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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Number	215904
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Submission Date	20-July, 2021
Submission Type	505(b)(1) New Molecular Entity (Priority Review)
Brand Name	ZTALMY
Generic Name	Ganaxolone
Dosage form (Strength)	Oral Suspension (50 mg/mL)
Proposed Indication	Seizures associated with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder (CDD).
Applicant	Marinus Pharmaceuticals
Associated IND	IND 044020
OCP Review Team	Ramakrishna Samala, Ph.D., Dawei Li, Ph.D., Michael Bewernitz, Ph.D., Atul Bhattaram, Ph.D., Gopichand Gottipati, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

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1. Executive Summary

In this original New Drug Application (NDA), the Applicant, Marinus Pharmaceuticals, Inc., is seeking approval for ZTALMY® (Ganaxolone, GNX) via 505(b)(1) pathway for the treatment of seizures associated with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder (CDD) in patients 2 years of age and older. GNX is a selective positive allosteric modulator of Gamma Amino Butyric Acid type A ($GABA_A$) receptors. Currently, there are no approved therapies to treat CDD.

To evaluate the safety and efficacy of GNX in CDD patients 2 years and older, the applicant is relying on a double-blind, randomized, placebo-controlled study (1042-CDD-3001). This study demonstrated efficacy based on the primary endpoint, median percent change from baseline in 28-day major motor seizure frequency during the 17-week double-blind treatment phase.

The primary focus of this review is to evaluate the need for dose adjustment based on extrinsic factors, specifically, concomitant administration of GNX with CYP3A4 inducers and inhibitors.

1.1 Recommendation

The Office of Clinical Pharmacology reviewed the information submitted under this NDA and recommends approval of GNX in CDD patients 2 years and older. The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	The evidence of effectiveness of GNX for CDD in patients 2 years and older was demonstrated in a double-blind, randomized, placebo-controlled study (1042-CDD-3001) based on the reduction in the median percent change from baseline in 28-day major motor seizure frequency.

Review Issues	Recommendations and Comments
General dosing instructions	GNX is recommended to be administered with food. Dosage in CDD patients is based on weight cut-off (28 kg) and is titration-based (at weekly intervals). GNX Recommended Titration Schedule for Patients Weighing 28 kg or Less

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

GNX Recommended Titration Schedule for Patients Weighing More Than 28 kg

Dosage	mL per Dose	Total daily dosage	Days
150 mg three times daily	3	450 mg	1 to 7
300 mg three times daily	6	900 mg	8 to 14
450 mg three times daily	9	1350 mg	15 to 21
600 mg three times daily	12	1800 mg	22 to ongoing

Review Issues	Recommendations and Comments
Dosing in patient subgroups (extrinsic and intrinsic factors)	• **Strong and moderate CYP3A4 inducers:** Coadministration of GNX with strong or moderate CYP3A4 inducers will decrease GNX exposure, which may lower the efficacy of GNX. It is recommended to avoid coadministration of GNX with strong or moderate CYP3A4 inducers. When concomitant use with strong or moderate CYP3A4 inducers is unavoidable, consider an increase in GNX dosage; however, the maximum daily dosage of GNX (63 mg/kg and 1800 mg in patients weighing ≤ 28 kg and >28 kg, respectively) should not be exceeded. In patients on stable GNX dosage who are initiating or increasing the dosages for enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenytoin, phenobarbital, primidone), GNX dosage may need to be increased; however, the maximum daily dosage of GNX should not be exceeded (as noted above). • **CYP3A4 inhibitors:** Coadministration of GNX with strong CYP3A4 inhibitor, itraconazole, did not result in clinically significant impact on the pharmacokinetics of GNX. Drug-interaction with moderate and weak CYP3A4 inhibitors is not expected to be clinically significant. Therefore, no dose adjustment for GNX is needed when co-administered with CYP3A4 inhibitors. • **CYP3A4 Substrates:** No dosage adjustment for CYP3A4 substrates is needed. • **Hepatic Impairment:** The impact of hepatic impairment on PK of GNX is being evaluated in an ongoing study. Since GNX undergoes clearance via hepatic route, hepatic impairment can increase GNX exposures. Patients with impaired hepatic function should be monitored for incidence of adverse reactions and GNX dosage may need to be reduced**.**

Review Issues	Recommendations and Comments
Dosing in patient subgroups (extrinsic and intrinsic factors)	• **Renal Impairment:** The impact of renal impairment on PK of GNX is being evaluated in an ongoing study. Renal excretion is a minor pathway in the elimination of GNX. Therefore, renal impairment is unlikely to result in clinically significant changes in GNX exposures**.**
Bridge between the "to-be-marketed" and clinical trial formulations	The final to-be-marketed formulation was used in the phase 3 clinical trial.

1.2 Post-Marketing Requirements

Four post-marketing studies are required to meet the clinical pharmacology requirements of this application. These studies include:

1) Hepatic impairment study

In-vitro studies indicate that GNX is metabolized by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6. In a mass balance study in humans, 55% of the total radioactivity was recovered in feces (2% as unchanged GNX) and 18% of the total radioactivity dose was recovered in urine (undetected as unchanged GNX). This suggests that GNX is cleared via hepatic route and hepatic impairment may increase its systemic exposures. Therefore, a hepatic impairment study is necessary to understand the impact of hepatic impairment on the PK of GNX. In the Type C meeting minutes dated 01/11/2018, the Agency agreed with the applicant's plan to submit the clinical study reports of a hepatic impairment study (1042-IHF-1001, full study design) after filing the NDA. This study is ongoing and once completed, the clinical study report should be submitted.

2) Renal impairment study

In the Type C meeting minutes dated 01/11/2018, the Agency agreed with the applicant's plan to submit the clinical study reports of a renal impairment study (1042-IRF-1001, reduced study design) after filing the NDA. This study is ongoing and once completed, the clinical study report should be submitted.

3) Thorough QT (TQT) study

Given the submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of GNX, the QT-IRT recommends that the

applicant conduct a thorough QT trial to evaluate the effect of GNX on the QTc interval. 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

In-vivo mass balance study (1042-GNX.AME-1001) indicated that the exposure of M47 (also noted as M15 in some study reports), a sulfate conjugated metabolite of GNX, accounted for 24.4% of total plasma radioactivity exposure (based on 0-30 days radioactivity data). GNX is a methyl substituted derivative of endogenous nerosteroid allopregnanolone. Literature searches suggest that sulfate metabolite of allopregnanolone, pregnenolone sulfate, modulates a variety of ion channels, transporters, and enzymes. (b) (4) M47 could modulate transporters and enzymes like that of allopregnanolone sulfate. Therefore, an *in-vitro* DDI study is needed to evaluate the potential of M47 as a perpetrator of major enzymes and transporters.

2. Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

GNX is a selective positive allosteric modulator of gamma-aminobutyric acid type A ($GABA_A$) receptors located in the CNS.

Pharmacokinetics

Absorption

Following oral administration, GNX is absorbed with a T_{max} of 2-3 h. When administered with high-fat meal, GNX C_{max} and $AUC_{0\text{-}inf}$ increased by 3-fold and 2-fold, respectively. GNX was administered with food in the pivotal clinical safety/efficacy study. The efficacy of GNX when administered in fasted state is unknown.

Distribution

GNX is highly plasma protein bound (99%).

Elimination

GNX is eliminated with a terminal half-life of 34 h and with a clearance of 430 L/h.

Metabolism

In-vitro studies indicate that GNX is metabolized by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6. However, the relative contribution of each of the pathways towards the metabolism of GNX is not clear. Multiple metabolites M60b, M18, M73, M62, M43 and M47 were identified from mass-balance and lactation studies. The exposures of a sulfated metabolite M47, and two non-conjugated metabolites M60b, M18 exceeded the exposures of GNX, while the exposures of the rest of the metabolites were lower than parent GNX (please see Section 3.2 for additional details).

M60b did not show drug-interaction liability as a perpetrator with major CYP enzymes or transporters. The applicant did not assess the drug interaction liability of M18 and M47 as a perpetrator, noting low abundance (M18), structural similarities with parent GNX (which did not show drug-interaction liabilities) [M18] or being a sulfate conjugate (M47) and challenges to synthesize and test them as isolated compounds (Ref. response to Information Request dated 08/17/2021, sequence #4, section 1.11.3). Other metabolites were reported to be conjugated metabolites and/or minor, and not expected to be active.

