.2%	(-65.1, -7.2)
Rest of World	27	-11.6%	32	-27.5%	-19.7%	(-53.1, 4.5)

Reviewer Comment: Examination of the percent change in seizure frequency by demographic subgroups reveals a more prominent seizure reduction in males than females. However, the sample size of the male population is notably smaller than the population of females. This female predominance is driven by the x-linked characteristic of CDD. There was also a more prominent seizure reduction in the USA compared to the rest of the World. The US GNX

treatment arm was smaller than the ROW. This may have contributed to the imbalance in the treatment difference.

Data Quality and Integrity

OSI report pending

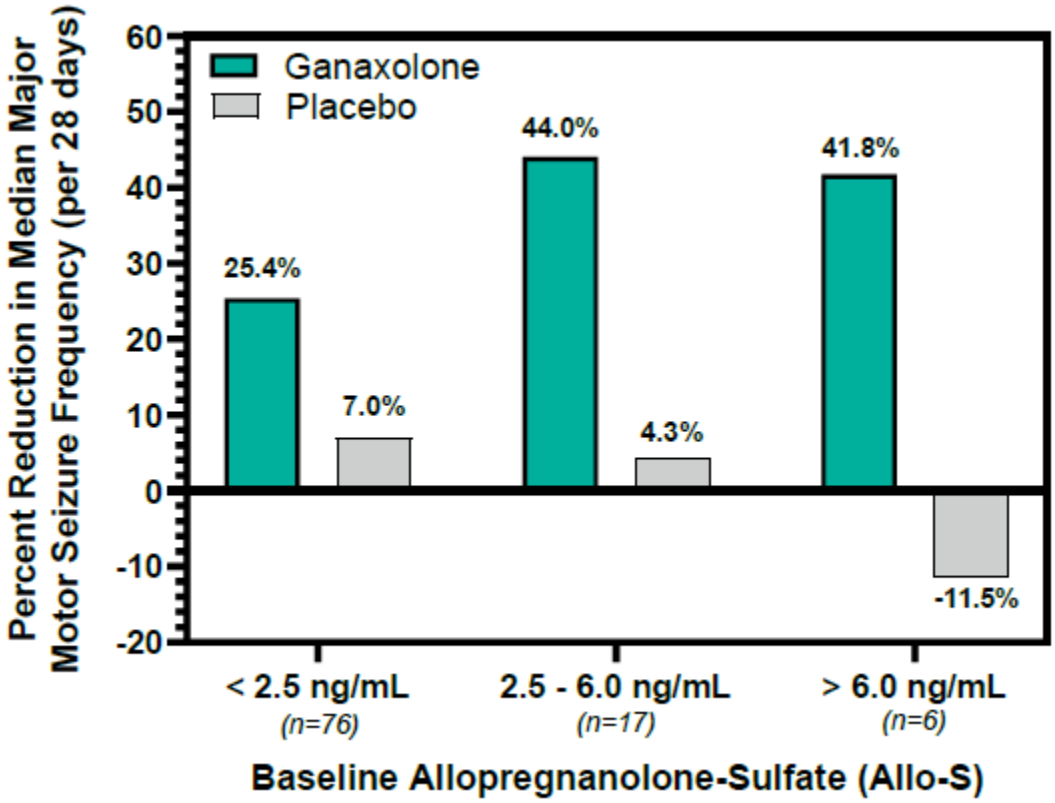
Efficacy Results – Secondary and other relevant endpoints

Applicant Analysis- Baseline Allo-S Level

Reduction in 28-day major motor seizure frequency by patient baseline major motor seizure frequency.

The Applicant reports that the Baseline Allopregnanolone-sulfate (Allo-S) Subgroup Preliminary data from the open-label Phase 2 study 1042-0900 suggested that reduced baseline Allo-S concentrations may predict a better seizure frequency reduction in those patients. To evaluate the effect of baseline Allo-S concentrations in patients with CDD, GNX- and PBO-treated patients were stratified into various Allo-S concentrations that were selected based on previous data from a different patient population. GNX patients experienced a directional improvement in major motor seizure frequency reduction in all Allo-S subgroups relative to PBO and the magnitude of effect numerically increased in patients with Allo-S concentrations > 2.5 ng/mL. These data suggest that patients treated with ganaxolone demonstrated an improvement relative to placebo across all Allo-S subgroups analyzed and there are no meaningful differences between the GNX effect across all Allo-S subgroups, see Figure 4.

Figure 4 Reduction in 28-day major motor seizure frequency by patient baseline major motor seizure frequency by Baseline Allopregnanolone-sulfate (Allo-S) Subgroup.[11]



Applicant Analysis, Influence of Baseline Allopregnanolone Sulfate (Allo-S) Level: Subgroups with Low, Mid and High Allo-S Levels

- For subjects with low Allo-S levels (39 subjects in the GNX group, 37 subjects in the PBO group), the median percent change from baseline in seizure frequency was -25.37% for subjects in the GNX group and -9.53% for subjects in the PBO group (p = 0.0706) with a median shift from the PBO group to the GNX group of -20.99%, indicating improvement in the GNX group compared to the PBO group.

- For subjects with mid Allo-S levels (5 subjects in the GNX group, 12 subjects in the PBO group), the median percent change from baseline in seizure frequency was -40.89% for subjects in the GNX group and -3.53% for subjects in the PBO group, with a median shift from the PBO group to the GNX group of -47.97%, indicating improvement in the GNX group compared to the PBO group.

- For subjects with high Allo-S levels (4 subjects in the GNX group, 2 subjects in the PBO group), the median percent change from baseline in seizure frequency was -39.03% for subjects in the GNX group and 8.90% for subjects in the PBO group, with a median shift

[11] IND 044020- 11/16/2020 Type C Meeting Request and Briefing Document Page 31, Figure 8

from the PBO group to the GNX group of -47.93%, indicating improvement in the GNX group compared to the PBO group.

Reviewer Comment: The Applicant's analysis of GNX efficacy across the low, mid and high range of baseline Allo-S levels does not identify a relationship between baseline Allo-S level and efficacy of GNX treatment.

Responder Analysis (Applicant's Analysis)

The 50% responder rate analysis did not identify a significant difference between the GNX and PBO treatment arms. The number (%) of subjects with a greater than or equal to 50% reduction from baseline in major motor seizure frequency (response rate) numerically favored the GNX group (12 [24.5%] subjects in the GNX group, 5 [9.8%] subjects in the PBO group; p = 0.0643). There was significance seen in the 25% responder rate where 57.1% of patients in the GNX treatment arm and 23.5% of patients in the PBO treatment arm met the ≥25% response threshold, p = 0.001 based on Fisher Exact test.

Reviewer Comment: The 50% responder rate is not in alignment with the primary endpoint of the median percent change in 28-day major motor seizure from baseline in seizure frequency during the 17-week double-blind treatment phase. There is support for a biologic effect on seizures in CDD based on the observation of a positive 25% responder.

CGI-I (Parent/Caregiver) scores (Applicant's Analysis)

The CGI-I (Parent/Caregiver) scores numerically favored the GNX group (p = 0.0971). Higher proportions of parents/caregivers of subjects in the GNX group rated the response to treatment at the end of the 17-week double blind period as "Minimally Improved" or "Much Improved" compared to parents/caregivers of subjects in the PBO group. In addition, a lower proportion of parents/caregivers of subjects in the GNX group rated the response to treatment as "No Change" compared to parents/caregivers of subjects in the PBO group, Table 24.

CGI-I (Clinician) scores (Applicant's Analysis)

There was no statistically significant difference for the CGI-I (Clinician) scores between the GNX and PBO groups (p = 0.3518). Higher proportions of clinicians of subjects in the GNX group rated the response to treatment at the end of the 17-week double blind period as "Minimally Improved" compared to clinicians of subjects in the PBO group. In addition, a lower proportion of clinicians of subjects in the GNX group rated the response to treatment as "No Change" compared to clinicians of subjects in the PBO group, Table 24.

Table 24 Response Rate and CGI-I Scores at End of 17-week Double-blind Treatment Phase (ITT Population)[12]

Variable	Placebo	Ganaxolone
50% Response Rate, N	51	49
n (%)	5 (9.8)	12 (24.5)
Difference (95% CI)		14.7 (-4.7, 33.8)
p-value[a]		0.0643
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[b]	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[b]		0.3518

[a] Response was defined as at least 50% reduction from baseline in 28 day Seizure Major Motor Seizures Frequency. P value was based on Fisher's Exact test.

[b] CGI-I analysis was based on ordinal logistic regression model adjusted for treatment group as a fixed factor. The analysis is based on the CGI-I values reported at the last scheduled visit in the 17-weeks Double-Blind treatment phase.

Seizure counts were based on the sum of the individual seizures, the countable seizures, and the clusters with uncountable seizures (each cluster with uncountable seizures counts as 1 seizure). Within the baseline and post baseline intervals, 28 day seizure frequency was calculated as the total number of seizures in the interval divided by the number of days with available seizure data in the interval, multiplied by 28.

The types included bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic clonic.

The baseline interval consisted of the 6 weeks prior to the first dose.
Duplicate seizure diary entries were excluded from this analysis.

Reviewer Comment: The CGI-I patient/caregiver and clinician responses are not robustly

[12] 1042-CDD-3001 Study Report Page 46, Table 9

positive; however, the results are in alignment with a treatment benefit due to GNX treatment.

Dose/Dose Response

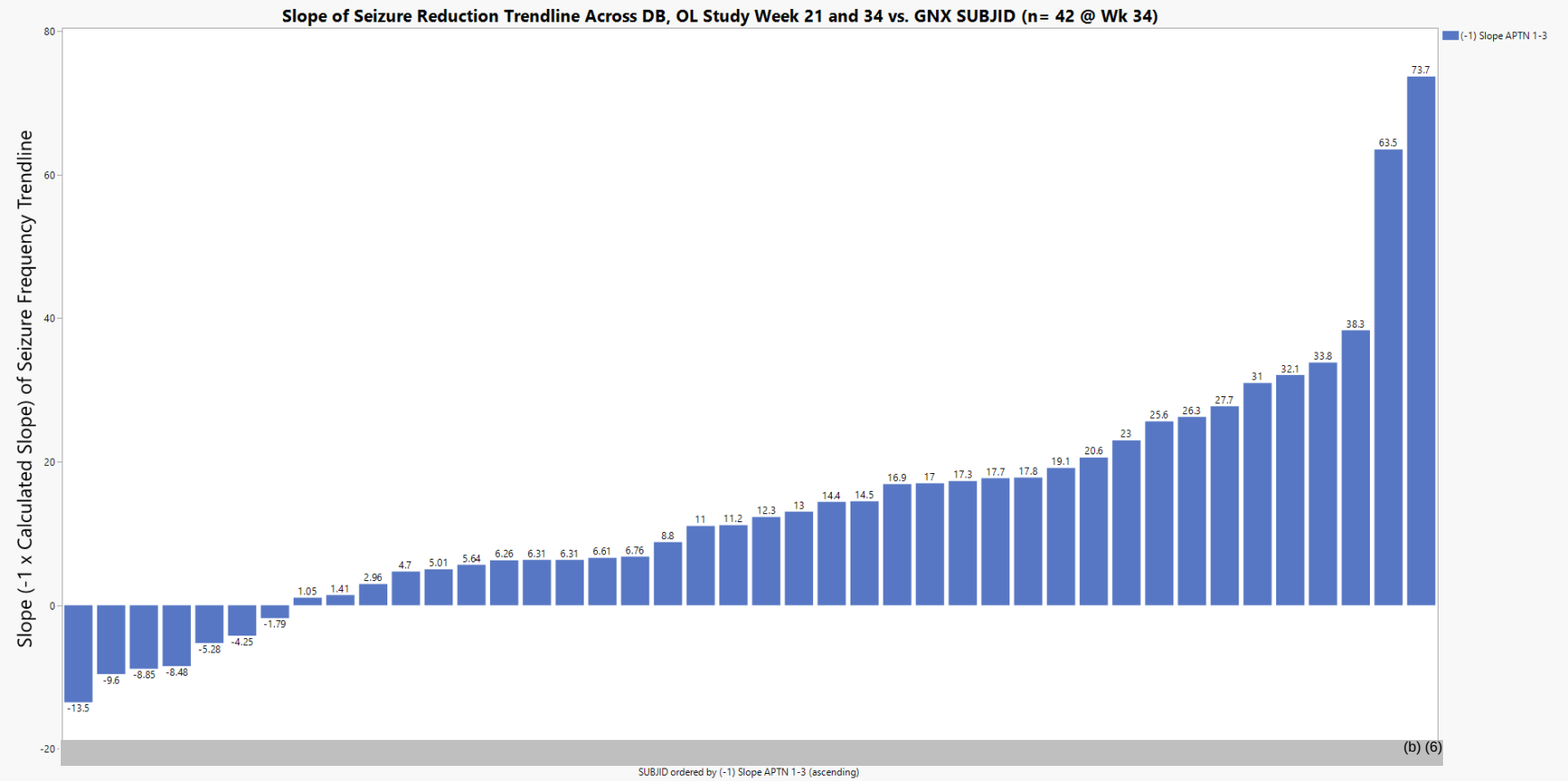
Clin-Pharm Review Pending at the time of this writing

Durability of Response

The durability of response was examined by analysis of the percent change in seizure frequency from baseline to the double-blind treatment interval, as well as OL Study Week 21 and week 34. A trendline was generated for each of 43 patients treated with GNX in the double-blind interval who have continued seizure frequency data to week 34 in the open label treatment period. This trendline incorporated the percent change measurements identified at the three 28-day seizure frequency calculation intervals (DB, wk 21, wk 34). The slopes of these trendlines may be considered a representation of seizure frequency trend, where a positive slope indicates an increasing frequency trend compared to baseline and a zero or negative slope is associated with a sustained or continued improvement in seizure frequency compared to baseline frequency. This analysis is shown in Figure 5 where an improving trend in percent change in baseline is displayed as a positive result (multiply raw value by (-1) for ease of visualization, although an increase in a negative percent change from baseline has a negative slope. It is seen that 35 of 42 patients (83%) have a trendline that is consistent with sustained or improving seizure control compared to baseline.

Reviewer Comment: The analysis of seizure frequency counts from the double blind into the open label treatment period are consistent with durability of treatment response.

Figure 5 Slope (multiply by -1) of Seizure Reduction Trendline @ DB and OL Study Week 21 and 34 vs. GNX SUBJID (n= 42 @ Wk 34)



7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Study 1042-0900

As discussed in Section 6 above the efficacy evidence supporting the use of GNX for the adjunctive treatment of CDD is based on data from the pivotal Study 1042-CDD-3001 (N = 101). A second, open label, proof of concept study, 1042-0900, that included 7 subjects with CDD will be examined to determine if the results are in alignment with the pivotal study.

Study Title: A 26-Week Multicenter, Open-Label Proof-of-Concept Trial of Ganaxolone in Children with PCDH19 Female Pediatric Epilepsy and Other Rare Genetic Epilepsies Followed by a 52-Week Open-Label Treatment.

7.1.1. Primary Endpoints

Study 1042-0900

Primary efficacy will be percent change in seizure frequency per 28 days relative to the baseline. This efficacy metric is examined at 13- and 26-weeks post baseline, Table 25. The median percent change in seizure frequencies at the 13- and 26-week interval are in alignment with the median percent change in seizure frequency of -30.7 seen in the pivotal study.

Table 25 Study 1042-0900, 28-day Median Percent Change in Seizure Frequency from Baseline at 13 and 26 Weeks.

Post-Baseline Thru Month 3 (Day 91)	% Change from Baseline
Median	-47.3
Mean	-31.2
Std Dev	41.4
Post-Baseline 26 Week Open Label Period	
Median	-37.7
Mean	-20.6
Std Dev	60.6

Reviewer Comment: The seizure reduction seen in the small sample of CDD patients in open label study 1042-0900 are in alignment with a treatment benefit established in pivotal study

1042-CDD-3001.

7.1.2. Subpopulations

Study 1042-0900

Patients with CDD represent a subpopulation, seven of 31 total patients. Further subdivision of the CDD population is not meaningful in this study.

7.1.3. Onset, Duration, and Durability of Efficacy Effects

Study 1042-0900

The median 28 day precent seizure reduction over baseline at 13 weeks is -47.3% while at 26 weeks post baseline the 28 day seizure reduction is -37.7%. Durability is present based on the continued although reduced reduction of seizure frequency.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The small population of this rare disease increases the likelihood that the findings from study 3001 will be generalizable to the broader CDD population.

7.3. Integrated Assessment of Effectiveness

Efficacy is established by pivotal Study 3001 where the 28 day median percent reduction in seizure frequency over baseline was 30.7% with an effect size of 27.1%. This effect size is in the range seen for other approved ASMs. The statistical reviewer concluded that the primary efficacy endpoint results are robust with key secondary endpoints that show numerical findings in favor of the efficacy of GNX as adjunctive treatment of seizures in CDD. The post hoc subgroup analyses for the primary endpoint all very clearly favored drug with respect to gender, age, baseline allopregnanolone-sulfate plasma concentrations, and region. The seizure reduction observed in Study 0900 is not derived from a design of sufficient rigor to serve as a pivotal supporting study, however, the findings offer reassurance of a positive biologic benefit on seizure frequency in CDD.

8. Review of Safety

8.1. Safety Review Approach, see Table 27

Assessment of deaths is performed for all 46 studies included in the NDA submission. Eight deaths (7 in subjects who received GNX) occurred across the completed and ongoing company-sponsored studies.

The core safety review is performed on the CDD patient population from studies 1042-CDD-3001 and 1042-0900. The DB component of Study 3001 is examined for differential between safety characteristics of the PBO and GNX treatment arms. Safety review is then performed on the pooled open label study 0900 and open label extension of Study 3001 GNX treated populations. The safety review of the Study 3001 and Study 0900 safety pool incudes reviewer generated serious adverse effects (SAE), treatment emergent adverse effects (TEAE), Laboratory Shift and outlier analysis, Hy's Law analysis as well as a reviewer analysis of the ECG interpretation and QTcF during the DB treatment period of Study 3001. The applicant analysis is relied upon for assessment of vital signs in Studies 3001 and 0900.

Additional supportive safety review is performed on SAE's and TEAE of a subset of legacy studies in adult epilepsy (Study 0603, Cohort 2)), and PTSD (Study 0700) that include an additional 471 adult patient safety data across PBO and GNX treatment arms. To further explore potential hepatic function abnormalities, in light of the report of hepatic injury of patient (b) (6) in Study 0900, a Hy's law analysis is performed on bilirubin and ALT laboratory data from studies 0603, 0600, and 0700, see Table 26 for characteristics of these studies.

A pooled adverse event dataset (entitled Pooled Study Elementary Signal Analysis) from the ADAE datasets from Studies 0601, 0603, 0700, 0900 -52wk, 2002-C6, and 3001 DB & OL also including Study 0700 STDM ae.xpt dataset is created to amplify potential safety signals. Due to variation in construction of the dataset, such as where study 0700 is lacking an ADAM adverse event dataset, only the adverse event term, subject IDD, study day of AE, severity assignment and SAE flag variable are included in the pooled dataset. The divergent array of variable construction created limitations in the dataset and did not allow a more granular pooled dataset to include adverse event dates, dose, and precise patient counts or patient age at intervals of the open label interval for each study. The core purpose of this dataset was to capture as many patients as possible on GNX treatment for evaluation of safety events.

A screening analysis for systematic – sequential increase in ALP and related hepatic associated chemistries is performed on the DB interval of study 600 and on the subset of patients on GNX treatment in the DB period of study 0603 that continued in the OL extension study, see ALP and Associated ALT, Bilirubin Screening.

Table 26 Supportive Safety Studies in Other Indications

Study Number	Sort #	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	study Area	Year	exposure months	additional note	deaths	SAE n	SAE % (GNX)
1042-0603, Cohort 2	603	POS- DB	Phase 3, double-blind, randomized, PBO-controlled, add-on, safety, tolerability, PK, and efficacy study of GNX in adults with uncontrolled partial-onset seizures followed by long-term OL treatment	Cohort 1: 1200 mg/day, Cohort 2: 1800 mg/day	GNX capsules (200 mg & 225 mg capsules for Cohort 1 and 225 mg capsules for Cohort 2) dosed BID	180	179	Adult Epilepsy	2013	2	death due to vehicle collision	0	9	5
1042-0601	601	POS	OL extension of 1042-0600 up to 2 years	200mg to 500mg TID	GNX oral suspension (50mg/ml)	0	124	Adult Epilepsy	**2007**	**24**		0	15	12
1042-0600	600	POS	DB, randomized PBO controlled, add on, safety, tolerability, PK, efficacy	200mg to 500mg TID	GNX oral suspension (50mg/ml)	49	98	Adult Epilepsy	2007	3		0	5	5.1
1042-PPD-2002	2002	Post partum depression	DB, PBO controlled multiple dose escalation study to evaluate safety PK and efficacy	IV infusion over 60 hours (IV injection 2-12 mg/h; IV bolus 12 mg) IV injection 20 mg/h for 6 hours / 900mg/day	GNX injection / GNX oral Capsule	45	46	PPD	2017	1		0	1	2
1042-0700	700	PTSD	POC, 6 Week DB randomized study followed by 6 wk OL RX in adults	400 - 1200mg/day	GNX 200mg capsules BID	53	59	PTSD	2011	3		0	3	5.1
1042-TSC-2001	2001	Status Epilepticus	DB, randomized, PBO controlled study to evaluate safety, tolerability and efficacy of IV GNX as adjunctive therapy for Status epilepticus	Study drug administered as a 3-minute bolus, with a continuous infusion at the rate between 20-80 mg/hour for 36 hours, and a 12-hour study drug taper. Daily doses of ganaxolone of ≤ 830 mg/day and Captisol of ≤ 50 g/day	Intravenous with captisol		17	SE	2018	36 hours plus taper	deaths due to background critical illness	3		

Study Number	Sort #	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	study Area	Year	exposure months	additional note	deaths	SAE n	SAE % (GNX)
1042-0104	1996	Epilepsy	DB PBO controlled 8 day multiple dose study , safety tolerability, AED activity	500mg TID to 625mg TID	Oral suspension	28	24	Adult epilepsy	1996	.26	SUDEP 2 months after Placebo assignment study completion	1		

Table 27 Safety Review Outline of Analysis Strategy

Safety Review Outline of Analysis Strategy- see Table 26 for study description

1. Deaths: total development program
2. SAE- Reviewer analysis
    a. CDD
        i. Pivotal 3001
        ii. OL 3001 & 0900
    . 603 DB
    . 0700 DB
    a. Any GNX Pool: Studies 0601, 0603, 0700, 0900 -52wk, 2002-C6, and 3001 DB & OL
3. Dropout & Discontinuation- Reviewer Analysis
    a. CDD Pooled Studies 0900 and 3001- DB, OL
4. TEAE – Reviewer Analysis
    a. DB 3001
    b. DB 0603 Cohort 2
    c. DB 0700
    d. Any GNX Pool: Studies 0601, 0603, 0700, 0900 -52wk, 2002-C6, and 3001 DB & OL
5. Laboratory Assessments
    a. Applicant- overview
        i. DB 3001 -Hematology
        ii. DB 3001 Chemistry
        iii. DB 3001 Urinalysis
        iv. DB 3001 Vital Signs
        v. OL 3001, 0900 - Vital Signs
        vi. DB 3001 - ECG

b. Reviewer analysis
   i. 3001 Hematology -Chemistry
      1. Shifts & Outliers
      2. Hy's Law
      3. Bicarbonate
      4. QT
   ii. Hy's Law
      1. 0603, 0600, 0700
   iii. Bicarbonate
      1. 0700
   iv. QT 3001 DB

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Exposure for the indication of CDD is provided by studies 1042-CDD-3001 and 1042-0900 in Table 28. There were 83 patients with exposure ≥ 6 months and 50 patients with exposure ≥ 12 months. Fourteen patients with mass greater than 28kg had a modal dose 1800mg/day of while among patients with a body mass less than or equal to 28kg there were 62 patients with a modal dose of 63mg/kg/day.

Table 28 Duration of Exposure to Study Treatment (Pooled, All Treated CDD Subjects)

Exposure duration categories,	**GNX n (%)**
Any exposure	102 (100)
≥ 1 month	99 (97.1)
≥ 2 months	94 (92.2)
≥ 3 months	92 (89.2)
≥ 4 months	91 (89.2)
≥ 5 months	85 (83.3)
≥ 6 months	83 (81.4)
≥ 9 months	65 (63.7)
≥ 12 months	50 (49.0)
≥ 15 months	27 (26.5)
≥ 18 months	16 (15.7))
≥ 21 months	9 (8.8)
≥ 24 months	3 (2.9
≥ 27 months	1 (1.0)
≥ 30 months	1 (1.0)
≥ 33 months	1 (1.0)
≥ 36 months	1 (1.0)
≥ 39 months	1 (1.0)
≥ 42 months	1 (1.0)
Exposure duration (days)	
n	102
Mean	351.4
SD	206.90
Min	14
Median	358.5
Max	1337
Sum	35847
Subjects > 28 kg (30 kg)a: Modal dose (dose of longest exposure), n (%)	
< 1800 mg/day	8 (7.8)
1800 mg/day	14 (13.7)
Subjects ≤ 28 kg (30 kg)a: Modal dose (dose of longest exposure), n (%)	
< 63 mg/kg/day	18 (17.6)
63 mg/kg/day	62 (60.8)

Table 29 Exposure In GNX Treatment Studies of Epilepsy, Post-Partum Depression & Post Traumatic Stress Disorder, 1995 to 2018 (Pivotal Study shaded row)

Study Number	Study Area	Year	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	Duration exposure months
1042-0101	Pediatric Epilepsy	1996	refractory seizures & history of IS	OL, 3-month addon, flex dose, dose escalation study of safety tolerability and efficacy	1.5mg/kg TID escalation to max tolerated of 3,6,9, or 12 mg/kg TID by week 4	GNX beta cyclodextrin suspension (following meals)	0	0	20	3
1042-0104	Adult Epilepsy	1996	surgical treatment of epilepsy	DB PBO controlled 8-day multiple dose study, safety tolerability, AED activity	500mg TID to 625mg TID	GNX oral suspension (25mg/ml)	28	24		0.26
1042-0500	Pediatric Epilepsy	2007	infantile spasms	DB, PBO controlled add on, dose escalation, incomplete crossover study to evaluate the safety, tolerability and antiepileptic activity of GNX in IS	3mg/kg to 18mg/kg TID	GNX oral suspension	19	38		0.5
1042-0501	Pediatric Epilepsy	2007	infantile spasms	OL extension of 1042-0500- up to 2 years	3mg/kg to 18mg/kg TID	GNX oral suspension	0	54		24
1042-0600	Adult Epilepsy	2007	Uncontrolled POS	DB, randomized PBO controlled, add on, safety, tolerability, PK, efficacy	200mg to 500mg TID	GNX oral suspension (50mg/ml)	49	98		3
1042-0601	Adult Epilepsy	2007	Uncontrolled POS	OL extension of 1042-0600 up to 2 years	200mg to 500mg TID	GNX oral suspension (50mg/ml)	0	124		24
1042-0602	Adult Epilepsy	2009	Uncontrolled POS	OL extension for patients deriving benefit from 1042-0601	200mg to 500mg TID	GNX oral suspension (50mg/ml)	0	11		24
1042-0603, Cohort 1	Adult Epilepsy	2013	Uncontrolled POS-DB	Phase 3, double-blind, randomized, PBO-controlled, add-on, safety, tolerability, PK, and efficacy study of GNX in adults with uncontrolled partial-onset seizures followed by long-term OL treatment	Cohort 1: 1200 mg/day, Cohort 2: 1800 mg/day	GNX capsules (200 mg & 225 mg capsules for Cohort 1 and 225 mg capsules for Cohort 2) dosed BID	22	24		2
1042-0603, Cohort 2	Adult Epilepsy	2013	Uncontrolled POS-DB	Phase 3, double-blind, randomized, PBO-controlled, add-on, safety, tolerability, PK, and efficacy study of GNX in adults with uncontrolled partial-onset seizures followed by long-term OL treatment	Cohort 1: 1200 mg/day, Cohort 2: 1800 mg/day	GNX capsules (200 mg & 225 mg capsules for Cohort 1 and 225 mg capsules for Cohort 2) dosed BID	180	179		2
1042-0604	Adult Epilepsy	2015	drug resistant POS	Second year OL extension study of GNX in subjects with Drug resistant POS	GNX oral 900-1800mg/day	GNX 225mg capsules BID	0	26		17
1042-0700	PTSD	2011	PTSD	POC, 6 Week DB randomized study followed by 6 wk OL RX in adults	400 - 1200mg/day	GNX 200mg capsules BID	53	59		3

Study Number	Study Area	Year	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	Duration exposure months
1042-0800	Pediatric Epilepsy	2012	Fragile X syndrome	POC DB, crossover trial of GNX and PBO	9mg/kg/day up to 36 mg/kg/day to max 1800mg/day	GNX oral suspension (50mg/ml) TID	30	29		1.3
1042-0900, CDKL5	Pediatric Epilepsy	2015	PCDH19 & rare genetic	A Phase 2A, OL, proof-of-concept study of GNX in children with PCDH19 female pediatric epilepsy and other rare genetic epilepsies	oral, 900 - 1800mg/day	GNX oral suspension (50 mg/mL), TID or GNX 200mg or 225mg Capsules BID	0	7		43
1042-0900, Total	Pediatric Epilepsy	2015	PCDH19 & rare genetic	A Phase 2A, OL, proof-of-concept study of GNX in children with PCDH19 female pediatric epilepsy and other rare genetic epilepsies	oral, 900 - 1800mg/day	GNX oral suspension (50 mg/mL), TID or GNX 200mg or 225mg Capsules BID	0	30		43
1042-CDD-3001	Pediatric Epilepsy	2018	CDD	A Phase 3, double-blind, randomized, PBO-controlled trial of adjunctive GNX treatment in children and young adults with CDD which consists of a 6-week prospective baseline period to collect seizure data, followed by a 17-week double-blind treatment phase, which is then followed by a long-term OL phase	GNX oral ,≤ 1800 mg/day, (dosing bases on mg/kg and mg/kg/day)	GNX oral suspension (50 mg/mL)	51	50		4.25
1042-CDD-3001	Pediatric Epilepsy	2018	CDD	A Phase 3, long-term OL phase of study 1042-CDD-3001	GNX oral ,≤ 1800 mg/day, (dosing bases on mg/kg and mg/kg/day)	GNX oral suspension (50 mg/mL)			88	17.5
1042-PPD-2002	PPD	2017	Postpartum depression	DB, PBO controlled multiple dose escalation study to evaluate safety PK and efficacy	IV infusion over 60 hours (IV injection 2-12 mg/h; IV bolus 12 mg) IV injection 20 mg/h for 6 hours / 900mg/day	GNX injection / GNX oral Capsule	45	46		1
1042-PPD-2003	PPD	2018	Postpartum depression	Double-blind, PBO-controlled multicenter study to evaluate safety, tolerability, and efficacy of GNX in women with PPD	675 - 1350mg/day	GNX oral capsules at HS or TID	0	84		
1042-SE-2001	Adult Epilepsy	2018	Status epilepticus	P2 CB, Randomized, PBO controlled study to evaluate the safety, tolerability, efficacy and PK of adjunctive IV GNX in patients ≥12 years with SE	GNX IV ≤713 mg/day	GNX IV solution 3mg/ml	0	17		0.16
CA042-9408.01	Pediatric Epilepsy	1996	Refractory partial or generalized seizures	OL, 17-week, flexible escalating dose add on study of the safety , optimal dose and potential efficacy of GNX (same population)	variable escalating dose to max total of 36mg/kg	GNX beta cyclodextrin suspension	0		45	48
CA042-9408.01	Pediatric Epilepsy	1995	Refractory partial or generalized seizures	OL, 2-month flexible escalating dose add on study of safety tolerability, dose range and efficacy in	variable escalating dose to max total of 36mg/kg	GNX beta cyclodextrin suspension			15	24

Study Number	Study Area	Year	Indication	Design & Purpose	GNX Dose	Formulation	PBO	GNX	OL	Duration exposure months
				pediatric or adolescent patients with refractory partial or generalized seizures						
Total Patients								900	168	**All GNX, DB and OL** 1068

Reviewer Comment: The CDD exposure is adequate. CDD is a rare disease. These exposures represent a meaningful proportion of the currently identified CDD population. The additional studies of other indications and age ranges presented in Table 29 identify additional extensive exposure to GNX.

