Office of Clinical Pharmacology (OCP) Review

Applicant	Zogenix, Inc.
Product (Generic Name)	Fenfluramine
Product (Trade Name)	FINTEPLA® (fenfluramine) oral suspension
Link to EDR	\\CDSESUB1\evsprod\NDA212102\0106
NDA Submission	212102 Supplement-3 (Sequence 0106)
Dosage Form (Strength)	Oral suspension (2.2 mg/ mL)
Route of Administration	Oral
Proposed Dosing regimen	The proposed starting and maintenance dose is 0.1 mg/kg twice daily. The dose can be increased weekly based on efficacy and safety to a maximum recommended maintenance dose of 0.35 mg/kg twice daily (maximum daily dose of 26 mg/day). For patients taking concomitant stiripentol plus clobazam, the dose can be increased weekly based on efficacy and safety to a maximum recommended maintenance dose of 0.2 mg/kg twice daily (maximum daily dose of 17 mg/day).
Indication	Treatment of seizures associated with Lennox Gastaut Syndrome (LGS) in patients 2 years of age and older.
Submission Date	09/27/2021
OCP Review Team	Anantha Ram Nookala, Ph.D., Jie Liu, Ph.D., Atul Bhattaram, Ph.D., Gopichand Gottipati, Ph.D.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology II (DN2)

Table of Contents

1. Executive Summary

In this current efficacy supplement (Supplment-3) for the New Drug Application (NDA) 212102 for FINTEPLA® (fenfluramine) oral solution, the Applicant (Zogenix Inc.) is seeking approval for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age and older. In June 2020, FINTEPLA® (ZX008)[1] was originally approved for the treatment of seizures associated with Dravet syndrome (NDA 212102) in patients 2 years of age and older.

In this sNDA, the applicant conducted one pivotal phase 3 randomized, placebo-controlled trial that evaluated two fixed doses of 0.2 and 0.7 mg/kg/day of ZX008 (ZX008-1601 Part 1 Cohort A). This study demonstrated efficacy of 0.7 mg/kg/day ZX008 dose on the primary efficacy endpoint, median percent change from baseline in the frequency of drop seizures per 28 days compared to placebo during the 14-week treatment period. The applicant also submitted the results of a drug-drug interaction (DDI) study with fluvoxamine (strong CYP1A2 inhibitor), paroxetine (strong CYP2D6 inhibitor), and rifampin (strong CYP1A2, CYP2B6 and CYP3A inducer), and a renal impairment study (in subjects with severe renal impairment). The applicant proposed labeling revisions to *Drug Interactions* (Section 7.1), *Specific Populations* (Section 8.6), and *Clinical Pharmacology* (Section 12) to update the results from the clinical pharmacology studies noted above.

The primary focus of this review is to evaluate the appropriateness of dosing recommendations 1) for DDI with strong inhibitors of CYP1A2 or CYP2D6; 2) strong inducers of CYP1A2, CYP2B6 or CYP3A; and 3) in subjects with severe renal impairment.

1.1 Recommendation

The Office of Clinical Pharmacology team reviewed the information submitted under this sNDA 212102 and recommends approval of FINTEPLA® for treatment of seizures associated with LGS patients 2 years of age and older.

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	The evidence of effectiveness of fenfluramine for the treatment of seizures associated with LGS patients 2 years of age and older was demonstrated in a double-blind, randomized, placebo-controlled study (ZX008-1601 Part 1 Cohort A) based on median percent change from baseline

[1] ZX008 and FINTEPLA® are used interchangeably in this review document.

(reduction) in the frequency of drop seizures per 28 days during the 14-week treatment period.

APPEARS THIS WAY ON ORIGINAL

Review Issues	Recommendations and Comments

- The initial starting fenfluramine dosage for patients with LGS is 0.1 mg/kg twice daily, which should be increased weekly based on tolerability. The recommended titration schedule is shown in table below.
- Patients with LGS not on concomitant stiripentol who are tolerating fenfluramine should be titrated to the recommended maintenance dosage of 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients with LGS taking concomitant stiripentol plus clobazam who are tolerating fenfluramine should be titrated to the recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg)

General dosing instructions

	Without concomitant stiripentol*		**With concomitant stiripentol plus clobazam**	
	Weight-based dosage	**Maximum total daily dosage**	**Weight-based dosage**	**Maximum total daily dosage**
Initial dosage	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily		0.15 mg/kg twice daily	
Day 14	0.35 mg/kg twice daily		0.2 mg/kg twice daily	

For patients not on concomitant stiripentol in whom a more rapid titration is warranted, the dose may be increased every 4 days.

Review Issues	Recommendations and Comments
Dosing in patient subgroups (extrinsic and intrinsic factors)	• **Strong inducers of CYP1A2, CYP2B6, or CYP3A:** Concomitant administration of ZX008 with strong inducers of CYP1A2, CYP2B6, or CYP3A will decrease fenfluramine exposures, which may lower the efficacy of ZX008. It is recommended to avoid concomitant use with strong inducers of CYP1A2, CYP2B6, or CYP3A. If concomitant administration of strong inducers of CYP1A2, CYP2B6, or CYP3A with ZX008 is necessary, monitor the patient for reduced efficacy and consider increasing the dosage of ZX008 as needed; however, do not exceed the maximum daily dosage of ZX008 [Please refer table above for specific dose titration scheme]. If a strong inducer of CYP1A2, CYP2B6, or CYP3A is discontinued during maintenance treatment with ZX008, consider gradual reduction in the ZX008 dosage to the dose administered prior to initiating the inducer. • **Strong inhibitors of CYP1A2 or CYP2D6:** Concomitant administration of ZX008 with strong inhibitors of CYP1A2 or CYP2D6 will increase fenfluramine and decrease norfenfluramine plasma exposures. When co-administering with strong inhibitors of CYP1A2 or CYP2D6, do not exceed the maximum daily dosage of 20 mg of ZX008. If a strong inhibitor of CYP1A2 or CYP2D6 is discontinued during maintenance treatment with ZX008, consider gradual increase in the ZX008 dosage to the dose administered prior to initiating the inhibitor. If ZX008 is coadministered with stiripentol and with or without strong CYP1A2 or CYP2D6 inhibitors, do not exceed the maximum daily dosage of ZX008 of 17 mg. • **Renal Impairment:** Administration of ZX008 in patients with severe renal impairment (eGFR between 15 - 29 ml/min/1.73m^2) will increase fenfluramine and norfenfluramine plasma exposures. Therefore, in patients with severe renal impairment, do not exceed the maximum daily dosage of 20 mg of ZX008. If ZX008 is coadministered with stiripentol in patients with severe renal impairment, do not exceed the maximum daily dosage of 17 mg of ZX008. ZX008 was not studied in patients with eGFR < 15 ml/min/1.73m^2.

2. Summary of Labeling Recommendations

- Concomitant administration of ZX008 with fluvoxamine, a strong CYP1A2 inhibitor, increased fenfluramine AUC_{inf} by 102% and Cmax by 22%, and decreased norfenfluramine AUC_{inf} by 22% and Cmax by 44%. The net increase in sum of molar exposures (AUC_{inf}) of fenfluramine and norfenfluramine is estimated to be 1.35-fold (i.e., 35% increase). When co-administering with strong CYP1A2 inhibitor, ZX008 maximum daily dosage should not exceed 20 mg. If a strong CYP1A2 inhibitor is discontinued during maintenance treatment with ZX008, consider gradual increase in the ZX008 dosage to the dose administered prior to initiating the inhibitor.
- Concomitant administration of ZX008 with paroxetine, a strong CYP2D6 inhibitor, increased fenfluramine AUC_{inf} by 81% and Cmax by 13%, and decreased norfenfluramine AUC_{inf} by 13% and Cmax by 29% respectively. The net increase in sum of molar exposures (AUC_{inf}) of fenfluramine and norfenfluramine is estimated to be 1.31-fold (i.e., 31% increase). When co-administering with strong CYP2D6 inhibitor, ZX008 maximum daily dosage should not exceed 20 mg. If a strong CYP2D6 inhibitor is discontinued during maintenance treatment with ZX008, consider gradual increase in the ZX008 dosage to the dose administered prior to initiating the inhibitor.
- If ZX008 is coadministered with stiripentol and with or without strong inhibitors of CYP1A2 or CYP2D6, maximum daily dosage of ZX008 should not exceed 17 mg.
- Concomitant administration of ZX008 with rifampin, a strong inducer of CYP3A4, CYP1A2 and CYP2B6, decreased fenfluramine AUC_{inf} by 58% and Cmax by 40%, and decreased norfenfluramine AUC_{inf} by 50% and increased Cmax by 13%. It is recommended to avoid concomitant use of ZX008 with strong inducers of CYP1A2, CYP2B6, or CYP3A. If concomitant use of strong inducers of CYP1A2, CYP2B6, or CYP3A cannot be avoided, consider an increase in ZX008 dosage; however, do not exceed the maximum daily dosage of ZX008 (as noted in table in section 1). If strong inducer of CYP1A2, CYP2B6, or CYP3A is discontinued during maintenance treatment with ZX008, consider gradual reduction in the ZX008 dosage to the dose administered prior to initiating the inducer.
- Administration of ZX008 in subjects with severe renal impairment (estimated glomerular filtration rate (eGFR) 15 - 29 mL/min/1.73m^2) increased fenfluramine AUC_{inf} and Cmax by 88% and 20%, respectively; and increased norfenfluramine AUC_{inf} by 13% and decreased Cmax by 21%. The net increase in sum of molar exposures (AUC_{inf}) of fenfluramine and norfenfluramine is estimated to be 1.44-fold (i.e., 44% increase). In patients with severe renal impairment, ZX008 maximum daily dosage should not exceed 20 mg. In patients with severe renal impairment who are also on concomitant stiripentol, ZX008 maximum daily dosage should not exceed 17

mg. ZX008 was not studied in subjects with eGFR < 15 mL/min/1.73m^2. It is not known if fenfluramine or norfenfluramine are dialyzable.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

The drug product of ZX008 is supplied as a colorless and cherry-flavored liquid, containing 2.5 mg/mL fenfluramine hydrochloride (equivalent to (b) (4) mg/mL of fenfluramine free base) in a high-density polyethylene bottle for oral administration. Fenfluramine is a racemic compound containing equal amounts of dexfenfluramine (S enantiomer) and levofenfluramine (R enantiomer). Oral administration of fenfluramine results in the formation of norfenfluramine, an active metabolite. The exact mechanism of action of fenfluramine and norfenfluramine in reducing seizures is unknown, but they are thought to act as agonist at serotonin or 5-hydroxytryptamine (5-HT) receptors in the brain, including the 5-HT1D, 5-HT2A, and/or 5-HT2C receptors, and as positive modulators of the sigma-1 receptor. In response (information amendment 1.11.3, dated 02-16-2022, eCTD 0124) to an information request, the applicant reported that the norfenfluramine showed equipotent agonist activity at 5-HT2A, 5-HT2C receptors, and similar affinity at 5-HT1D (although no functional activity data were available); while at sigma-1 receptor, norfenfluramine showed approximately 10-fold less affinity than fenfluramine.