Excretion

GNX and its metabolites are excreted in feces and urine. Following single oral dose of 300 mg [^{14}C]-GNX to healthy male subjects, 55% of the total radioactivity was recovered in feces (2% as unchanged GNX) and 18% of the total radioactivity dose was recovered in urine (undetected as unchanged GNX).

In addition, GNX and its metabolites were evaluated in a lactation study. Following a single oral dose of ^{14}C-GNX to 5 healthy adult lactating women, unchanged GNX exposures ($AUC_{(0\text{-}24\ h)}$) in breast milk were approximately 4 times that in maternal plasma, resulting in an estimated daily dose in the infant of less than 1% of the maternal dose.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

Dosage in CDD patients is based on weight cut-off (28 kg) and is titration-based (at weekly intervals). In patients ≤ 28 kg, dosing is weight-based and maximum daily dose is 63 mg/kg, and in patients > 28 kg, fixed doses are to be administered and the maximum daily dose is 1800 mg. Details of dose titration are summarized in section 1.1, and this titration schedule is the same as that studied in the phase 3 pivotal safety and efficacy study (1042-CDD-3001).

2.2.2 Therapeutic Individualization

Therapeutic individualization is necessary for the following extrinsic/intrinsic factors:

Drug-Drug Interactions as a victim

CYP3A4 Inhibitors

In study 1042-DDI-1001, concomitant administration of itraconazole at steady state (200 mg once daily) and GNX (200 mg) increased GNX AUC by 17%, while C_{max} was unchanged. The applicant did not conduct drug-interaction studies to evaluate the impact of coadministration of GNX with moderate and weak CYP3A4 inhibitors.

Overall, given that changes in GNX exposures with concomitant administration with strong CYP3A4 inhibitors are as noted above, moderate or weak CYP3A4 inhibitors are not expected to result in clinically significant changes in GNX exposures. Therefore, GNX dosage adjustment is not needed with strong, moderate or weak inhibitors.

CYP3A4 Inducers

Based on the *in-vitro* characterization of the metabolic pathways, CYP3A4, CYP2B6, CYP2D6 and CYP2C19 were identified as the enzymes involved in GNX metabolism, however the relative contribution of each pathway is not clear.

In a phase 1 study (1042-DDI-1001), concomitant administration of GNX with rifampin showed a 57% reduction in Cmax and 68% reduction in AUC. Rifampin is a strong inducer of CYP2C19 and CYP3A4, and a moderate inducer of CYP2B6. The drug-drug-interaction study with rifampin provides a composite effect of induction of multiple CYP enzymes on GNX PK.

Therefore, it is recommended to avoid concomitant administration of GNX with inducers of CYP450 enzymes such as strong or moderate CYP3A4 inducers. When co-administering GNX with strong or moderate CYP3A4 inducers is unavoidable, consider an increase in GNX dosage; however, do not exceed the maximum daily dosage, i.e., 63 mg/kg and 1800 mg for patients weighing ≤ 28 kg and >28 kg, respectively.

In patients on stable GNX dosage who are initiating or increasing dosages for enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenytoin, phenobarbital and primidone) GNX dosage may need to be increased; however, do not exceed the maximum daily dosage of GNX (as noted above).

Drug-Interactions as a perpetrator

CYP3A4 Substrates

In-vitro CYP3A4 induction and inhibition evaluation showed that, at clinically relevant concentrations, GNX is unlikely to be an inhibitor or inducer of CYP3A4 substrate. In study 1042-0402, concomitant administration of GNX at steady state (a subtherapeutic dose of 400 mg twice daily) with midazolam (2 mg orally) did not show clinically significant impact on midazolam exposures C_{max} or AUC.

Specific Populations

Hepatic Impairment

The impact of hepatic impairment on PK of GNX is being evaluated in an ongoing study. Since GNX undergoes clearance via hepatic route, hepatic impairment can increase GNX exposures. Patients with impaired hepatic function should be monitored for incidence of adverse reactions and GNX dosage may need to be reduced.

Renal Impairment:

The impact of renal impairment on PK of GNX is being evaluated in an ongoing study with reduced study design (i.e., healthy controls and severe renal impairment). However, renal excretion is a minor pathway in the elimination of GNX and therefore, renal impairment is unlikely to result in clinically significant increase in GNX exposures.

Other Specific Populations

Age, sex, and race are not expected to have a clinically relevant effect on GNX pharmacokinetics, after accounting for bodyweight.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

- When administered with high-fat meal, GNX C_{max} and $AUC_{0\text{-}inf}$ increased by 3-fold and 2-fold, respectively. GNX was administered with food in clinical safety/efficacy study. The efficacy of GNX when administered in fasted state is unknown. Therefore, GNX should be administered with food.
- The results from *in-vitro* characterization studies showed that CYP3A4, CYP2B6, CYP2D6 and CYP2C19 were involved in GNX metabolism. However, the relative contribution of each pathway towards overall GNX metabolism is not clear. Concomitant administration of GNX with strong CYP3A4 inducer rifampin reduced GNX Cmax by 57% and AUC by 68%. Rifampin is a strong inducer of CYP2C19 and CYP3A4, and a moderate inducer of CYP2B6, suggesting that the results from rifampin drug-interaction study are a composite effect of induction of multiple enzymes on GNX PK. Therefore, it is recommended to avoid concomitant administration with inducers of CYP450 enzymes such as strong or moderate CYP3A4 inducers. When concomitant use of strong or moderate CYP3A4 inducers is unavoidable, consider an increase in GNX dosage; however, do not exceed the maximum daily dosage of GNX i.e., 63 mg/kg and 1800 mg for patients weighing ≤ 28 kg and >28 kg, respectively. In patients on stable GNX dosage who are

initiating or increasing dosages for enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenytoin, phenobarbital and primidone) GNX dosage may need to be increased; however, do not exceed the maximum daily dosage of GNX.

- Concomitant administration of GNX with strong CYP3A4 inhibitor itraconazole increased GNX AUC by 17% and C_{max} was unchanged. No dose adjustment for GNX is needed when co-administered with strong CYP3A4 inhibitors. Coadministration of GNX with moderate and weak CYP3A4 inhibitors was not evaluated. Drug-interaction with moderate and weak CYP3A4 inhibitors is not expected to be clinically significant, and therefore no dose adjustment for GNX is needed.
- *In-vitro* studies showed that, GNX at clinically relevant concentrations is unlikely to be an inhibitor or inducer of CYP3A4. Therefore, no dosage adjustment for CYP3A4 substrates is needed. Additionally, coadministration of GNX at steady state (400 mg twice daily) with midazolam, a sensitive CYP3A4 substrate, did not result in clinically relevant changes in exposures of the substrate in healthy subjects.
- The impact of hepatic impairment on the PK of GNX is being evaluated in an ongoing study. Since GNX undergoes clearance via hepatic route, hepatic impairment can increase GNX exposures. Patients with impaired hepatic function should be monitored for incidence of adverse reactions and GNX dosage may need to be reduced.
- The impact of renal impairment on PK of GNX is being evaluated in an ongoing study. However, renal excretion is a minor pathway in the elimination of GNX. Therefore, renal impairment is unlikely to result in clinically significant changes in GNX exposures

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

GNX is a methyl substituted analog of allopregnanolone and it is a positive allosteric modulator of GABAA receptors. Over the course of the clinical development, several formulations, e.g., (b) (4) solution, β-CD suspension, tablet, capsule, and (b) (4) suspension, were developed and evaluated in clinical studies. The applicant noted that (b) (4) suspension (50 mg/mL) was the final to-be-marketed formulation and was used in Phase 1 studies (1042-DDI-001, 1042-0400), a proof-of-concept study (1042-0900), and a Phase 3 study (1042-CDD-3001).

In the Type C meeting minutes DARRTS dated 1/11/2018, the agency agreed with the applicant that hepatic impairment study (full study design) and renal impairment study (reduced design) may be conducted post NDA submission. On August 11, 2020, in an email communication, the Agency informed the applicant that, a Thorough QT (TQT) study (1042-TQT-1001) results can be submitted post NDA submission, if the data are not available by the time of NDA review. These three studies are ongoing, and the applicant agreed to submit the data as they become available.

The clinical development program includes a Phase 3 study (1042-CDD-3001) in CDD patients to evaluate the safety/efficacy for ZTALMY®, and 6 relevant phase 1 studies evaluating the drug-interaction potential with itraconazole (strong CYP3A4 inhibitor) and rifampin (strong CYP3A4 inducer), grapefruit juice (CYP3A4 inhibitor), midazolam (CYP3A4 substrate), food-effect study, a mass-balance study, and a lactation study.