8.2.2. Relevant characteristics of the safety population:

CDD Safety Population

The safety population of CDD patients has 108 participants where there are 101 from study 1042-CDD-3001 and 8 from study 1042-0900. Examination of the distribution of patients by sex reveals there were 86 (79.6%) females and 22 (20.4%) males where the distribution between GNX and PBO treatment arms was similar, Table 30. The nearly 4:1 female to male predominance reflects the distribution of the disease in the population. CDD is an X-linked disorder that affects females more than males (approximately 4:1) as males with germline variants have no normal CDKL5 gene and may not survive fetal life.[13]

Examination of the racial distribution of the safety population reveals a predominance of white patients where ethnicity is predominantly "NOT HISPANIC OR LATINO", Table 30.

The mean and median ages of the study population were 7.3 years and 6 years respectively where the age distribution across treatment arms was similar. The mean and median weight of the safety population were 21.5kg and 18.5kg respectively where the weight distribution across treatment arms was similar, Table 31.

Patients in the CDD safety population were enrolled from 8 countries. The distribution of patients by country of origin was examined and shows the largest proportion of study participants, 44 (40.7%) was from the US. From among the remaining 7 countries the proportion of patient enrollment from each of the remaining countries was 20%, 14%, 10%, 6%, 6%, and 1% from Italy, Russia, Poland, Germany, Australia, France and Israel respectively. The distribution of patients across each treatment arm by country was similar with the exception of Italy where 13% of patients were enrolled in the GNX treatment arm and 5.6% in the PBO treatment arm, Table 32. This divergence in the distribution of Italian patients across treatment arms is not likely to affect patient outcome.

Table 30 CDD Safety Population, Studies 1042-CDD-3001 & 1042-0900, Distribution of Sex, Race and Ethnicity

	Ganaxolone	% Patients	Placebo	% Patients	Total	% Patients
Sex[14]						
F	45	41.7	41	38.0	86	79.6
M	12	11.1	10	9.3	22	20.4
Race						

[13] H. E. Olson et al., "Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review," *Pediatric Neurology* 97 (Aug 2019), https://dx.doi.org/10.1016/j.pediatrneurol.2019.02.015.
[14] Ibid

	Ganaxolone	% Patients	Placebo	% Patients	Total	% Patients
White	53	49.1	47	43.5	100	92.6
Other	2	1.9	1	0.9	3	2.8
Asian	2	1.9	3	2.8	5	4.6
Ethnicity						
no entry	1	0.9		0.0	1	0.9
HISPANIC OR LATINO	6	5.6	4	3.7	10	9.3
NOT HISPANIC OR LATINO	43	39.8	51	47.2	94	87
NOT REPORTED	1	0.9	1	0.9	2	1.8
UNKNOWN			1	0.9	1	0.9

Table 31 CDD Safety Population, Studies 1042-CDD-3001 & 1042-0900, Distribution of Age & Weight

Treatment arm	# patients	Mean	SD	Median	Min	Max
Age						
Ganaxolone	57	6.8	4.7	5	2	19
Placebo	51	7.7	4.4	7	2	19
Total	108	7.3	4.6	6	2	19
Weight						
Ganaxolone	57	20.6	9.3	17	9.7	42
Placebo	51	22.4	9.1	19.1	8.7	46.5
Total	108	21.5	9.2	18.5	8.7	46.5

Table 32 CDD Safety Population, Studies 1042-CDD-3001 & 1042-0900, Patient Distribution by Country

	GNX		PBO		Total	
COUNTRY	# Patients	% Patients	# Patients	% Patients	# Patients	% Patients
USA	20	18.5	24	22.2	44	40.7
ITA	14	13.0	6	5.6	20	18.5
RUS	7	6.5	7	6.5	14	13
POL	5	4.6	5	4.6	10	9.3
GBR	4	3.7	3	2.8	7	6.5
AUS	4	3.7	2	1.9	6	5.6
FRA	3	2.8	3	2.8	6	5.6
ISR			1	0.9	1	0.9

Reviewer Comment: Examination of patient demographics reveals the most notable imbalance in proportion of Caucasian (white) participants. This distribution likely represents the predominantly European and US study site distribution and possibly an imbalance in access due to difference in resource distribution across racial subpopulations in these nations. Overall, due to the known genetic basis of this developmental encephalopathy it is not likely that there will be a differential effect of treatment across racial groups.

8.2.3. Adequacy of the safety database:

As noted above in Section 8.2.1, Overall Exposure, the CDD exposure is adequate. CDD is a rare disease. These exposures represent a meaningful proportion of the currently identified CDD population. The additional studies of other indications and age ranges presented in Table 29 identify additional extensive exposure to GNX. In addition, the distribution of demographic variables across treatment arms is acceptable to support generalizable safety conclusions.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

8.3.2. Categorization of Adverse Events

All CDD Study Population Study 1042-CDD-3001 and 1042-0900

All AEs and medical history terms were coded to MedDRA® version 23.0.

The definition of an adverse event and SAE were equivalent in protocols 1042-CDD-3001 and 1042-0900 as follows while assignment of severity were divergent and both will be presented:

Definition: "An AE is any untoward medical occurrence in a clinical investigation subject who has been administered a pharmaceutical product; it does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] Guidance E2A March 1995)."

"All AEs are collected from the time the informed consent is signed until the defined follow-up period. This includes events occurring during the screening phase of the study, regardless of whether or not the investigational product has been administered. All AEs reported after the initiation of investigational product will be considered treatment-emergent AEs."

Severity:

Study 1042-CDD-3001

"The severity of AEs must be recorded during the course of the event, including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event.

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or

therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research subject.
Severe: A type of AE that interrupts usual activities of daily living, that significantly affects clinical status, or that may require intensive therapeutic intervention.

Study 1042-0900:

Severity of AEs will be graded by the Investigator using the following criteria as guidelines:

- **Mild**: Nuisance, barely noticeable.
- **Moderate**: Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.
- **Severe**: Symptoms significantly interfere with daily activities or sleep.

Relationship to Study Drug

A physician/investigator must make the assessment of relationship between the investigational product and each AE. The investigator should decide whether, in their medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, the AE should be classified as “not related.” If a relationship between the AE and the investigational product is at least reasonably possible (i.e. the relationship cannot be ruled out) the AE should be considered "related.”

Term	Relationship definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject’s medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors, such as the subject’s underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between the investigational product and the event.

SAE Definition: A serious adverse event (SAE) is any untoward medical occurrence that at any dose (including overdose) that meets one or more of the following criteria (these are in alignment with CFR 312.32 IND safety reporting. (a) Definitions.)

- Death
- A life-threatening adverse event
- Requires or prolongs inpatient hospitalization

- Results in permanent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Reviewer Comment: the differences in severity definition between studies 1042-CDD-1042 and 1042-0900 will have a limited impact on assessment of AE severity due to the small contribution of study 1042-0900 to this pooled safety dataset.

8.3.3. Routine Clinical Tests

Assessment of clinical status was by an appropriate sampling and testing of vital signs, physical and neurologic exam, clinical laboratory and ECG capture at regular intervals that were appropriately spaced.

8.4. Safety Result

8.4.1. Deaths

There were a total of 9 deaths reported in the 46 pediatric and adult studies from the development program that were included in the NDA submission. The Applicant reports 4 deaths during pediatric development of GNX. There was a total exposure of 376 patients in GNX pediatric epilepsy studies with 4 deaths that yield a 1.06% frequency of death combining both DB and OL study intervals. None of the reports has a causal relation to GNX.

All CDD Study Population Study 1042-CDD-3001 and 1042-0900

Study 1042-CDD-3001

In the All Ganaxolone CDD population, 1 death (Study 1042-CDD-3001), 1% of total, 2% of GNX treatment arm) was reported by the cutoff date.

- (b) (6) (Subject (b) (6) randomized to GNX in the DB phase, was receiving 33 mg/kg/day GNX. On Day 381 during the OL phase, (b) (6) experienced severe meningococcal sepsis and died on Day 382. The investigator assessed the death as unlikely related to study drug.

Study 1042-0900

One death was reported for a subject in Study 1042-0900.

- (b) (6) (patient (b) (6) (b) (6) with LGS was receiving 54 mg/kg/day GNX at the time of hepatic failure. At birth, (b) (6) experienced necrotizing enterocolitis resulting in short gut syndrome. The subject had additional co-morbidities of hepatic dysfunction, hypotonia (all extremities), left eye ptosis, urinary incontinence,

developmental delay, and static encephalopathy with resultant seizure disorder. On Day 157, the subject was hospitalized due to hepatic failure. [redacted] took [redacted] last dose of study drug on Day 159 and was withdrawn from the study on Day 160 due to hepatic failure. Between Days 160 and 355, the subject was hospitalized several times for various medical reasons including hepatic failure, jaundice, hyperbilirubinemia, and liver enlargement. On Day 355, the subject died due to hepatic failure. The investigator assessed the hepatic failure as unlikely related to study drug, see also Section 8.5.1Hepatic Failure Case.

Other Pediatric Epilepsy Studies

Two deaths were reported during Study 1042-0501 (Infantile Spasms Open Label Extension)

- [redacted] (patient [redacted] was receiving > 36 to ≤ 45 mg/kg/day GNX. The subject 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 related to study drug.

- An [redacted] (patient [redacted] was receiving > 54 mg/kg/day GNX. The subject had co-morbidities including microcephaly and lobar holoprosencephaly in addition to IS. The subject had [redacted] last dose of study medication on Day 262. On Day 263, [redacted] died due to respiratory failure. The investigator assessed the death as not related to study drug.

No deaths were reported the remaining pediatric studies (Studies CA042-9408.01 Stages 1 and II, 1042-0101, 1042-0500, and 1042-0800).

Reviewer Comment: In study 1042-CDD-3001 the single death occurred in open label treatment day 382 due to meningococcal sepsis. The long duration of treatment greatly reduces support of casualty due to the absence of temporal relationship. In study 1042-0900 there was a death due to possible hepatic failure. This occurrence has been subject to addition focus with evaluation by the DILI team. The DILI team concluded the death was not due to primary hepatic failure but a general systemic decline from comorbidities of short bowel syndrome and underlying disease. The primary support for this conclusion is the recovery of INR to normal range following treatment with vitamin K. This response was seen with concurrent elevated bilirubin of 15.9mg/dl. The two deaths in the study of Infantile Spasms do not have a causal relationship. In the first case, patient [redacted] the event was due to a mechanism not related to study drug while in the second case, patient [redacted] there was no support due to absence of temporal relationship.

Adult Studies

Five deaths occurred in adult epilepsy studies where four occurred in GNX treated patients.

1042-SE-2001

(DB, Randomized, placebo-controlled study of Safety, Tolerability and Efficacy of GNX as adjunctive therapy for treatment of Status Epilepticus in ages 12 years of age and older)

There were three deaths in study 2001. All deaths occurred in the context of serious, advanced underlying medical illness and were unrelated to GNX treatment. A brief description of each is provided below.

Patient (b) (6) a (b) (6) with no history of epilepsy presented with nonconvulsive status epilepticus due to a subdural hematoma. Two days prior to the start of study drug infusion, the patient had a level 1 trauma due to a mechanical fall and was noted to have subdural haematoma. The patient underwent a right frontal craniotomy for evacuation of acute subdural hematoma on the same day (Study Day -2). On physical examination, the patient was unresponsive to both verbal and noxious stimuli; pupils were equal and reactive to light, there was no gag, and vestibule-ocular reflex was intact. Her blood pressure and oxygen saturation were stable. The patient also had rhonchorous breathing and was treated with mannitol. A computed tomogram on (b) (6) (1 day prior to the start of study drug infusion) showed stable re-accumulation of the hematoma. On study day 4 the patient was discontinued due to lack of efficacy. Fifteen days later the patient's family decided to withdraw life support.

Patient (b) (6) an (b) (6) with a positive history of epilepsy (status epilepticus beginning 2 days prior to enrollment) presented non-convulsive status epilepticus due to a subdural hemorrhage/traumatic brain injury. Four days prior to initiating study drug the patient was also noted to have peripheral oedema, cytotoxic cerebral edema, intermittent hypotension, and respiratory distress. The patient was intubated and placed on propofol. The patient had a complex medical course and prolonged hospitalization with respiratory failure and sepsis. While hospitalized, consultations were held with the family regarding the subject's expected poor prognosis. At the direction of the family, the subject was extubated and measures to ensure the subject's comfort were taken. The subject subsequently died on Study Day 28, 22 days after completing study drug infusion. Per death report, the preliminary cause of death was septic shock.

Patient (b) (6) a (b) (6) with a positive history of epilepsy (seizures beginning approximately 2 months prior to enrollment) presented non-convulsive status epilepticus due to neoplasia. The patient had relevant history of metastatic non-small cell lung cancer. There was also evidence of progressive metastatic lung cancer to multiple soft tissue sites, liver, and adrenal glands, lymph nodes, and spine. Nine hours after completing study drug infusion, the subject was diagnosed with intestinal perforation (perforated bowel), and the investigator considered the event to be severe in intensity and life-threatening. The surgery

service was consulted and expressed concern for potential post-operative complications as the subject was on high dose steroids and also for the overall prognosis from an oncological perspective. After a discussion with the subject's family, neurology, oncology, and radiation oncology, noting the risk of complications from a surgical intervention and poor long-term prognosis from the non-small cell lung cancer, a decision was made to defer surgical intervention. Later, the palliative care service was consulted, and the subject was transferred to an intensive palliative care unit for ongoing symptomatic management. The patient died nine days after completing study drug infusion. Per death report, the main causes of death were bowel perforation and enteritis.

Study 0603

There were no deaths in the double-blind phase of study 0603. There was a death in the open label treatment phase on study day 480 where a a (b) (6)

Study 0104

This was an eight day double blind PBO controlled multiple dose study in patients awaiting surgical treatment of epilepsy. There was one death assessed as SUDEP two months after the patient completed the study who was treated with PBO during the study.

Reviewer Comment: none of the five deaths identified in adult studies had a causal relationship to GNX treatment.

8.4.2. Serious Adverse Events

All CDD Study Population Study 1042-CDD-3001 and 1042-0900

Double blind treatment interval of study 1042-CDD-3001

During the double blind treatment interval of study 1042-CDD-3001 There were 16 SAE from among 11 (10.1%) patients with 6 (10.5%) patients in the GNX treatment arm and 5 (9.8%) in the PBO treatment arm (note: there was no double blind interval in OL study 1042-0900) .

There was no overlap in the SAE preferred terms between the GNX and PBO treatment arms. There was also no recurrence of preferred terms among patients in each treatment arm with an SAE. This is likely due to the small overall count of SAEs. There were 2 (3.5%) respiratory infections in the GNX arm and 3 (5.8%) in the PBO arm, one hypoxia preferred term in each treatment arm. There was one seizure in the PBO arm with no occurrence in the GNX arm.

Table 33 SAE by PT, Number and Percent of Patients, Study 1042-CDD-3001

Treatment Arm	Preferred Term	# Patients	% Patients
GNX	FOOD REFUSAL	1	1.8
	RHINOVIRUS INFECTION	1	1.8
	PNEUMONIA ASPIRATION	1	1.8
	URINARY TRACT INFECTION	1	1.8
	BRONCHITIS	1	1.8
	OXYGEN SATURATION DECREASED	1	1.8
PBO	FAECALOMA	1	2.0
	HYPOTONIA	1	2.0
	HYPOXIA	1.0	2.0
	PNEUMONIA MYCOPLASMAL	1.0	2.0
	PNEUMONIA VIRAL	1	2.0
	RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS	1	2.0
	SEIZURE	1	2.0
	UNRESPONSIVE TO STIMULI	1	2.0

Reviewer Comment: The frequency of SAE that occurred during double blind treatment was very similar between GNX and PBO treatment arms. The frequency of respiratory infections was greater in the PBO arm while frequency of hypoxia was equal across the arms with a single occurrence in each. Overall, there is no differential safety signal between the treatment arms.

Open Label Treatment Interval of Pooled Studies 1042-CDD-3001 and 1042-0900

One hundred and one (101) CDD patients entered the pooled OL treatment phase of studies 1042-CDD-3001 and 1042-1042-0900. In the OL treatment interval of the pooled CDD studies 1042-CDD-3001 and 1042-0900 there were 55 SAEs from among 23 (22.7%) patients. SAEs from the Pooled OL studies with TTO are shown in Table 34. Acute events that occur on the OL timeline with a shorter TTO have a more likely causal relationship. The shortest TTO may be seen in the "minimum" column of Table 34.

Table 34 SAE in Open Label Treatment Interval of Pooled Studies 1042-CDD-3001 and 1042-0900 by Number and Percent of Patients with Mean, Median and Minimum Time on GNX Treatment for Each PT.

			Time on GNX Treatment by PT		
Preferred Term	# Patients in OL	% Patients in OL	Mean	Median	Minimum
SEIZURE	5	5	164	62	16
DEHYDRATION	3	3	134	62	56
PNEUMONIA ASPIRATION	3	3	214	201	136
ACUTE RESPIRATORY FAILURE	2	2	239	239	192

			Time on GNX Treatment by PT		
Preferred Term	**# Patients in OL**	**% Patients in OL**	**Mean**	**Median**	**Minimum**
ASPIRATION	2	2	113	113	16
INFLUENZA	2	2	290	290	270
PNEUMONIA	2	2	355	355	285
PNEUMONIA VIRAL	2	2	288	288	192
STATUS EPILEPTICUS	2	2	345	345	232
VOMITING	2	2	38	38	19
ACUTE KIDNEY INJURY	1	1	-	-	189
ANAEMIA MACROCYTIC	1	1	-	-	167
ARTHRALGIA	1	1	-	-	145
CHOREA	1	1	-	-	189
DYSPHAGIA	1	1	-	-	276
ENDOTRACHEAL INTUBATION COMPLICATION	1	1	-	-	441
GAIT DISTURBANCE	1	1	-	-	450
HYPERCALCAEMIA	1	1	171	171	167
HYPOTONIA	1	1	-	-	276
LETHARGY	1	1	-	-	455
LOSS OF CONSCIOUSNESS	1	1	-	-	247
LOWER RESPIRATORY TRACT INFECTION	1	1	-	-	90
MENINGOCOCCAL SEPSIS	1	1	-	-	381
OXYGEN SATURATION DECREASED	1	1	-	-	583
PROCEDURAL COMPLICATION	1	1	-	-	441
RENAL FAILURE	1	1	-	-	406
RESPIRATORY FAILURE	1	1	-	-	984
RESPIRATORY SYNCYTIAL VIRUS TEST POSITIVE	1	1	-	-	140
SEPSIS	1	1	-	-	462
SKIN LACERATION	1	1	-	-	455
SOMNOLENCE	1	1	-	-	276
SOPOR	1	1	-	-	232
UNINTENTIONAL MEDICAL DEVICE REMOVAL	1	1	-	-	411
UNRESPONSIVE TO STIMULI	1	1	-	-	3
UPPER RESPIRATORY TRACT INFECTION	1	1	-	-	20
URINARY TRACT INFECTION	1	1	-	-	62
VIRAL INFECTION	1	1	-	-	145
WEIGHT DECREASED	1	1	-	-	455

Table 35 Any SAE in Open Label Treatment Interval of Pooled Studies 1042-CDD-3001 and 1042-0900 with One Occurrence < 56 days on GNX Treatment with Examination of All Events (across exposure interval) of Same PT to Assess Causal Relationship.

Subject ID	Preferred term	Days of GNX Treatment	Study	DX	History of SAE	Comment
(b) (6)	SEIZURE	16	3001	X-linked chromosomal disorder	(b) (6). Medical history included visual impairment, exaggerated startle response, hypotonia, muscle spasticity, irritability, and walking disability and Infantile Spasms Difficulty in swallowing the study drug followed by gasping. It was reported that the gasping became worse due to the large volume of suspension of the study drug according to the titration regimen. The subject then experienced a generalized seizure, lasting approximately half an hour, characterized by rolling of eyes and involuntary movement of arms and legs. Discontinued	**Conclusion: GNX API non causal,** GNX delivery volume possibly causal to aspiration due to liquid volume. Seizure secondary to effects of primary event of aspiration. Background liquid tolerances unknown.
(b) (6)	SEIZURE	20		CDD	(b) (6), increased seizures in a setting of acute febrile illness, which was suspected to be secondary to either a viral upper respiratory infection or pneumonia bacteremia. A chest x-ray on the same date revealed patchy bibasilar opacities suggestive of atelectasis or pneumonia. The SARS (severe acute respiratory syndrome) and COVID (coronavirus disease) test results were negative. 1 day hospitalization. Study drug continued.	**Conclusion: GNX non causal** increased seizures in a setting of acute febrile illness.
(b) (6)	SEIZURE	62	3001	CDD	(b) (6), Medical history included constipation, CDD, scoliosis, and epilepsy. Additional medical history included epileptic encephalopathy, gene mutation, and autism spectrum disorder and dysphagia. On extension day 62 during an unscheduled visit the subject was hospitalized due to increased seizures, change in urine smell, and dehydration. (b) (6) denied being febrile, or having cough, congestion or running nose, but had lost 2 pounds and 4 ounces of weight since the last visit on (b) (6) (Extension Day 35). Urine analysis result revealed the subject's urine was cloudy and amber in color. The SAEs of dehydration and seizure of moderate severity and UTI of severe severity were reported. Study drug continued.	**Conclusion: GNX non causal** Seizure increase is embedded in an episode of infection. Diaper hygiene possible related. GNX possibly indirectly related if level of alertness reduced although temporal relationship to even is not strong.

					Investigator proposes an etiology could be explained by the subject's daily use of diapers which can cause urinary tract infections if not changed frequently.	
(b) (6)	SEIZURE	271	3001	CDD	(b) (6) Medical history included constipation; epilepsy; infantile spasms (since (b) (6)); intellectual disability; developmental delay ; X-linked chromosomal disorder; hypotonia, congenital nystagmus; cortical visual impairment; hypermetropia, Lennox-Gastaut syndrome (LGS). The subject was diagnosed with SAEs of influenza with an onset date of Day 270, increased seizure frequency with an Day 271. Study drug continued	**Conclusion: GNX non-causal** Seizure increase embedded in an episode of infection. Poor temporal relationship.
(b) (6)	SEIZURE	450	3001	CDD	(b) (6) Medical history includes infantile spasms, unsteady gait, epileptic encephalopathy, and language disorder. the subject had increased seizures and worsened gait disturbance and the serious adverse events (SAEs) of seizure and gait disturbance were reported. On study day 475 study drug was discontinued at parents request due to loss of efficacy.	**Conclusion: GNX non causal** no temporal relationship. Seizure increase without clear cause, GNX dose reduced prior to event (reason unreported), was it somnolence, loss of appetite?
(b) (6)	Dehydration	62	3001	CDD	Reported in seizure above	**Conclusion: GNX non-causal**
(b) (6)	Dehydration	284	3001	CDD	Reported in seizure above	**Conclusion: GNX non-causal**
(b) (6)	Dehydration	56	3001	CDD	(b) (6) with medical history of developmental delay, stereotypic movement disorder and hypotonia. On GNX treatment day 56 the patient experienced progressive lack of appetite. On GNX treatment day 57 the patient refused oral intake including food, liquid, water or medications. There were repeated bouts of vomiting and increase in seizure frequency and duration. Intravenous rehydration was started. An abdominal x-ray revealed distension of the stomach and abundant colic coprostasis without intestinal air-fluid levels. The investigator assessed the events of vomiting and dehydration as serious due to hospitalization and unrelated to study drug.	**Conclusion: GNX non causal** An AE of dehydration occurred during PBO treatment in DB day 76. Weak temporal relationship to GNX. This may be a spontaneous GI dysfunction

(b) (6)	Aspiration	210	3001	CDD	(b) (6) medical history includes impaired gastric emptying, GERD, developmental delay, and esophageal stent. The patient has SAEs of Aspiration pneumonia reported on study days 31, 136, and 231 (all GNX treatment, patient in GNX arm). This patient was also captured as "pneumonia aspiration" in SAE during DB period, see Table 33. Pulmonology and ear-nose-throat specialist were further consulted for sialorrhea and excess secretions believed to be causing the aspiration events and was advised that the subject could benefit from salivary gland botox injections. GNX continued.	**Conclusion: GNX causality uncertain**, recurrent aspiration events began in DB period on day 31, a plausible temporal relationship. Pre-existing vulnerability to aspiration of salivary contents is also supported by the findings of ENT consultation.
(b) (6)	Aspiration	16	3001	CDD	Reported in "seizure" above. (b) (6) medical history includes visual impairment, hypotonia, muscle spasticity, walking disability and infantile spasms.	**Conclusion: GNX API non causal,** GNX delivery volume possibly causal to aspiration due to liquid volume. Background liquid tolerances unknown.
(b) (6)	Vomiting	19	3001	CDD	(b) (6) medical history includes cortical visual impairment, dysphagia, GE reflux, hypotonia, bronchitis, asthma and restrictive pulmonary disease, feeding intolerance, G tube placement. Faecaloma during DB (PBO) phase. On study day 136-extension OL day 19 the patient. Vomiting improved on day 21 and patient was discharged. No change in GNX treatment.	**Conclusion: GNX non causal**, underlying bowel dysmotility.
(b) (6)	Vomiting	56	3001	CDD	Reported in "dehydration" above.	**Conclusion: GNX non causal** An AE of dehydration occurred during PBO treatment in DB day 76. Weak temporal relationship to GNX. This may be a spontaneous GI dysfunction
(b) (6)	Unresponsive to stimuli	3	3001	CDD	(b) (6) medical history includes developmental delay, corpus callostomy, g-tube. The subject received the study drug at 11:30 AM and approximately 15 minutes after receiving the study	**Conclusion: GNX causality due to sedation plausible**

					drug, he had convulsive seizure of typical semiology for about 20 seconds. The subject then fell asleep, and remained in a state of deep sleep, and unresponsive to stimuli for hours. An ambulance was called, and his blood pressure was low (value not reported) during the event and the subject did not respond to cold compresses. The subject woke up after a needle stick in the ambulance. In the ambulance, the subject's oxygen, blood pressure, and heart rate were all within normal limits (values not reported). Post-ictal state cannot be excluded. GNX was continued	
(b) (6)	upper respiratory tract infection	20	3001	CDD	(b) (6) medical history includes rett syndrome and dysphagia. the subject presented to the emergency room (ER) due to increased seizures in a setting of acute febrile illness, which was suspected to be secondary to either a viral upper respiratory infection or pneumonia bacteremia. It was reported that (b) (6) also had respiratory distress, cough for 4 days, and congestion since 2 days, but denied having fever. On the date of admission, the subject presented three episodes of non bloody, non-bilious emesis. A chest x-ray on the same date revealed patchy bibasilar opacities suggestive of atelectasis or pneumonia. The SARS (severe acute respiratory syndrome) and COVID (coronavirus disease) test results were negative. Patient hospitalized one day. GNX continued	**Conclusion: GNX non causal** Causality confounded by the occurrence of viral URI on day 31 of DB PBO treatment, Coughing on day 65 of DB PBO treatment (although non SAE)

Reviewer Comment: Analysis of SAEs that occurred with a plausible temporal relationship to GNX treatment in the OL study period (< 8 weeks, [56 days]) identified 14 events from among 9 patients. There were 5 preferred terms that contributed to the 14 events, these terms were seizure (5), dehydration (3), aspiration (2), and one each "unresponsive to stimuli" and "upper respiratory tract infection". From among these 14 events there are two that have possible causal relationship to GNX treatment, one event each of "aspiration" and "Unresponsive to stimuli". Both events may be related to the underlying potential of GNX related sedation. The "aspiration" event is however, confounded by "sialorrhea and excess secretions believed to be causing the aspiration events". Sedation will be a labeled AE for GNX.