Currently, the US FDA approved treatments for LGS include cannabidiol (Epidiolex), clobazam (Onfi), felbamate (Felbatol), lamotrigine (Lamictal), rufinamide (Banzel) and topiramate (Topamax).

ZX008 was approved in Europe in the 1960s and in the US in the 1970s as an appetite suppressant at a dose of 60 to 120 mg/day for the treatment of adult obesity. However, it was withdrawn from the global markets in the late 1990s due to its association with cardiac valve abnormalities. In the current efficacy supplement, ZX008 is recommended at a maximum daily dose of 26 mg (without concomitant stiripentol) which is approximately one quarter of the previously approved maximum recommended dose (not to exceed 120 mg/day).

In a Type B meeting in January 2017, the agency noted that a single positive safety and efficacy study may be sufficient to support ZX008 for treatment of LGS. In a type C meeting held in September 2020, the agency agreed that a final clinical study report for the phase 1 PK study in subjects with hepatic impairment is not required to support the filing of the current supplement for LGS. In the pre-NDA meeting held on 22 June 2021, agency recommended the sponsor to conduct a popPK and E-R analysis.

3.2 General Pharmacological and Pharmacokinetic Characteristics

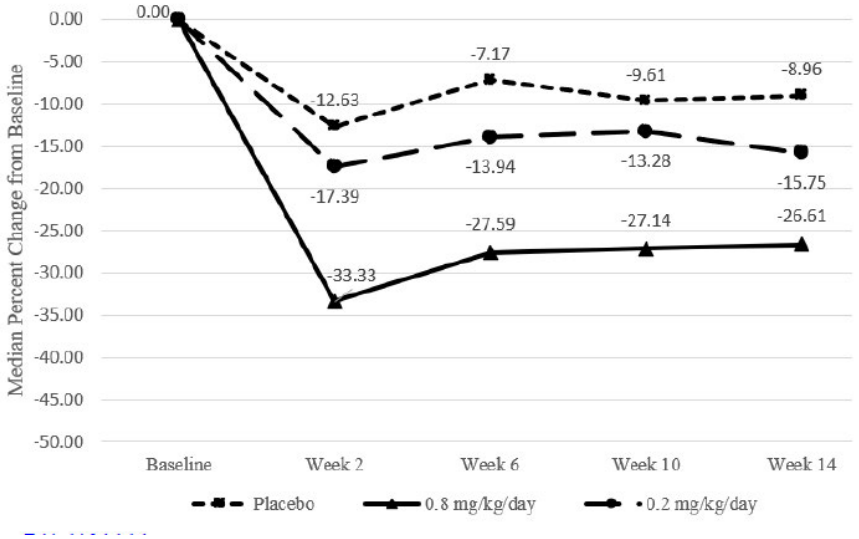
Please refer to Clinical Pharmacology Review of FINTEPLA for the treatment of Seizures associated with Dravet syndrome in DARRTS dated 06/25/2020 for more details on the general pharmacology and clinical pharmacokinetics.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of efficacy was evaluated in a pivotal phase 3 (Study 1601 Part 1, Cohort A) randomized, double-blind, and placebo-controlled study in subjects with LGS. A total of 263 subjects were randomized to the placebo or 1 of 2 doses of ZX008: 0.2 mg/kg/day or 0.7 mg/kg/day. The subjects entered a 2-week titration period followed by a 12-week maintenance period, for a total of 14 weeks treatment. The primary efficacy endpoint, percentage change from baseline in the frequency of drop seizures per 28 days (shown in Figure 1), showed statistically significant benefit (placebo-corrected) for the 0.7 mg/kg/day group, but not the 0.2 mg/kg/day group. Please refer to the statistical review by Drs. Xiangmin Zhang, and John Lawrence, and clinical efficacy review by Drs. Amy Kao and Phillip Sheridan for additional details on the pivotal phase 3 efficacy data.

Figure 1: Median Percentage Change in Drop Seizure Frequency (mITT Population)



Source: Clinical Study Report ZX008-1601-part-1; pg-118

3.3.2 Is the proposed general dosing regimen appropriate?

Yes, ZX008 dosing evaluated in a pivotal efficacy/safety study (Study 1601 Part 1, Cohort A) in LGS patients demonstrated significant reduction in median percentage change from baseline in the frequency of drop seizures per 28 days compared to placebo. The applicant's proposed dosing regimen is identical to that evaluated in efficacy/safety study and is therefore considered acceptable.

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

Extrinsic factors

Fenfluramine undergoes hepatic metabolism to norfenfluramine by cytochrome P450 (CYP450) enzymes, primarily by CYP1A2, CYP2B6, and CYP2D6. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5. Norfenfluramine is further metabolized by deamination and oxidation to inactive metabolites. Since, fenfluramine is metabolized by multiple CYP enzymes, dedicated studies with CYP inhibitors and inducers were conducted to assess the changes in the exposures of fenfluramine and norfenfluramine.

Effect of Strong CYP1A2, CYP2B6, or CYP3A Inducers

The applicant conducted a dedicated DDI study (Study 1904) to evaluate the impact of rifampin, a strong inducer of CYP1A2 and moderate inducer of CYP2B6 and a strong inducer of CYP3A at steady state (600 mg QD) on ZX008 (single dose of 0.4 mg/kg) in healthy adult subjects (N=19). The study results showed that concomitant administration of rifampin at steady state decreased the $AUC_{0\text{-}inf}$ and C_{max} of fenfluramine by 58% and 40%, respectively and, decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 50%, and increased the C_{max} of norfenfluramine by 13%. Based on these changes in exposures, the applicant recommended to increase ZX008 dose as needed, not exceeding (b) (4) the maximum daily dosage.

The OCP review team recommends avoid concomitant use of strong inducers of CYP1A2, CYP2B6, or CYP3A. If concomitant use of strong inducers of CYP1A2, CYP2B6, or CYP3A is necessary, monitor the patient for reduced efficacy and consider increasing the dosage of FINTEPLA as needed; however, do not exceed the maximum daily dosage of FINTEPLA, since there is no long-term safety data with subjects receiving ZX008 doses greater than 26 mg/day (Please refer to dosing table in section 1 for more details).

Effect of CYP1A2 Inhibitors

The applicant conducted a dedicated DDI study (Study 1904) to evaluate the impact of fluvoxamine (a strong CYP1A2 inhibitor) at steady state (50 mg BID) on ZX008 (single dose of 0.4 mg/kg) in healthy adult subjects (N=18). The study results showed that concomitant administration of fluvoxamine at steady state increased the geometric mean ratios of $AUC_{0\text{-}inf}$ and C_{max} of fenfluramine by 102% and 22%, respectively; and the $AUC_{0\text{-}inf}$ and C_{max} of norfenfluramine decreased by 22% and 44%, respectively. As noted in section 3.1, norfenfluramine is an active metabolite with equipotent agonist activity at 5-HT2A, 5-HT2C receptors, and similar affinity at 5-HT1D receptors. Therefore, the OCP review team conducted independent analyses (please refer to section 4.2 in Appendix for specific details), and the key findings are summarized below:

1. When ZX008 is co-administered with strong CYP1A2 inhibitor compared to without strong CYP1A2 inhibitor (reference scenario), the net increase in sum of molar exposures (AUC_{inf}) of fenfluramine and norfenfluramine was estimated to be 1.35-fold (i.e., 35% increase in AUC_{inf}). This is considered a more clinically relevant approach than considering the magnitude of interaction based on fenfluramine exposures alone.
2. If ZX008 is not adjusted based on the magnitude of the interaction (i.e., 1.35-fold increase), the 26 mg maximum daily dose translates to a maximum daily dose of 35.1 mg (~35% higher than 26 mg, the reference scenario without concomitant strong CYP1A2 inhibitor use).
3. Based on the magnitude of the interaction (i.e., 1.35-fold increase), if ZX008 is adjusted to 17 mg maximum daily dose, it translates to a maximum daily dosage of 22.9 mg (~12% lower than 26 mg, the reference scenario without concomitant strong CYP1A2 inhibitor use).
4. If ZX008 is adjusted to 20 mg maximum daily dose, it translates to a maximum daily dosage of 26.7 mg, ~3% higher than 26 mg, the reference scenario without concomitant strong CYP1A2 inhibitor use. This regimen is considered optimal based on minimal difference relative to reference scenario. Additionally, given the strength of 2.2 mg/mL ZX008 oral solution, it is equivalent of ~9 mL and is also practical for administration, potentially minimizing dosing errors.

In conclusion, when ZX008 is co-administered with a strong CYP1A2 inhibitor drug, OCP review team recommends that ZX008 maximum daily dosage should not exceed 20 mg. If ZX008 is co-administered with stiripentol and with or without strong CYP1A2 inhibitor drug, ZX008 maximum daily dosage should not exceed 17 mg. If a strong CYP1A2 inhibitor is discontinued during maintenance treatment with ZX008, consider gradual increase in the ZX008 dosage to the dose administered prior to initiating the inhibitor.