3.2 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and pharmacokinetics information of GNX are summarized below.

Pharmacology	
Mechanism of Action	GNX is a selective positive allosteric modulator of gamma-aminobutyric acid type A ($GABA_A$) receptors located in the CNS.
Active Moieties	GNX is the only identified active moiety.
QT Prolongation	A Thorough-QT TQT study (1042-TQT-1001) is currently ongoing.
General Information	
Bioanalysis	GNX was measured using validated LC/MS/MS method. The accuracy, precision, and other relevant assay parameters are summarized in Appendix 4.1.

Dose proportionality	In study 1042-DDI-1001 in adult healthy volunteers, a 3-fold increase in single dose (from 200 mg to 600 mg) of GNX resulted in 2.4-fold increase in mean Cmax, and 3.6-fold increase in mean $AUC_{0\text{-}inf}$.
Enzyme Inhibitor/Inducer [in-vitro]	GNX is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 at the clinically relevant concentrations. GNX is not an inducer of CYP1A2, CYP2B6 or CYP3A4/5 at the clinically relevant concentrations. GNX is not an inhibitor of SULT1E1 at clinically relevant concentrations.
Transporter [in-vitro]	GNX is not a substrate of P-gp, BCRP, OCT1, OCT2, OATP1B1 and OATP1B3 at clinically relevant concentrations. GNX is not an inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp and BSEP at clinically relevant concentrations.
Absorption	
Tmax	T_{max} of 2-3 h.
Food effect (high-fat)	Coadministration of GNX with high-fat meal increased Cmax and AUC by 3-fold and 2-fold, respectively.
Distribution	
Plasma Protein Binding	GNX binds extensively to human plasma proteins >84% and > 99% at 50 ng/mL and 500 ng/mL, respectively.
Elimination	
Elimination Half-life	The half-life for GNX was about 34 hours. GNX is eliminated with a clearance of 430 L/hr.

Metabolism / Excretion	The results from *in-vitro* characterization studies showed that CYP3A4, CYP2B6, CYP2D6 and CYP2C19 were involved in GNX metabolism. However, the relative contribution of each pathway towards overall GNX metabolism is not clear. Multiple metabolites M60b, M18, M73, M62, M43 and M47 have been identified from mass-balance study: **Metabolites** / **% Total Radioactivity (0-30 days)** M60a/M60b — 23 M18 — 4.6 M73 — 2.3 M62 — 3.0 M47* — 24 M43* — 2.0 Ganaxolone — 4.1 *Sulfate conjugates The exposures of a sulfated metabolite M47, and two non-conjugated metabolites M60b, M18 exceeded the exposures of GNX. M60b did not show drug-interaction liability as a perpetrator with major CYP enzymes or transporters. The applicant did not assess the drug interaction liability of M18 and M47 as a perpetrator. In response (dated 08/17/2021, sequence #4, section 1.11.3) to an information request, the applicant noted that M18 was generally similar structurally with parent GNX, and M47 is sulfate conjugate of parent GNX. Given that parent GNX did not show drug-interaction potential and the low abundance of M18, it is considered not to pose any significant drug-interaction liability. Further, the applicant noted that synthesis of these metabolites and evaluation of drug-interaction liability as isolated compounds is impractical. Therefore, no additional post-marketing studies are being issued to assess the DDI liability of these metabolites. Following single oral dose of 300 mg [^{14}C]-GNX to healthy male subjects, 55% of the total radioactivity was recovered in feces (2% as unchanged GNX) and 18% of the total radioactivity dose was recovered in urine (undetectable as unchanged GNX).

	In addition, GNX and its metabolites were evaluated in a lactation study. Following a single oral dose of ^{14}C-GNX to 5 healthy adult lactating women, unchanged GNX exposures ($AUC_{(0\text{-}24\ h)}$) in breast milk were approximately 4 times that in maternal plasma, resulting in an estimated daily dose in the infant of less than 1% of the maternal dose.

3.3 Clinical Pharmacology Review Questions

3.3.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The evidence of effectiveness of GNX is based on a double blind, placebo-controlled Phase 3 trial (1042-CDD-3001) in CDD subjects. GNX-treated subjects showed statistically significant reduction in median percent change from baseline in 28-day seizure frequency for major motor seizure types compared to subjects who received PBO:

Table 1. Median Percent Reduction in Primary Seizure Frequency (per 28 days)

	Treatment		
	GNX	Placebo	Difference
Median Percent reduction in Primary Seizure Frequency (per 28 days)	30.7%	6.9%	Δ = 27.1% p = 0.0036*

Source: Table-8 on Page 40, Clinical Study Report 1042-CDD-3001

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, GNX dosing evaluated in pivotal efficacy/safety study (1042-CDD-3001) in CDD patients demonstrated significant reduction in seizure frequency compared to the placebo. The applicant's proposed dosing for GNX in CDD patients is identical to that evaluated in efficacy/safety study and is therefore considered acceptable. Please review Clinical review by Drs. Steven Dinsmore and Phillip Sheridian and Statistics reviews by Drs. Xiang Ling and John Lawrence for additional details on efficacy and safety evaluation of GNX.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Clinical studies evaluating the impact of hepatic impairment (full-study design) and renal impairment (reduced study design) on the PK of GNX are currently ongoing.

GNX undergoes clearance via hepatic route. Therefore, hepatic impairment can increase GNX exposures. Patients with impaired hepatic function should be monitored for incidence of adverse reactions and GNX dosage may need to be reduced.

Renal excretion is a minor pathway in the elimination of GNX and therefore, renal impairment is unlikely to result in clinically significant increase in GNX exposures

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-Drug Interaction

The applicant conducted a dedicated PK study (1042-0400) in healthy subjects to evaluate the impact of high-fat meal on the PK of GNX. The study results showed that coadministration of high-fat meal increased GNX C_{max} by 3-fold, and AUC by 2-fold when compared to fasting conditions. In addition, in the pivotal efficacy/safety study, GNX was administered with food. The efficacy of GNX when administered in fasted state is not known. Therefore, GNX should be administered with food in CDD patients.

Drug-Drug Interactions

In-Vivo Studies – Effect of Other Drugs on GNX

CYP3A4 Inhibitors

The applicant conducted two dedicated PK studies to evaluate the impact of grapefruit juice (1042-0115) and itraconazole (1042-DDI-1001) on PK of GNX.

The applicant conducted study 1042-0115 to evaluate the impact of consumption of grapefruit juice on a single 400 mg dose of GNX oral tablet (which is not the final to-be-marketed formulation) in 4 healthy female volunteers. The study results showed that concomitant administration of grapefruit juice with GNX increased GNX exposures C_{max} by 2-fold and AUC by 2.6-fold. The review team identified a few challenges in verifying the accuracy of these PK data: 1) the applicant did not submit the individual-level PK data, noting that the study was conducted in 1998, and did not have access to the raw datasets; 2) the applicant did not submit the bioanalytical validation reports; 3) the sample size of subjects was relatively low (n=4), and %CV in the exposures was 50-95% and therefore, reliability of complete inhibition of CYP3A4 is not clear. Owing to these concerns, the

review team considered the data from study 1042-DDI-1001 (described below) more reliable to inform dosing recommendations for concomitant use of GNX with strong CYP3A4 inhibitors.

The applicant conducted cross-over study 1042-DDI-1001 in healthy subjects to evaluate the impact of itraconazole at steady state (200 mg once daily, oral capsules) on GNX (200 mg oral suspension, to-be-marketed formulation) in healthy adult subjects (n=16). Both, GNX and itraconazole were administered approximately 30 minutes after the beginning of a meal. The study results showed that concomitant administration of itraconazole with GNX increased GNX AUC by 17%, while C_{max} was unchanged.

The applicant did not conduct drug-interaction studies to evaluate the impact of coadministration of GNX with moderate and weak CYP3A4 inhibitors.

Overall, given the small changes in GNX exposures with concomitant administration of strong CYP3A4 inhibitors, moderate or weak CYP3A4 inhibitors are not expected to result in clinically significant changes in GNX exposures. Therefore, GNX dosage adjustment is not needed with strong, moderate or weak CYP3A4 inhibitors.