120 Day Update, SAE CDD Study Population Study 1042-CDD-3001 and 1042-0900

See Table 49, Section 8.4.5, Treatment Emergent Adverse Events and Adverse Reactions.

Study 0603 Adult POS, see Table 26

SAE

In the GNX treatment arms of Cohort 1 and 2 there were 14 SAEs from among 9 (4.4%) patients while there were 11 SAEs from among 9 (4.5%) patients. The only SAE of overlap between the treatment arms was "convulsion" occurring in 1% of patients in each arm. The remaining 12 SAEs in the GNX treatment arm had a frequency of a single patient occurrence (0.5%) of patients.

There was a no overlap between the SAE's observed in the GNX treatment arm of study 0603 and study 3001. In 4 of 6 SAEs in study 3001 the SAE was associated with a term aligned with infection while the remaining two were "food refusal" and "oxygen saturation decreased" (thought to be due to sedation). The study population of 0603 is a numerically larger population of adults with POS where the SAEs are from a broader range of clinical conditions. There was a small excess of SAE in the PBO treatment arm compared to the GNX treatment arm, 4.4% vs 4.6% respectively. There was a single SAE, convulsion, that occurred in both the GNX and PBO treatment arms with an equal frequency of 1% of patients in each. If all seizure related terms are considered in the count, there remains an excess in the PBO treatment arm. The remaining SAE preferred terms in both treatment arms occur in a single patient each with no overlap. This small number of non-overlapping preferred terms does not support an identifiable safety signal distinct for the GNX treatment arm, see Table 36.

Table 36 Study 0603 SAE in GNX and PBO Treatment Arms

GNX SAE; 9 (4.4%) patients			**PBO SAE; 9 (4.6%) patients**		
Preferred Term	# Patients	% Patients	Preferred Term	# Patients	% Patients
Convulsion	2	1	Convulsion	2	1
Breast cancer	1	0.5	Appendicitis	1	0.5

GNX SAE; 9 (4.4%) patients			PBO SAE; 9 (4.6%) patients		
Preferred Term	# Patients	% Patients	Preferred Term	# Patients	% Patients
Depression	1	0.5	Coronary artery disease	1	0.5
Gait disturbance	1	0.5	Epilepsy	1	0.5
Hypokalaemia	1	0.5	Fall	1	0.5
Oesophageal obstruction	1	0.5	Grand mal convulsion	1	0.5
Pulmonary tuberculosis	1	0.5	Ligament rupture	1	0.5
Respiratory failure	1	0.5	Postictal psychosis	1	0.5
Small intestinal obstruction	1	0.5	Psychogenic seizure	1	0.5
Somnolence	1	0.5	Suicidal ideation	1	0.5
Speech disorder	1	0.5			
Status epilepticus	1	0.5			
Tongue injury	1	0.5			

Study 0700, PTSD, see Table 26

There were 3 SAE's in the DB portion of Study 0700 all in the GNX treatment arm. This represents 5.1% of patients. These events are presented in narrative form as follows:

- Subject (b) (6) experienced SAEs of severe fever, myalgia, and arthralgia during Week 6 that resolved after 5 days. The subject was hospitalized for pneumonia. The events were considered not related to the study drug according to the investigator. While hospitalized, the subject had received Valium, and (b) (6) tested positive for benzodiazepines at (b) (6) subsequent study visit. As a result, the subject was discontinued from the study drug.

- Subject (b) (6) was hospitalized overnight for observation during Week 6 due to SAEs of moderate intensity dizziness, confusion, and balance issues. (b) (6) had taken his morning dose of study without food. (b) (6) reported having experienced the events since the study drug was last increased 16 days earlier. The study drug was discontinued, and all of the events resolved the following day. The events were considered probably related to the study drug according to the investigator.

- Subject (b) (6) had an SAE of an episode of suicidal ideation on Day 22 that resolved without clinical intervention. While on a hunting trip, the subject reported putting a loaded gun in his mouth with intent of self-harm. (b) (6) did not harm (b) (6) self. Upon reporting the incident to the study site and after consultation with the site psychiatrist, (b) (6) was permitted to remain in the study. The incident was considered unlikely related to study drug since the subject stated the event was precipitated by discussions at a group session and the approaching anniversary of (b) (6) trauma. The event resolved on the same day. The subject completed the study without further incident.

There were no SAEs during the OL extension phase of study 0700.

Reviewer Comment: The SAE analysis of studies 0603 and 0700 does not reveal unique safety signals with causal relationship to GNX treatment that were not previously identified in the review of studies 3001 and 0900.

Pooled Study Elementary Signal Analysis[15]

A pooled adverse event dataset from the ADAE datasets from Studies 0601, 0603, 0700, 0900 -52wk, 2002-C6, and 3001 DB & OL also including Study 0700 STDM ae.xpt dataset is created to amplify potential safety signals (see Table 29 for individual study information). Due to variation in construction of the dataset, where study 0700 is lacking an ADAM adverse event dataset, only the adverse event term, subject ID, study day of AE, severity assignment and SAE flag variable are included in the pooled dataset. The core purpose of this dataset was to capture as many patients as possible on GNX treatment for evaluation of safety events. The divergent array of dataset variable construction did not allow a more granular pooled dataset to include adverse event dates, dose, and precise patient counts or patient age at intervals of the open label interval for each study. The study day variable does provide a measure of the TTO for the adverse event while on GNX treatment. Study 0700 had only verbatim adverse event terms and subject ID available in the posted STDM, ae.xpt dataset. There was a degree of splitting of "somnolence" related preferred and verbatim (study 0700) entry terms. To accurately evaluate this signal the preferred terms "lethargy", "sedation", "fatigue" as well as the lower-level terms (LLT) "drowsiness", "sleepiness", "daytime sleepiness" and "day fatigue" were all coded to the term "somnolence". Similar recoding of terms related to "Gait Disturbance" was performed. The related terms "balance disorder" and "coordination abnormal" were recoded to the preferred term "Gait disturbance". To accurately evaluate the frequency of the PT "rash" there were six specific rash terms that were recoded to the term "rash". These terms were "rash macular", "rash maculo-papular", "rash maculovesicular", "rash on abdomen", "rash papular" and "rash pruritic".

The pool included 569 patients with an AE entry. This patient count will be utilized (as denominator) to generate percent of patients but does not equal the exact number of patients on GNX participating in the studies. As noted above the precise patient count of individual studies corresponding to the open label AE count could not be ascertained. The percent count of an AE based on number of patients with an AE entry does serve as a rough index of the frequency of the AE in the study population.

From among the pool there were 138 SAE entries from 129 patients. The top ten of all SAE by preferred term is presented in Table 37. There were 4.0% of patient entries for the seizure

[15] Pooled AE from Studies 0601, 0603, 0700, 0900 -52wk, 2002-C6, and 3001 DB & OL ADAM- ADAE datasets with Subject ID, AEDECOD, Study Day, Severity and Serious AE variables, on GNX treatment with Study 0700 STDM ae.xpt dataset containing only event term and subject ID.

related PT's (Convulsion, Seizure and Status Epilepticus) with 0.9% for "Pneumonia", 0.7% "somnolence". There were 3 patients with an SAE event entry for "Gait Disturbance". One patient had this entry with a TTO that supports a plausible causal relationship. The narrative for this patient ((b) (6) reveals the gait disturbance resolved with GNX dose reduction, also supportive of a causal relationship. The overall profile of SAE's does not change substantially from the profile of the individual study analysis of adult POS study 0603.

Table 37 Ten Most Frequent PT with SAE Entry, Pooled Study Elementary Signal Analysis, pooled adverse event dataset from the ADAE datasets from Studies 0601, 0603, 0700, 0900 - 52wk, 2002-C6, and 3001 DB & OL also including Study 0700 STDM ae.xpt dataset.

AEDECOD- Pool Somnolence, Gait disturbance	# Patients	% of Patients = # Patients with AE / All Patients Contributing an AE entry
CONVULSION	12	2.1
SEIZURE	7	1.2
PNEUMONIA	5	0.9
SOMNOLENCE	4	0.7
STATUS EPILEPTICUS	4	0.7
DEHYDRATION	3	0.5
GAIT DISTURBANCE	3	0.5
PNEUMONIA ASPIRATION	3	0.5
PNEUMONIA VIRAL	3	0.5
ACUTE RESPIRATORY FAILURE	2	0.4

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations in the CDD Pooled Studies 0900 and 3001

There were 6 patient discontinuations during Study 3001 double blind treatment interval, 5 if these were due to adverse events and 1 due to withdrawal by subject. The adverse event withdrawals occurred in the interval from day 4 to day 104 of the DB study period. Four of the five patients with discontinuation due to AE were in the PBO treatment arm while one was in the GNX arm with a withdrawal on study day 11 due to seizure. The patient with an entry "withdrawal by subject" occurred on day 58.

During open label extension period there were 6 patients who withdrew due to an adverse event. The temporal relationship to the adverse event withdrawal ranges from 142 to 239 days. This range of latency reduces causal likelihood. There were 8 patient withdrawals during the open label extension due to "lack of efficacy". The duration of treatment to time of withdrawal ranged from 24 to 57 weeks. There were 88 patients that continued in the Study 3001 OL extension, the 8 withdrawals due to lack of efficacy represents 9%. (see section 7.1.3 – durability)

Table 38 Discontinuations in Study 3001 by Discontinuation Event, Study Period and Study Day

Patient ID	Discontinuation Event	Study Period	Study Day
(b) (6)	ADVERSE EVENT	BLINDED TREATMENT	51
	ADVERSE EVENT	BLINDED TREATMENT	4
	ADVERSE EVENT	BLINDED TREATMENT	33
	ADVERSE EVENT	BLINDED TREATMENT	104
	ADVERSE EVENT	BLINDED TREATMENT	100
	ADVERSE EVENT	OPEN LABEL TREATMENT	149
	ADVERSE EVENT	OPEN LABEL TREATMENT	187
	ADVERSE EVENT	OPEN LABEL TREATMENT	170
	ADVERSE EVENT	OPEN LABEL TREATMENT	156
	ADVERSE EVENT	OPEN LABEL TREATMENT	239
	ADVERSE EVENT	OPEN LABEL TREATMENT	142
	LACK OF EFFICACY	OPEN LABEL TREATMENT	367
	LACK OF EFFICACY	OPEN LABEL TREATMENT	321
	LACK OF EFFICACY	OPEN LABEL TREATMENT	254
	LACK OF EFFICACY	OPEN LABEL TREATMENT	243
	LACK OF EFFICACY	OPEN LABEL TREATMENT	341
	LACK OF EFFICACY	OPEN LABEL TREATMENT	400
	LACK OF EFFICACY	OPEN LABEL TREATMENT	166
	LACK OF EFFICACY	OPEN LABEL TREATMENT	176
	PHYSICIAN DECISION	OPEN LABEL TREATMENT	496
	WITHDRAWAL BY SUBJECT	BLINDED TREATMENT	58
	WITHDRAWAL BY SUBJECT	OPEN LABEL TREATMENT	317
	WITHDRAWAL BY SUBJECT	OPEN LABEL TREATMENT	274
	WITHDRAWAL BY SUBJECT	OPEN LABEL TREATMENT	325
	WITHDRAWAL BY SUBJECT	OPEN LABEL TREATMENT	232
	WITHDRAWAL BY SUBJECT	OPEN LABEL TREATMENT	180

There were two discontinuations in study 0900 from among the 7 patients with a diagnosis of CDD. One discontinuation due to lack of efficacy on study day 182 and one patient withdrew consent on study day 153.

Table 39 Discontinuations in Study 0900 by Discontinuation Event, Study Period and Study Day

Patient ID	Discontinuation Event	DSDY
(b) (6)	LACK OF EFFICACY	182
	WITHDREW CONSENT	153

Reviewer Comment: discontinuations from study 3001 due to an AE were more frequent in the PBO treatment arm. This observation points away from study drug intolerance associated with GNX treatment. There were 6 patients who withdrew due to an adverse event during GNX treatment in the OL extension phase of study 3001 where duration of treatment until

withdrawal ranged from 142 to 239 days. This range of latency reduces causal likelihood. There were no discontinuations due to "lack of efficacy" during double blind treatment. There were 8 (9%) patient withdrawals during the open label extension due to "lack of efficacy" where the duration of treatment to withdrawal ranged from 24 to 57 weeks. This rate of withdrawal over a one-year period does not provide substantive data to evaluate durability of treatment, see 7.1.3 Onset, Duration, and Durability of Efficacy Effects.

8.4.4. Significant Adverse Events

Reproductive system, breast disorders and Rash

The Applicant reports in the ISS that Rash and Hormonal effects reported as AEs related to the MedDRA highest or broadest level SOC of reproductive system and breast disorders were initially identified as warranting special attention to better characterize the safety profile of the compound. At the time the AESI groups were included as a cautionary safety oversight measure, these theoretical hormonal effects were not considered to be potential precursors or prodromes of more serious medical conditions nor is there a mechanism or rationale proposed that these hormonal based reactions would be expected or be serious or life-threatening. To date, these AESI groups have generated only 2 SAEs of rash.

The Applicant concludes that given the paucity of evidence and the absence of a safety signal related to 'Rash', there seem to be insufficient grounds to continue to retain 'Rash' as an AESI in future clinical trials.

Rash

To explore the risk related to the AE of "rash" the ADAE Dataset for the DB period of Study 3001 is examined. This analysis revealed there were 3 (6%) patients and 7 (13.7%) patients in the GNX and PBO treatment arms respectively that had an AE entry under the SOC "Skin and Subcutaneous Tissue Disorders". From among these AEs, it was found that 3 (6%) patients in the GNX treatment arm had an AE of "rash". In the PBO treatment arm there were 2 (3.9%) patients with an AE of "alopecia", 4 (7.8%) patients with an AE of rash, 1 (2%) patient with an AE of "blister" and 1 (2%) patient with an AE of "psoriasis", Table 40. None of these events in either treatment arm was entered as an SAE.

Table 40 Frequency of Patients with AE in by SOC "Skin and Subcutaneous Tissue Disorders " and by Preferred Term

Frequency of Patients with AE in the SOC "Skin and Subcutaneous Tissue Disorders "			
ARM	# Patients	% Patients	
Ganaxolone	3	6	
Placebo	7	13.7	

Frequency of Patients with AE in the SOC "Skin and Subcutaneous Tissue Disorders "			
ARM	# Patients	% Patients	
Ganaxolone	3	6	
Placebo	7	13.7	
Frequency of Patients with AE in the SOC "Skin and Subcutaneous Tissue Disorders " by Preferred Term			
	Preferred Term	# Patients	% Patients
Ganaxolone	RASH	3	6
Placebo	ALOPECIA	2	3.9
	BLISTER	1	2.0
	PSORIASIS	1	2.0
	RASH	4	7.8

The OL treatment period of the Pooled CDD, Study 3001 and 0900 ADAE dataset was examined for AE entries in the "Skin and Subcutaneous Tissue Disorders "SOC. There were 6 entries from 5 (4.6%) patients with preferred terms related to skin reaction. Three patients (2.8%) had an AE of "rash", 1 (0.9%) patient had an AE of "rash maculovesicular", and 1 (0.9%) patient had an AE of "urticaria". None of these was entered as an SAE.

Reviewer Comment: Analysis of the Pooled CDD safety dataset does not reveal a safety signal for AEs in the "Skin and Subcutaneous Tissue Disorders "or for the preferred term "rash".

Reproductive System and Breast Disorders

Due to the early concern about potential hormonal effects of GNX as noted in the Applicant's discussion above an analysis of AE in the SOC "Reproductive System and Breast Disorders" was performed on these occurrences in study 3001 and the pooled studies 0900 and 3001, see Table 41.

During the DB period of study 3001 there was a single entry in the SOC "Reproductive System and Breast Disorders" in the GNX treatment arm and none in the PBO arm. This was not an SAE. This was an AE of "Spontaneous Penile Erection" in a (b) (6) at two days after initiation of GNX treatment. The significance of this event with a short latency to effect is of uncertain relationship to GNX treatment.

On examination of the AE that occurred in the "Reproductive System And Breast Disorders" SOC during open label treatment there were 13 entries from among 8 patients. These were entered from one patient in study 0900 and 7 patients in study 3001. In study 0900 there were three sequential monthly entries of "Pain due to Menstrual Cycle" and one entry of "Malaise due to Menstrual Cycle" from a (b) (6) patient with the initial entry on day 12 of GNX treatment. The background history of menstrual experience is not known.

From among the remaining entries in "Reproductive System and Breast Disorders" during the OL period the temporal relationship ranged from day 30 to day 368. Those events entered at treatment day 79 and less will be examined further due to the closer temporal relationship to

GNX treatment. These three events were entered from three patients. The preferred term entries were “menorrhagia”, “Oligomenorrhoea” “Polymenorrhoea” at days 30, 31 and 79 respectively. GNX treatment was discontinued due to “menorrhagia”.

Table 41 Any AE from the SOC Reproductive System And Breast Disorders From Pooled Studies 1042-CDD-3001 and 1042-0900, OL and DB. None Entered as SAE.

STUDYID	SUBJID	AGE	SEX	Preferred Term	GNX Treatment Days	Phase	Comment
		(b) (6)	F	MENSTRUAL DISCOMFORT	12	Double-Blind Phase/Open Label Period	
			F	DYSMENORRHOEA	40	Double-Blind Phase/Open Label Period	
			F	DYSMENORRHOEA	73	Double-Blind Phase/Open Label Period	
			F	DYSMENORRHOEA	98	Double-Blind Phase/Open Label Period	
			M	SPONTANEOUS PENILE ERECTION	2	Double-Blind Phase/Open Label Period	
			F	MENSTRUATION IRREGULAR	368	Open Label Extension Phase	
			F	MENORRHAGIA	368	Open Label Extension Phase	
			F	MENORRHAGIA	30	Open Label Extension Phase	GNX discontinued
			F	POLYMENORRHOEA	79	Open Label Extension Phase	
			F	POLYMENORRHOEA	194	Open Label Extension Phase	
			F	OLIGOMENORRHOEA	31	Open Label Extension Phase	
			F	BREAST ENLARGEMENT	392	Open Label Extension Phase	
			F	DYSMENORRHOEA	123	Open Label Extension Phase	
			F	DYSMENORRHOEA	126	Open Label Extension Phase	

Study 142-0603 (Efficacy And Safety Of Ganaxolone As Adjunctive Therapy For Adults With Drug Resistant Partial-Onset Seizures)

An additional analysis of the frequency of AE in the SOC “Reproductive System And Breast Disorders” is performed on the controlled treatment interval study 0603. There were 9 patients each with an AE occurrent in the PBO and GNX treatment arms representing 4.4% and 4.5% of

patients in the GNX and PBO treatment groups respectively. The frequency of patients with each of the preferred terms by treatment arm in this SOC was also examined, see Table 42. The proportion of patients with an entry in this SOC from the PBO treatment arm is greater than the GNX treatment arm. The frequency of patients with any of the preferred term entries is greater in the GNX arm for the term "Vaginal haemorrhage" with 1% of patients having an AE and 0.5% of patients in the PBO arm. All other preferred term entries have an equal or higher proportion of patients in the PBO arm with an AE entry. The analysis reveals no difference in overall frequency of terms from the SOC "Reproductive System And Breast Disorders". Preferred terms associated with menstrual dysfunction are examined and there is higher proportion of patients with relevant entries in the PBO treatment arm.

Table 42 Study 142-0603 Frequency of Preferred terms from SOC "Reproductive System And Breast Disorders" by % of Patients for each Preferred Term by Treatment Arm

	GNX		PBO	
Preferred Term	**# Patients**	**% Patients**	**# Patients**	**% patients**
Vaginal haemorrhage	2	1.0	1	0.5
Amenorrhoea	1	0.5	0	0.0
Benign prostatic hyperplasia	1	0.5	0	0.0
Dysmenorrhoea	1	0.5	4	2.0
Menstruation irregular	1	0.5	0	0.0
Metrorrhagia	1	0.5	0	0.0
Polymenorrhoea	1	0.5	1	0.5
Uterine polyp	1	0.5	0	0.0
Vaginal inflammation	1	0.5	0	0.0
Breast cyst	0	0.0	1	0.5
Breast tenderness	0	0.0	1	0.5
Menopausal symptoms	0	0.0	1	0.5
Erectile dysfunction	0	0.0	1	0.5
Menorrhagia	0	0.0	1	0.5
Uterine haemorrhage	0	0.0	1	0.5
Total	10	4.9	12	5.9

Reviewer Comment: Analysis of potential hormone effects by examination of the frequency of entries in the SOC "Reproductive System And Breast Disorders" from among the CDD population reveals only one event in the GNX arm of the DB treatment interval. This single event does not support a hormonal effect of GNX treatment in the controlled study interval. There were 4 (3.7%) patients during open label treatment with events in the "Reproductive System and Breast Disorders" SOC with a supportive temporal relationship. These AE were "Menorrhagia", "polymenorrhoea" and "Oligomenorrhoea". These events occurred from among 10 female patients potentially past the age of menarche. This results in a 30% rate of AE in the SOC group of interest. Although the frequency of patients with these preferred term entries is high, the sample size is small and the background rate of these terms in the CDD population is uncertain. An additional examination of the AE in the "Reproductive System And

Breast Disorders" from study 0603 did not reveal a signal for hormonal effects associated with GNX treatment. These AE do not rise to a level of evidence to include in labeling.

Somnolence / Level of Alertness

A prominent AE identified in assessment of TEAE was somnolence. This AE is explored further in this section. Entries in study 3001 DB period AE dataset under the SOC "Nervous System Disorders" are examined for preferred terms similar to or related to somnolence. Five terms were identified in this search. These terms include "hypersomnia", "lethargy", "sedation", "unresponsive to stimuli" and "somnolence". There were 43 AE captured by these terms from 35 patients where 29 (58%) patients were from the GNX treatment arm and 14 (23.5%) patients were in the PBO treatment arm. From among these AE there was a single SAE of "unresponsive to stimuli" in a patient in the PBO treatment arm. The breakout of the five individual somnolence terms is shown in Table 43. Somnolence is the predominant AE preferred term where 36% of patients in the GNX arm experience this AE and 15.7% in the PBO treatment arm. This analysis demonstrates somnolence and sedation are a prominent AE effect seen in GNX treatment. This AE is presented in Section 5 of the proposed label.

No somnolence or sedation TEAE were identified on examination of the ISS dataset of 7 patients in study 0900.

Table 43 Study 3001 for preferred terms similar to or related to somnolence

	GNX		PBO	
Preferred Term	# Patients	% Patients	# Patients	% Patients
SOMNOLENCE	18	36	8	15.7
SEDATION	3	6	2	3.9
HYPERSOMNIA	2	4	0	0.0
LETHARGY	2	4	2	3.9
UNRESPONSIVE TO STIMULI	1	2	1	2.0

Aspiration

Due to the prominence of sedation the reviewer has a concern that the AE "aspiration" may be associated with sedation. The frequency of this preferred term is examined in the ISS ADAE dataset of the pooled studies 0900 and 3001. There were three instances of this preferred term identified in the dataset. There were 2 SAE reports of "aspiration" that occurred in study 3001 during the OL extension period, one after 16 days of GNX treatment and the second on day 212 of GNX treatment. These 2 reports are discussed in Table 35 above and were considered causality uncertain. The third report of "aspiration" was a non-serious AE on day 43 of GNX treatment in study 0900.

An addition search for the preferred term "aspiration" and related term "choking" was performed on the larger ADAE dataset of Study 142-0603 (Efficacy And Safety Of Ganaxolone As Adjunctive Therapy For Adults With Drug Resistant Partial-Onset Seizures). No instances of these two preferred terms were identified in this ADAE dataset.

Reviewer Comment: although over sedation may be contributor to events of aspiration due to altered protective reflexes an examination of adverse events in the CDD population and an adult POS treatment dataset (study 0603) do not identify a safety signal for this event associated with GNX treatment.

Exploration of Preferred Terms dehydration", "Weight decreased", "decreased appetite" and "vomiting"

Because the preferred term "vomiting" was a high frequency TEAE term there is further exploration of potentially related preferred terms in this section. The terms "dehydration", "Weight decreased", "decreased appetite" and "vomiting" are examined in the double-blind phase of study 3001 to allow a comparison of GNX treatment to PBO. There were no instances of "weight decreased" in the DB period of study 3001. The combined frequency of the remaining three PT revealed that 6 (12%) patients in the GNX treatment arm and 11 (21.6%) patients in the PBO had an occurrence of one or more of these PT. The frequency of individual terms reveals the occurrence of "decreased appetite" and "vomiting" in 1 and 5 patients respectively in the GNX treatment arm. There was an instance of "dehydration" and "vomiting" in 1 and 10 patients respectively in the PBO arm, Table 44.

Table 44 Study 3001 DB Treatment period, Combined & Individual Frequencies of the PT "dehydration", "Weight decreased", "decreased appetite" and "vomiting" by Treatment Arm

Treatment Arm	# Patients	% Patients	
Ganaxolone	6	12	
Placebo	11	21.6	
Treatment Arm	Preferred Term	# Patients	% patients
Ganaxolone	DECREASED APPETITE	1	2
	VOMITING	5	10
Placebo	DEHYDRATION	1	2.0
	VOMITING	10	19.6

Reviewer Comment: There was a higher frequency of AEs associated with vomiting, dehydration and weight loss in the PBO treatment arm than in the GNX treatment arm. Examination of these adverse events in the DB period of study 3001 does not identify a safety signal for these terms associated with GNX treatment.

Gait Disturbance and Ataxia

(b) (4). In the DB period of the pivotal study 3001 this AE occurs in 4% of GNX treated patients and 2% of PBO treated patients. None of these adverse events were entered as an SAE. To further assess the risk of the AE "gait disturbance" additional analysis of the DB period of pivotal study 3001 and pooled ADAE dataset for studies 3001 and 0900 are performed. The closely related AE of "fall" and "ataxia" are evaluated in both the DB period of study 3001 and the OL pooled dataset of studies 3001 and 0900. A pertinent negative is the absence of the preferred term "dizziness" in the DB treatment period of study 3001. This term would also be associated with "gait disturbance".