Effect of CYP2D6 Inhibitors

The applicant conducted a dedicated DDI study (Study 1904) to evaluate the impact of paroxetine, a strong CYP2D6 inhibitor, at steady state (30 mg QD) on ZX008 (single dose of 0.4 mg/kg) in healthy adult subjects (N=18). The study results showed that concomitant administration of paroxetine at steady state increased the geometric mean ratio of fenfluramine $AUC_{0\text{-}inf}$ and C_{max} by 81% and 13%, respectively; and decreased norfenfluramine $AUC_{0\text{-}inf}$ and C_{max} by 13% and 29%, respectively. The OCP review team conducted independent analyses (please refer to section 4.2 in Appendix for specific details), and the key findings are summarized below:

1. When ZX008 is co-administered with strong CYP2D6 inhibitor compared to without strong CYP2D6 inhibitor (reference scenario), the net increase in sum of molar exposures (AUC_{inf}) of fenfluramine and norfenfluramine was estimated to be 1.31-fold (i.e., 31% increase in AUC_{inf}). This is considered a more clinically relevant approach than considering the magnitude of interaction based on fenfluramine exposures alone.
2. If ZX008 is not adjusted based on the magnitude of the interaction (i.e., 1.31-fold increase), the 26 mg maximum daily dose translates to a maximum daily dose of 34 mg (31% higher than 26 mg, the reference scenario without concomitant strong CYP2D6 inhibitor use).
3. Based on the magnitude of the interaction (i.e., 1.31-fold increase), if ZX008 is adjusted to 17 mg maximum daily dose, it translates to a maximum daily dosage of 22.3 mg (~14% lower than 26 mg, the reference scenario without concomitant strong CYP2D6 inhibitor use).
4. If ZX008 is adjusted to 20 mg maximum daily dose, it translates to a maximum daily dosage of 26 mg, the reference scenario without concomitant strong CYP1A2 inhibitor use. Additionally, given the strength of 2.2 mg/mL ZX008 oral solution, it is equivalent of ~9 mL and is also practical for administration, potentially minimizing dosing errors.

In conclusion, when ZX008 is co-administered with a strong CYP2D6 inhibitor drug, OCP review team recommends that ZX008 maximum daily dosage should not exceed 20 mg. If ZX008 is co-administered with stiripentol and with or without strong CYP2D6 inhibitor, ZX008 maximum daily dosage should not exceed 17 mg. If a strong CYP2D6 inhibitor is discontinued during maintenance treatment with ZX008, consider gradual increase in the ZX008 dosage to the dose administered prior to initiating the inhibitor.

The review team also considered the impact of concomitant administration of strong inhibitors of CYP1A2 and CYP2D6 based on fenfluramine exposures alone, and the magnitude of the interaction was higher than that based on sum of molar exposures of fenfluramine and norfenfluramine noted above. If ZX008 maximum daily dosage is adjusted to 20 mg, the higher magnitude (based on fenfluramine exposures alone) translates to up to 40.3 mg (55% higher maximum daily dosage of ZX008 than the reference scenario without concomitant strong CYP1A2 or CYP2D6 inhibitor use). If the

maximum daily dosage of ZX008 is capped at 13.2 mg (6 mL) or 15.4 mg (7 mL) to match the reference scenario, based on the magnitude of the interaction using fenfluramine exposures alone, it translates to 20-33% lower dose relative to reference scenario, when calculated based on sum of molar exposures of fenfluramine and norfenfluramine. Overall, based on relative benefit/risk assessment, the review team notes that sum of molar exposures of fenfluramine and norfenfluramine is an appropriate approach and controlling the seizure frequency is an important consideration, while adverse events except for long-term cardiovascular events were generally manageable (please refer to clinical review by Drs. Amy Kao and Phillip Sheridan for additional details). The maximum daily dosage estimated based on fenfluramine exposures alone is much lower than the previously approved doses of 60 to 120 mg/day, where cardiovascular events were reported. Based on these considerations, the review team recommends maximum daily dosage cap of 20 mg with strong inhibitors of CYP1A2 or CYP2D6, and a cap of 17 mg with strong inhibitors of CYP1A2 or CYP2D6 with or without stiripentol use.

Intrinsic factors

ZX008 undergoes hepatic metabolism to norfenfluramine and inactive metabolites. Most of an orally administered dose of fenfluramine (greater than 90%) is excreted in the urine as fenfluramine, norfenfluramine, or other metabolites with fenfluramine and norfenfluramine accounting for less than 25% of the total.

Renal impairment: The applicant conducted a dedicated renal impairment study (Study 1902) to evaluate the impact of severe renal impairment (eGFR 15 – 29 ml/min/1.73m^2, based on MDRD equation) on the PK of fenfluramine and norfenfluramine. The study results showed that the geometric mean ratio of fenfluramine $AUC_{0\text{-}inf}$ and C_{max} increased by 88% and 20%, respectively, and norfenfluramine $AUC_{0\text{-}inf}$ increased by 13% and C_{max} by 21%, in the severe renal impairment group compared to the healthy controls.

The OCP review team conducted independent analyses (please refer to section 4.2 in Appendix for specific details), and the key findings are summarized below:

1. The net increase in sum of molar exposures (AUC_{inf}) of fenfluramine and norfenfluramine was estimated to be 1.44-fold (i.e., 44% increase in AUC_{inf}) when ZX008 is administered in patients with severe renal impairment compared to healthy controls. This is considered a more clinically relevant approach than considering the magnitude of interaction based on fenfluramine exposures alone.
2. If ZX008 is not adjusted based on the magnitude of the increase in exposures (i.e., 1.44-fold increase), the 26 mg maximum daily dose translates to a maximum daily dose of ~37.5 mg (44% higher than 26 mg, the reference scenario of healthy controls).

3. Based on the magnitude of the increase in exposures (i.e., 1.44-fold increase), if ZX008 is adjusted to 17 mg maximum daily dose, it translates to a maximum daily dosage of 24.5 mg (6% lower than 26 mg, the reference scenario of healthy controls).
4. If ZX008 is adjusted to 20 mg maximum daily dose, it translates to a maximum daily dosage of 28.5 mg, 10% higher than 26 mg, the reference scenario of healthy controls. Additionally, given the strength of 2.2 mg/mL ZX008 oral solution, it is equivalent of ~9 mL and is also practical for administration, potentially minimizing dosing errors.

In conclusion, OCP review team recommends that when ZX008 is administered in patients with severe renal impairment, ZX008 maximum daily dosage should not exceed 20 mg. In patients with severe renal impairment who also take stiripentol concomitantly, ZX008 should not exceed 17 mg. ZX008 was not studied in patients with eGFR < 15 ml/min/1.73 m^2. It is unknown if fenfluramine or norfenfluramine is dialyzable.

As noted above for concomitant use with strong inhibitors of CYP1A2 or CYP2D6, the review team considered the impact of severe renal impairment based on fenfluramine exposures alone, which was higher than that calculated based on sum of molar exposures of fenfluramine and norfenfluramine noted above.

If ZX008 maximum daily dosage is adjusted to 20 mg, the higher magnitude based on fenfluramine exposures alone, translates to up to 37.7 mg (45% higher maximum daily dosage of ZX008 than the reference scenario in healthy controls). If the maximum daily dosage of ZX008 is capped at 13.2 mg (6 mL) or 15.4 mg (7 mL) to match the reference scenario, based on the magnitude of the interaction based on fenfluramine exposures alone, it translates to 15-27% lower dose relative to reference scenario, when calculated based on sum of molar exposures of fenfluramine and norfenfluramine. Overall, based on relative benefit/risk assessment, the review team notes that sum of molar exposures of fenfluramine and norfenfluramine is an appropriate approach and controlling the seizure frequency is an important consideration while adverse events except for long-term cardiovascular events were generally manageable (please refer to clinical review by Drs. Amy Kao and Phillip Sheridan for additional details). The maximum daily dosage estimated based on fenfluramine exposures alone is much lower than the previously approved doses of 60 to 120 mg/day, where cardiovascular events were reported. Based on these considerations, the review team recommends maximum daily dosage cap of 20 mg in patients with severe renal impairment, and a cap of 17 mg in patients with severe renal impairment who also take stiripentol concomitantly.

Hepatic Impairment: Subjects with moderate or severe hepatic impairment were excluded from the pivotal phase 3 clinical trial. (b) (4) .

Other Intrinsic Factors

PopPK analysis conducted using data from only study 1601 to evaluate the impact of intrinsic factors on exposure parameters for fenfluramine and norfenfluramine. No significant effects of intrinsic factors such as age, sex, body mass index, race, and creatine clearance (>76mL/min/1.73m^2) were identified based on the results of popPK analysis from study 1601.

4. Appendices

4.1 Summary of Bioanalytical Method Validation

The applicant used a validated liquid chromatography coupled with tandem mass spectrometry bioanalytical method to quantify the exposures of fenfluramine and norfenfluramine. This is the same method that was used in the original NDA submission for Dravet syndrome and was reviewed by the OCP review team and was considered acceptable. For more details on the bioanalytical method validation, please refer to Clinical Pharmacology Review of FINTEPLA for the treatment of seizures associated with Dravet syndrome that was put in DARRTS on 06/25/2020. The validated method is deemed suitable for the determination of fenfluramine and norfenfluramine exposures (range 0.250-100 ng/mL).

In the current submission, the sponsor has conducted the additional bioanalytical method validation studies for assessing the hepatic and renal impaired plasma matrix effect and interference, freeze/thaw stability, and bench-top stability in the presence of 200 ng/mL fluvoxamine, 60 ng/mL paroxetine, and 10 mcg/mL rifampin. The accuracy, precision, stability, and other relevant parameters for the additional bioanalytical method validation studies are described in Table 1 below.