CYP3A4 Inducers

The applicant conducted cross-over study 1042-DDI-1001 in healthy subjects to evaluate the impact of rifampin at steady state (600 mg once daily) on GNX (600 mg oral suspension, to-be-marketed formulation) in healthy adult subjects (n=16). The study results showed that concomitant administration of rifampin with GNX decreased GNX AUC by 68%, and C_{max} by 57%. Rifampin is a strong inducer of CYP2C19 and CYP3A4, and a moderate inducer of CYP2B6. Therefore, the results from rifampin drug-interaction study are a composite effect of induction of multiple enzymes on GNX PK. Further, the results from *in-vitro* characterization studies showed that CYP3A4, CYP2B6, CYP2D6 and CYP2C19 were involved in GNX metabolism, but the relative contribution of each pathway towards overall GNX metabolism is not clear.

The reduction in GNX exposure when administered with strong/moderate CYP inducers is considered clinically significant and may result in reduced efficacy. Therefore, it is recommended to avoid concomitant administration with inducers of CYP450 enzymes such as strong or moderate CYP3A4 inducers. When concomitant use of strong or moderate CYP3A4 inducers cannot be avoided, GNX dosage may need to be increased, but should not exceed the maximum daily dosage of GNX, i.e., 63 mg/kg and 1800 mg for patients weighing ≤ 28 kg and >28 kg, respectively.

In the pivotal efficacy/safety study (1042-CDD-3001), CDD patients were allowed to take antiepileptic drugs [AEDs] that were moderate or strong inducers or inhibitors, so long as patients are stabilized on AEDs for a month prior to initiating GNX. Besides AEDs, concomitant use of strong or moderate CYP3A4/5/7 inducers or inhibitors were not

permitted. Use of dietary supplements or herbal preparations were not permitted if subject had been using them consistently for less than 3 months prior to screening or did not plan on remaining on stable doses for the duration of the double-blind phase. Use of St. John's Wort was not permitted.

The results from study 1042-CDD-3001 showed that 12% of CDD patients in placebo group and 10% CDD patients in GNX group were on Enzyme-Inducing AED (EIAEDs). Within the GNX arm, out of the 5 subjects who were on concomitant EIAEDs, 3 subjects were ≤ 28 kg (all three maintained at maximum daily dosage of 63 mg/kg): 2 were on phenobarbital, 1 subject was on carbamazepine; 2 subjects were > 28 kg: both on phenobarbital, one maintained at 450 mg and another at 1050 mg total GNX daily dosage.

The distribution of the final GNX doses at the end of the double-blind period in GNX arm stratified by weight cut-off are shown below. Overall, by the end of 17 weeks, in the GNX arm, 30-40% of the CDD subjects were not at respective maximum daily dosage likely due to tolerability. Therefore, in some CDD subjects who take concomitant strong or moderate CYP3A4 inducers, GNX daily dosage can be increased until they reach the maximum limit proposed by the applicant.

Subjects weighing ≤ 28 kg		**Subjects weighing > 28 kg**	
Dose (mg/kg/day)	**Number of Subjects**	**Dose (mg/day)**	**Number of Subjects**
8	2	450	1
11	1	900	1
16	1	1050	1
18	2	1350	1
33	2	1800	6
42	1		
48	2		
63	29		
Total number of subjects	40		10
Percentage of subjects at maximum GNX daily dosage by the end of week 17	72.5		60
Percentage of subjects not at maximum GNX daily dosage by the end of week 17	27.5		40

In summary, when patients are on stable background EIAEDs, the GNX titration scheme, as proposed, is similar to that evaluated in the pivotal phase 3 efficacy/safety study and is appropriate.

For CDD patients on stable GNX dosage who are initiating or increasing dosages for EIAEDs, GNX dosage may need to be increased but should not exceed the maximum daily dosage of GNX.

Effect of GNX on Other Drugs

CYP3A4 Substrates - Midazolam

The applicant conducted study 1042-0402 in healthy subjects to evaluate the impact of GNX at steady state (400 mg twice daily [total daily dosage of 800 mg], oral capsules) on midazolam (2 mg orally) in healthy adult subjects (n=17). The study results showed no clinically significant impact on midazolam exposures C_{max} or AUC. However, it should be noted that this study evaluated interaction potential of GNX (as a perpetrator) at a lower dose level (maximum GNX total daily dose is 1800 mg) and used GNX capsule formulation (the final product is a suspension). Therefore, at the pre-NDA meeting (minutes DARRTS dated 03/11/2021) agency noted the interaction potential of GNX as perpetrator for CYP3A4 based on study 1042-0402 is likely an underestimation (additionally: oral capsules showed ~18-36% lower exposures than to-be-marketed formulation at fasted state). The applicant provided supporting *in-vitro* CYP3A4 induction and inhibition study (XT155147) and concluded that GNX was not a CYP3A4 inducer or inhibitor. The review team considered both *in vitro* and *in vivo* study results and based on a totality of evidence of approach, concluded that it is unlikely that GNX, at clinically relevant concentrations, is an inhibitor or inducer of CYP3A4 substrates. Therefore, no dosage adjustment is needed for CYP3A4 substrates when concomitantly administered with GNX.

Oral Contraceptives

Oral contraceptives usually contain 2 synthetic steroid hormones, an estrogen, typically ethinyl estradiol (EE) and a progestin (e.g., norethindrone, levonorgestrel, drospirenone, and gestodene). CYP3A4 is considered the major enzyme for the oxidative metabolism of oral contraceptives and CYP2C9 and CYP2C19 are involved to a minor extent.

At the Pre-NDA meeting, the applicant submitted a waiver request for clinical drug interaction studies with oral contraceptives, citing *in-vitro* (XT155147, XT15312, OPT-2016-020) and *in-vivo* (1042-0402) studies that demonstrated no DDI potential of GNX either as a victim or perpetrator of major CYP enzymes. As noted above, the Agency requested for additional justification in the correspondence dated 03-11-2021. The Agency also recommended that the applicant investigate inhibitory potential on

sulfotransferase 1E1 (SULT1E1), enzyme that affects disposition of ethinyl estradiol (EE), the most commonly used estrogen in oral contraceptives. The applicant conducted *in-vitro* study (B21A34-R), evaluating the inhibition potential of GNX for SULT1E1. The study results indicated that IC_{50} of SULT1E1 inhibition by GNX was 2.2 µM, while the *in-vivo* steady state unbound C_{max} was 0.0088 µM (125-fold lower than the IC_{50}). The applicant also summarized (**Table 2**) a literature survey of the effects of reference compounds on AUC of CYP3A4-sensitive probe substrates and oral contraceptives and compared the impact with GNX. Based on these results, the applicant considered these data, along with the completed midazolam clinical drug interaction study, are adequate to characterize the risk of GNX acting as a perpetrator of a drug interaction and no additional studies are required. The review team, based on totality of information, agrees that clinically significant interaction between GNX and oral contraceptives is unlikely at clinically relevant concentrations.

Table 2 Effect of reference compounds and GNX on AUC of CYP3A4-sensitive probe substrates and oral contraceptives

Potential CYP3A4 Inducer	CYP3A4 Sensitive Probe	Effect of Inducer on Sensitive Probe	Effect on OC	Reference
Rifampin	MDZ	↓95%	↓64%	Backman-1996a, Lebel-1998
Carbamazepine	MDZ	↓94%	↓41%	Backman-1996b, Crawford-1990, Rip-2006
St. John's Wort	MDZ	↓45%	↓12% (NE) ↓32% (EE)	Hall-2003
NUVIGIL (armodafinil)	MDX	↓32%	Not reported	Darwish-2008, NUVIGIL label (28 Jun 2013)
ONFI (clobazam)	MDZ	↓27%	Not reported	ONFI label (21 Nov 2013)
ACTOS Pioglitazone	MDZ	↓26%	↑3% (NE) ↓11% (EE)	ACTOS label (12 Nov 2013)
AVANDIA Rosiglitazone	NIF	↓13%	No effect	Harris-1999, Inglis-2001, AVANDIA label (30 May 2012)
VIMPAT (lacosamide)	MDZ	No influence	No influence	VIMPAT label (25 Sep 2013)
GNX	MDZ	↓12% (not significant)		Marinus Study 1042-0402 – copy available upon request

EE = ethinyl estradiol; GNX = ganaxolone; NE = norethindrone; NIF = nifedipine; MDZ = midazolam.