Examination of the frequency of "fall", "gait disturbance", "ataxia" and "balance disorder" in the DB period of study 3001 reveals no events of "ataxia". There were 2 patients in the GNX treatment arm and 1 in the PBO treatment arm of "gait disturbance" and 1 patient in the PBO treatment arm had an AE of "balance disorder". One patient in the GNX treatment arm accounts for an AE of both "fall" and "gait disturbance", Table 45.

Table 45 3001 DB Treatment period, Frequencies of the PT "fall", "gait disturbance", and "balance disorder".

Treatment Arm	Preferred term	# patients	% patients
Ganaxolone	FALL	1	2
	GAIT DISTURBANCE	2	4
Placebo	BALANCE DISORDER	1	2.0
	GAIT DISTURBANCE	1	2.0

Examination of the OL interval of the pooled studies 3001 and 0900 for the terms "gait disturbance" and related terms "ataxia", "balance disorder", and "fall" reveal one instance of "ataxia" and 4 unique patient instances of "gait disturbance". In the instance of "ataxia" and one of the instances of "gait disturbance" the event occurred within the first 21 days of GNX treatment. This temporal relationship is consistent with a causal relationship. The remaining AEs occurred greater than 4 months after initiation of GNX treatment. There was an SAE of "gait disturbance" on day 450 of GNX treatment. This prolonged latency of greater than one year before occurrence of the AE does not support a causal relationship. The patient had an increase in concomitant VPA dose within the same month of the AE. This concomitant VPA may have contributed to the event of "gait disturbance".

Table 46 Examination of OL Period of Pooled Studies 1042-CDD-3001 and 1042-0900 for Entries of "ataxia", "balance disorder", "fall" and "gait disturbance".

SUBJID	Preferred Term*	Study Day	SAE
(b) (6)	ATAXIA	21	N
	GAIT DISTURBANCE	450	Y
	GAIT DISTURBANCE	15	N
	GAIT DISTURBANCE	239	N
	GAIT DISTURBANCE	135	N

*each single instance represents 2.0% of Patients

Further exploration of the risk of "gait disturbance" and related adverse events is assessed by examination of the larger adult AEAE dataset of study 142-0603, see Table 26, (Efficacy and Safety Of Ganaxolone As Adjunctive Therapy For Adults With Drug Resistant Partial-Onset Seizures). Analysis of the GNX treatment arm reveals there were 8, 11, 1, and 7 patients with AE entries of "ataxia", "balance disorder", "fall" and "gait disturbance" respectively. This is compared to the PBO treatment arm where there were 3,2,8, and 5 patients with AE entries of ataxia", "balance disorder", "fall" and "gait disturbance" respectively, Table 47. One of the PT entries of "gait disturbance" in the GNX treatment was a (b) (6) patient where the event was an SAE.

Table 47 Study 142-0603 DB Period, Frequency of Preferred terms "ataxia", "Balance disorder", "fall" and "gait disturbance" by Treatment arm and Percent of Patients for each Preferred Term

	GNX (n= 203)		PBO (n= 202)		
Preferred Term	**# patients**	**% patients**	**# patients**	**% patients**	**Comment**
Ataxia	8	3.9	3	1.5	No SAE in GNX arm
Balance disorder	11	5.4	2	1.0	No SAE in GNX arm
Fall	1	0.5	8	4.0	No SAE in GNX arm
Gait disturbance	7	3.4	5	2.5	1 (0.5%) Gait disturbance SAE in GNX arm ((b) (6) study day 37), none in PBO
Any Term	27	13.3	18	9.0	

Reviewer Comment: There is a low frequency of "gait disturbance" and related preferred terms and no SAE among these entries in the adverse event dataset of pooled CDD patients, however, the overall population is small. (b) (4) Additional examination of the adult POS population in study 603 reveals an excess of 4.3% GNX over PBO for "Gait disturbance" related terms where one entry is an SAE. This frequency over placebo is consistent with the presence of a signal for "gait disturbance" and related terms (b) (4)

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study 3001 DB

In Study 3001 DB period the TEAE with frequency greater than 2% in the GNX treatment arm with an excess over PBO were somnolence, constipation, salivary hypersecretion, seasonal allergy, sedation, bronchitis, ear infection, gait disturbance, hypersomnia, influenza, insomnia, irritability, lethargy, nasal congestion, and rhinitis. The preferred terms with the largest

frequency margin greater than 4%, GNX over PBO, were “somnolence”, “pyrexia”, “salivary hypersecretion”, “seasonal allergy”, and “upper respiratory tract infection” where the percent difference between GNX and PBO arms for these preferred terms were 20.3, 10.2, 6, 6, and 4.1 respectively, Table 48.

Table 48 Study 3001 DB Period, TEAE Occurrence of 1 Event or More in GNX Treatment Arm by Frequency and Percent of Patients, GNX vs PBO

PT	GNX (n= 50)		PBO (n= 51)		
Preferred Term	GNX # patients	GNX % Patients	PBO # Patients	PBO % patients	Difference GNX % - PBO %
SOMNOLENCE	18	36	8	15.7	20.3
PYREXIA	9	18	4	7.8	10.2
SEIZURE	7	14	9	17.6	-3.6
UPPER RESPIRATORY TRACT INFECTION	5	10	3	5.9	4.1
VOMITING	5	10	10	19.6	-9.6
CONSTIPATION	3	6	3	5.9	0.1
RASH	3	6	4	7.8	-1.8
SALIVARY HYPERSECRETION	3	6	1	2.0	4.0
SEASONAL ALLERGY	3	6	0	0.0	6.0
SEDATION	3	6	2	3.9	2.1
BRONCHITIS	2	4	0	0.0	4.0
EAR INFECTION	2	4	3	5.9	-1.9
GAIT DISTURBANCE	2	4	1	2.0	2.0
HYPERSOMNIA	2	4	0	0.0	4.0
INFLUENZA	2	4	1	2.0	2.0
INSOMNIA	2	4	2	3.9	0.1
IRRITABILITY	2	4	2	3.9	0.1
LETHARGY	2	4	2	3.9	0.1
NASAL CONGESTION	2	4	1	2.0	2.0
RHINITIS	2	4	4	7.8	-3.8
ABDOMINAL DISCOMFORT	1	2	0	0.0	2.0
ABNORMAL WEIGHT GAIN	1	2	0	0.0	2.0
ANAL FUNGAL INFECTION	1	2	0	0.0	2.0
ANTICONVULSANT DRUG LEVEL DECREASED	1	2	0	0.0	2.0
ANXIETY	1	2	1	2.0	0.0
ASTHENIA	1	2	0	0.0	2.0
BENIGN BREAST NEOPLASM	1	2	0	0.0	2.0
CHOKING	1	2	0	0.0	2.0
CONJUNCTIVITIS	1	2	0	0.0	2.0
DECREASED APPETITE	1	2	0	0.0	2.0
DIARRHOEA	1	2	4	7.8	-5.8
DISTURBANCE IN ATTENTION	1	2	0	0.0	2.0
DROOLING	1	2	0	0.0	2.0
DYSPNOEA	1	2	0	0.0	2.0
FALL	1	2	0	0.0	2.0
FATIGUE	1	2	1	2.0	0.0

PT	GNX (n= 50)		PBO (n= 51)		
Preferred Term	GNX # patients	GNX % Patients	PBO # Patients	PBO % patients	Difference GNX % - PBO %
FOOD REFUSAL	1	2	0	0.0	2.0
GASTROENTERITIS	1	2	1	2.0	0.0
GASTROINTESTINAL DISORDER	1	2	1	2.0	0.0
GASTROINTESTINAL VIRAL INFECTION	1	2	2	3.9	-1.9
HEADACHE	1	2	0	0.0	2.0
HEPATIC ENZYME INCREASED	1	2	0	0.0	2.0
HEPATIC STEATOSIS	1	2	0	0.0	2.0
HICCUPS	1	2	0	0.0	2.0
HYPOPHAGIA	1	2	0	0.0	2.0
HYPOTONIA	1	2	1	2.0	0.0
INAPPROPRIATE AFFECT	1	2	0	0.0	2.0
INCREASED APPETITE	1	2	0	0.0	2.0
INCREASED BRONCHIAL SECRETION	1	2	0	0.0	2.0
INCREASED UPPER AIRWAY SECRETION	1	2	0	0.0	2.0
INFLUENZA VIRUS TEST POSITIVE	1	2	0	0.0	2.0
LACRIMATION DECREASED	1	2	0	0.0	2.0
LARYNGITIS	1	2	0	0.0	2.0
LIP INJURY	1	2	0	0.0	2.0
LOWER RESPIRATORY TRACT CONGESTION	1	2	0	0.0	2.0
LOWER RESPIRATORY TRACT INFECTION	1	2	0	0.0	2.0
MIDDLE INSOMNIA	1	2	0	0.0	2.0
NASAL FLARING	1	2	0	0.0	2.0
NAUSEA	1	2	0	0.0	2.0
NERVOUSNESS	1	2	0	0.0	2.0
OCULAR HYPERAEMIA	1	2	0	0.0	2.0
OEDEMA PERIPHERAL	1	2	0	0.0	2.0
ORAL CANDIDIASIS	1	2	0	0.0	2.0
OXYGEN SATURATION DECREASED	1	2	0	0.0	2.0
PNEUMONIA	1	2	0	0.0	2.0
PNEUMONIA ASPIRATION	1	2	0	0.0	2.0
PRODUCTIVE COUGH	1	2	0	0.0	2.0
RESPIRATORY DISORDER	1	2	0	0.0	2.0
RESPIRATORY TRACT INFECTION	1	2	0	0.0	2.0
RESPIRATORY TRACT INFECTION VIRAL	1	2	3	5.9	-3.9
RHINORRHOEA	1	2	2	3.9	-1.9
RHINOVIRUS INFECTION	1	2	0	0.0	2.0
SEDATION COMPLICATION	1	2	0	0.0	2.0
SLEEP DISORDER	1	2	1	2.0	0.0
SPONTANEOUS PENILE ERECTION	1	2	0	0.0	2.0
UNRESPONSIVE TO STIMULI	1	2	1	2.0	0.0
URINARY RETENTION	1	2	0	0.0	2.0

PT	GNX (n= 50)		PBO (n= 51)		
Preferred Term	**GNX # patients**	**GNX % Patients**	**PBO # Patients**	**PBO % patients**	**Difference GNX % - PBO %**
URINARY TRACT INFECTION	1	2	3	5.9	-3.9
URINE OUTPUT DECREASED	1	2	0	0.0	2.0
VIRAL INFECTION	1	2	0	0.0	2.0
VIRAL UPPER RESPIRATORY TRACT INFECTION	1	2	1	2.0	0.0

120 Day Safety Update

At the 120 day safety update there were 39 new adverse event entries that included 24 preferred terms from among 13 patients, see Table 49. Five adverse events, 4 from one patient, were entered as an SAE. The most frequent TEAE was "toothache" from patient (b) (6) An additional 3 patients had two events each of "vomiting", "somnolence" and "weight decreased". The two most frequent adverse events were "somnolence" and "vomiting".

Table 49 120 Day Safety Update, Additional TEAE and SAE by Patient ID, SAE / TEAE status and Number of Events.

Subject ID	Preferred Term	Serious (Y/N)	# Events
(b) (6)	TOOTHACHE	N	11
	VOMITING	N	2
	SOMNOLENCE	N	2
	WEIGHT DECREASED	N	2
	WEIGHT DECREASED	N	1
	VOMITING	N	1
	UPPER RESPIRATORY TRACT INFECTION	N	1
	TOOTHACHE	N	1
	SEIZURE	N	1
	SEIZURE	Y	1
	SOMNOLENCE	N	1
	STOMA SITE HAEMORRHAGE	Y	1
	UPPER RESPIRATORY TRACT INFECTION	Y	1
	VIRAL UPPER RESPIRATORY TRACT INFECTION	N	1
	VOMITING	Y	1
	VIRAL UPPER RESPIRATORY TRACT INFECTION	N	1
	SLEEP DISORDER	N	1
	SOMNOLENCE	N	1
	VOMITING	Y	1
	SOMNOLENCE	N	1
	WEIGHT DECREASED	N	1
	THROMBOCYTOSIS	N	1
	VOMITING	N	1
	SEDATION COMPLICATION	N	1
	UPPER RESPIRATORY TRACT INFECTION	N	1
	SOMNOLENCE	N	1

Reviewer Comment: The 39 new adverse event entries identified in the 120-day safety update are similar to the profile of adverse events at the time of the original submission. A new safety signal is not identified.

Study 0603 TEAE, Adult POS, see Table 26

There were 404 TEAE from among 136 (67%) patients in the GNX treatment arm of Cohort 1 and 2 while there were 242 TEAE from among 98 (49%) patients in the PBO treatment arm of Cohort 2. There were 26 preferred terms in the GNX treatment arm with a frequency greater than 1% of patients, see Table 50. The four most frequent TEAE in both treatment arms were "somnolence", "dizziness", "fatigue", and "headache", with an excess of 17.2%, 13.7%, 5.4% and 1.5% of patients respectively in the GNX treatment arm for each term. The greatest differences in GNX over PBO of more than 2% were for the terms "somnolence", "dizziness", "fatigue", "ataxia", "balance disorder", and "vision blurred".

Table 50 Study 0603, Cohorts 1 & 2, GNX vs PBO Where TEAE > 1% in GNX treatment Arm

Preferred Term	GNX UNIQUE PATIENTS	GNX % PATIENTS COHORT2	PBO UNIQUE PATIENTS	% PBO COHORT 2	Difference in % Patients
Somnolence	45	22.2	10	5	17.2
Dizziness	37	18.2	9	4.5	13.7
Fatigue	23	11.3	12	5.9	5.4
Headache	18	8.9	15	7.4	1.5
Balance disorder	7	3.4	1	0.5	2.9
Convulsion	7	3.4	7	3.5	-0.1
Vision blurred	7	3.4	2	1	2.4
Ataxia	6	3	0	0	3
Gait disturbance	6	3	2	1	2
Upper respiratory tract infection	6	3	3	1.5	1.5
Aphasia	5	2.5	2	1	1.5
Nasopharyngitis	5	2.5	9	4.5	-2
Alopecia	4	2	0	0	2
Rash	4	2	2	1	1
Sedation	4	2	0	0	2
Tremor	4	2	1	0.5	1.5
Vertigo	4	2	1	0.5	1.5
Anxiety	3	1.5	3	1.5	0
Constipation	3	1.5	1	0.5	1
Contusion	3	1.5	4	2	-0.5
Diarrhoea	3	1.5	5	2.5	-1
Dysarthria	3	1.5	1	0.5	1
Dyspnoea	3	1.5	0	0	1.5
Insomnia	3	1.5	0	0	1.5

Preferred Term	GNX UNIQUE PATIENTS	GNX % PATIENTS COHORT2	PBO UNIQUE PATIENTS	% PBO COHORT 2	Difference in % Patients
Sinusitis	3	1.5	2	1	0.5
Urinary tract infection	3	1.5	2	1	0.5

PBO from ADAE dataset, Variables TRT01A, TRTA and APHASE set to "placebo", "placebo" and "On-treatment" with ASTDY set to range 1 – 117.
GNX from ADAE dataset, Variables TRT01A, TRTA and APHASE set as follows:

TRT01A	TRTA	APHASE
Ganaxolone 1200 mg	Ganaxolone 1200 mg	On-treatment
Ganaxolone 1200 mg	Ganaxolone 1800 mg	On-treatment
Ganaxolone 1800 mg	Ganaxolone 1800 mg	On-treatment

with ASTDY set to range 1 – 100.

Reviewer Comment: Somnolence is the most frequent TEAE in the GNX treatment arms of both Studies 3001 and 0603 while the most preferred terms next in order of frequency in Study 3001 are "pyrexia", "seizure", "upper respiratory tract infection", "vomiting", "constipation" and "rash". The more frequent preferred terms observed in Study 0603 are CNS associated adverse effects of "dizziness", "fatigue", "headache" and "balance disorder". The difference in the high frequency preferred terms is likely associated with the age of the patient population, where the CDD cohort is younger and prone to a higher frequency of respiratory and gastroenterological infections. There is no evidence of new safety signal of concern on examination of the Study 0603 adult POS population.

Study 0700 PTSD, see Table 26

There were 66 TEAE entries in the GNX treatment arm of the DB period 01 from among 28 patients and 45 TEAE in the PBO arm of the DB period 01 from among 22 patients. Examination of events that occurred in greater than one patient in the GNX treatment arm revealed there was an excess of occurrences (unique patient) over PBO for the terms "ataxia", "diarrhea", "slurred speech", and "strep throat". The terms "headache" and "somnolence" were most frequent in the GNX arm but were more frequent in the PBO treatment arm. For the purpose of this analysis the terms "sleepiness" and "sedation" were combined. There is no novel safety profile emergent in the analysis of the TEAE from study 0700 compared with the CDD population.

Table 51 Study 0700, TEAE, GNX vs PBO During Treatment Period 01.

AEHEVNT (AE Term)	GNX # Patients	% patients	PBO # Patients	% patients
Headache	4	7.3	6	11.8
Somnolence	3	5.5	4	7.8
ataxia	2	3.6	0	0
daytime drowsiness	2	3.6	2	3.9
diarrhea	2	3.6	0	0.0
slurred speech	2	3.6	0	0.0
Strep throat	2	3.6	0	0.0

AEHEVNT (AE Term)	GNX # Patients	% patients	PBO # Patients	% patients
blurred vision	1	1.8	1	2.0
Common Cold	1	1.8	0	0.0
confusion	1	1.8	0	0.0
depression	1	1.8	0	0.0
difficulty focusing eyes	1	1.8	0	0.0
Dizziness	1	1.8	0	0.0
dizziness, confusion and balance issues.	1	1.8	0	0.0
Drowsiness	1	1.8	0	0.0
Drowsiness	1	1.8	0	0.0
Dry mouth	1	1.8	0	0.0
elevated ALT	1	1.8	0	0.0
fatigue	1	1.8	1	2.0
GI upset	1	1.8	0	0.0
increased shakiness of hands and legs	1	1.8	0	0.0
Leg cramping	1	1.8	0	0.0
lethargy	1	1.8	0	0.0
Lethargy	1	1.8	0	0.0
Light Headed	1	1.8	0	0.0
Mid Calf Pain	1	1.8	0	0.0
mild decreased alertness in a.m.	1	1.8	0	0.0
mild sedation	1	1.8	0	0.0
muscle aches	1	1.8	0	0.0
nightmare	1	1.8	0	0.0
nightmares	1	1.8	0	0.0
Participant took vicodin	1	1.8	0	0.0
positive blood in urine	1	1.8	0	0.0
Rash on abdomen	1	1.8	0	0.0
Reduced balance	1	1.8	0	0.0
rt hand tremor	1	1.8	0	0.0
sedation	1	1.8	1	2.0
sinus congestion	1	1.8	1	2.0
sleepiness	1	1.8	0	0.0
slowed motor skills	1	1.8	0	0.0
Sore thigh muscles	1	1.8	0	0.0
Suicidal Ideation	1	1.8	0	0.0
Suicide of family friend	1	1.8	0	0.0
temporary confusion	1	1.8	0	0.0
Tics	1	1.8	0	0.0
transient mild euphoria	1	1.8	0	0.0
Trouble falling asleep	1	1.8	0	0.0
upper respiratory infection (URI)	1	1.8	1	2.0
Upper respiratory syndrome	1	1.8	1	2.0
urinary tract infection	1	1.8	0	0.0
vertigo	1	1.8	0	0.0
Vertigo	1	1.8	0	0.0
vomiting	1	1.8	0	0.0

Pooled Study Elementary Signal Analysis

The pooled signal analysis safety dataset (see description above) is examined for overall AE frequency. From within this pool there were 3017 Adverse event entries from 596 patients in the AE pooled dataset. The most frequent TEAE, "somnolence" occurred in 47% of patients who had an AE entry although only 1.5% (4 patients) of these entries was flagged as an SAE. The preferred term "dizziness" and "headache" were the following most frequent AE entries among entries with a frequency greater than 10%, see Table 52.

Although there was a high frequency of "somnolence" only 1.5% (4 patients) were flagged as an SAE while a high proportion of patients with seizure related AE entries (PT= "convulsion", "seizure") were also flagged as an SAE. The preferred term "gait disturbance" (with inclusive recoding to include the terms "coordination abnormal" and "balance disorder") is included in the Warnings and Precautions section of proposed labeling. In this pooled analysis "gait disturbance" has an AE frequency that includes 43 patients (7.6%) where 3 (7%) of these patients have the event also flagged as an SAE. Fall is examined as a term likely to be associated with "gait disturbance". There were 23 (4% of patents in the AE pool) patients with an AE of "fall" with none entered as an SAE.

The patients with a PT of "rash" flagged as an SAE are further examined. Patient (b) (6) a patient in study 0601 had a rash appear on "stomach and arms" that was identified as mild severity. The GNX dose was reduced, and the patient listed as recovered. The causal relation to GNX is confounded by the concomitant treatment with several other AEDs including phenytoin. A second patient (b) (6) in study 0900 had an entry of rash as an SAE. The brief narrative on this event from study report is presented below.

"*On study Day 27, patient* (b) (6) *was hospitalized due to a rash. Study drug was discontinued that same day due to the rash. On* (b) (6) *(Day 28), the subject prematurely discontinued the 26-week open label study due to the rash, which was resolving at that time. The subject began treatment with topical triamcinolone on* (b) (6) *(Day 32) and received 1 dose of intravenous ceftriaxone that same day. No further information was available. The investigator assessed the event of rash as severe in intensity and possibly related to the study drug."*

Table 52 Most Frequent TEAE Entry with Frequency ≥3%, Pooled Study Elementary Signal Analysis, adverse event dataset from the ADAE datasets from Studies 0601, 0603, 0700, 0900 -52wk, 2002-C6, and 3001 DB & OL also including Study 0700 STDM ae.xpt dataset.

Column 1	Column 2	Column 3	Column 4	Column 5
Preferred term-Somnolence, Gait disturbance and rash have additional term inclusive recoding.	**# Patients**	**% Patients with AE**	**# Patients Flagged as an SAE**	**% Patients with AE flagged as an SAE= (Col 4/Col 2)*100**
SOMNOLENCE	265	46.6	3	1.1

Column 1	Column 2	Column 3	Column 4	Column 5
Preferred term-Somnolence, Gait disturbance and rash have additional term inclusive recoding.	**# Patients**	**% Patients with AE**	**# Patients Flagged as an SAE**	**% Patients with AE flagged as an SAE= (Col 4/Col 2)*100**
DIZZINESS	96	16.9	0	0.0
HEADACHE	80	14.1	0	0.0
NASOPHARYNGITIS	47	8.3	0	0.0
GAIT DISTURBANCE	43	7.6	3	7.0
UPPER RESPIRATORY TRACT INFECTION	42	7.4	1	2.4
VOMITING	41	7.2	2	4.9
PYREXIA	39	6.9	0	0.0
CONVULSION	38	6.7	12	31.6
SEIZURE	31	5.4	7	22.6
RASH	31	5.4	2	6.5
URINARY TRACT INFECTION	27	4.7	2	7.4
NAUSEA	25	4.4	0	0.0
CONTUSION	24	4.2	0	0.0
DIARRHOEA	23	4	0	0.0
FALL	23	4	0	0.0
COUGH	21	3.7	0	0.0
SINUSITIS	20	3.5	0	0.0
BACK PAIN	18	3.2	0	0.0
DECREASED APPETITE	18	3.2	0	0.0
IRRITABILITY	17	3	0	0.0

Reviewer Comment: Analysis of the pooled adverse events from the ADAE study 0601, 0603, 0700, 0900 -52wk, 2002-C6, 3001 DB & OL and the ae.xpt dataset of study 0700 STDM reveal a strong signal for somnolence. From among the “somnolence” adverse events there was a small proportion (1.1%) of that were flagged as an SAE. There is a strong signal for terms “dizziness” and “headache” where there was a frequency of greater than 10% of all patients with an AE dataset entry. None of these latter two terms had an entry that was flagged as an SAE. Gait disturbance was notable as an adverse event with a frequency of 7.6% because it may be expected as an associated central nervous system AE given the high frequency of “somnolence” and “dizziness”. There was a higher proportion of gait disturbance events flagged as an SAE compared to the proportion of “somnolence”, “dizziness” and “headache” TEAE were flagged as SAE but less than the total proportion of “somnolence” events when all TEAE are taken as denominator, see Table 37 . The preferred terms with the largest proportion that are flagged as an SAE occurs in the terms “convulsion” and “seizure”. Overall, the profile of adverse event terms in the pooled AE dataset is similar to the profile seen in the GNX treatment arm of pivotal study 3001 with no new safety signal identified in this larger patient pool with a broader age representation.

8.4.6. Laboratory Findings

Study 3001

Hematology

Applicant Report:

Overall, no patterns or trends were observed in hematology laboratory values and shifts from baseline in Study 1042-CDD-3001, Study 1042-0900, or the All Ganaxolone CDD population.

Applicant Shift Analysis Study 1042-CDD-3001: Hematology laboratory values at baseline and at the end of the 17-week DB phase were similar between the GNX and PBO groups. There were no significant findings related to shifts in hematology values. Overall, the proportion of subjects with shifts from normal values at baseline to abnormal (low or high) values at the end of the 17-week DB phase were similar between the GNX and PBO groups.

No abnormal hematology laboratory test parameters were reported as TEAEs for subjects in the GNX group.

Reviewer Analysis

Shifts and Outliers

The change in select hematology parameters including neutrophils, WBC (leukocytes), hemoglobin, eosinophils, and platelets during the double-blind treatment period are examined. The frequency of patients who had one or more shifts to a maximum OORR high value or OORR low value maximum and minimum values in the double-blind intervals are shown in Table 53. The analysis does not identify an outstanding difference in shift magnitude from normal to high or normal to low in the assessment of neutrophils and WBC in the GNX treatment arm. The assessment of eosinophils, platelets and hemoglobin revealed a higher frequency of shift from normal to high compared to normal to low in the GNX arm. When comparing these three parameters between GNX and PBO arm there are similar frequencies of shift from normal to high in both GNX and PBO arms.

Reviewer Comment: overall there is no notable difference in frequencies of normal to high and normal to high shift between treatment arms during DB treatment where this shift would be of clinical concern.

Table 53 Select Hematology Parameters, Study 3001 DB Shift to Max / Min Values During Double Blind Interval by Treatment Arm†

Neutrophils				Eosinophils x10^9/L			
Arm	**Shift**	**# patients**	**% patients**	**Arm**	**Shift**	**# patients**	**% patients**
GNX	NORMAL to HIGH	8	16	GNX	NORMAL to HIGH	7	14
Placebo	NORMAL to HIGH	6	12	Placebo	NORMAL to HIGH	8	16
GNX	NORMAL to LOW	9	18	GNX	NORMAL to LOW	0	0
Placebo	NORMAL to LOW	10	20	Placebo	NORMAL to LOW	4	8
Leukocytes				**Platelets 10^9/L**			
GNX	NORMAL to HIGH	8	16	GNX	NORMAL to HIGH	15	30
Placebo	NORMAL to HIGH	12	24	Placebo	NORMAL to HIGH	14	27
GNX	NORMAL to LOW	6	12	GNX	NORMAL to LOW	0	0
Placebo	NORMAL to LOW	10	20	Placebo	NORMAL to LOW	4	8
hemoglobin							
GNX	NORMAL to HIGH	7	14				
Placebo	NORMAL to HIGH	10	20				
GNX	NORMAL to LOW	2	4				
Placebo	NORMAL to LOW	1	2				

† Derived from Study 3001 double blind ADSL dataset using the "SHIFT1" variable

High outliers identified as greater than 2 times ULN and low outliers identified as 50% of LLN are identified in the GNX and PBO treatment arms for the select hematology parameters during the DB treatment period. This analysis is shown in Table 54. Individual patient results are examined across measurements at baseline and all DB treatment visits where there is potential clinical concern. These instances of additional examination were performed for elevation of eosinophils, both elevation and low values for neutrophils and elevations of WBC in the GNX treatment arm. There were no identified 50% LLN values for WBC in the GNX treatment arm. The results of additional exploration are reported in the "comment" column of Table 54. Overall, the elevations or low values were found to be sporadic occurrences and were not associated with a sustained trend except in the case of two patients with elevations of neutrophils in the GNX arm. These patients also had adverse event entries for infection events.