Table 1:Bioanalytical Method Performance Parameters: Fenfluramine and Norfenfluramine

Method Parameter	Acceptance Criteria	Results	Conclusion
Selectivity			
Analyte – Fenfluramine, Norfenfluramine	Interferences at ≤ 20% LLOQ (at least 5 of 6 screened)	Complies (16 lots interference free)	Acceptance criteria met.
Internal Standard – Fenfluramine-d_5, Norfenfluramine-d_6	Interferences at ≤ 5% mean IS (at least 5 of 6 screened)	Complies (16 lots interference free)	Acceptance criteria met.
Matrix Effect (6 spiked matrix lots)	the % CV for IS Normalized MF must be ≤ 15% over all 6 lots	Complies	Acceptance criteria met.
Hemolytic Effect Evaluation Lipemic Effect Evaluation	± 15.0% Bias; ≤ 15.0% CV	Complies. Results indicate that hemolytic and lipemic plasma does not affect the analysis of the fenfluramine or norfenfluramine in human plasma	Acceptance criteria met.
Hepatic Impaired Subjects in Plasma Matrix Effect (6 spiked matrix lots)	the % CV for IS Normalized MF must be ≤ 15% over all 6 lots	Complies	Acceptance criteria met.
Renal Impaired Plasma Matrix Effect (6 spiked matrix lots)	the % CV for IS Normalized MF must be ≤ 15% over all 6 lots	Complies	Acceptance criteria met.
Comedications (Valproic Acid, Stiripentol, Levetiracetam, Topiramate, Phenobarbital, Clonazepam, Phenytoin, Carbamazepine, Eslicarbazepine, Retigabine, Lamotrigine, Zonisamide, N-desmethylclobazam, Clobazam, Cannabidiol, Fluvoxamine, Paroxetine, Rifampin)	± 15.0% Bias; ≤ 15.0% CV	Complies. Results indicate that the presence of the co-medications does not affect the accuracy or precision of the data.	Acceptance criteria met.
Carry-Over	≤ 20.0% LLOQ, ≤ 5.0% mean IS	Complies. Data were required to give ≤ 20.0% of LLOQ peak area for each drug and ≤ 5.0% for their corresponding internal standard.	Acceptance criteria met.
Linearity			
Fenfluramine			
Weighting		$1/x^2$	Acceptance criteria met.
Bias at LLOQ	±20.0% Bias	-1.8%	
Bias above LLOQ	±15.0% Bias	-2.5 to 3.6%	
Bioanalytical Range	0.250 to 100 ng/mL	Complies	
Norfenfluramine			
Weighting		$1/x^2$	Acceptance criteria met.
Bias at LLOQ	±20.0% Bias	-1.9%	
Bias above LLOQ	±15.0% Bias	-2.6 to 4.0%	
Bioanalytical Range	0.250 to 100 ng/mL	Complies	
Precision			
Intra-assay (Fenfluramine)	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	3.5 to 10.0% (LLOQ); 1.2 to 8.8% (above LLOQ)	Acceptance criteria met.
Inter-assay (Fenfluramine)	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	8.9 % (LLOQ); 3.5 to 6.2% (above LLOQ)	Acceptance criteria met.
Intra-assay (Norfenfluramine)	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	4.8 to 5.9% (LLOQ); 1.2 to 6.4% (above LLOQ)	Acceptance criteria met.
Inter-assay (Norfenfloramine)	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	5.3% (LLOQ); 3.4 to 4.0% (above LLOQ)	Acceptance criteria met.

Accuracy			
Intra-assay (Fenfluramine)	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	4.3 to 7.1% (LLOQ); -3.8 to 6.6% (above LLOQ)	Acceptance criteria met.
Inter-assay (Fenfluramine)	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	1.7% (LLOQ); -0.9 to 2.6% (above LLOQ)	Acceptance criteria met.
Intra-assay (Norfenfluramine)	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	1.3 to 4.7% (LLOQ); -2.8 to 2.1% (above LLOQ)	Acceptance criteria met.
Inter-assay (Norfenfluramine)	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	2.6% (LLOQ); -1.3 to 1.0% (above LLOQ)	Acceptance criteria met.
Dilution (2x, 5x)			
Fenfluramine			
Precision	≤ 15.0% CV	1.6%, 5.3%	Acceptance criteria met.
Accuracy	± 15.0% Bias	0.6%, 1.3%	
Norfenfluramine			
Precision	≤ 15.0% CV	1.4%, 3.9%	Acceptance criteria met.
Accuracy	± 15.0% Bias	-2.7%, 2.1%	
K_3EDTA Human Plasma			
Fenfluramine			
Precision	≤20.0% CV (LLOQ); ≤15.0% CV (above LLOQ)	8.6 to 9.6% 1.5 to 8.0%	Acceptance criteria met.
Accuracy	±20.0% Bias (LLOQ); ±15.0% Bias (above LLOQ)	-9.6 to 0.7% -3.2 to 2.0%	
Norfenfluramine			
Precision	≤20.0% CV (LLOQ); ≤15.0% CV (above LLOQ)	4.3 to 6.1% 0.7 to 4.1%	Acceptance criteria met.
Accuracy	±20.0% Bias (LLOQ); ±15.0% Bias (above LLOQ)	-5.9 to 2.2% -1.8 to 4.6%	
Lithium Heparin Human Plasma			
Fenfluramine			
Precision	≤20.0% CV (LLOQ); ≤15.0% CV (above LLOQ)	5.7 to 17.7% 0.9 to 6.0%	Acceptance criteria met.
Accuracy	±20.0% Bias (LLOQ); ±15.0% Bias (above LLOQ)	-16.0 to 6.2% -4.6 to 1.6%	Acceptance criteria met.
Large Batch Size	For QC sample results to be accepted, at least 1 QC at each concentration level and two- thirds of the total number of QC samples were required to interpolate with dev [%] within ± 15.0% from nominal.	168 samples	Acceptance criteria met.
Norfenfluramine			
Precision	≤20.0% CV (LLOQ); ≤15.0% CV (above LLOQ)	3.8 to 6.8% 0.7 to 2.3%	Acceptance criteria met.
Accuracy	±20.0% Bias (LLOQ); ±15.0% Bias (above LLOQ)	-7.3 to 0.1% -0.9 to 3.0%	Acceptance criteria met.
Large Batch Size	For QC sample results to be accepted, at least 1 QC at each concentration level and two- thirds of the total number of QC samples were required to interpolate with dev [%] within ± 15.0% from nominal.	168 samples	Acceptance criteria met.
Stability for Both Fenfluramine and Norfenfluramine			
Matrix (in polypropylene tubes)			
Freeze/Thaw (-20 °C and -70 °C/room temperature) (with and without valproic acid, stiripentol, levetiracetam, topiramate, N-desmethylclobazam, clobazam) - K_3EDTA	± 15.0% Bias; ≤ 15.0% CV	Stable 4 cycles	Acceptance criteria met.
Freeze/Thaw (-20 °C and -70 °C/room temperature) lithium heparin	± 15.0% Bias; ≤ 15.0% CV	Stable 4 cycles	Acceptance criteria met.
Freeze/Thaw (-20 °C and -70 °C/room temperature) (with cannabidiol)	± 15.0% Bias; ≤ 15.0% CV	Stable 4 cycles	Acceptance criteria met.

Method Parameter	Acceptance Criteria	Results	Conclusion
Freeze/Thaw (-20 °C and -70 °C/room temperature) (with fluvoxamine, paroxetine, rifampin)	± 15.0% Bias; ≤ 15.0% CV	Stable 4 cycles	Acceptance criteria met.
Room Temperature (RT) (with and without valproic acid, stiripentol, levetiracetam, topiramate, N-desmethylclobazam, clobazam) - K_2EDTA	± 15.0% Bias; ≤ 15.0% CV	Stable 9.5 hours	Acceptance criteria met.
Room Temperature (RT) K_3EDTA and lithium heparin	± 15.0% Bias; ≤ 15.0% CV	Stable 6 hours	Acceptance criteria met.
Room Temperature (RT) (with cannabidiol	± 15.0% Bias; ≤ 15.0% CV	Stable 9.25 hours	Acceptance criteria met.
Room Temperature (RT) (with fluvoxamine, paroxetine, rifampin)	± 15.0% Bias; ≤ 15.0% CV	Stable 16 hours	Acceptance criteria met.
Long-term (-20 °C) - K_2EDTA	± 15.0% Bias; ≤ 15.0% CV	Stable 416 days	Acceptance criteria met.
Long-term (-70 °C) - K_2EDTA	± 15.0% Bias; ≤ 15.0% CV	Stable 416 days	Acceptance criteria met.
Long-term (-20 °C and -70 °C) (with valproic acid, stiripentol, levetiracetam, topiramate, N-desmethylclobazam, clobazam)- K_2EDTA	± 15.0% Bias; ≤ 15.0% CV	Stable 422 days (valproic acid, stiripentol, levetiracetam, topiramate) Stable 381 days (N-desmethylclobazam, clobazam)	Acceptance criteria met.
Long-term (-20 °C and 70 °C) - lithium heparin	± 15.0% Bias; ≤ 15.0% CV	Stable 168 days	Acceptance criteria met.
Long-term (-20 °C and 70 °C) - K_3DTA	± 15.0% Bias; ≤ 15.0% CV	Stable 168 days	Acceptance criteria met.
Long-term (-20 °C and -70 °C) (with cannabidiol)	± 15.0% Bias; ≤ 15.0% CV	Stable 133 days	Acceptance criteria met.
Individual Sample Re-injection	± 15.0% Bias; ≤ 15.0% CV	Reproducible	Acceptance criteria met.
Whole Batch Re-Injection Integrity	± 20.0% Bias; ≤ 20.0% CV (LLOQ) ± 15.0% Bias; ≤ 15.0% CV (above LLOQ	Reproducible	Acceptance criteria met.
Column Ruggedness	± 20.0% Bias; ≤ 20.0% CV (LLOQ) ± 15.0% Bias; ≤ 15.0% CV (above LLOQ)	Reproducible	Acceptance criteria met.
System Upgrade			
Precision - Fenfluramine	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	6.2% 1.7 to 5.3%	Acceptance criteria met.
Precision - Norfenfluramine	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	5.3% 1.3 to 3.0%	Acceptance criteria met.
Accuracy - Fenfluramine	±20.0% Bias (LLOQ); ± 15.0% Bias; (above LLOQ)	3.2% -2.9 to -0.3%	Acceptance criteria met.
Accuracy - Norfenfluramine	±20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	-1.5% -0.4 to 3.0%	Acceptance criteria met.
Extraction Recovery			
Fenfluramine	Report as found	Overall: 106.7%, 6.3 %CV	Not applicable
Fenfluramine-d_5 (IS)	Report as found	Overall: 110.6, 4.2 %CV	Not applicable
Norfenfluramine	Report as found	Overall: 93.4%, 3.2 %CV	Not applicable
Norfenfluramine-d_6 (IS)	Report as found	Overall: 107.7%, 3.5 %CV	Not applicable