Source: Table 29, pre-NDA meeting briefing document

***In-Vitro* Studies**

The results from *in-vitro* characterization studies showed that CYP3A4, CYP2B6, CYP2D6 and CYP2C19 were involved in GNX metabolism. However, the relative contribution of each pathway towards overall GNX metabolism is not clear.

The applicant conducted *in-vitro* drug-interaction studies, and showed that at clinically relevant exposures:

- GNX is not a substrate of efflux transporters: P-gp and BCRP and hepatic uptake transporters: OCT1, OCT2, OATP1B1 and OATP1B3.
- GNX is not an inhibitor of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP.
- GNX is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.
- GNX is not an inducer of CYP1A2, CYP2B6 and CYP3A4/5.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes. GNX oral suspension, the to-be-marketed formulation, was used in the pivotal efficacy/safety study (1042-CDD-3001). Therefore, no additional formulation bridging studies are necessary.

4. Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods used for the essential clinical pharmacology studies of GNX are summarized in the Tables below,

Summary of Bioanalytical Method Measuring GNX in Plasma

Method ID	QSP 199-1503	QSP 199-0506
Study Number Supported	Study 1042-DDI-1001, Study 1042-C14GNX-lac-1001, Study 1042-GNX.AME-1001	Study 1042-0400 Study 1042-0402
LLOQ (ng/mL)	2	1
Linear Range (ng/mL)	2 - 1000	1 - 1000
QC Concentrations (ng/mL)	2, 6, 50, 500, and 750	1, 3, 25, 270, and 900
Intra-day Accuracy for QC (%RE)	-0.4 to 12.0	-5.9 to 6.4
Intra-day Precision for QC (%CV)	0.9 to 4.1	2.2 to 19.6*
Inter-day Accuracy for QC (%RE)	2.2 to 8.0	-8.8 to 3.5
Inter-day Precision for QC (%CV)	2.8 to 4.4	4.2 to 18.8*
Processed Sample Stability	166 Hours at 4°C	149 Hours at 4 °C
Freeze/Thaw Stability in Plasma	11 Cycles at -20°C, 10 Cycles at -70°Ce	5 Cycles at -20°C
Long-term Storage Stability in Plasma	999 Days at -20°C, 369 Days at -70°Ce	To Be Determined at-20°C

* With precision of LLOQ

Summary of Bioanalytical Method Measuring GNX in Breast Milk

Method ID	**199-1705**
Study Number Supported	1042-C14GNX-lac-1001
LLOQ (ng/mL)	1 ng/mL
Linear Range (ng/mL)	1 ng/mL to 1000 ng/mL
Analytical QC Inter-run Precision Range (%CV)	2.0 to 5.9
Analytical QC Inter-run Accuracy Range (%RE)	-1.8 to 6.7

Reviewer's comments:

The validated assay performance was reviewed individually for the key clinical pharmacology studies. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits.

4.2 Population Pharmacokinetic Analyses

The Applicant submitted two population pharmacokinetic (PK) analysis reports. The first report is the main pharmacokinetic PK (PPK) report *1042-cdd-poppk-001-study-report.pdf*, titled "*Modeling Report: Population PK Modeling of Ganaxolone in Pediatric Patients with Seizure Disorders*", submitted to sequence 0001 module 5335. The second report is the supplemental PPK report *09-0600-pop-pk-01-study-report.pdf*, titled "*Population Pharmacokinetic (PK) Analysis of Ganaxolone (GNX) Following Oral Liquid Suspension Administration in Adult Refractory Epilepsy Patients (PK data from Phase 2, Clinical Study No.1042-0600)*", submitted to sequence 0001 module 5335.

4.2.1 Supplemental PPK Report

The supplemental PPK report (09-0600-pop-pk-01-study-report.pdf) describes PPK analyses of GNX oral liquid suspension to adult patients with refractory epilepsy from a Phase 2 Clinical Study number 1042-0600. This study was not reviewed for the following reasons:

- The applicant does not have access (and cannot gain access) to one of the key data files involved in the analyses (gnx-nca-of-simulated-poppk.kbd).
- The applicant does not have access to the software used to conduct the PK simulations described in the report. The aforementioned .kbd file is a Kinetica database file. The software, Kinetica Version 5.0, was previously discontinued by the developer, Thermofisher Scientific. The Applicant indicates that they do not have a copy of the Kinetica software required to access the file.
- The PK parameter estimate for ka in the Supplemental PPK report (4620 h^-1) is over 10,000 times higher than the ka estimate in the Main PPK report (0.34 h^-1). The estimate of 4620 h^-1 from the Supplemental PPK report is physiologically implausible.

For these reasons, the analyses in the supplemental Pk report will not be reviewed and will not be further discussed in this review.

4.2.2 Main PPK Report

The main PPK report (1042-cdd-poppk-001-study-report.pdf), submitted to sequence 0001 module 5335, is titled "*Modeling Report: Population PK Modeling of Ganaxolone in Pediatric Patients with Seizure Disorders*". The objective of these analyses is to estimate GNX exposures in pediatric patients using a population PK model (potentially supported with data from healthy adult subjects). There were 694 samples 146 subjects included in the analyses. The studies from which the data were collected are summarized in the table below:

Table 3: Clinical Studies From Which Data Were Collected for Inclusion in the Analyses in the Main PPK Report (1042-cdd-poppk-study-report.pdf)

Study Number, Phase, Type	Subject Population	Number of Subjects	Drug Dose and Regimen	PK and/or PD Sampling
1042-DDI-1001 Phase 1 DDI	Healthy adult subjects	N=32 (planned)	A: 200 mg GNX B: 200 mg itraconazole QD for 11 days + 200 mg GNX on Day 12 C: 600 mg GNX D: 600 mg rifampin QD for 16 days + 600 mg GNX on Day 10	PK: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose after each dose of GNX Efficacy: None
1042-0900 Phase 2a Safety and efficacy	Children with PCDH19 female pediatric epilepsy	N=30 including 7 CDD patients	Up to 63 mg/kg but not more than 1800 mg/day	PK: Baseline, Weeks 2, 8, and 26 Efficacy: Baseline and end of 26 weeks of treatment
1042-CDD-3001 Phase 3 Safety and efficacy	Children and young adults with cyclin-dependent kinase-like 5 deficiency disorder	N=100 (planned)	Up to 63 mg/kg but not more than 1800 mg/day	PK: Sparse samples in double blind period (Planned: Weeks 5, 9, 17, but some missing). Efficacy: Baseline and end of the 17-week treatment phase

Abbreviations: CDD=CDKL5 Deficiency Disorder; DDI=drug-drug interaction; GNX=ganaxolone; N=number of subjects; PCDH19=protocadherin-19; PK=pharmacokinetics; QD=once daily.

Source: Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf, page 13 of 87

The final model included two compartments and first-order absorption with time lag. The model is parameterized in terms of clearance (CL), volume of distribution of the central compartment (V2), volume of distribution of the peripheral compartment (V3), intercompartmental clearance (Q), first-order absorption rate constant (ka), relative bioavailability (F), and maximum absorbed dose.

Allometric Scaling: Model models with fixed exponents of 0.75 for clearance terms (Cl and Q) and 1 for volume terms (V2, V3) was body weight normalized to 70 kg.

Inter-Individual Variability: Exponential

Residual Variability: Additive and Proportional

Covariates: Weight is a covariate on the maximum absorbed dose.

Parameter estimates for the final model (Run finalpk) are shown in the table below.