Table 54 Core Hematology Parameters, Study 3001, DB Outlier Analysis, >2 x ULN & < 50% LLN, GNX vs PBO

Laboratory Parameter	Treatment Arm	2 X ULN	50% LLN	# Patients	% Patients	Comment
EOS	GNX	0	1	1	2	
EOS	GNX	1	0	2	4	Patient (b) (6) had a high baseline with all subsequent measurements below baseline but remaining > 2 ULN. Patient (b) (6) also had a high baseline with all subsequent measurements below baseline but remaining > 2 ULN
EOS	Placebo	0	1	3	6	

Laboratory Parameter	Treatment Arm	2 X ULN	50% LLN	# Patients	% Patients	Comment
EOS	Placebo	1	0	5	10	
NEUT	GNX	0	1	4	8	All patients had improvement in neutrophil count at subsequent measurement. Three of 4 patients were low at baseline. Patients: (b) (6) (b) (6) (b) (6) (b) (6)
NEUT	GNX	1	0	4	8	Two of 4 patients have a return to OORR low but not neutropenic at subsequent visit while the remaining two patients have a trajectory of continued increase. These patients have TEAE entries for pyrexia or infection events. Patients (b) (6) (b) (6) (b) (6) (b) (6)
NEUT	Placebo	0	1	3	6	
NEUT	Placebo	1	0	1	2	
PLAT	Placebo	1	0	1	2	
WBC	GNX	1	0	2	4	both patients return to reference range WBC count at subsequent visits. The outlier increase is an isolated event rather than a systematic sustained elevation. Patients (b) (6) (b) (6)

Chemistry

Applicant Report:

Overall, no patterns or trends were observed in chemistry laboratory values and shifts from baseline in Study 1042-CDD-3001, Study 1042-0900, or the All Ganaxolone CDD population. No Hy's law cases were reported.

Values at baseline and at the end of the 17-week DB phase were similar between the GNX and PBO groups. There were no significant findings related to chemistry laboratory values in either the GNX or PBO groups.

There were no significant findings related to shifts in chemistry laboratory values. Overall, the proportion of subjects with shifts from normal values at baseline to abnormal (low or high) values at the end of the 17-week DB phase were similar between the GNX and PBO groups. As is common with CDD, 47 (95.9%) subjects in the GNX group and 49 (96.1%) subjects in the PBO group had low creatinine levels at baseline (not clinically significant); these levels did not change over the course of the 17-week DB phase.

Chemistry laboratory test abnormalities reported as TEAEs for subjects in the GNX and PBO groups included hepatic enzyme increased reported in 1 (2.0%) subject in the GNX group and blood urea increased in 1 (2.0%) subject in the PBO group, neither of which were related to study drug.

Hy's Law Analysis

A Hy's law analysis is performed on the 120-day safety update ADLB dataset, Figure 6 and Figure 7. This analysis includes patients from open label study 0900 and DB to OL study 3001. The set of laboratory Bili and ALT values captured in treatment period 2 are examined. This represents the open label portion of study 3001 and the entire GNX treatment period for study 0900. There were no Hy's law cases identified from peak hepatic function test values during this period. The longest duration GNX treatment in the OL interval was 4.2 years while 50 patients were treated for greater than one year. No Hy's law cases were identified in this analysis.

Figure 6 ISS Dataset CDD Study 3001, 120 day, Hy's Law Analysis, PBO in DB then GNX in OL, n= 45 (0900 patients do not fit category)

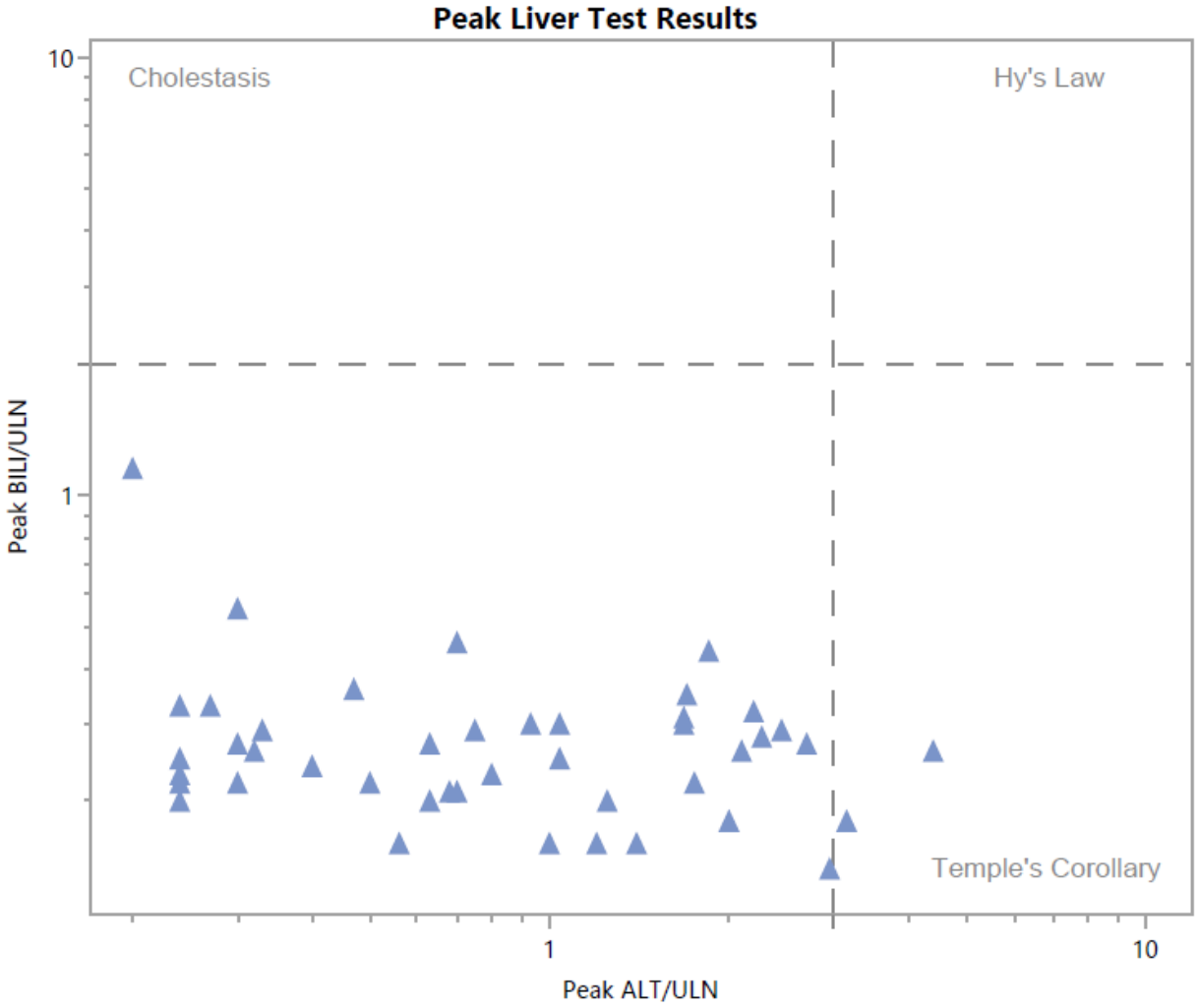
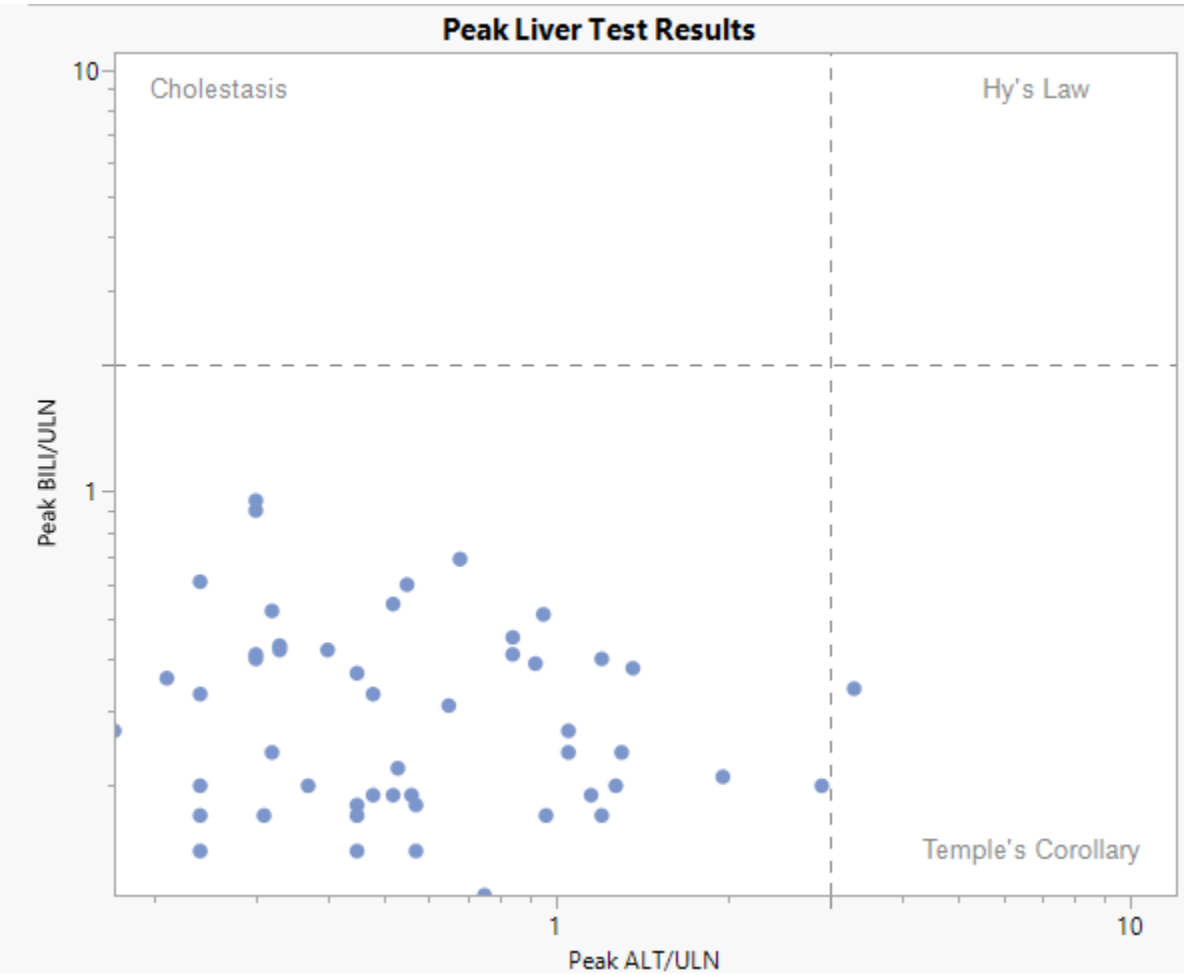


Figure 7 ISS Dataset CDD Study 3001 & 0900, 120 day, Hy's Law Analysis, GNX in DB and OL, n= 50 (includes 0900)



Shifts and Outliers

The change in select clinical chemistry parameters including alanine Aminotransferase, bilirubin, sodium, potassium, chloride, creatinine, glucose and bicarbonate during the double-blind treatment period are examined. The frequency of patients who had one or more shifts to a maximum OORR high value or OORR low value maximum and minimum values in the double-blind intervals are shown in Table 55 and Table 56.

The analysis reveals no notable difference in magnitude of frequencies in the normal to low and normal to high shifts for GNX compared to PBO or normal to low and normal to high shifts within the GNX treatment arm including alanine Aminotransferase, bilirubin, sodium, potassium, chloride, creatinine, and glucose. There was a notable difference in magnitude of the frequencies of normal to low shift between GNX and PBO treatment arms for bicarbonate.

Near double the frequency of patients in the GNX treatment arm 13 (26%) of patients in the GNX treatment arm had an occurrence of normal to OORR low shift for bicarbonate during the DB treatment period compared to 7 (14%) patients in the PBO treatment arm. The slope of the bicarbonate value from baseline through the DB treatment interval for all patients in the GNX and PBO treatment arms is generated. This analysis reveals that 52% of patients in the GNX treatment arm have a trendline with negative slope compared to 39% in the PBO treatment arm, see Table 57.

This differential in shift to low bicarbonate is explored further by assessing the mean change from baseline bicarbonate values for all patients in the GNX treatment arms compared to the mean change from baseline for all patients in the PBO treatment arm, see Figure 8 and Figure 9. This analysis reveals little overall difference in the change from baseline to treatment bicarbonate values between the GNX and PBO treatment arms. An additional approach to explore the effect of GNX on serum bicarbonate was to examine the distribution of minimum bicarbonate measurements during the double-blind treatment period in the GNX treatment arm compared to the PBO treatment arm, see Figure 10 and Figure 11. This analysis reveals little difference in the distribution of minimum values between the two treatment arms.

There was also a notably higher frequency of normal to OORR high shift in the potassium values among patients in the GNX (n= 4, 8%) treatment arm compared to those in the PBO (n=1, 2%) arm with no patients in the GNX arm having a normal to low shift. The maximum potassium measurement in the “normal to high” shift group was 5.7mmol/L from a baseline of 4.6mmol/L. This differential in shift to high is explored further by assessing the mean change from baseline potassium value for all patients in the GNX treatment arms compared to the mean change from baseline for all patients in the PBO treatment arm, see Figure 12 and Figure 13. This analysis reveals little overall difference in the change from baseline to treatment period potassium values between the GNX and PBO treatment arms.

Table 55 ALT & BILI, Study 3001 DB Shift to Max / Min Values During Double Blind Interval by Treatment Arm†

ALT & Bilirubin, Normal to High				
Arm	**Lab Parameter**	**Shift**	**# subjects**	**% Subjects**
GNX	ALT	NORMAL to HIGH	4	8
Placebo	ALT	NORMAL to HIGH	3	6
GNX	BILI	NORMAL to HIGH	1	2
Placebo	BILI	NORMAL to HIGH	1	2
† Derived from Study 3001 double blind ADSL dataset using the “SHIFT1” variable				

Table 56 Select Chemistry Parameters, Study 3001 DB Shift to Max / Min Values During Double Blind Interval by Treatment Arm†

Sodium mmol/L				Glucose mmol/L			
Arm	**Shift**	**# Subjects**	**% Subjects**	**Arm**	**Shift**	**# Subjects**	**% Subjects**
GNX	NORMAL to HIGH	2	4	GNX	NORMAL to HIGH	3	6

Sodium mmol/L			
Arm	**Shift**	**# Subjects**	**% Subjects**
Placebo	NORMAL to HIGH	2	4
GNX	NORMAL to LOW	3	6
Placebo	NORMAL to LOW	5	10
Potassium mmol/L			
GNX	NORMAL to HIGH	4	8
Placebo	NORMAL to HIGH	1	2
GNX	NORMAL to LOW	0	0
Placebo	NORMAL to LOW	1	2
chloride mmol/L			
GNX	NORMAL to HIGH	7	14
Placebo	NORMAL to HIGH	7	14
GNX	NORMAL to LOW	2	4
Placebo	NORMAL to LOW	3	6
Creatinine umol/L			
GNX	NORMAL to HIGH	0	0
Placebo	NORMAL to HIGH	0	0
GNX	NORMAL to LOW	1	2
Placebo	NORMAL to LOW	2	4

Glucose mmol/L			
Arm	**Shift**	**# Subjects**	**% Subjects**
Placebo	NORMAL to HIGH	1	2
GNX	NORMAL to LOW	19	38
Placebo	NORMAL to LOW	15	29
Bicarbonate mmol/L			
GNX	NORMAL to HIGH	0	0
Placebo	NORMAL to HIGH	0	0
GNX	NORMAL to LOW	13	26
Placebo	NORMAL to LOW	7	14

† Derived from Study 3001 double blind ADSL dataset using the "SHIFT1" variable (local and Central Lab)

Bicarbonate slope analysis

Table 57 Slope of Bicarbonate Value Trend, Baseline to Week 17 (Visit 6), GNX vs PBO

Slope State, positive/negative	GNX # Patients	GNX % Patients	PBO # Patients	PBO % Patients
Positive	19	38	25	49
Negative	26	52	20	39.2
Insufficient data/measurement	5	10	6	11.8

Figure 8 Study 3001 Bicarbonate Mean Change from Baseline During Treatment Interval (Visit 1- 6) (mmol/L) for Each Patient in PBO Treatment Arm, with Mean of Means (summary statistics)

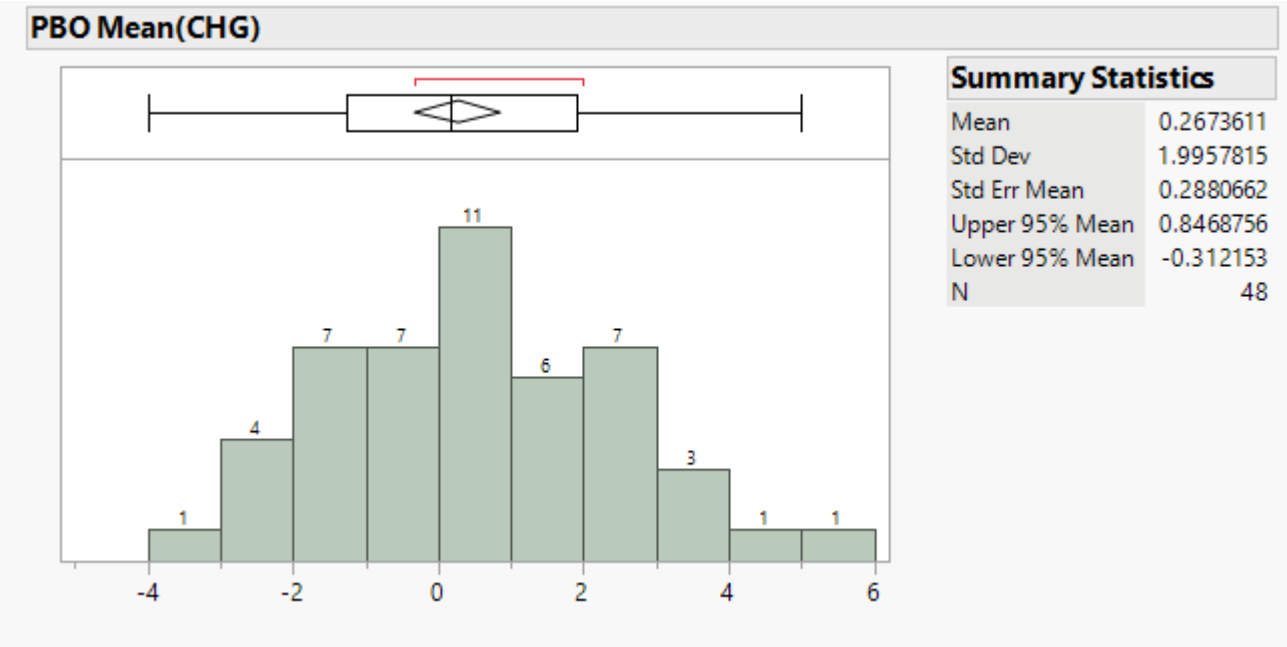


Figure 9 Study 3001 Bicarbonate Mean Change from Baseline During Treatment Interval (Visit 1- 6) (mmol/L) for Each Patient in GNX Treatment Arm, with Mean of Means (summary statistics)

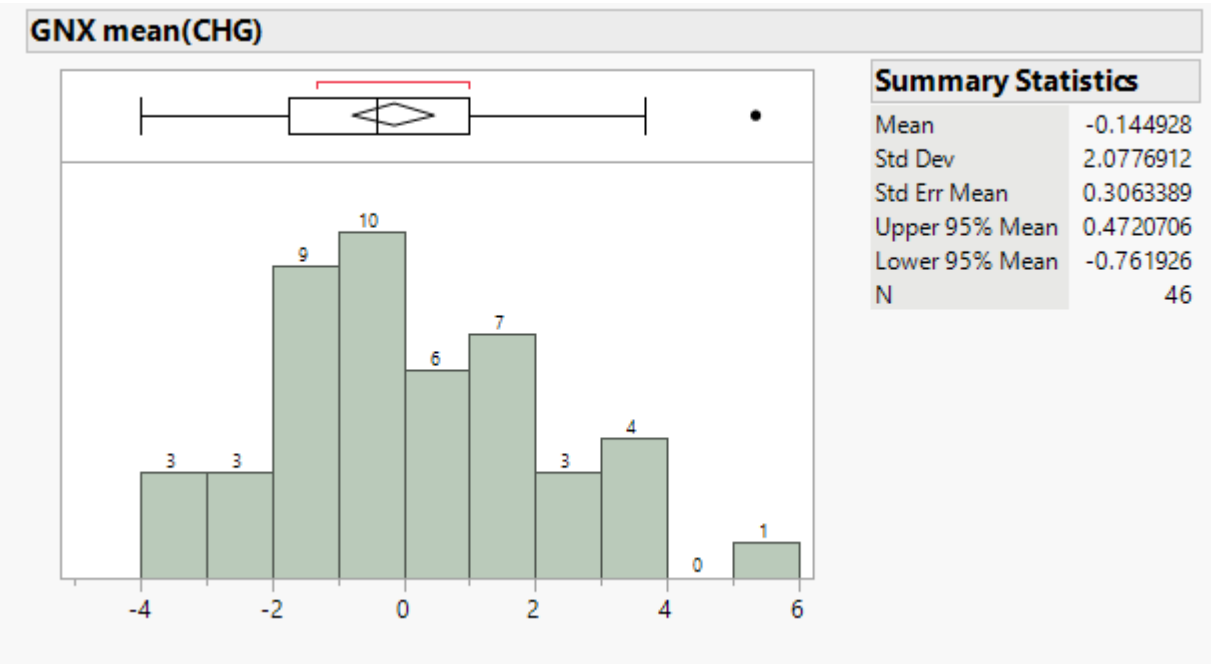


Figure 10 Study 3001 Bicarbonate, Distribution of Minimum Value During Treatment Interval (Visit 1- 6) (mmol/L) for Each Patient in GNX Treatment Arm, with Median and Mean (summary statistics)

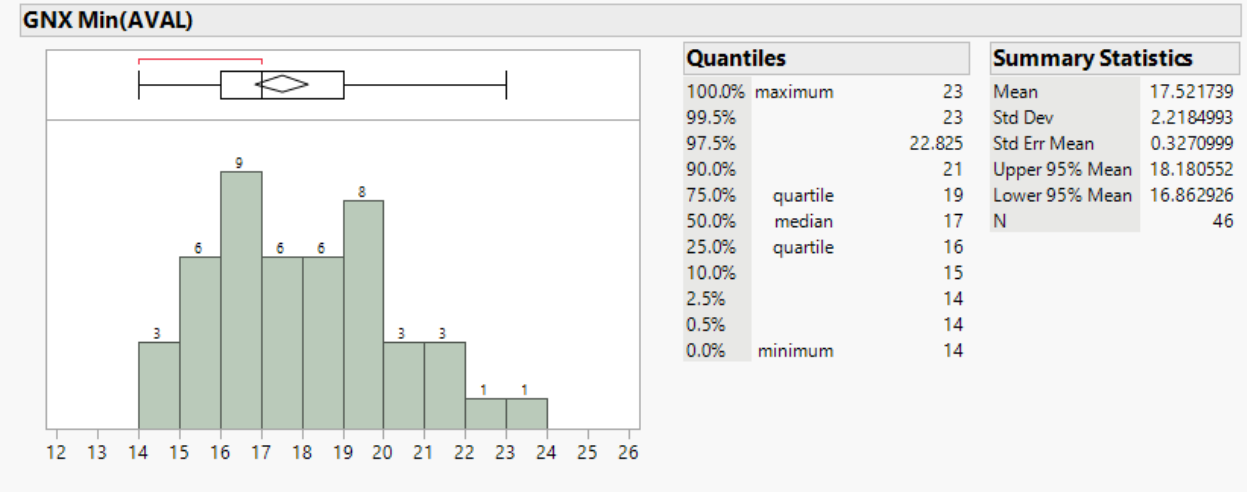


Figure 11 Study 3001 Bicarbonate, Distribution of Minimum Value During Treatment Interval (Visit 1- 6) (mmol/L) for Each Patient in PBO Treatment Arm, with Median and Mean (summary statistics)

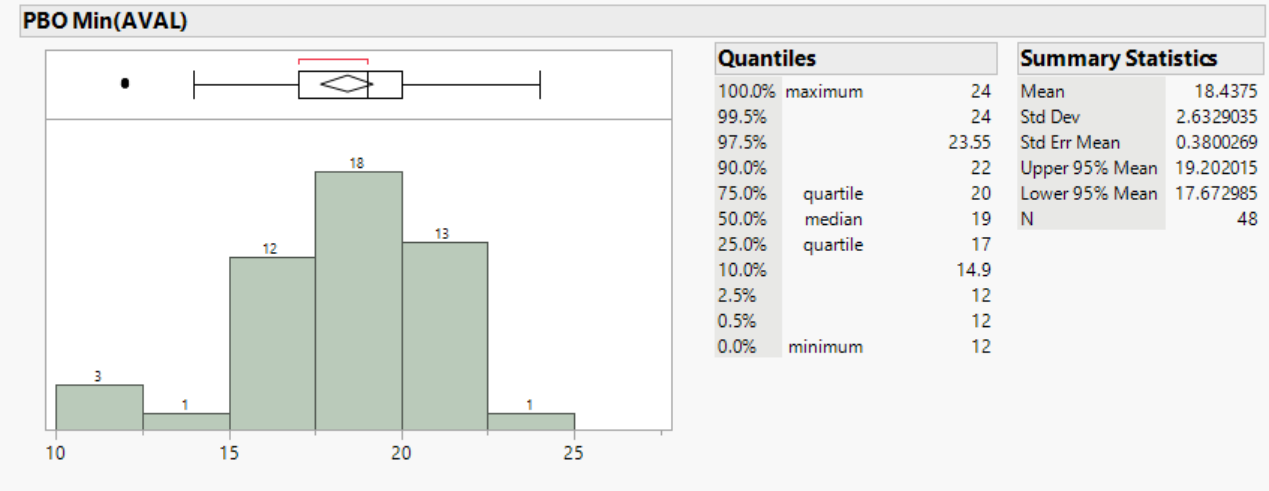


Figure 12 Study 3001 Potassium Mean Change from Baseline During Treatment Interval (Visit 1- 6) (mmol/L) for Each Patient in GNX Treatment Arm, with Mean of Means (summary statistics)

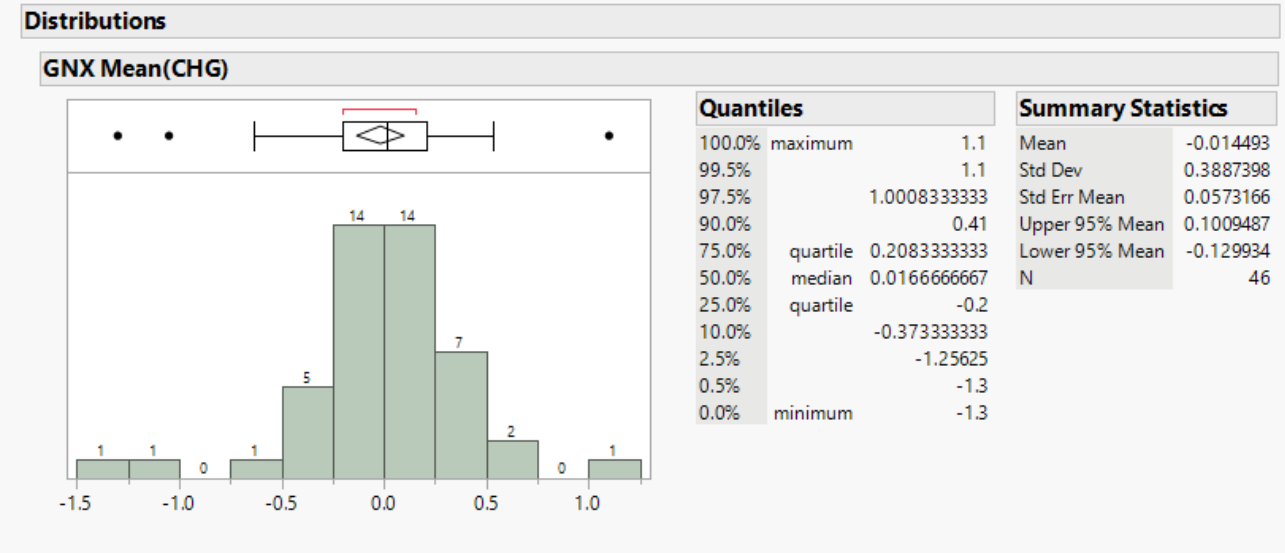
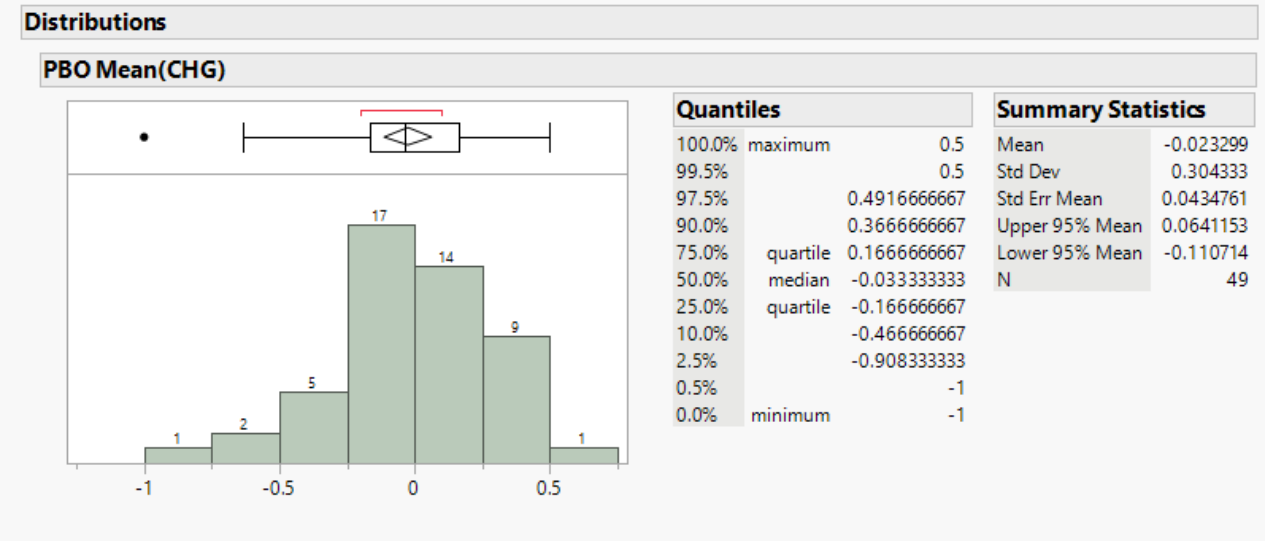


Figure 13 Study 3001 Potassium Mean Change from Baseline During Treatment Interval (Visit 1- 6) (mmol/L) for Each Patient in PBO Treatment Arm, with Mean of Means (summary statistics)



Study 0900
Hy's Law Screen

Bilirubin / ALT analysis performed on the Study 1042-0900 52W ADLB dataset. Laboratory

values for ALT, AST, ALP and bilirubin that span study day 1 (baseline) to as long as 1040 days were examined using the JMP Clinical "Hy's Law Screening" function. The timeline of the distribution of available laboratory values by subject ID is shown in Figure 15 where 11 patients have relevant chemistry data for greater than 293 days and two patients each have relevant chemistry data for 1038 and 1040 days respectively. This data examination reveals no Hy's law cases. Patient (b) (6) had ALP values that were OORR high at all measurements but less than baseline except for final value on study day 303 that was 2 U/L over baseline. There was also an entry for bilirubin on study day 303 that was 2.5 x ULN while all previous post baseline values were at LLN (1.71umol/L). The final value was 10 x greater at 17.1 umol/L while the corresponding day 303 ALT and AST were within normal limits with little change from baseline which raises the possibility of a data entry error, see Figure 14.