Source: Appendix-1, Pg-11, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Reviewer's comments: The applicant has conducted the additional bioanalytical method validation studies in compliance with the 2018 bioanalytical method validation guidance. The results indicated that the method is sensitive, selective, accurate, and reproducible for the quantitation of fenfluramine and norfenfluramine in the presence or absence of concomitant medications and hepatic or renal impaired plasma.

4.2 Reviewer's Independent Analyses to Support Labeling Changes

The reviewer summarized the geometric means of the PK exposures (AUC_{inf}) of the impact of concomitant administration of strong inhibitors of CYP1A2 or CYP2D6, and in patients with renal impairment. Next, the molar exposures of fenfluramine and norfenfluramine were calculated to the evaluate the impact of the drug-interaction with concomitant administration of strong inhibitors of CYP1A2 or CYP2D6, and in patients with renal impairment. Subsequently, based on the magnitude of the fold-change, "adjusted" doses were derived to match exposures with respective reference scenario, i.e., without concomitant use of strong inhibitors of CYP1A2 or CYP2D6 or healthy controls (without renal impairment).

ZX008 Exposures	**Fenfluramine**	**Norfenfluramine**	
AUC_{inf} (w/o Fluvoxamine)	725	740	
AUC_{inf} (w Fluvoxamine)	1460	575	
Fold-change	2.01	0.78	
Molar exposures			**Sum of molar exposures (Fen+Norfen)**
Molecular weight	231	203	
Molar AUC_{inf} (w/o Fluvoxamine)	3.14	3.65	6.78
Molar AUC_{inf} (w Fluvoxamine)	6.32	2.83	9.15
Fold-change in Molar AUC_{inf} w vs. w/o Fluvoxamine			**1.35**
Adjusted ZX008 dose (9 mL of 2.2 mg/mL solution)	1.35*19.8 = 26.7 mg (+3% relative to reference scenario)		

Source: Clinical Study Report of ZX008-1904, Table 11-4 on pages 59 and 60.

ZX008 Exposures	**Fenfluramine**	**Norfenfluramine**	
AUC_{inf} (w/o Paroxetine)	681	669	
AUC_{inf} (w Paroxetine)	1230	580	
Fold-change	1.81	0.87	
Molar exposures			**Sum of molar exposures (Fen+Norfen)**
Molecular weight	231	203	
Molar AUC_{inf} (w/o Paroxetine)	2.95	3.30	6.24
Molar AUC_{inf} (w Paroxetine)	5.32	2.86	8.18
Fold-change in Molar AUC_{inf} w vs. w/o Paroxetine			**1.31**
Adjusted ZX008 dose (9 mL of 2.2 mg/mL solution)	1.31*19.8 = 25.9 mg (-0.2% relative to reference scenario)		

Source: Clinical Study Report of ZX008-1904, Table 11-4 on page 61.

ZX008 Exposures	**Fenfluramine**	**Norfenfluramine**	
AUC_{inf} (severe renal impairm.)	669	851	
AUC_{inf} (healthy controls)	1260	966	
Fold-change	1.88	1.14	
Molar exposures			**Sum of molar exposures (Fen+Norfen)**
Molecular weight	231	203	
Molar AUC_{inf} (severe RI)	2.90	4.19	7.09
Molar AUC_{inf} (healthy controls)	5.45	4.76	10.21
Fold-change in Molar AUC_{inf} severe RI vs. healthy controls			**1.44**
Adjusted ZX008 dose (9 mL of 2.2 mg/mL solution)	1.44*19.8 = 28.5 mg (+10% relative to reference scenario)		

Source: Clinical Study Report of ZX008-1902, Tables 11-3 and 11-4 on pages 50 and 51.

4.3 Pharmacometrics Review

4.3.1 Applicant's Analysis

4.3.1.1 Population PK Analysis

The final PopPK model was developed from a dataset of 1260 evaluable plasma concentrations (628 fenfluramine (FEN) concentration and 632 norfenfluramine (NFEN) concentration) from 164 subjects enrolled in Cohort A of Study 1601, Part 1 to quantitatively describe the clinical PK of and identify sources of interindividual variability. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4 (ICON, Maryland) was used for the PopPK analysis.

Study 1601 is a two-part study of ZX008 in children and adults with LGS. Part 1 was a double-blind, parallel-group, placebo-controlled, study to assess the efficacy and safety of two doses of ZX008 when used as adjunctive therapy for seizures in children and adult subjects with LGS. Part 2 is an open-label extension to assess long-term safety of ZX008 in children and adults with LGS. Part 1 included two cohorts: Cohort A included randomized subjects from North America, Europe, and Australia while Cohort B includes randomized subjects from Japan. Only data obtained from Part 1, Cohort A was used for PopPK analysis.

Part 1 consisted of a 4-week baseline, 2-week titration, 12-week maintenance, and 2-week taper or transition period. Approximately 340 subjects were to be screened and approximately 250 subjects were to be randomized into Part 1, Cohort A. Upon completion of the Baseline Period, subjects who qualified for the study were randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day [or 0.5 mg/kg/day, maximum 20 mg/day, for subjects taking concomitant STP]) or placebo. PK Samples were to be collected at the following times: prior to the dose and 1, 2, and 4 to 6 hours after dose administration. A listing of the baseline demographics for these subjects is given in **Table 6**.

Table 6. Summary statistics or counts of the subject demographic characteristics of the PK analysis population in Part 1, Cohort A of Study 1601

Variable	Stratified by ZX008 Dose		Stratified by Age	
	0.2 mg/kg/day n = 84	0.8 mg/kg/day n = 80	≤18 years n = 129	>18 years n = 35
Age (yr)	13.3 (7.54) 13.0 (3.00 - 33.0)	13.3 (7.40) 13.0 (2.00 - 35.0)	10.3 (4.78) 11.0 (2.00 - 18.0)	24.2 (4.98) 23.0 (19.0 - 35.0)
Height (cm)	142 (24.7) 148 (98.0 - 191)	142 (25.3) 147 (78.0 - 188)	135 (23.7) 137 (78.0 - 188)	165 (12.0) 167 (140 - 191)
Weight (kg)	42.5 (20.7) 41.6 (13.0 - 108)	41.7 (21.8) 39.0 (11.0 - 127)	36.2 (18.0) 34.0 (11.0 - 127)	64.0 (17.5) 60.8 (36.0 - 108)
BSA (m^2)	1.27 (0.409) 1.32 (0.598 - 2.22)	1.26 (0.419) 1.27 (0.507 - 2.51)	1.15 (0.369) 1.15 (0.507 - 2.51)	1.70 (0.252) 1.72 (1.26 - 2.22)
BMI (kg/m^2)	19.9 (5.36) 19.4 (11.9 - 47.3)	19.4 (5.00) 18.4 (9.91 - 37.2)	18.6 (4.41) 17.7 (9.91 - 36.5)	23.4 (6.06) 22.2 (13.9 - 47.3)
CLcr ($mL/min/1.73\ m^2$)	142 (36.3) 136 (76.3 - 252)	138 (31.6) 134 (84.2 - 219)	139 (33.1) 135 (76.3 - 252)	143 (37.9) 135 (93.9 - 221)
Age Category				
≤18 years	65/84 (77.4%)	64/80 (80.0%)	—	—
>18 years	19/84 (22.6%)	16/80 (20.0%)	—	—
Weight Category				
<37.5 kg	39/84 (46.4%)	38/80 (47.5%)	76/129 (58.9%)	1/35 (2.86%)
≥37.5 kg	45/84 (53.6%)	42/80 (52.5%)	53/129 (41.1%)	34/35 (97.1%)
Gender				
Male	43/84 (51.2%)	51/80 (63.8%)	71/129 (55.0%)	23/35 (65.7%)
Female	41/84 (48.8%)	29/80 (36.2%)	58/129 (45.0%)	12/35 (34.3%)
Race				
White	64/84 (76.2%)	67/80 (83.8%)	100/129 (77.5%)	31/35 (88.6%)
Black	5/84 (5.95%)	2/80 (2.50%)	7/129 (5.43%)	0/35 (0%)
Asian	2/84 (2.38%)	4/80 (5.00%)	5/129 (3.88%)	1/35 (2.86%)
Native-Hawaiian/ Pacific Islander	1/84 (1.19%)	0/80 (0%)	1/129 (0.775%)	0/35 (0%)
Other[a]	12/84 (14.3%)	7/80 (8.75%)	16/129 (12.4%)	3/35 (8.57%)

Note: Abbreviations are provided in the Abbreviation Listing.
Summary statistics presented as mean (standard deviation [SD]) and median (Min. – Max.) or n/N (%). The PK analysis population is defined as those subjects that were included in the non-compartmental PK analysis.