Table 4: Parameter Estimates for the Final PPK Model (Run finalpk-mod.txt)

Parameters	**Model Estimate**	**95% CI**	**Bootstrap Median**	**Bootstrap 95% CI**
CL (L/hr)	430	381-479	433	388-504
V2 (L)	823	471-1174	767	539-2452
V3 (L)	8854	6756-10950	228	6557-10991
Q (L/hr)	228	194-262	8847	197-267
k_a (hr^{-1})	0.34	0.28-0.40	0.33	0.3-0.4
Lag time (hr)	0.18	0.16-0.19	0.18	0.16-0.2
Maximum Absorbed Dose (mg)	266	208-323	272	215-369
Weight effect on Maximum Absorbed Dose	0.81	0.40-1.2	0.80	0.4-1.2
Random effects	**Model Estimate**	**95% CI**	**Bootstrap Median**	**Bootstrap 95% CI**
IIV on V2	74	0-114	49.4	
IIV on ka for healthy volunteers	8.9	0-23	2.3	
IIV on F	75	60-88	55	
Residual error	**Estimates**			
Proportional	35%	30-40		
Additive (ng/mL)	0.01 FIX	--	--	--

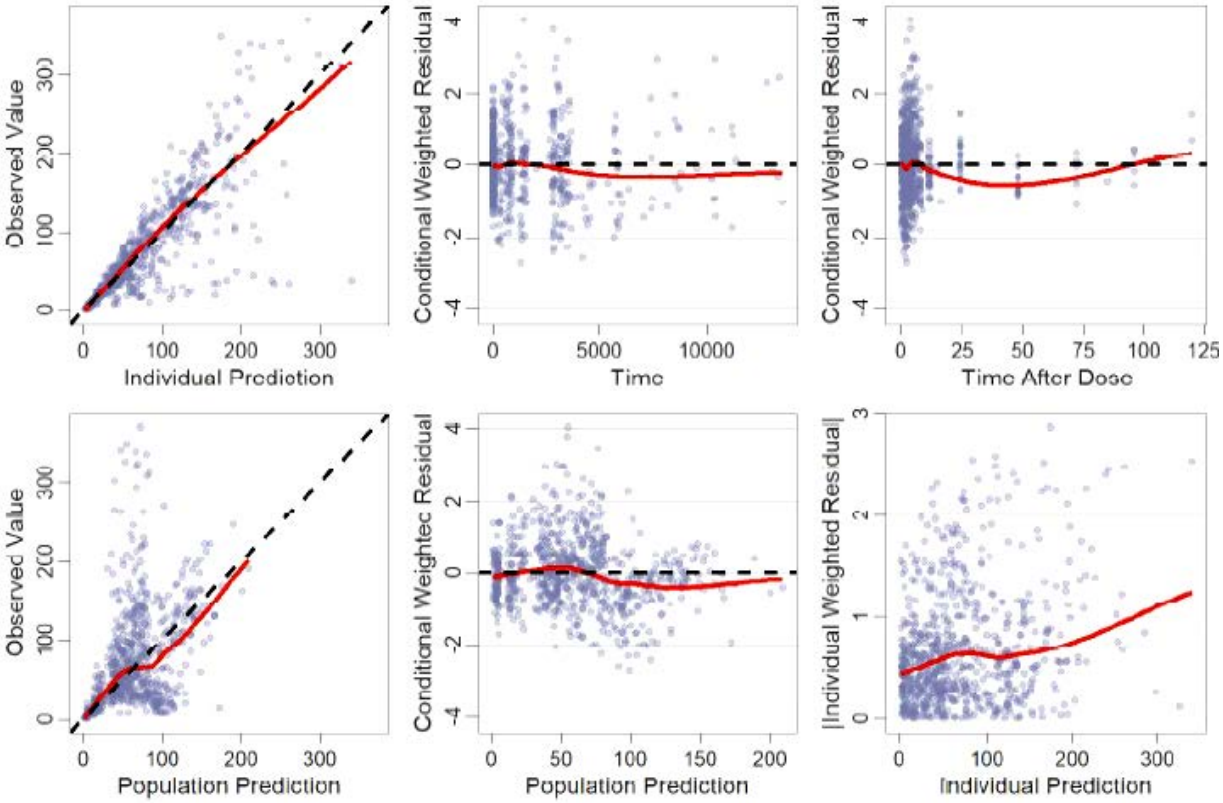
Source: n14v11.lst

Abbreviations: CI=confidence interval; CL=clearance; CV=coefficient of variation; F=relative bioavailability; FIX=fixed parameter; IIV=inter-individual variability; ka=absorption rate constant; Q=inter-compartmental clearance; RSE=relative standard error; V2=central volume of distribution; V3=peripheral volume of distribution

Source: Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf, page 35, Table 10

Model diagnostics are presented in **Figure 1** and **Figure 2**.

Figure 1: Goodness-of-fit plots for the final Population PK Model



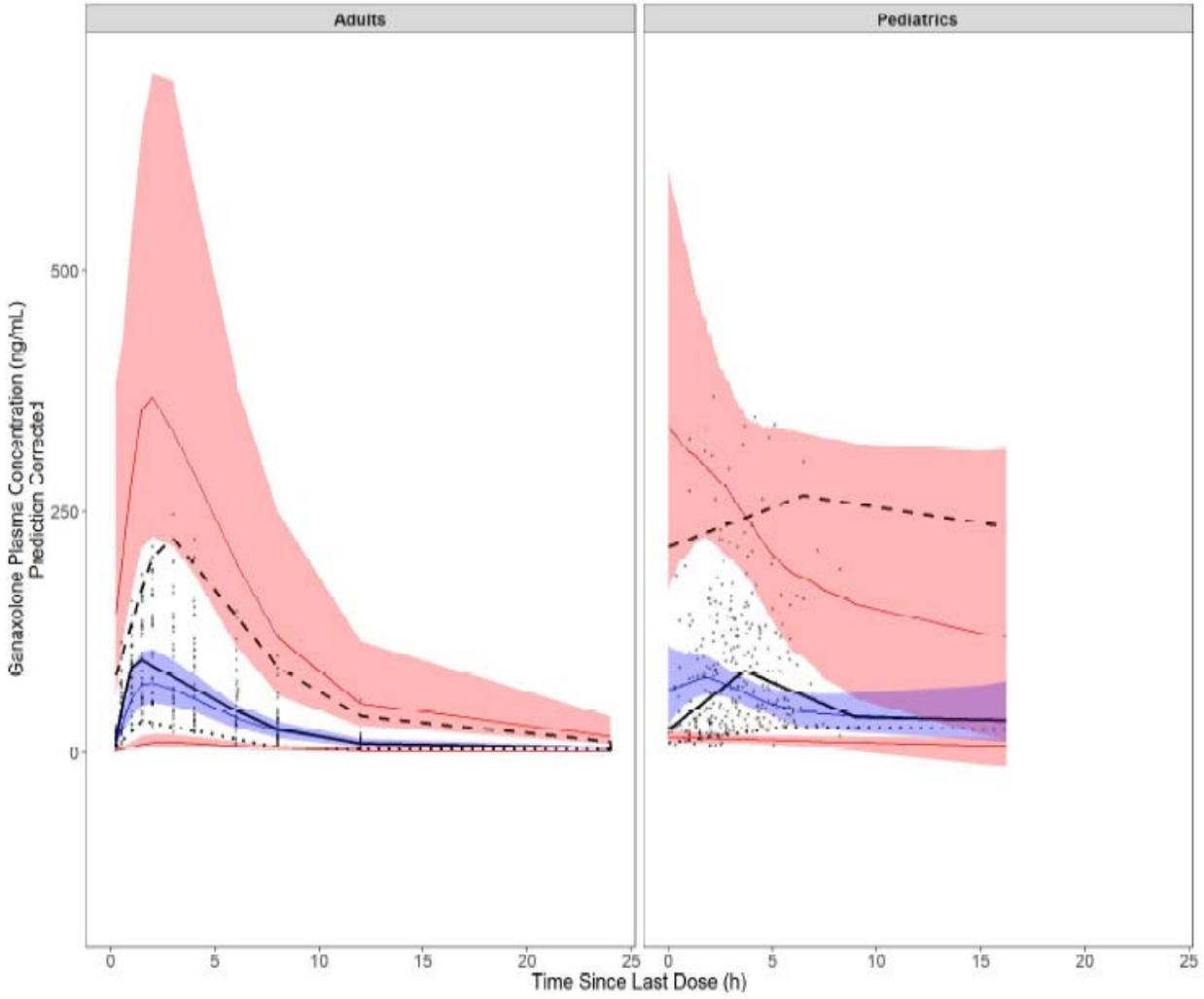
Source: Mari-update26Mar2021.Rmd

Notes: Dots are individual data points, and solid red lines are smoothed LOESS lines. In the two plots in the left column, dashed lines are lines of identity, while in the two plots in the center column and the top plot in the right column, dashed lines show the CWRES=0.