Figure 14 Study 0900, OL GNX Treatment, Hy's Law Analysis of Peak Bilirubin/ULN by Peak ALT/ULN Maximum Number of, Study Days 1 to 1040.

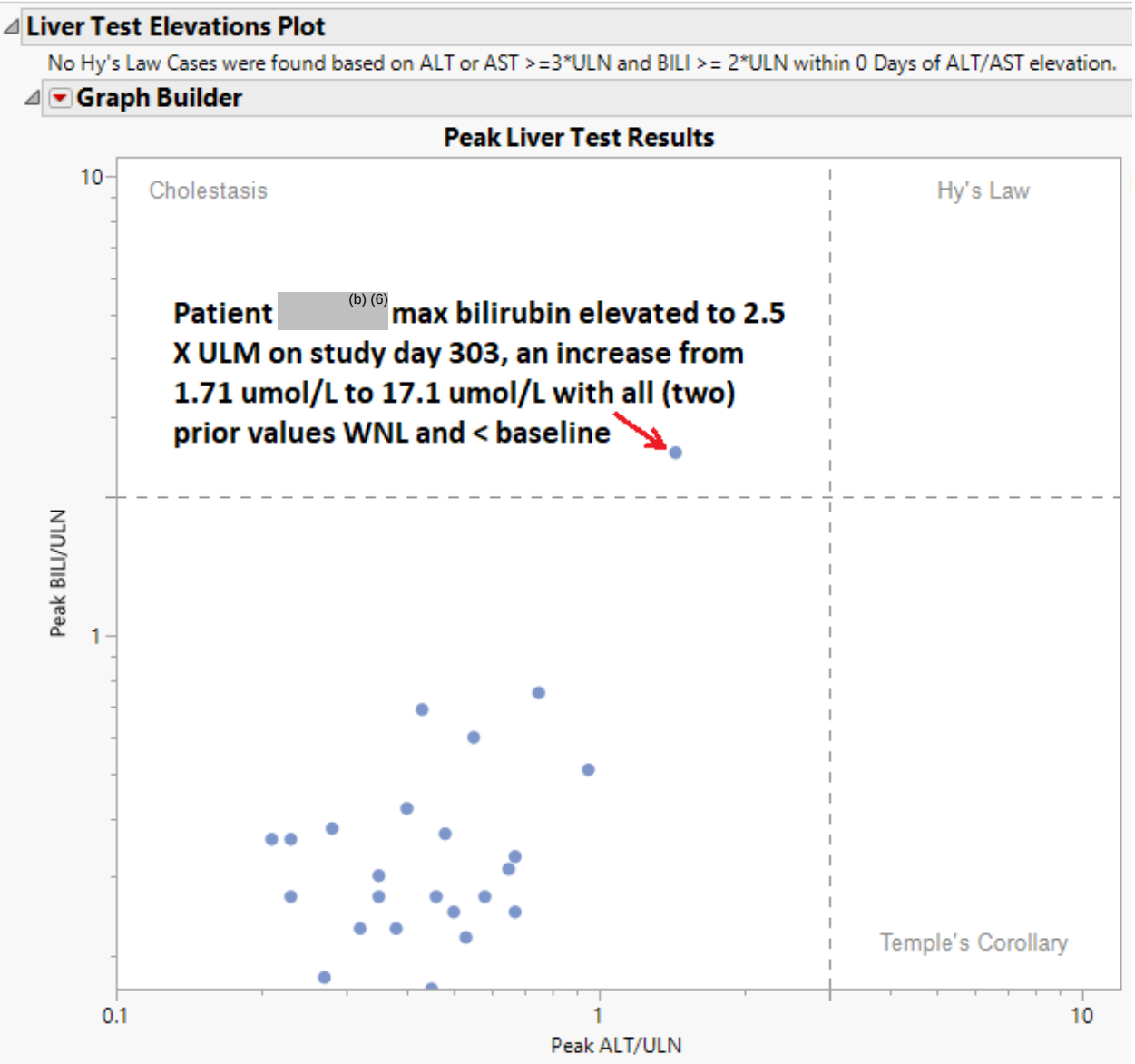
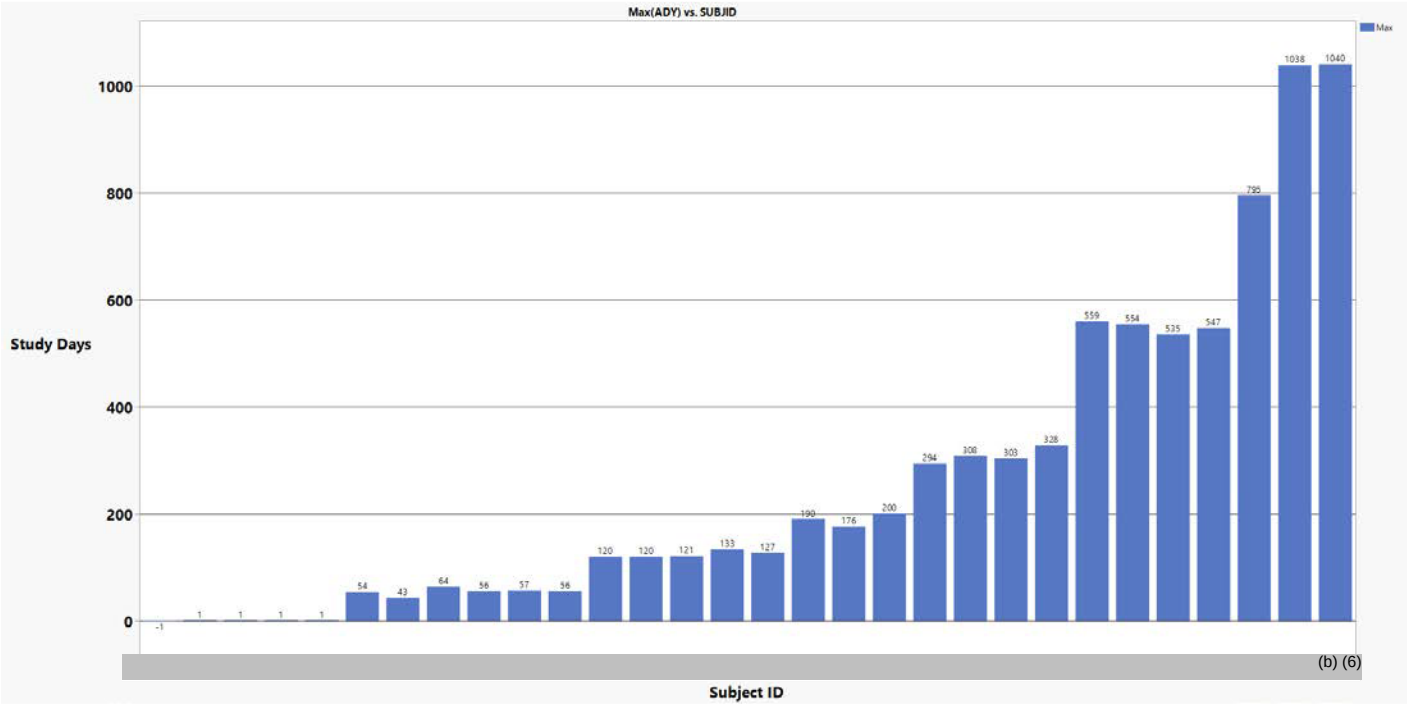


Figure 15 Study 0900, Distribution of ALT, AST, ALP and Bilirubin Measurements by Maximum Number of Days of Blood Chemistry Sampling During the Study.



Study 0603, see Table 26
Hy's Law Screen

A screen for Hy's law cases is performed on the entire ADLB dataset containing all visits for both Cohorts 1 and 2. A variable is created to capture any laboratory value ≥2 x ULN and ≥3 x ULN. Examination of this variable yields 32 entries that have a value ≥2 x ULN and 15 entries with values that are both ≥2 x ULN and ≥3 x ULN for a total of 47 entries from 31 patients that are examined. From among these entries there are two bilirubin values > 2 x ULN. One of these is a baseline value of 47.3umol/L while the second is found at visit 5 week 14 in a second patient where the ALT, AST and ALP values all remain in reference range and bilirubin is found to be 1.4 x ULN at screening. The Hy's Law screen of study 0603 does not reveal any instances of simultaneous elevation of ALT greater than or equal to 3 X ULN with bilirubin greater than or equal to 2 x ULN.

Study 0600, see Table 26
Hy's Law Screen

The STDM, LB dataset for study 0600 is examined for ALT entries that exceed 3 X ULN or Bilirubin values that exceed 2 X ULN. The maximum value for a bilirubin entry was 1.1mg/dl with an OORR high threshold of 1.3mg/dl. The maximum value for an ALT entry was 2.02 x ULN at screening. This analysis does not reveal an ALT -Bilirubin entry that could meet Hy's Law

criteria.

Study 0700, see Table 26
Hy's Law Screen

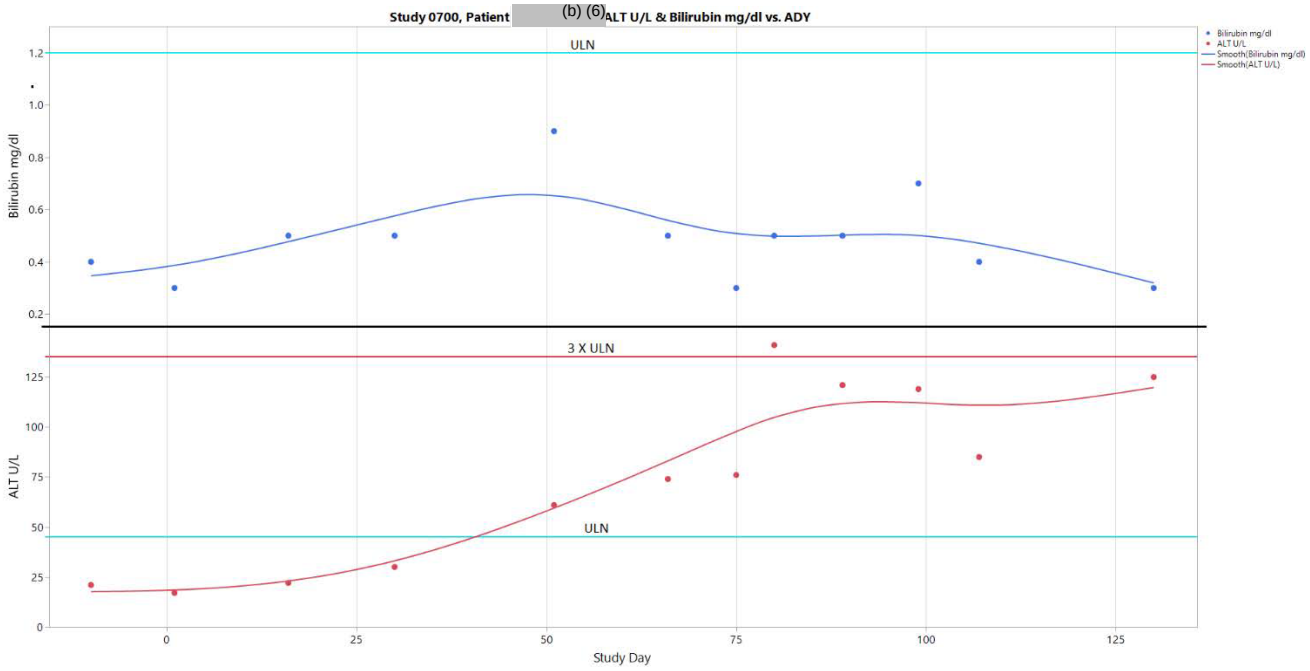
The ADLB dataset is examined for ALT entries that exceed 3 X ULN or Bilirubin values that exceed 2 X ULN.

There was a single entry with a bilirubin value > 2 X ULN. Patient (b) (6) had a bilirubin value 3 x ULN at study visit number 9- study day 57, six days following the final GNX treatment. This patient had no OORR high value of ALT, AST or ALP and the abnormal bilirubin value was bracketed by a normal value 6 days before and 18 days following the abnormal result. There were no AE entries related to the Hepatobiliary disorders SOC. This value is not explained by drug treatment or any clear clinical basis and may be a laboratory or recording error, see Table 58. A second patient, (b) (6) had an entry for ALT that was 3 x ULN on study day 80, Study Visit #7, Week 10. After study day 50 this patient had multiple entries for ALT that were greater than the ULN, with the maximum occurring on day 80. There were no elevations of bilirubin over the upper limit of normal, see Figure 16.

Table 58 Study 0700, Patient (b) (6) ALT, ALP, AST & Bilirubin vs. Study Day. (GNX treatment through study day 50)

Study Day	ALT (NR= 11 – 45 U/L)	ALP (NR= 30 - 130 U/L)	AST (NR= 10 - 30 U/L)	Bilirubin (NR= 0.4 - 1.2 mg/dl)	Comment
-10	20	69	20	0.39	
1	18	76	21	0.33	
15	18	80	19	0.39	
29	14	85	17	0.53	
33	15	79	16	0.28	
51	11	76	16	0.3	
57	14	83	17	3.6	6 days following final treatment day
85	12	86	14	0.57	

Figure 16 Study 0700, Patient (b) (6) ALT U/L & Bilirubin mg/dl vs. Study Day (with smoother line), blue y axis = ULN, red y axis = 3 x ULN. (GNX treatment through study day 106)



There were two entries in the ADLB dataset of ALT values greater than or equal to 3 X ULN. In one patient this was identified at a screening visit. The second patient ((b) (6) had a value that was 3.1 x ULN at study visit 7, week 10, study day 80.

Reviewer Comment: The analysis of ALT and bilirubin measurements does not identify any Hy's law cases.

Bicarbonate (CO2) Analysis

As an additional test of the effect of GNX on serum bicarbonate the CO_2 values obtained during GNX treatment period in Study 0700 are examined. An analysis of the frequency of measurements with a value less than the baseline value are compared to the frequency of measurements with a value greater than or equal to baseline. During GNX treatment there were 274 instances from among 75 (69%) patients where the CO2 value was greater than or equal to baseline while there were 142 instances from among 53 (49%) patients with a CO2 value less than the baseline measurement. This analysis is not in alignment with a systematic trend of declining bicarbonate.

Study 3001

Urinalysis

Applicant Report:

In Study 1042-CDD-3001 DB phase, urinalysis values at baseline and at the end of the 17-week DB phase were similar between the GNX and PBO groups. There were no significant findings related to urinalysis values in either the GNX or PBO groups. Abnormal urinalysis laboratory values reported as TEAEs in the DB phase included urine output decreased reported by 1 (2.0%) subject in the GNX group and polyuria reported by 1 (2.0%) subject in the PBO group, both considered by the investigator as study drug related.

For the Study 1042-CDD-3001 OL phase, a summary of urinalysis laboratory values and changes from baseline are presented in Study 1042-CDD-3001 OL Table 14.3.4.3A. Overall, there were no significant findings related to shifts in urinalysis laboratory values.

Abnormal urinalysis laboratory values reported as TEAEs in the OL phase included urine analysis abnormal reported by 1 (1.1%) subject in the GNX group that was considered unrelated to study drug.

No new trends or changes due to long-term exposure were identified.

In Study 1042-0900, the mean changes from baseline in urinalysis parameters were small with no consistent pattern over time. There were no notable differences between cohorts. There were no changes in urinalysis parameters that were considered clinically significant.

8.4.7. Vital Signs

Applicant Report:

Study 1042-CDD-3001 Double-Blind

There were no significant findings related to vital signs. Potentially clinically significant abnormalities were similar between the GNX and PBO groups (Study 1042-CDD-3001 DB CSR, Section 12.5.1).

TEAEs of vital signs abnormalities were reported for 2 subjects in the GNX group (abnormal weight gain for 1 (2.0%) subject, moderate in severity; oxygen saturation decreased for 1 (2.0%) subject, moderate in severity, also classified as an SAE and 3 subjects in the PBO group (body temperature increased for 2 [3.9%] subjects, hypertension for 1 [2.0%] subject; all were mild in severity. One TEAE of vital signs abnormalities (oxygen saturation decreased) was related to study drug sedation and dose escalation. Dose was reduced and GNX continued.

All Ganaxolone CDD Population (Pooled OL Portion of Study 3001)

There were no significant findings related to vital signs and the overall trends were consistent

with Study 1042-CDD-3001 DB phase.

Study 1042-CDD-3001 Open-Label

Overall, there were no significant findings related to shifts in vital signs values.

Study 1042-0900

Mean changes from baseline in vital signs were generally small with no consistent patterns observed over time. Very few vital sign abnormalities were observed.

8.4.8. Electrocardiograms (ECGs)

Applicant Report:

No clinically meaningful signals of QTc prolongation or other cardiovascular toxicities have been observed in clinical trials to date. Based on the cardiac safety assessment, there was no clear correlation between GNX exposure and QTc prolongation.

Reviewer analysis of the overall ECG interpretation from the ADEG dataset reveals there was a higher frequency of abnormal interpretations in the PBO treatment arm at baseline and a higher proportion of normal overall interpretations in the GNX treatment arm, see Table 59. The proportions did not change in either treatment arm by visit 3 (end of week 5). By visit 6 (end of week 17), the frequencies of normal and abnormal ECG in each treatment arm were similar. Overall, there was no signal for development of an abnormal ECG interpretation associated with GNX treatment in the DB interval.

Table 59 Study 3001, DB, ECG Interpretation by Treatment Arm and Visit Number

Treatment Arm	ECG Overall Interpretation	Visit Number (1= baseline)	# patients
GNX	ABNORMAL	1	4
GNX	NORMAL	1	45
Placebo	ABNORMAL	1	13
Placebo	NORMAL	1	38
GNX	ABNORMAL	3	4
GNX	NORMAL	3	41
Placebo	ABNORMAL	3	15
Placebo	NORMAL	3	33
GNX	ABNORMAL	6	6
GNX	NORMAL	6	27
Placebo	ABNORMAL	6	6
Placebo	NORMAL	6	29

8.4.9. QT

While the 40+ clinical trials of GNX have not raised concerns about QTc prolongation, none were designed to specifically exclude small QTc effects of GNX. The applicant has two planned clinical trials intended to provide significantly more information related to the effects of GNX on QTc and other ECG parameters. These studies include a phase 1 thorough QT/QTc study (1042-TQT-1001) evaluating the highest GNX exposures feasible with oral dosing and a sub-study of the planned phase 3 double-blind study evaluating IV ganaxolone at high doses for the treatment of patients with status epilepticus (1042-SE-3003).

Reviewer Analysis Study 3001 DB

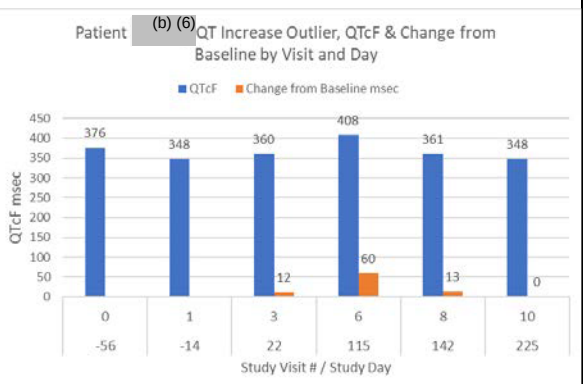
The group mean, median and maximum QTcF by study visit during the DB treatment period are examined. At visit 3 (Week 5) the GNX treatment group has a mean and median of -1.5msec and 1.5msec change from baseline respectively with a maximum change from baseline of 26 msec identified. The PBO arm had a group mean and median of 2.8msec and 3msec change from baseline respectively with a maximum change from baseline of 53 msec identified. At the visit 6 (week 17) measurements the GNX treatment group had a mean and median of 4.9msec and 5.5msec change from baseline respectively with a maximum change from baseline of 60 msec identified. The PBO arm had a group mean and median of 2.1msec and 3msec change from baseline respectively with a maximum change from baseline of 37 msec identified, see Table 60.

The mean and SD for all change from baseline entries in both GNX and PBO treatment arms at visits 3 and 6 is computed. The mean change from baseline is 1.99msec with an SD of 18.4. The maximum positive change from baseline of 60msec is an outlier, 3.3 SD from the mean. The range of values for QTcF for all measurements from this patient ((b) (6) are examined. The maximum QTcF of 408msec with a 60msec change from baseline occurred at visit 6. While on treatment at visits 8 and 10 the sequential QTcF values were 361 and 348 respectively. These observations do not reveal a significantly prolonged QT. Examination of the QTcF values for all entries at visit 3 and 6 in the GNX and PBO treatment arm reveal a maximum QTcF of 422msec and 443msec respectively.

Reviewer Comment: Analysis of the QTcF during the study 3001 DB treatment period dose not reveal evidence of a differential effect on QTc between the GNX and PBO treatment arms.

Table 60 Study 3001 DB: QTcF Group Mean, Median & Maximum by Treatment Arm and Study Visit,.

Arm	**Visit #**	# Patients @ Visit	Mean(CHG) QTcF	Median(CHG) QTcF	Max(CHG) QTcF	Comment
GNX	3	44	-1.3	1.5	26	

GNX	6	34	4.9	5.5	60	 Pt. (b) (6) had a single prolongation of 60msec from baseline to a QTcF of 408msec on Study day 115.
PBO	3	49	2.8	3	53	
PBO	6	35	2.1	3	37	

8.4.10. Immunogenicity

Not Applicable, small molecule drug

8.5. Analysis of Submission-Specific Safety Issues

Not Applicable

8.5.1. Hepatic Failure Case

Patient (b) (6) a (b) (6) has a past medical history of premature birth. At birth, (b) (4) experienced necrotizing enterocolitis resulting in short gut syndrome. The patient's surgical history includes gastrostomy, tracheostomy, cataract operation, intestinal resection, and myringotomy. Additional ongoing medical conditions included hepatic dysfunction, hypotonia (all extremities), left eye ptosis, urinary incontinence, developmental delay, and static encephalopathy with resultant seizure disorder, due to anoxic brain injury sustained while undergoing cataract surgery. The patient was wheelchair-bound and non-verbal.

This patient was entered in the LGS cohort of open label treatment study 1042-0900 and developed jaundice on study day 146. There was no scheduled clinical laboratory assessment between study day 56 and study day 182. Unscheduled clinical laboratory evaluation was performed on **day 156** when the patient developed yellowish-brown, foul smelling urine and was taken to the emergency department. Physical examination findings included that the subject was non-verbal, in no obvious distress and non-toxic; sclera icterus was present, tracheostomy was in place, with increased secretions that required suctioning, along with surrounding erythema. A gastrostomy tube (G-tube) was in place. The subject also exhibited bilateral coarse breath sounds, hyperactive bowel sounds, generalized jaundice, and redness to buttocks and labium majora.

Laboratory results on **day 156** [redacted]) included ALT 22 IU/L (NR 10-35), AST 91 IU/L (NR 15-40; 2.3 ×ULN), ALP 247 IU/L (NR 175-420), bilirubin 5.2 mg/dL (NR 0.0-1.0; 5.2 ×ULN), direct bilirubin 4.3 mg/dL (NR 0.0-0.4; 10.8 ×ULN), gamma glutamyl transferase (GGT) 159 IU/L (NR 13-25; 6.4 ×ULN), ammonia 94 (units and NR not reported), prothrombin time (PT) 61.4 sec (NR 12.2-14.4), partial thromboplastin time (PTT) 105.9 sec (NR 23.4-38.9), and international normalized ratio (INR) 6.62 (NR 0.80-1.20), see Figure 17. Ongoing concomitant medications are listed in Table 61. Phenobarbital is a potentially confounding concomitant AED treatment but had been ongoing for two years.

The patient was then admitted to the hospital on **study day 157** due to hepatic failure. The patient was treated for UTI and macrocytic anemia and also received daily vitamin K infusions. [redacted] was discharged on **study day 195** in stable condition. Study drug was withdrawn due to hepatic failure; the last dose was taken on [redacted] (Day 159).

The patient was again hospitalized on **study day 207** due to worsening jaundice and hyperbilirubinemia. Treatment was started with Zosyn (Piperacillin/tazobactam) to treat possible cholangitis, but this was ineffective in improving bilirubin levels. Testing for Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Hepatitis A, Hepatitis B, Hepatitis C, alpha-1 antitrypsin test, and autoimmune hepatitis antibodies were all negative. Ceruloplasmin was found to be low, and the patient had a normal 24-urine copper test.

During this hospitalization, on **study day 211** [redacted]), the laboratory results included **ALT 85 IU/L (2.4 ×ULN),** AST 529 IU/L (13.2 ×ULN), ALP 160 IU/L, **bilirubin 15.7 mg/dL (15.7 ×ULN), PT 15.6 sec (NR 12.3-14.4), PTT 34.3 sec, and INR 1.23, see** Figure 17. Additional results included glucose 111 mg/dL (NR 70-126), blood urea nitrogen (BUN) 12 mg/dL (NR 7-17), creatinine 0.4 mg/dL (NR 0.2-0.7), sodium 144 mmol/L (NR 134-143), potassium 3.4 mmol/L (NR 3.5-5.2), chloride 97 mmol/L (NR 96-109), anion gap 28.4 (NR 8-16), total protein 8.5 g/dL (NR 6.2-8.1), and C-reactive protein (CRP) 4.2 mg/dL (NR 0-0.8). The [redacted] (Day 212), the subject remained jaundiced; however, there was no vomiting or diarrhea, and the subject was tolerating G-tube feeds per home regimen. Physical examination findings were unremarkable. Vital signs included blood pressure 112/58 mmHg, pulse 106 bpm, respiratory rate 28 breaths per minute, temperature 98°F, and oxygen saturation 97%. On study day 216 the patient was discharged from the hospital.

On [redacted] (Day 336), the subject was placed on comfort care measures, including continuous infusion hydromorphone and lorazepam. A do not resuscitate (DNR) order was also put in place for the patient. On [redacted] (Day 355), the subject died due to hepatic failure. An autopsy was not performed.