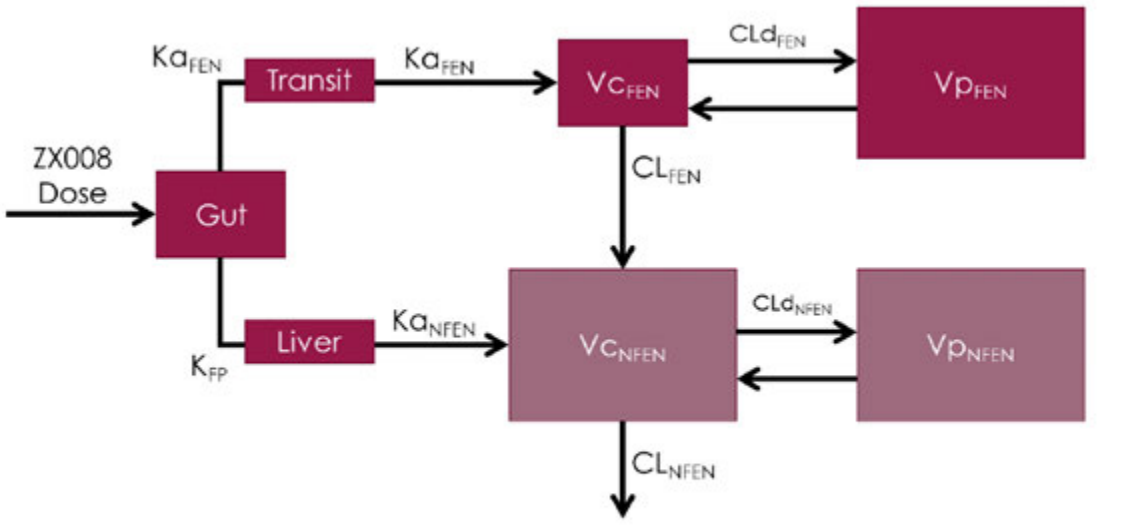
a. Includes multiracial (n = 1), unknown race (n = 3), and "not reported" (n = 15)

Source: Applicant's PopPK report 00619-2, Page 30, Table 2

Population PK Model

Structural Model: The structure of the previous population PK model (developed using data from healthy volunteers and patients with DS) was retained and updated using data from Study ZX008-1601. The PK of FEN and NFEN was best described by first-order absorption for FEN for a portion ofadministered FEN, pre-systemic formation of NFEN from a portion of administered FEN, 2 disposition compartments for FEN, 2 disposition compartments for NFEN, linear clearance for FEN (via 100% conversation to NFEN), and linear clearance of NFEN, as illustrated in **Figure 2**.

Figure 2. Schematic representation of the base structural model for FEN and NFEN



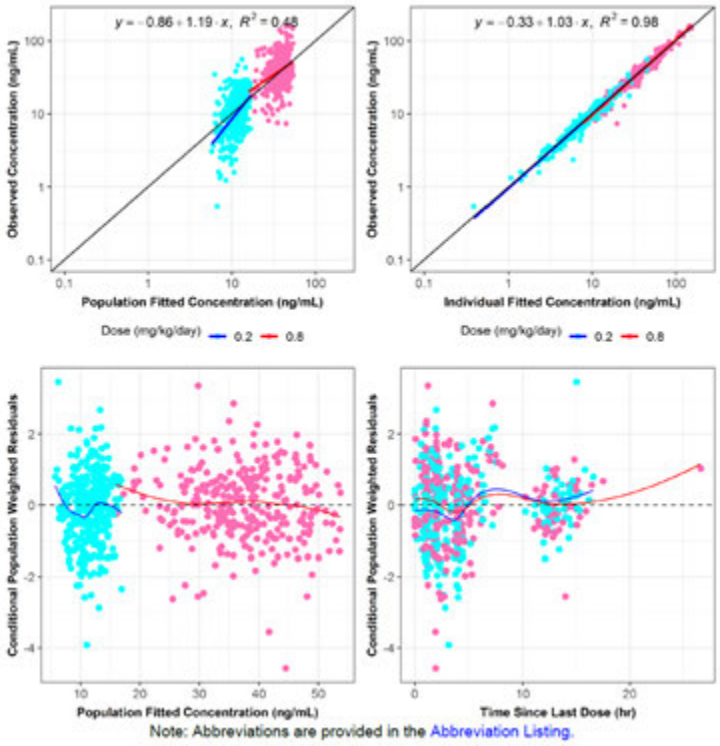
Note: Abbreviations are provided in the Abbreviation Listing.
All clearance and volume terms were conditioned on the unknown absolute bioavailability of FEN.
K_{FP} was set equal to CL_{FEN}/Vc_{FEN}, the elimination rate constant of FEN

Source: Applicant's PopPK report 00619-2, Page 18, Figure 1

The PopPK model was parameterized in terms of clearance (CL), volume of the central compartment (Vc), inter-compartmental clearance (CLd), volume of the peripheral compartment (Vp), presystemic (first-pass) metabolism rate (K_{FP}) and first-order absorption rate constant (Ka) for FEN and NFEN.

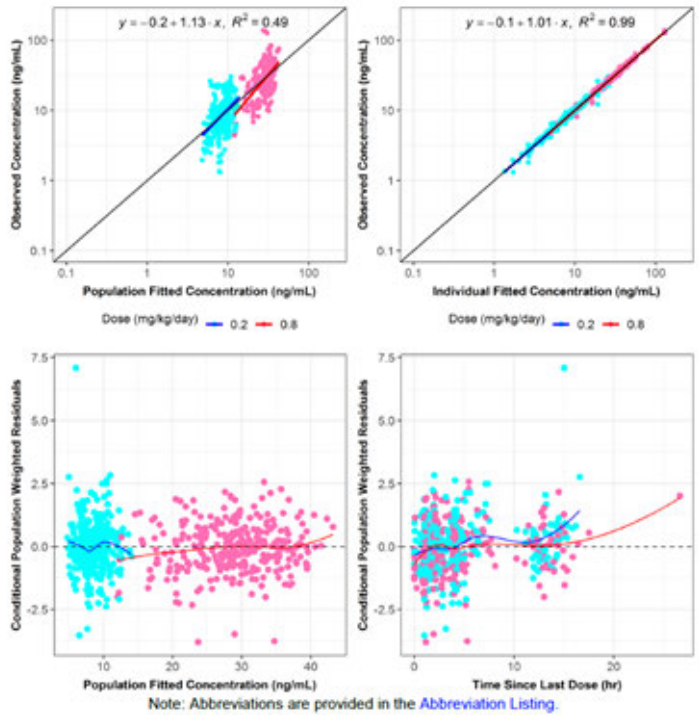
The final PK model for FEN and NFEN was assessed with diagnostics plots including goodness-of-fit (**Figure 3** and **Figure 4**) and pcVPC (**Figure 5**).

Figure 3: Goodness-of-fit plots for the final popPK model -FEN concentration



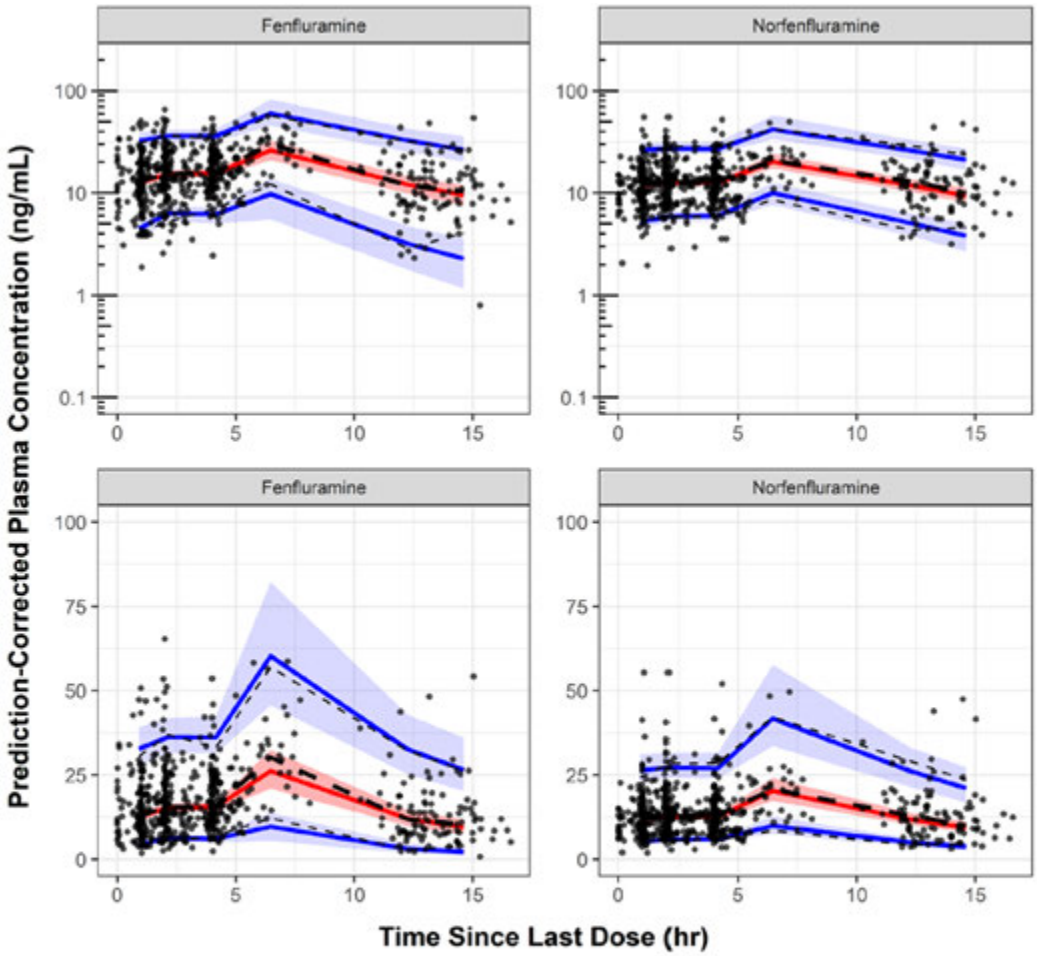
Source: Applicant's PopPK report 00619-2, Page 40, Figure 5

Figure 4: Goodness-of-fit plots for the final popPK model -NFEN concentration



Source: Applicant's PopPK report 00619-2, Page 41, Figure 6

Figure 5: Prediction-corrected visual predictive check for the final population PK model for FEN and NFEN for the entire study population on log-linear (top) and linear (bottom) scales



Note: Abbreviations are provided in the Abbreviation Listing.
Observed concentrations drawn more than 17 hr after the dose are excluded from these plots for visualization purposes (n = 4, 2 for FEN and 2 for NFEN, which were drawn 17.5 and 26.6 hr after the dose). These points fell within the same range as the observations drawn ~15 hr after a dose. Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations.