Abbreviations: CWRES=conditional weighted residuals; GOF=goodness-of-fit; LOESS=locally weighted scatterplot smoothing;

Source: Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf, page 30, Figure 4

Figure 2: Prediction-Corrected VPC Stratified by Adult and Pediatric Subjects Over The First 24 Hours After Dose Administration



Source: Mari-update26Mar2021.Rmd
Notes: Black dots are observed data points; black solid line is the observed median; black dashed line is the observed p95 and black dotted line is the observed p5. The blue solid line is the simulated median; red solid lines are simulated p5 and p95. The blue area is the 95% PI of the simulated median, and pink areas are the 95% PI of the simulated p5 and p95.
Abbreviations: p5=5th percentile; p95=95th percentile; PI=prediction interval; VPC=visual predictive check

Source: Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf, page 34, Figure 6

[*Reviewer comment: Based on the VPC (**Figure 2**) the model performance for pediatric patients may not be reliable. The Applicant addressed the performance in pediatric patients in the PPK report (Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf, page 33):*

> *"*The median concentration was not fully captured throughout the profile for the pediatric subjects with overpredictions between 0 and 3 hours post-dose, and underpredictions between 4 and 5 hours post-dose. The prediction bands for the p5 and p95 were more aligned with the observed values. The model misspecification for pediatric patients is likely due to the sparse data in pediatric subjects that prevented accurate estimation of the absorption profile in those subjects, and large interindividual variability in exposure for all subjects. Despite this model misspecification, the base pop PK model was considered the best model for the data.*"*

The reviewer agrees that sparse PK data sampling in the context of PK variability may have contributed to the model performance in pediatric patients.

The final model in the Main PPK Report does not include concomitant medications as a covariate on GNX PK. However, the final model in the Supplemental PPK Report includes concomitant carbamazepine and/or phenytoin (versus taking non-CYP-inducing AEDs) as a categorical covariate on GNX clearance. The information request was sent to the Sponsor on November 1st, 2021 seeking clarification on this matter:

> *"*The final model in the main PPK analysis report (1042-cdd-poppk-001-study-report.pdf in sequence 0001) does not include concomitant medication as a covariate on GNX PK. However, this result is inconsistent with the supplemental PPK model includes concomitant enzyme-inducing medications as a covariate on GNX PK. The main PPK analysis report does not provide details as to why concomitant medication use was not included in the final PPK model. You should clarify how you assessed the effect of concomitant medication on GNX PK and why concomitant medications were excluded from the final model in the main PPK report.*"*

The Applicant responded on November 4th, 2021 (sequence 0024) as follows:

> *"*The main PPK analysis (1042-CDD-POPPK-001) did not include use of enzyme induction antiepileptic drugs (EIAEDs) as a covariate on the PK of GNX, in part because only a small subset of subjects were taking EIAEDs (12 out of 82). The majority of the concomitant AEDs in 1042-CDD-3001 were non-enzyme inducing, were not expected to affect the PK of GNX, and dispersed over a large number of medicines, making it unfeasible to evaluate their effect the small number of subjects.

In the supplemental PPK there were PK data from 50 subjects not on EIAEDs and 44 subjects on EIAEDs, so the effect of the EIAEDs (carbamazepine, phenytoin, and phenobarbital in that study) was evaluated robustly.

Furthermore, since the supplemental PPK was completed, Marinus has since done a dedicated study of the effect of an index strong inducer (rifampin) on the PK of GNX (1042-DDI-1001) and the effect of induction on the PK of GNX was established clearly.

The data from the supplemental PPK and the dedicated DDI study provide substantial information to characterize the effect of CYP450 induction. The minimal information that could come from inducers as covariate in the 1042-CDD-POPPK-001 analysis was considered unlikely to provide useful information for the use of GNX.*"*

The applicant's response regarding drug interactions is reasonable. The reviewer agrees that robust estimation of drug interaction effect is not feasible.

Overall, the Applicant's PPK model ***performance in pediatric patients may not be reliable.***]

4.2.3 PK simulations

The Applicant conducted PK simulations to predict the PK in pediatric patients. The simulations were conducted in 4 age groups; 2 to < 6 years, 6 to < 12 years, 12 to < 18 years, and ≥ 18 years. The median weight within the age limits was obtained from the population PK dataset. Doses of 63 mg/kg/day as t.i.d. (maximum 1800 mg per day as maximum 600 mg three times daily) were administered in the simulations up to steady-state.

The key simulation results are described below. The detailed results can be found in the Main PPK report (Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf) on pages 35 to 36.

Table 5: Simulated GNX Steady-State Exposure in Pediatric and Adult Subjects

Age Group	Mean Body Weight (kg)	Dose (mg)	AUC_{24} (ng*hr/mL)	C_{min} (ng/mL)	C_{max} (ng/mL)
2 to <6 years	14.8	312	3903	85	247
6 to <12 years	22.6	475	3998	84	269
12 to <18 years	36.1	600	4106	84	293
≥18 years	35.1	600	4100	84	292

Source: Mari-sims20Apr2021.Rmd
Notes: Dose represents the dose amount in mg administered three times daily.
Abbreviations: AUC_{24}=24-hour area under the ganaxolone plasma concentration time curve; C_{max}=maximum ganaxolone plasma concentration; C_{min}=minimum ganaxolone plasma concentration.

The value presented for AUC24, Cmin, and Cmax represents the mean value within each age bin.

Source: Sequence 0001, module 5335, 1042-cdd-poppk-001-study-report.pdf, page 36, Table 11

The Applicant proposes to include the simulated AUC24 values for pediatric patients into section 12.3, specific populations, pediatric patients.

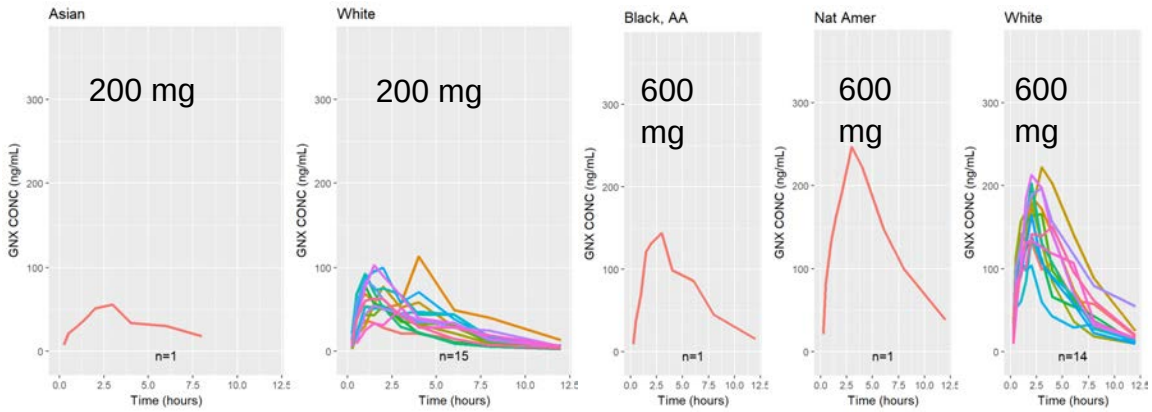
[*Reviewer comment: Section **4.2.2*** Main PPK Report *of this review describes concerns about the PPK model performance for pediatric patients. Considering these concerns, OCP recommends removing the statements based on the PK simulations from the label.*]

4.2.4 Reviewer's Assessment of Observed PK by Subgroup

The reviewer conducted a graphical assessment of the observed PK data by sub-group. Assessments were conducted for race, sex, and age.

The individual PK profiles stratified by race and by arm for study 1001 are presented in **Figure 3**.

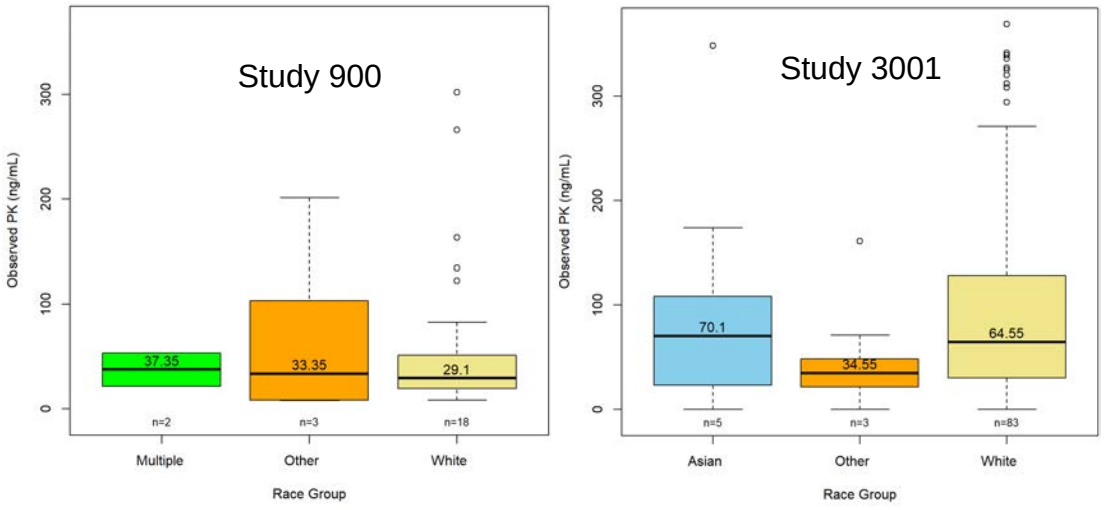
Figure 3: Observed PK Profile for Study 1042-DDI-1001 by Arm and by Race



Race is categorized as White, Black or African American, Asian, Native American or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, or Other.