Figure 17 Patient (b) (6) Study 0900, Hepatic Function Parameter Timeline

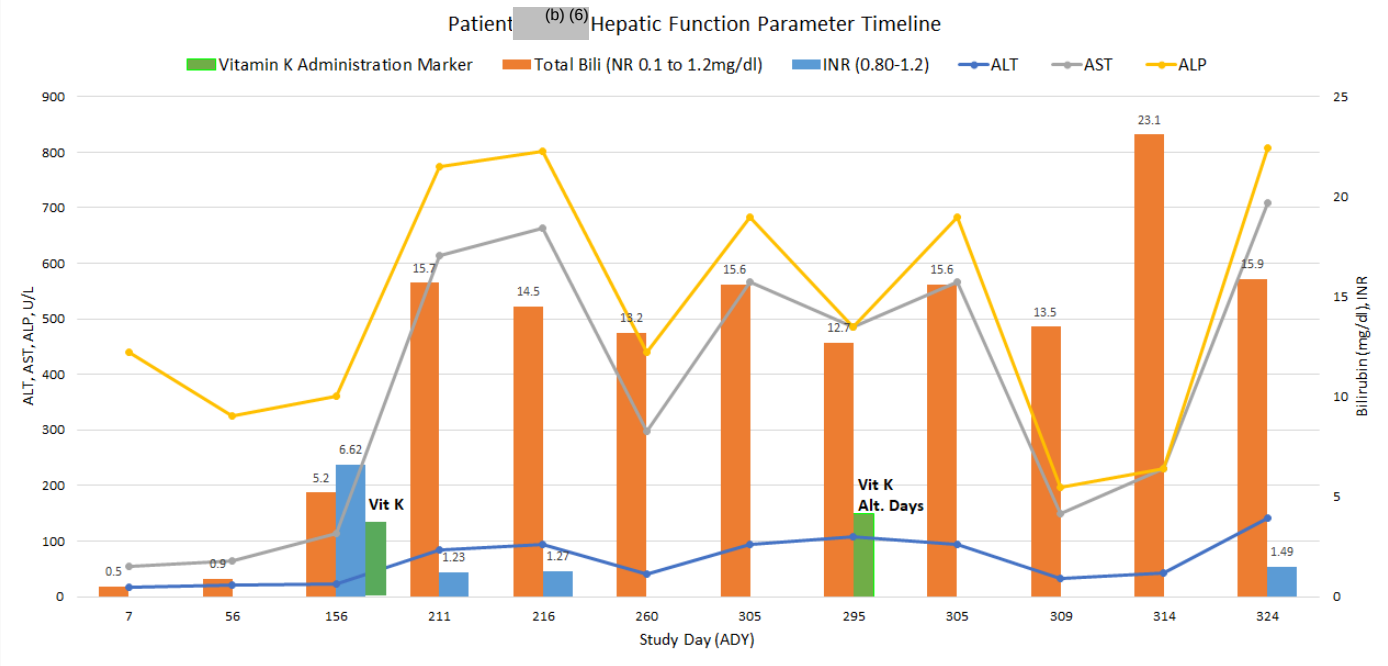


Table 61 Patient (b) (6) Study 0900 Day 156 Concomitant Medications

Medication	Dose	Start date
Phenobarbital	36mg BID	(b) (6)
Topiramate	30g TID	
Perampanel	3.5mg	
Diazepam	PRN	
Clonazepam	.25mg	
Budenoside		
Scopolamine patch		
Omeprazole	40mg	
Odansetron	4mg Q12 h PRN	
Albuterol	PRN	
Inhaled tobramycin	Q2 months	
Loperamide	Unknown	

Division of Hepatology and Nutrition Consultation, Drug-induced Liver Injury Team: "**Executive Summary**: We do not think this fatality should hold up approval for GNX treatment of the rare pediatric seizure disorder, CDD. The liver injury was only possibly related to GNX with cholestasis of sepsis competing as a reasonable alternate cause. If DILI occurred, the phenotype would be bland cholestasis, a phenotype that typically has a good prognosis upon holding the offending agent. However, this subject had recurrent infections making distinction between cholestasis of sepsis and bland cholestasis from DILI impossible. Moreover, we do not agree that the primary cause of death was liver failure based on near normal INR and albumin when the subject transitioned to comfort care. Indeed, cholestasis of sepsis is a more likely explanation of her persistent jaundice, and recurrent severe infections are also a more likely

proximal cause of death. In other words, this subject probably died with cholestasis rather than from it."

"Recommendations:
a) Approval should not be held up due liver injury risk.
b) No need for specific post-marketing requirements; routine post-marketing safety surveillance is sufficient."

Reviewer Comment: The patient did not succumb to hepatic failure but to multiple convergent factors deriving from a past medical history of short bowel syndrome a fragile medical status due to CDD and underlying infection. A diagnosis of primary hepatic failure is not supported by the observation of successful maintenance of near normal INR by Vitamin K treatment. The Applicant procured independent assessment of this case by two expert consultants, see Appendix, Section 13.3 Applicant Expert Consultation. One consultant concluded a possible causal relationship to study drug treatment (25-50% likely) although "*The patient's ultimate demise is likely to be multifactorial*.". The second consultant did not conclude a causal relationship. The DILI team concluded that the observed liver injury did not culminate in hepatic failure and was not the primary cause of death, but laboratory markers of hepatic dysfunction were present and due to "cholestasis of sepsis is a more likely explanation of her persistent jaundice".

8.5.2. Seizure Worsening

An analysis is performed on the DB ADAE dataset of study 3001 to assess seizure worsening. The dataset is examined for seizure related terms in the HLGT "Seizures (incl subtypes)", within the SOC "nervous system disorders" to identify the frequency distribution of relevant terms across treatment arms. The only HLGT for Seizures (incl subtypes) was the preferred term "seizure" with no other seizure PT entries identified in this analysis. There were 7 patients in the GNX treatment arm and 9 patients in the PBO treatment arm with AE of seizure where one of these entries in the PBO treatment arm was an SAE. The dataset is also examined for the preferred term "drug ineffective". There were no instances of this PT in the DB period.

Table 62 Study 3001 DB Period, Examination of TEAE Seizure Terms. Only "Seizure" Occurred in DB Period.

ARM (1042-CDD-3001)	# Patients	% Patients	Comment
Ganaxolone	7	14	
Placebo	9	17.6	1 Seizure event in PBO arm entered as an SAE

Reviewer Comment: there was no evidence of seizure worsening in the DB period of study 3001. The observation of a lower frequency of "seizure" AE in the GNX treatment arm compared to the PBO treatment arm as well as the occurrence of a "seizure" SAE in the PBO arm is in alignment with the evidence of GNX efficacy for treatment of CDD.

8.6. Safety Analyses by Demographic Subgroups

Examination of the frequency of TEAE by age strata in study 3001 DB period is performed. The distribution of TEAE frequency is similar to the overall study population age distribution, Table 63. Analysis of any TEAE frequency by unique patient occurrence and sex is performed, Table 64.

Table 63 Study 3001 DB Treatment, Distribution of Any TEAE by Treatment Arm Unique Patients and Age Strata, Compared to Study Age Distribution (ADSL)

ADAE				
Age group 2-6, 6-12, >12	TRT01A	N Rows	% patients	% ARM
2 to 6	Ganaxolone	28	56	60
6 to <12	Ganaxolone	10	20	26
12<	Ganaxolone	5	10	14
2 to 6	Placebo	21	41.2	43.1
6 to <12	Placebo	19	37.3	43.1
12<	Placebo	5	9.8	13.7

Table 64 Study 3001 DB Treatment, Distribution of Unique Patient TEAE Frequency by Treatment arm and Sex.

SEX	TRT01A	# Patients	Demographic distribution	% Patients with AE by Demographic
F	GNX	34	39	87.2
M	GNX	9	11	81.8
F	Placebo	35	41	85.4
M	Placebo	10	10	100.0

Reviewer Comment: Examination of TEAE frequency (unique patient) by age strata, and treatment arm does not reveal a notable divergence in the proportion of TEAE frequency from the proportion of patients that contribute to the age and treatment arm strata. Evaluation of the frequency of TEAE by sex and treatment arm does not reveal an increase in TEAE associated with sex. No differential safety signal is associated with age strata or sex in the study 3001 DB treatment period.

8.7. Specific Safety Studies/Clinical Trials

None Performed

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

None performed

8.8.2. Human Reproduction and Pregnancy

From Applicant ISS, Section 5.4, Page 80

Teratogenicity and effects on fertility were not evident in the animal studies completed to date, but studies in pregnant women have not been conducted.

From the entire GNX clinical safety database 6 events involving 5 subjects were observed. In Study 1042-PPD-2003 (DB, controlled study in post partum depression) there were 4 events of pregnancy (all non-serious and not related). In Study 1042-0601 (OL Safety & Efficacy in POS), 1 SAE of stillborn (not related- E. Coli septic shock) was reported and in Study 1042-PPD-2003, 1 SAE of miscarriage (not related) was reported.

8.8.3. Pediatrics and Assessment of Effects on Growth

From Applicant CSR Study 3001, Section 12.5.5 Developmental Examination, Page 79

The proportion of subjects who were able to perform any of the social (smiles appropriately to situation, makes eye contact), motor (sits with support, sits independently, crawls, stands with support, stands independently, takes steps with assistance, walks independently), or speech/language tasks (identifiable sounds for specific items, repeats sounds, single words, multiple words, makes a sentence, replies to question in an identifiable word) were similar in the GNX and PBO groups at screening and at the end of the 17-week double-blind phase. For most tasks, fewer subjects were able to perform the tasks at the end of the 17-week double-blind phase than at screening, but there were no differences between the GNX and PBO groups. There were no significant findings related to developmental examinations.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

From Applicant ISS, Section 5.6, Page 81

GNX is associated with CNS-effects and therefore AEs associated with abuse (eg, euphoric mood, somnolence, dizziness) have been reported with GNX treatment. No intentional overdose or misuse of GNX has been reported to date.

A clinical study was performed to evaluate the abuse potential of single oral doses of GNX in healthy recreational CNS depressant users (Study 1042-HAP-1001). GNX showed less abuse potential compared to lorazepam on the primary and secondary endpoints and greater abuse potential compared to PBO. Effects of GNX on cognitive or motor impairment were small, sporadic, and markedly lower than those of lorazepam. GNX at single oral doses up to 2000 mg was well tolerated in healthy recreational drug users.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

GNX is not marketed in any country

8.9.2. Expectations on Safety in the Postmarket Setting

Safety concerns in post marketing are centered around the well characterized central nervous system adverse event of somnolence and sedation covered in early discussions. Although there is a strong signal for these adverse reactions, with somnolence much greater than sedation, the frequency of SAEs under these preferred terms was not high. These AR will be sufficiently covered by labeling in Section 5.

There is also the issue of a trend of increase ALP that may portend a cholestatic lesion. Based on the reviewer's evaluation this remains only a potential consideration. The consultants from the Division of Hepatology and Nutritional Consultation consider this a reversible lesion where routine Post-marketing safety surveillance is considered sufficient.

8.9.3. Additional Safety Issues From Other Disciplines

None identified

8.10. Integrated Assessment of Safety

Deaths

There were a total of 9 deaths reported in the 46 pediatric and adult studies from the development program that were included in the NDA submission. The Applicant reports 4 deaths during pediatric development of GNX while none of the four deaths in pediatric epilepsy studies were adjudicated as causally related to GNX treatment. From among the 5 deaths reported in adult studies all were contained in epilepsy studies. One patient was in a PBO study arm. From among the remaining 4 patient deaths none was adjudicated as causally related to GNX treatment, see Section 8.4.1, Deaths.

There was a single death classified as hepatic failure in a pediatric LGS patient participating in study 1042-0900, however further analysis by the DILI team resulted in a conclusion that this event was not hepatic failure but alternatively was due to the comorbidity of short bowel syndrome and advancement of the underlying disease.

SAE

DB Study 3001

Assessment of SAEs in double blind study 1042-CDD-3001 does not reveal a notable differential safety signal between the PBO and GNX treatment arms. Four of six SAEs in the GNX treatment

arm were related to preferred terms from the “infections and infestations” SOC with one “food refusal” and the remaining entry “oxygen saturation decreased”, likely related to the sedative effect of GNX with a contribution from concomitant treatment with clonazepam. In this case GNX treatment was continued and the patient completed the double-blind phase of study 3001. This examination reveals a preponderance of SAE events related to the “infections and infestations” SOC. This observation is in alignment with the pediatric age range where increase in respiratory infection is greater than in the adult population. The event of oxygen saturation decreased was GNX specific and related to sedation. Sedation is presented in the Proposed Section 5, Warnings and Precautions of the proposed label. A new emergent GNX treatment specific safety issue was not identified.

In the open label phase of study 3001 and study 0900 there were 53 patients with SAEs from among 38 preferred terms. Patients had an occurrence of an SAE from among 10 preferred terms. The mean time to event for all of the SAEs with a frequency greater than one patient was 218 days with a minimum of 16 days for an SAE of “seizure” and “aspiration” with a TTO 19 days for an SAE of “vomiting”. From among the 10 preferred terms with an occurrence in greater than one patient the minimum TTO was 19 weeks with a range of minimum TTO from 19 to 41 weeks. The temporal relationship of these events does not support a causal relationship. Among the remaining 4 preferred terms, identified as “dehydration”, “vomiting”, “seizure” and “aspiration” the minimum TTO for an SAE entry ranged from 16 to 56 days, see Table 34. The most frequent preferred term from among these latter 4 was “seizure”. Seizure is an ongoing background event in this population and examination of Seizure Worsening Section 8.5.2 did not reveal a causal signal. The remaining preferred terms are consistent with the fragile underlying medical status of patient with CDD and the mean TTO for each “dehydration”, “vomiting” and “aspiration” do not support a specific GNX causal association, see Table 34.

Study 0603 and 0700

The SAE analysis of studies 0603 and 0700 does not reveal a unique safety signal with causal relationship to GNX treatment that was not observed in the review of studies 3001 and 0900. The terms identified in studies 3001 and 0900 were “somnolence” and “sedation”. These adverse reactions are included in proposed labeling.

Clinical Hematology and Chemistry

DB Study 3001

Analysis of the Clinical Chemistry and Hematology shift and outlier data from the double-blind interval of Study 3001 did not reveal a significant trend in any metric to suggest a safety signal within the laboratory measurements, see Section 8.4.6 - Study 3001.

ECG

DB Study 3001

Shifts and Outliers

Overall, there was no signal for development of an abnormal ECG interpretation associated with GNX treatment in the DB interval of study 3001.

Hepatic Function Assessment

Hy's Law Screen

Hy's Law screen was performed on the clinical laboratory data available from studies 3001, 0900, 0603, 0600, and 0700 using the JMP Clinical "Hy's Law Screening" function. There were no Hy's law cases identified in these assessments.

ALP and Associated ALT, Bilirubin Screening in an Adult POS DB and Open Label Extension Period

ALP Screening was performed on the double-blind interval of Study 600, derived from the STDM, lb.xpt dataset, to further evaluate the bland cholestasis signal identified by the DILI team in the assessment of hepatic failure in patient (b) (6) This assessment allowed for analysis of GNX treatment effect on this laboratory parameter in an adult POS population.

Patients with a minimum of 4 ALP measurements during the DB blind treatment interval of study 600, from baseline to study day 70 were included in the analysis. In the PBO treatment arm 47 of 52 contributed to the analysis while in the GNX treatment arm 86 of 89 patients were included in the trendline analysis. The slope of trendline analysis revealed an excess of positive over negative slope in the GNX treatment group where 67.5% of 86 patients had a positive slope trendline compared to a positive slope seen in 46.8% of 47 patients in the PBO treatment group, see Appendix 13.4, ALP Screening. This observation prompts further exploration for laboratory features of "bland cholestasis". The association of GNX treatment effect on ALT and Bilirubin is compared to PBO during the DB study interval.

Analysis of ALT trendline from 86 patients with up to 70 days participation in the GNX arm of the DB treatment interval reveals that 61.6% of patients had a negative trendline slope of ALT values where 53.2% of 47 patients in the PBO treatment arm (4 or more measurements) had a negative slope. Similarly, trendline analysis of the 86 patients with 4 or more total bilirubin measurements in the GNX treatment arm revealed there were 51.1% with a negative or zero slope compared with 48.9% of 47 patients in the PBO treatment arm with a trendline slope that was negative or zero. These analyses do not reveal a systematic trend of an increasing value of ALT and total bilirubin measurements associated with GNX treatment over the DB treatment interval. They also do not indicate a coupling between the observed trend of increasing ALP in associated with GNX treatment and broader range of hepatic function chemistries, ALT and total bilirubin, see Appendix 13.4, ALP Screening.

ALP Screening was performed on the open label treatment interval of Study 0603, derived from

the ADLB dataset, to further evaluate the bland cholestasis signal identified by the DILI team in the assessment of hepatic failure in patient (b) (6) This assessment allowed for analysis of GNX treatment effect on hepatic function chemistry parameters in a more extended treatment interval that ranged from 99 to 491 days with a median of 308 days in adult POS patients. There were 142 patients included in the analysis who were on continuous GNX treatment from Cohorts 1 and Cohorts 2 of the study that continued into the OL extension phase. These patients had a minimum of 6 ALP measurements during the interval from study visits 0 through 10. A minimum of 6 entries is needed to generate an interpretable trendline. This analysis revealed that 72.5% of 142 patients had a trendline with positive slope, a notable predominance over those with trendlines of declining slope, see Study 603 GNX in OL Extension, Figure 24. Patient (b) (6) with the trendline of maximum slope had a day 138 ALP value of 1.83 X ULN following a sequence of steadily increasing ALP values. This observation prompts further exploration for laboratory features of "bland cholestasis". The association of GNX treatment on ALT and Bilirubin from among the Cohorts 1 and Cohort 2 over the DB and OL study interval is examined.

There were 145 patients in study 0603 who received GNX during DB treatment and continued into the open label extension phase of study and had 6 or more measurements of ALT from study visits 0 to 10. ALT trendlines are created for these patients and the trendline slope generated. From among these patients 63.4% had negative trendline slopes while 36.6% had positive slopes. The entire sequence of ALT values is examined for patient (b) (6) who had the maximum trendline slope. From among 7 measurements there was an outlier value at study day 141 that was 3.4 x ULN with a second value, at last measurement of 1.09 x ULN. All other ALT values were within reference range and without sequential escalation of the value, see Study 603 GNX in OL Extension, Figure 25. The same analysis is performed for bilirubin values. There were 145 patients in study 0603 who received GNX during DB treatment and continued into the open label extension phase of study and had 6 or more measurements of Bilirubin from study visits 0 to 10. Bilirubin trendlines are created for these patients and the trendline slope generated. From among these patients 50.4% had negative trendline slopes while 49.6% had positive slopes. There were two patients, (b) (6) and (b) (6) with outlier positive slopes that were 44% and 41%, respectively, greater than the next lowest value. The full range of hepatic associated chemistry parameters is examined for each of these patients. Patient (b) (6) had maximum values for ALP and bilirubin that were both 1.04 X ULN occurring on study days 104 and 147 respectively. Patient (b) (6) had no ALP, ALT, AST or bilirubin values that were OORR high and there was no consistent escalating trend identified, see Study 603 GNX in OL Extension, Figure 26 .

These analyses do not reveal a systematic trend of an increasing value of ALT or total bilirubin measurements associated with GNX treatment over the extended interval examined in study 0603. They also do not indicate there is a coupling between the observed trend of increasing ALP in associated with GNX treatment and the broader range of hepatic function chemistries, ALT and total bilirubin, again over the extended period of GNX exposure.

Overall safety assessment:

Analysis of the Pooled CDD safety dataset does not reveal a safety signal for AESI of "Skin and Subcutaneous Tissue Disorders "or for the preferred term "rash" identified by the applicant. Risk of DILI was not substantiated based on examination of the potential DILI case of patient (b) (6) subsequent analysis of laboratory datasets from studies 3001, 0900, 0603, 0600, and 0700 or the trendline analysis of studies 600 and 603. Examination of shifts and outliers in the CDD safety clinical laboratory datasets did not reveal a signal for a systematic abnormal trend of any specific chemistry or hematology parameter. There was no notable emergence of safety signal on examination of ECG or QTc dataset from study 3001. The applicant reported no systematic trend of vital sign abnormality during study 3001.

Central nervous system adverse events including "somnolence", "dizziness", and "gait disturbance" had the overall strongest signal across the pediatric and adult safety populations where the adult populations contribute the largest proportion of the study participants. In the CDD populations, these adverse events were present but also admixed with a high frequency of events from the SOC "infections and infestations" that is in alignment with the higher frequency of infections in the pediatric age range.

9. Advisory Committee Meeting and Other External Consultations

Not Planned

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Reviewer Comment: The Applicant has proposed a Warnings & Precautions, Section 5.1 heading "Somnolence", "Sedation" (b) (4)

10.2. Nonprescription Drug Labeling

Not Applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

None Planned

12. Postmarketing Requirements and Commitments

GNX received orphan drug designation on 6/28/2017. As such, in accordance with Section 505B(k) of the Food, Drug and Cosmetic (FD&C) Act, the Applicant is exempt from the Pediatric Research Equity Act (PREA) requirements for NDA 215904

13. Appendices

13.1. References

See footnotes

13.2. Financial Disclosure

Study 1042-CDD-3001

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ **N/A**	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐ **N/A**	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐ **N/A**	No ☐ (Request explanation from Applicant)

13.3. Applicant Expert Consultation

Consultation with (b) (4), MD, PhD

On 4-Nov-2017, Marinus sought an independent assessment of this adverse event from Dr. (b) (4), who is Professor of (b) (4), and Professor of (b) (4) at the (b) (4). He also serves as the director of the (b) (4). He provided the following opinion:

"The bilirubin was documented to be normal prior to study drug treatment, the jaundice was treatment emergent, there was no evidence of chronic liver disease on biopsy, the biopsy is consistent with a rare form of drug-induced liver injury (Reye's Like Syndrome) that has not been attributed to the concomitant medications the patient received, and despite a thorough workup, there is no explanation other than study drug for the appearance of jaundice. However, the jaundice apparently occurred at relatively low exposure to drug, and progressed after stopping drug, and I am told that no other similar cases have been observed in the sizable number of patients who have received this drug. So I consider a role for study drug to be possible (25-50% likely) but not probable (>50% likely). The patient's ultimate demise is likely to be multifactorial. I have no experience with IgG4 cholangiopathy so cannot comment on this diagnosis."

Independent Consultation by Dr. (b) (4)

On 14-Nov, Marinus conducted a telephone consultation with Dr. (b) (4), Medical Director, (b) (4) and Professor of (b) (4) from the (b) (4). Dr. (b) (4) provided the following comments in correspondence following the consultation:

"The child was diagnosed with hepatic failure on the basis of elevated bilirubin and INR and low albumin. However, I noted that the INR appeared to …respond to vitamin K. That would NOT be the case in liver failure. It suggests a nutritional vitamin K deficiency (probably related to various courses of antibiotics the child was administered for reasons that were not entirely clear to me) and possibly the absence of a colon and the bacterial flora that would normally synthesize vitamin K, rather than liver failure. The albumin when it was in the 3's (ex 3.4) would not have reflected hepatic failure.

The child did not have IFALD (intestinal failure-associated liver disease). In order to have IFALD one has to have intestinal failure (IF). Intestinal failure is essentially defined as the inability to maintain nutritional autonomy such that parenteral nutrition is required. Now this child was under-weight, but there is no documentation of IF or that parenteral nutrition (PN) was required, despite the obvious fact there had to be some degree of malabsorption. Therefore, IFALD is not possible.

[The b]ottom line is between the issues of whether there was hepatic disease, how severe it actually was, many contributing causes, the low bioavailability of the study [drug] and [its] low blood concentrations, and the fact the bilirubin got worse – then substantially improved – the worsened again - all long after the study drug had been stopped suggest that at most the study drug was possibly a minor factor at most in any of the child's problems, and a significant potential exists study drug had no relationship with the liver or bilirubin issues whatsoever. However, due to the myriad of questions and missing or otherwise unavailable data, it is impossible to exclude any potential role for the study drug. If there is a role, that role is undefined and the mechanism unknown."

13.4. ALP Screening and Hepatic Chemistry Trendline Analysis

13.4.1. Study 600, GNX vs PBO in DB Interval

Figure 18 Study 600 DB, GNX Treatment, Slope of ALP Trendline Over Visit 4 to 8 - Study Day 70

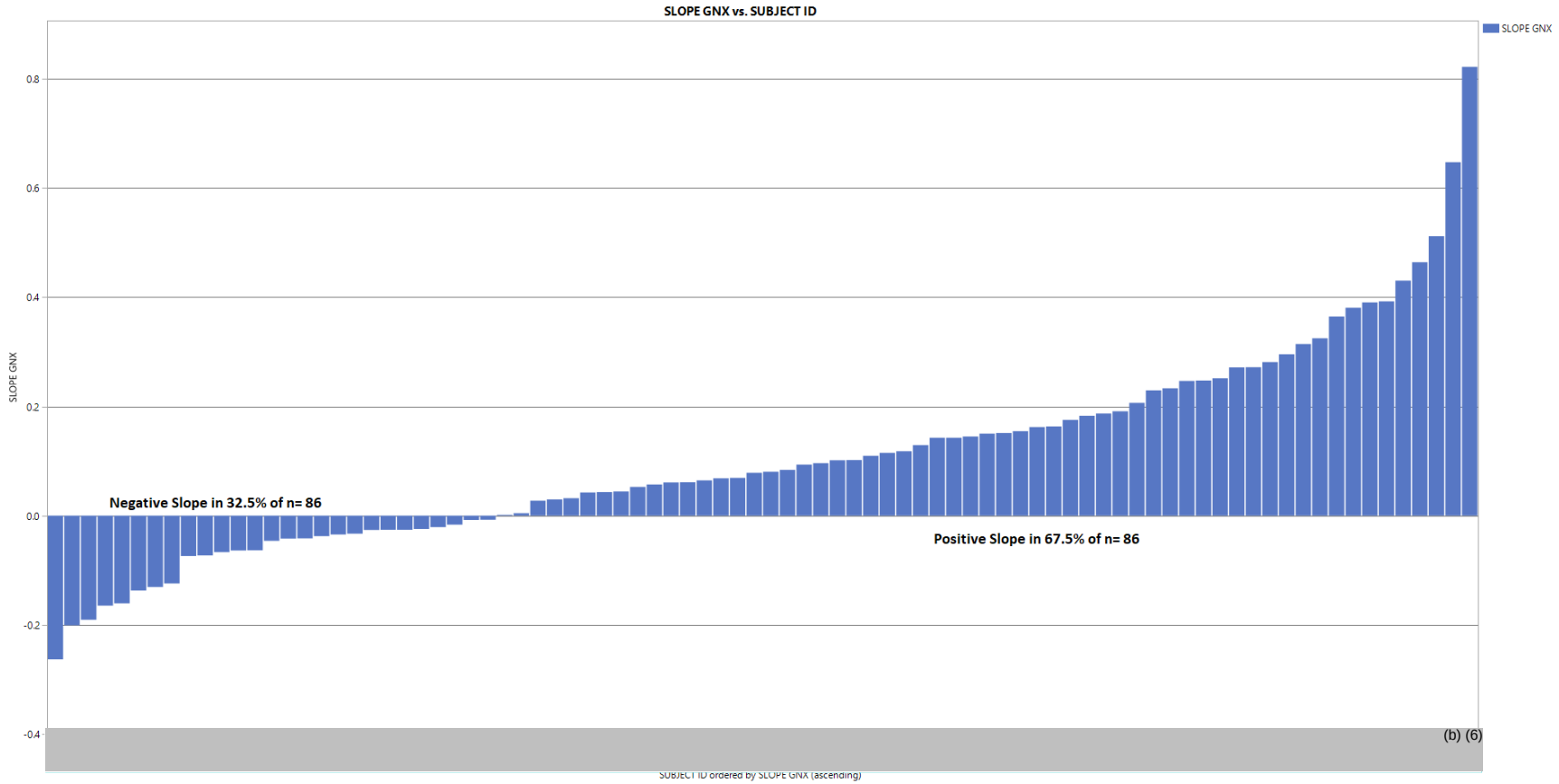


Figure 19 Study 600 DB, PBO Treatment, Slope of ALP Trendline Over Visit 4 to 8 - Study Day 70