Source: Applicant's PopPK report 00619-2, Page 43, Figure 8

Parameter estimates from the final population PK model are presented in **Table 7**. For a typical patient with body weight of 70 kg, the estimated CL was 37.3 L/hr, Vc was 498 L, CLd was 118 L/hr and Ka was 0.522 /hr for FEN, the estimated CL was 57.6 L/hr, Vc was 970 L, CLd was 150 L/hr and Ka was 1.03 /hr for NFEN. Interindividual variability on CL for FEN, Vc for FEN and CL for NFEN, were 23%, 81.3% and 23.2% respectively.

Table 7: Summary statistics of resampled population PK parameters in comparison to the model parameter estimates from the final population pharmacokinetic model

Parameter	Final model		Resample statistics (N=1000)			
	Final estimate	%SEE	Mean	Median	%CV[a]	90% CI
CL_{FEN} (L/hr/70kg)	37.3	6.68	37.8	37.8	5.46	[34.5,41.1]
Vc_{FEN} (L/70kg)	498	24.1	506	500	17.7	[376,660]
CLd_{FEN} (L/hr/70kg)	118	21.3	121	119	18.8	[89.3,162]
Vp_{FEN} (L/70kg)	500	—	500	500	—	—
CL_{NFEN} (L/hr/70kg)	57.6	4.4	57.7	57.7	3.61	[54.3,61.3]
Vc_{NFEN} (L/70kg)	970	66.8	975	984	25.5	[596,1370]
CLd_{NFEN} (L/hr/70kg)	150	274	175	152	63.9	[42.4,394]
Vp_{NFEN} (L/70kg)	500	—	500	500	—	—
Ka_{FEN} (hr^{-1})	0.522	11.1	0.526	0.523	9.69	[0.444,0.611]
Ka_{NFEN} (hr^{-1})	1.03	68	1.11	1.09	30	[0.624,1.67]
STP-CL_{FEN}	0.458	—	0.458	0.458	—	—
CLcr-CL_{NFEN}	0.581	27.3	0.599	0.596	22.6	[0.377,0.818]
$\omega^2_{CL, FEN}$	0.230 (48.0 %CV)[b]	14.2	0.243	0.241	11.7	[0.201,0.292]
$\omega^2_{Vc, FEN}$	0.813 (90.2 %CV)[b]	32.3	0.84	0.821	21.3	[0.577,1.17]
$\omega^2_{CL, NFEN}$	0.232 (48.1 %CV)[b]	11.7	0.236	0.234	11.2	[0.198,0.282]
Covariance ($\omega^2_{CL, FEN}$ $\omega^2_{CL, NFEN}$)	0.115 (r^2 = 0.246)	21.7	0.122	0.12	17.4	[0.089,0.159]
$\sigma^2_{FEN, Proportional}$	0.0178 (13.3 %CV)[c]	7.90	0.0182	0.0182	10.3	[0.0153,0.0214]
$\sigma^2_{FEN, Additive}$	0.253 (0.503 ng/mL)[c]	67.4	0.262	0.241	67.2	[0.0243,0.598]
$\sigma^2_{NFEN, Proportional}$	0.00467 (6.83 %CV)[c]	4.64	0.0048	0.00481	8.77	[0.00409,0.0055]
$\sigma^2_{NFEN, Additive}$	0.0875 (0.296 ng/mL)[c]	42.9	0.0913	0.088	34	[0.0441,0.149]

Note: Abbreviations are provided in the Abbreviation Listing.
a. Equivalent to the %SEE from the final model.
b. Shrinkage estimates were 1.93, 30.0, and 0.108% for IIV in CL_{FEN}, Vc_{FEN}, and CL_{NFEN}, respectively.
c. Shrinkage estimates were 18.1 and 15.6% for RV in FEN and NFEN concentrations, respectively.

Source: Applicant's PopPK report 00619-2, Page 44, Table 6

Reviewer's Comments

Overall, the applicant's popPK model appears to adequately characterize the PK profiles of fenfluramine and norfenfluramine in patients with Lennox-Gastaut syndrome (LGS).

4.3.2 Reviewer's Analysis

Methods

Data Sets

Data set used is listed in **Table 8**.

Table 8: Analysis Data Sets

Datasets

Study	Name	Link to EDR
Study ZX008-1601 Part 1(Cohort A)	ppkin1.xpt	\\CDSESUB1\evsprod\nda212102\0106\m5\datasets\00619-2\analysis\legacy\datasets\ppkin1.xpt

Software

PopPK model fitting was performed in NONMEM 7.4.3 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.0.2.

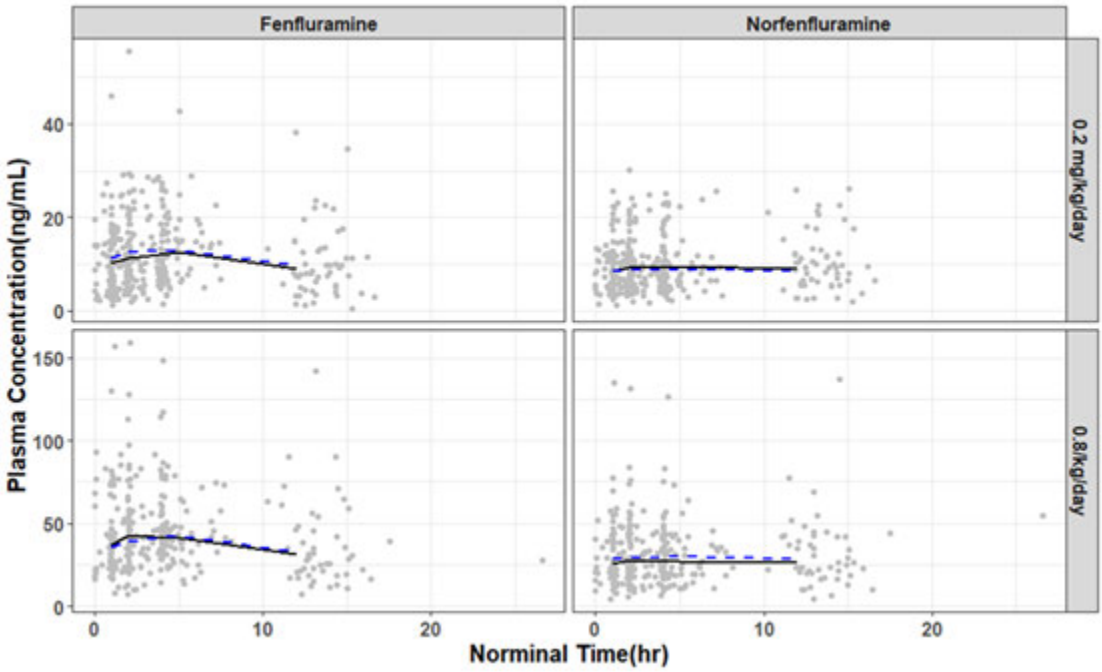
Results

The reviewer was able to reproduce the applicant's PopPK results with NONMEM (version:7.4.3). The applicant's PopPK analysis appears adequate for characterizing the PK profiles for FEN and NFEN. No additional modeling analysis was conducted.

Overview of Observed Data

Figure 6 presents PK profiles of FEN and NFEN for patients from at 0.2 mg/kg/day, and 0.8 mg/kg/day dose level. Overall, FEN and NFEN concentrations were consistently higher in subjects received the ZX008 0.8 mg/kg/day dose relatively to those observed in subjects received ZX008 0.2 mg/kg/day.

Figure 6: Observed FEN and NFEN Concentration Versus Nominal Time for 0.2 mg/kg/day, and 0.8 mg/kg/day Doses in Patients in Study ZX008-1601