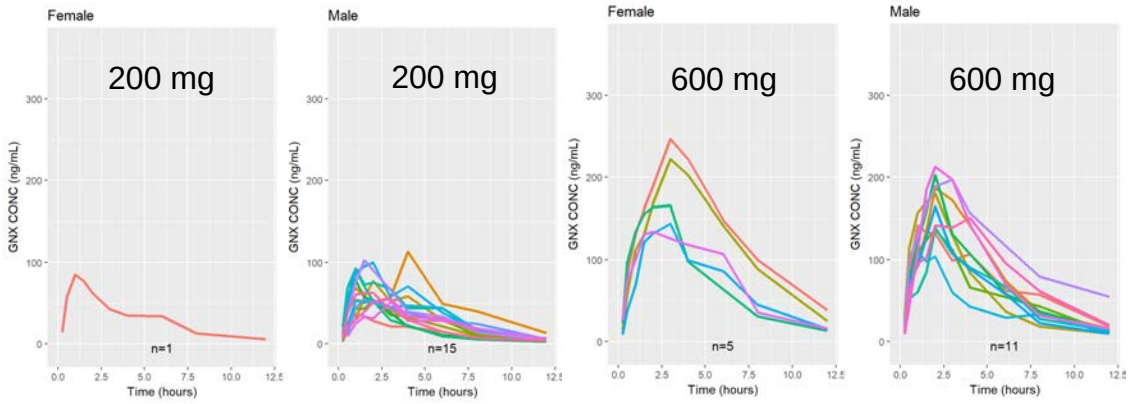
The observed PK profiles in studies 1042-0900 and 1042-CDD-3001 are presented by race in **Figure 4**.

Figure 4: Observed PK for Study 1042-0900 and Study 1042-CDD-3001 by Race



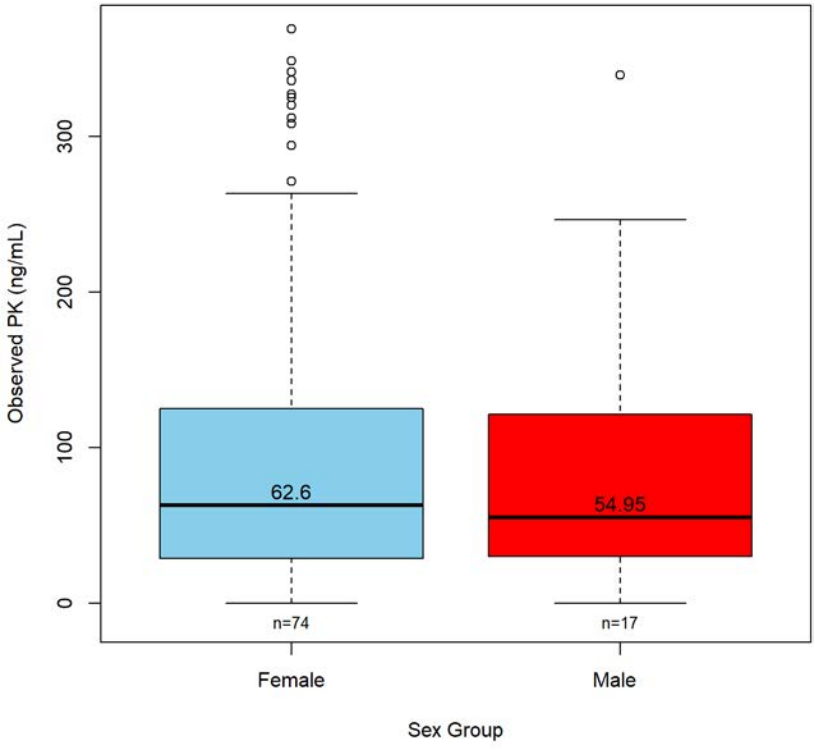
The individual PK profiles stratified by sex and by arm for study 1001 are presented in **Figure 5**.

Figure 5: Observed PK Profile for Study 1042-DDI-1001 by Arm and by Sex



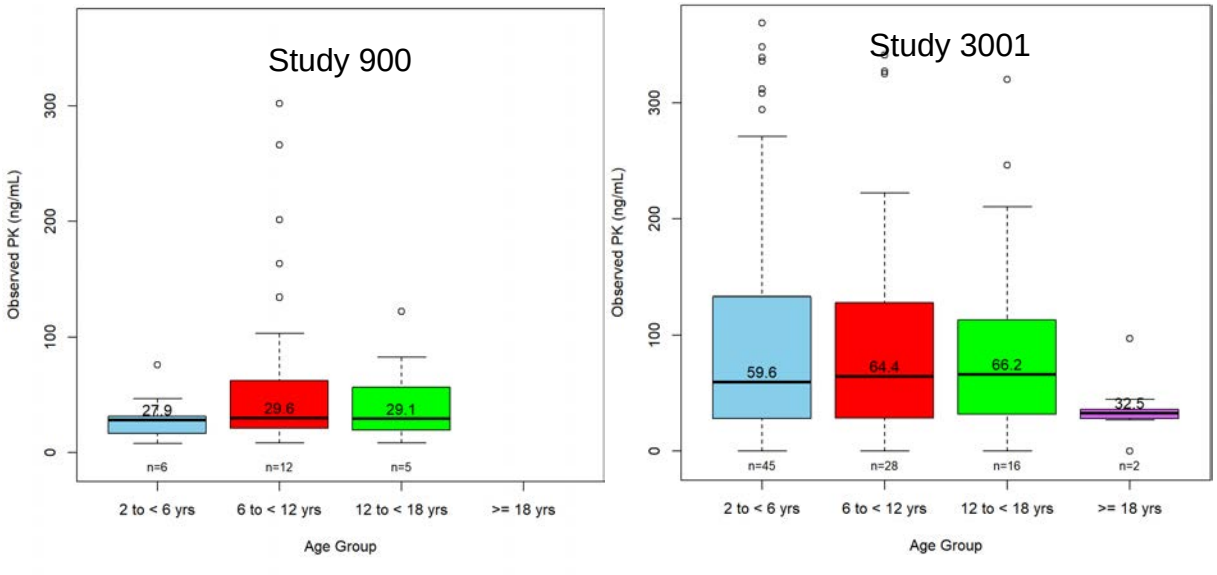
A PK comparison by sex is not feasible for Study 1042-0900 as this study enrolled only female subjects. The observed PK profiles in studies 1042-CDD-3001 is presented by sex in **Figure 6**.

Figure 6: Observed PK for Study 1042-CDD-3001 by Sex



The PK by age group was assessed for ages 2 to < 6 years, 6 to < 12 years, 12 to < 18 years, and ≥ 18 years. Study 1001 enrolled subjects ≥ 18 years (age range 25 to 53 years) and is not included in this comparison. The observed PK profiles in studies 1042-0900 and 1042-CDD-3001 are presented by age group in **Figure 7**.

Figure 7: Observed PK for Study 1042-0900 and Study 1042-CDD-3001 by Age Group



Overall, the graphical comparisons of exposure by race, sex, and age group suggest that these intrinsic factors do not affect GNX PK.

4.3 Exposure-Response Analyses

Report 1042-cdd-er-001-er-report.pdf submitted to sequence 0004, module 5335, is titled "*Efficacy and Safety Exposure-Response Analysis of GNX in Pediatric Patients with Seizure Disorders*". This report describes exposure-response analyses for both safety and efficacy. Data for these analyses came from study 3001. The Applicant's exposure-response analyses were not reviewed as they do not provide additional insight to inform regulatory decision-making.

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/s/

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