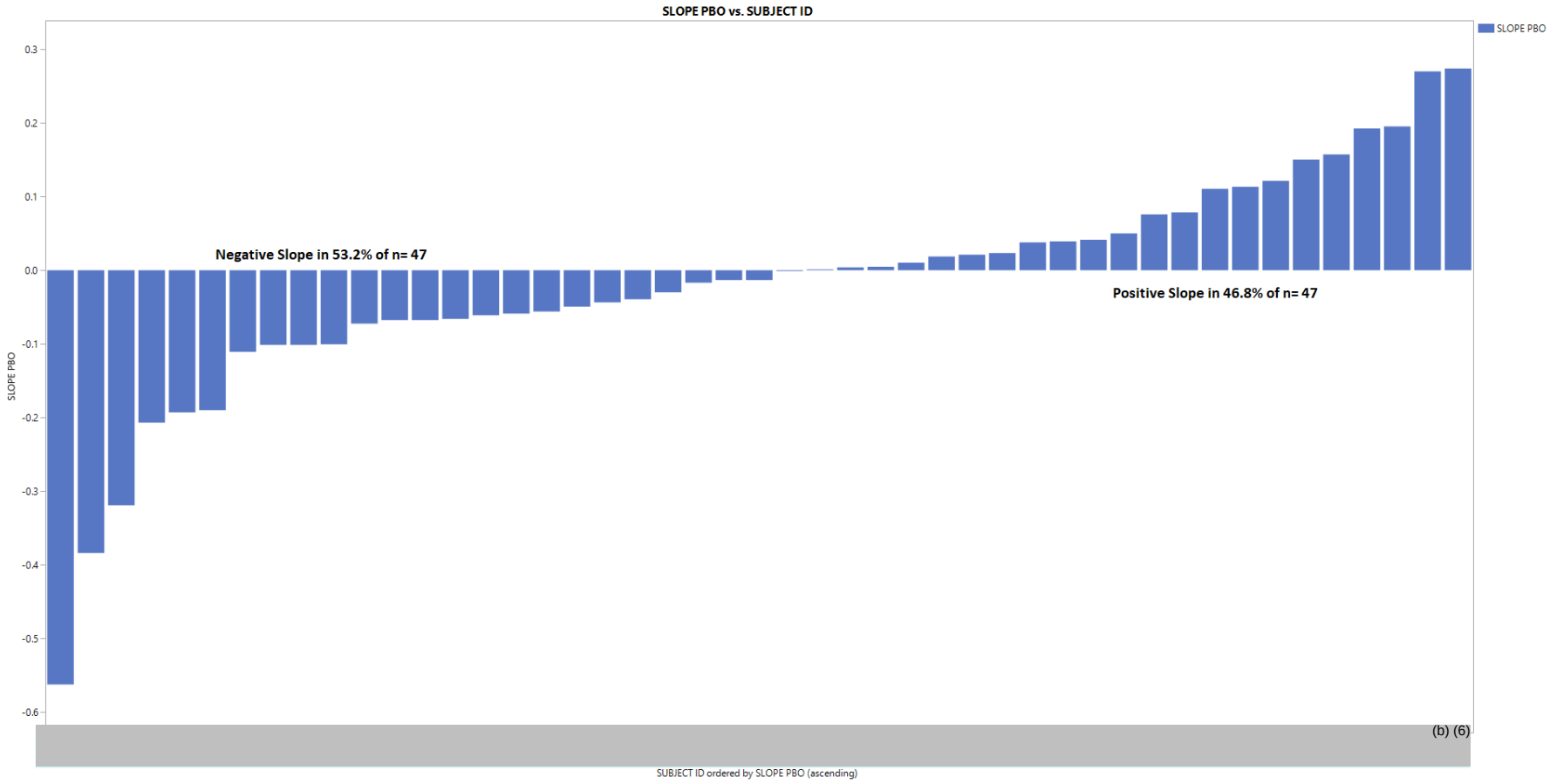


Figure 20 Study 600 DB, GNX Treatment, Slope of ALT Trendline Over Visit 4 to 8 - Study Day 70

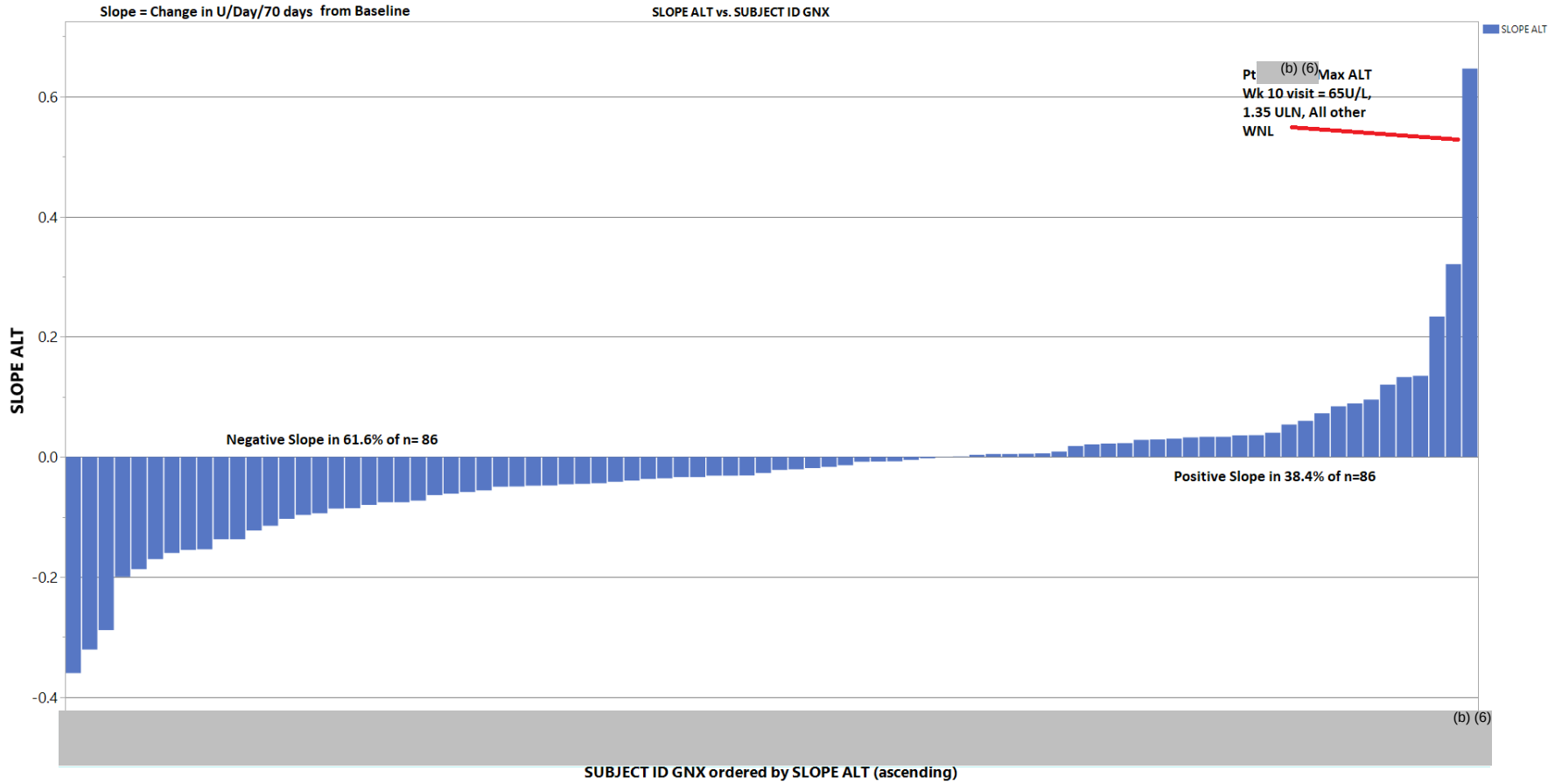


Figure 21 Study 600 DB, PBO Treatment, Slope of ALT Trendline Over Visit 4 to 8 - Study Day 70

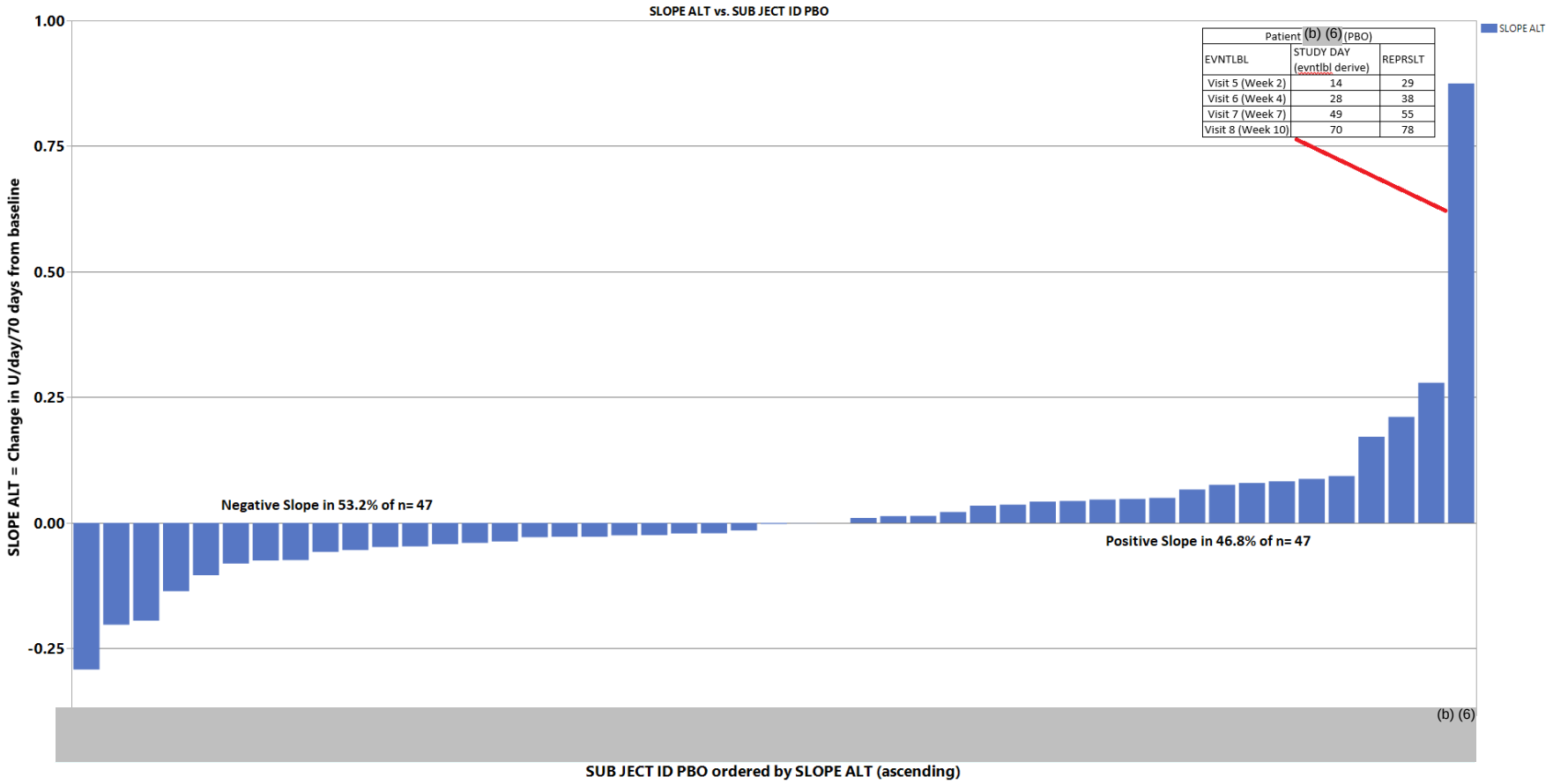


Figure 22 Study 600 DB, GNX Treatment, Slope of T Bilirubin Trendline Over Visit 4 to 8 - Study Day 70

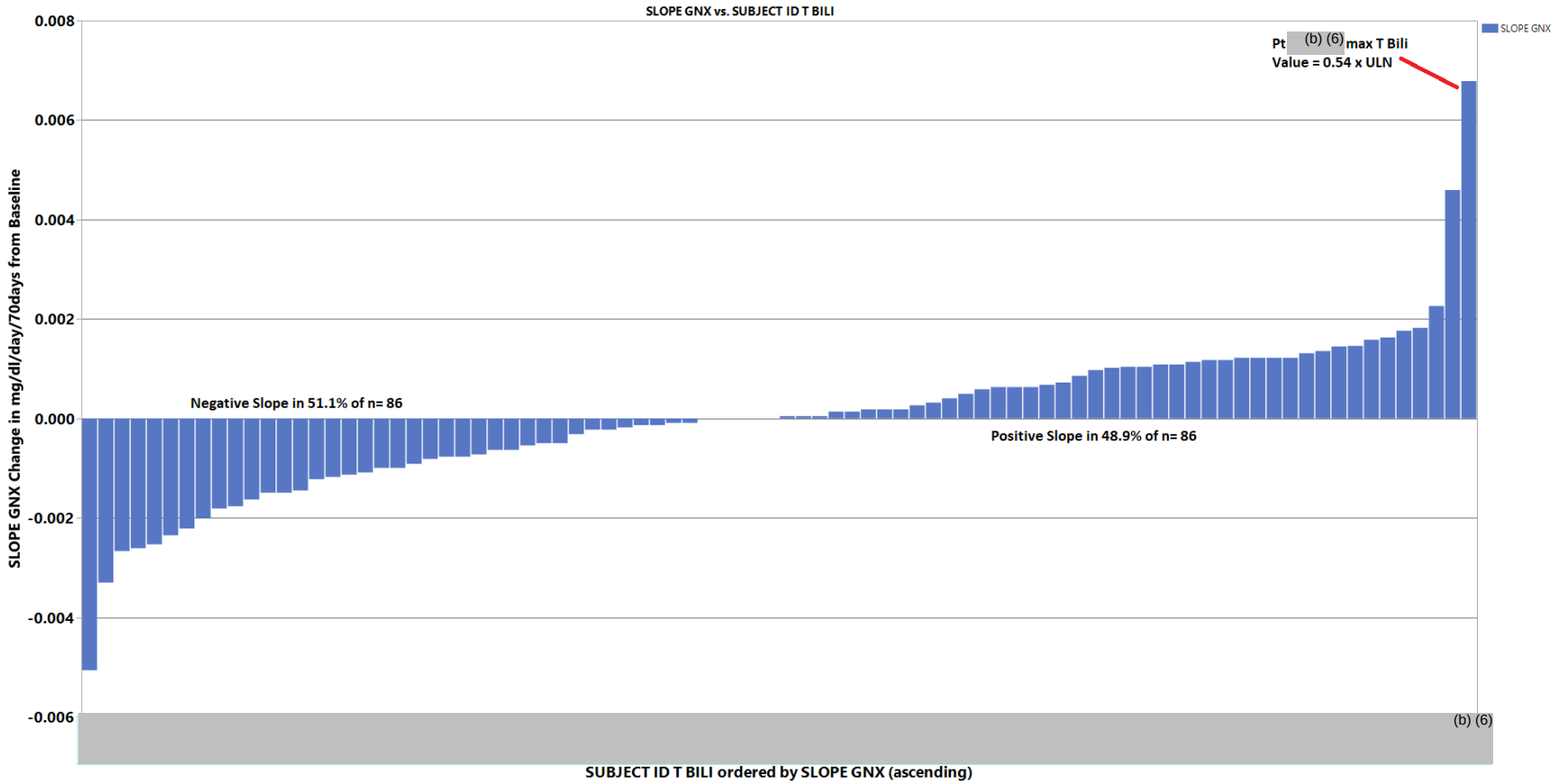
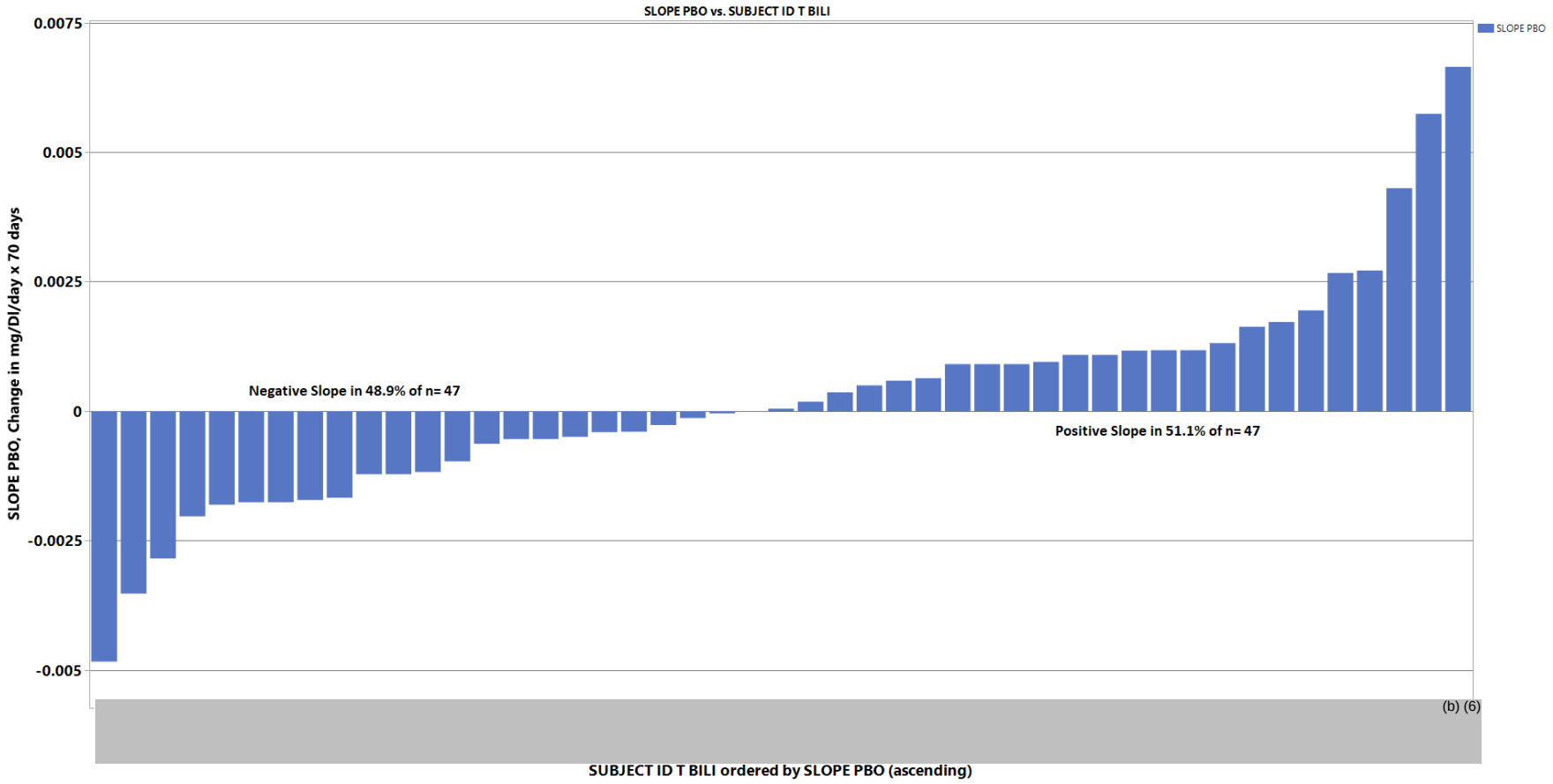


Figure 23 Study 600 DB, PBO Treatment, Slope of T Bilirubin Trendline Over Visit 4 to 8 - Study Day 70



13.4.2. Study 603 GNX in OL Extension

Figure 24 Study 0603 GNX Treated Patients from DB to OL extension (n=142), Slope of ALP Trendline Over Visit 0 to 10 - Study Day Range 99 to 491 days, median 308 days

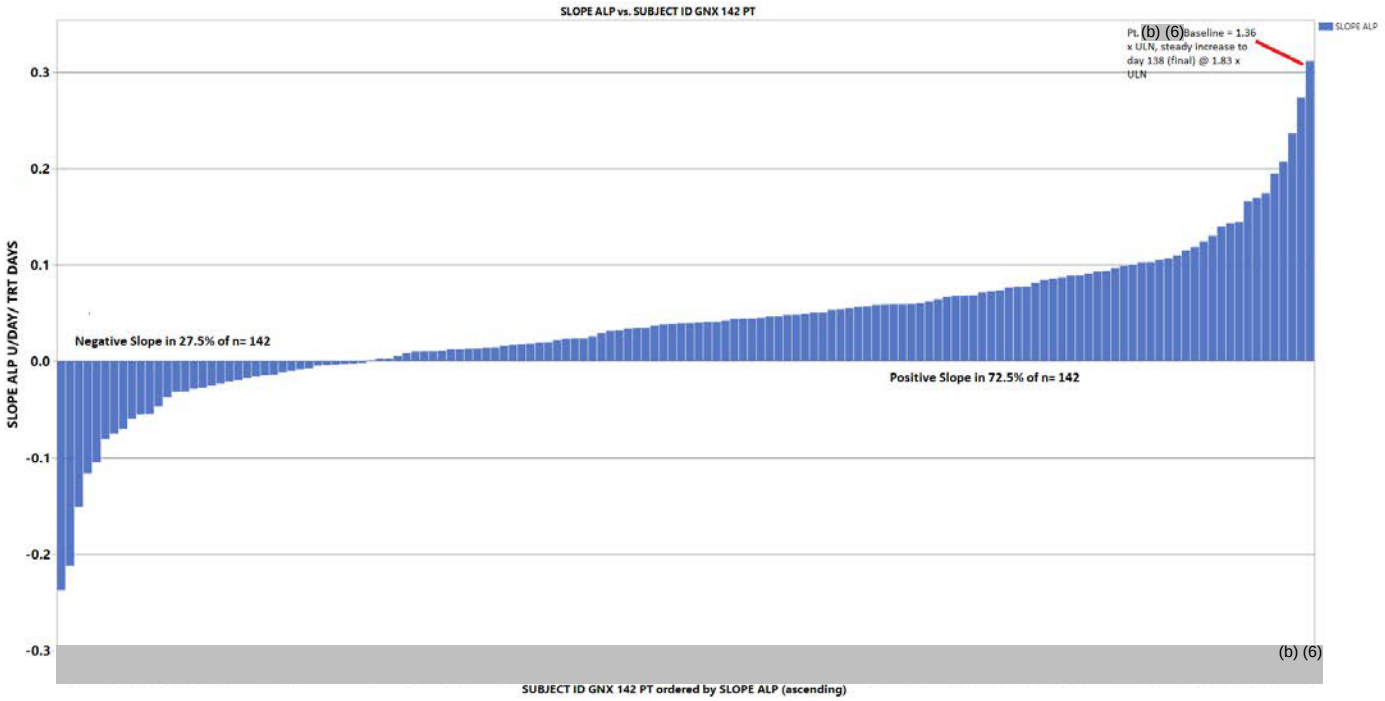


Figure 25 Study 0603 GNX Treated Patients from DB to OL extension (n=145), Slope of ALT Trendline Over Visit 0 to 10 - Study Day Range 99 to 491 days, median 308 days

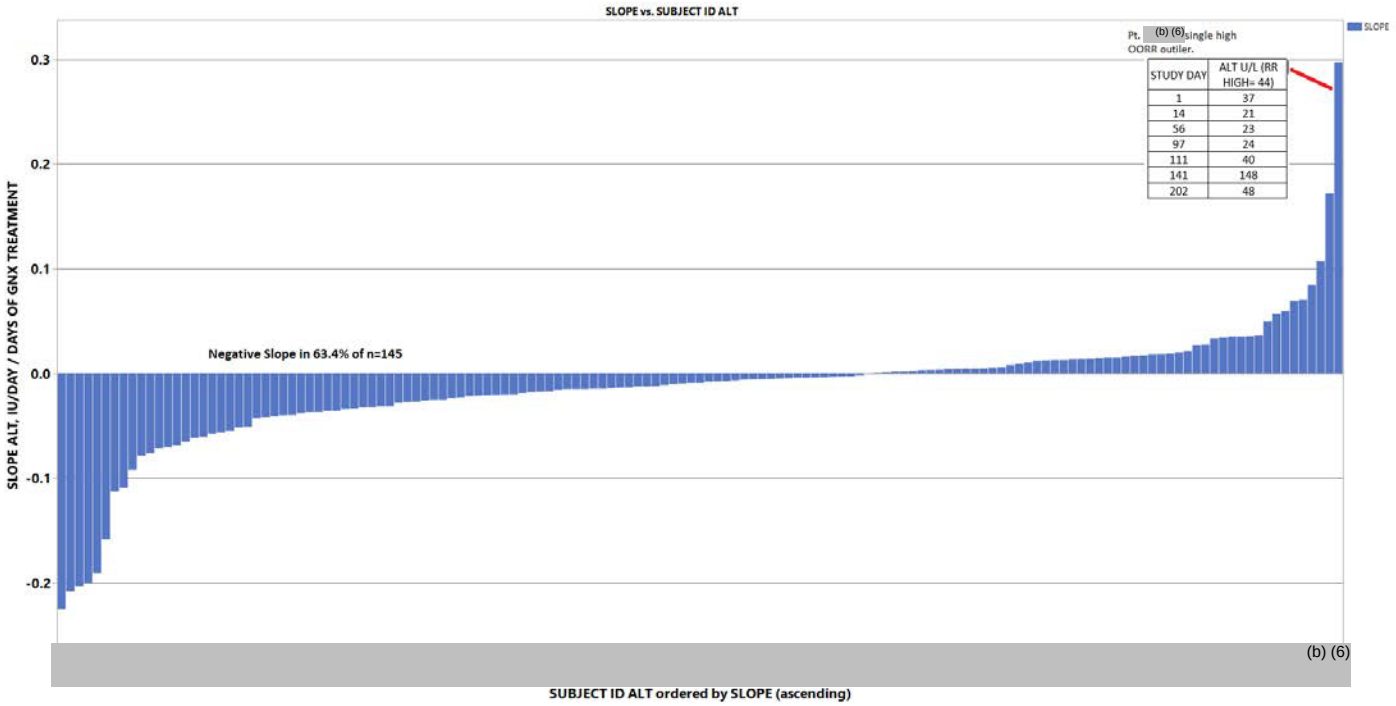
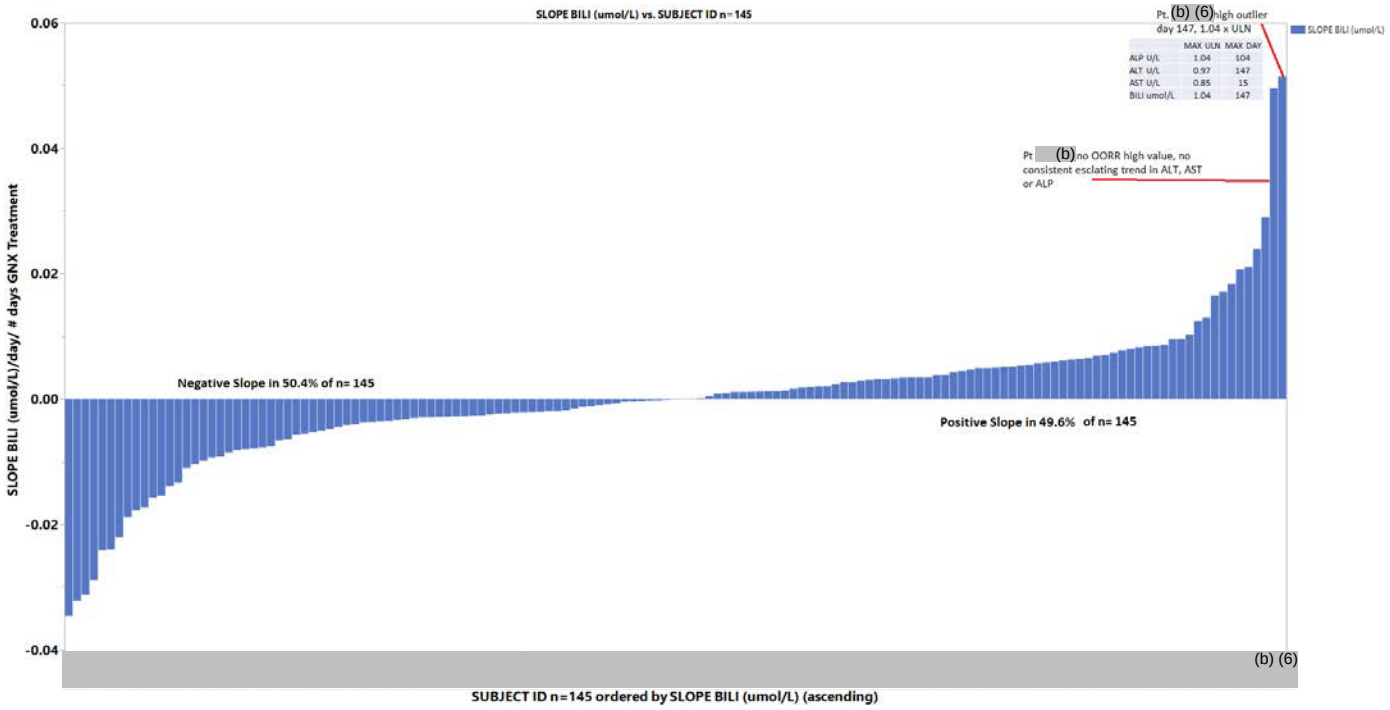


Figure 26 Study 0603 GNX Treated Patients from DB to OL extension (n=145), Slope of bilirubin Trendline Over Visit 0 to 10 - Study Day Range 99 to 491 days, median 308 days



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