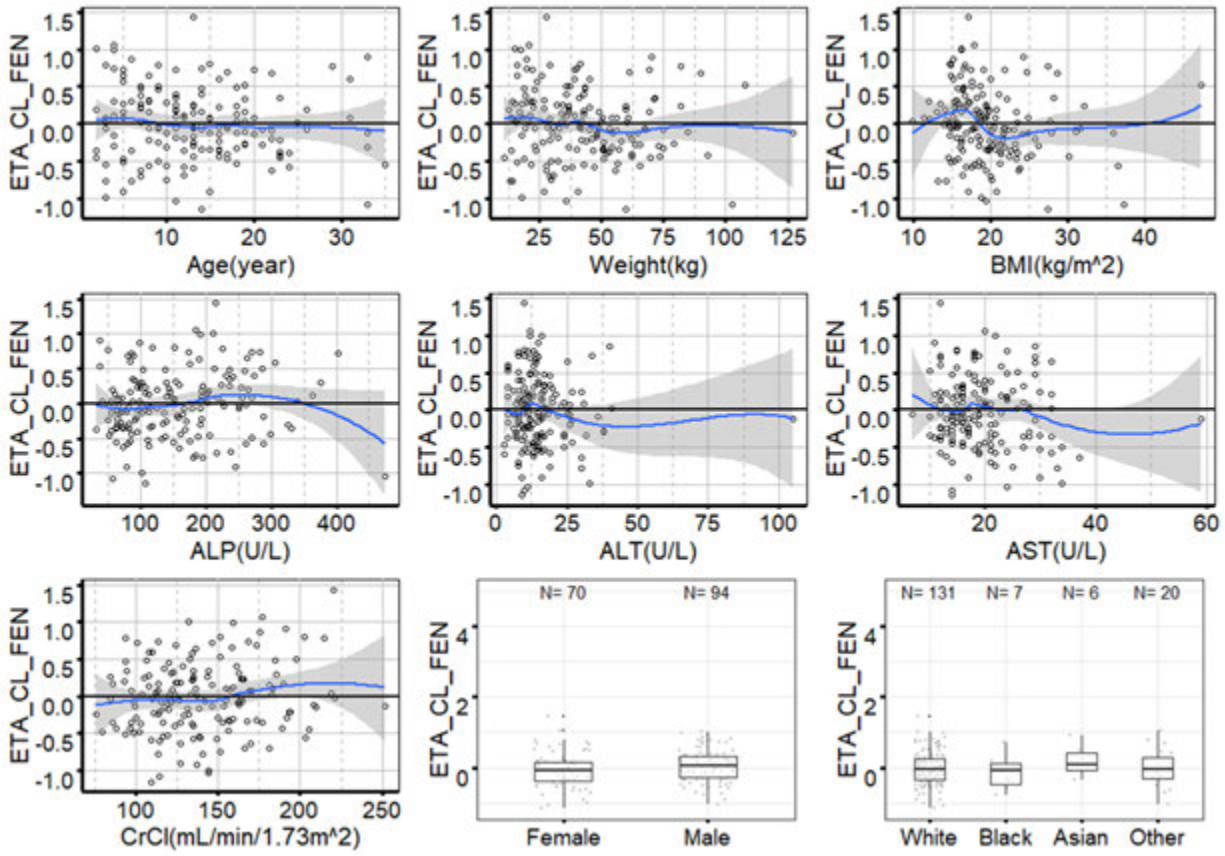


Note: Observed values are indicated by solid grey circles, the black solid lines represent the observed medians, and the blue dashed lines represent the population predicted medians.

Source: Reviewer's Analysis

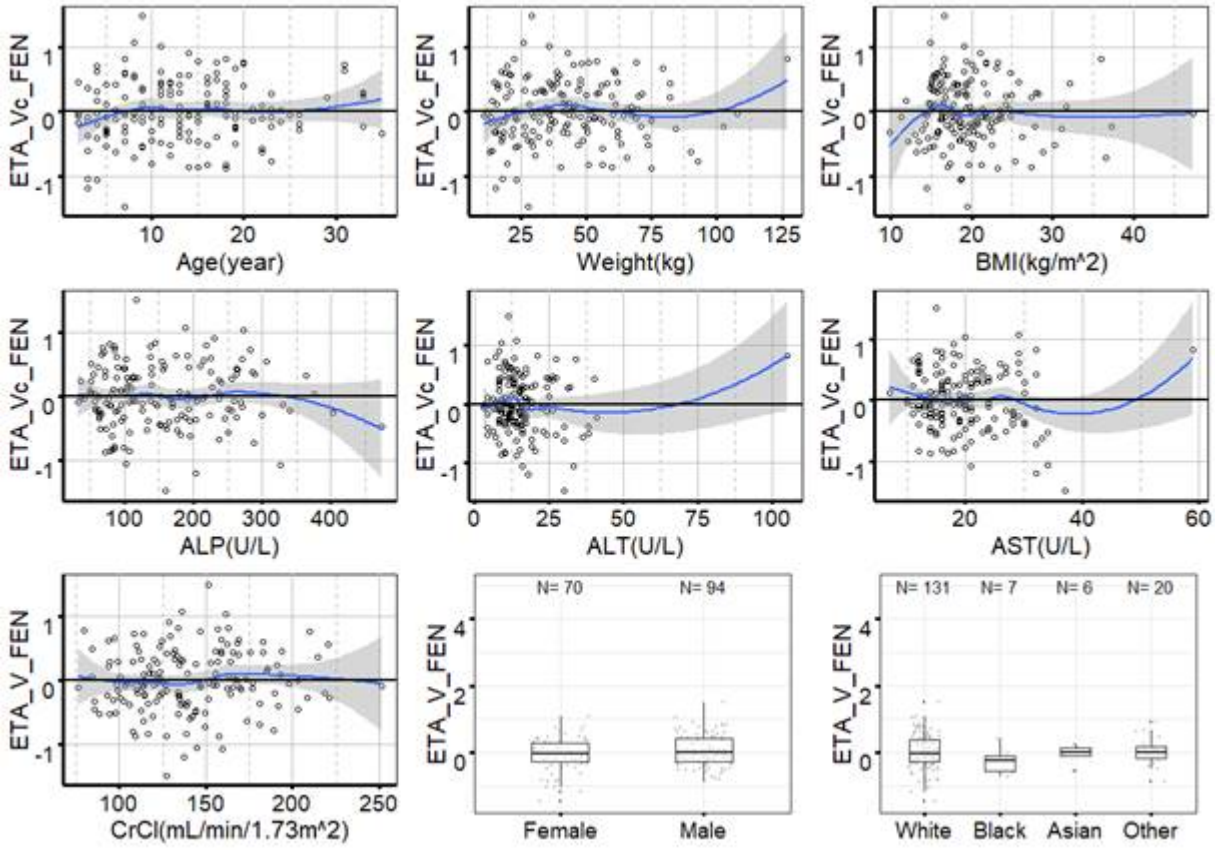
The impact of age, bodyweight, BMI, ALP, ALT, AST, CrCl (76-251 $mL/min/1.73m^2$), gender, race on the PK of FEN/NFEN were investigated. No clear trends in change in ETA with these covariates were observed with bodyweight allometric scaling in the final PopPK model (**Figure 7**, **Figure 8** and **Figure 9**). Therefore, after inclusion of body weight in the PopPK model, other covariates were not found to influence PK of FEN/NFEN.

Figure 7: Individual random effects versus Covariates Plots for Clearance of FEN



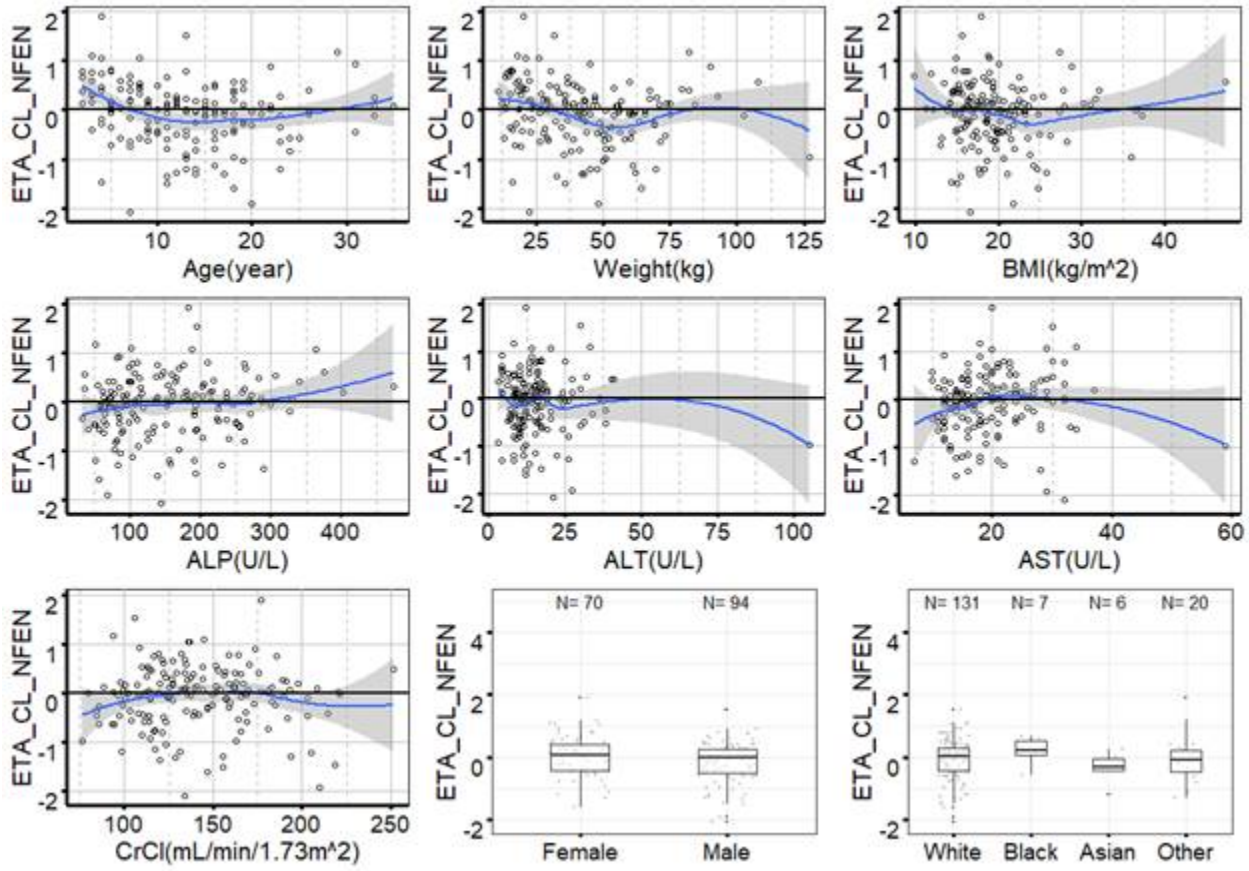
Source: Reviewer's Analysis

Figure 8: Individual Random Effects versus Covariate for Central Volume of Distribution (Vc) of FEN



Source: Reviewer's Analysis

Figure 9: Individual random effects versus Covariates Plots for Clearance of NFEN



Source: Reviewer's Analysis

Listing of Analyses Codes and Output Files

File Name	Description	Location
Fenfluramine pk analysis.R	PK and PopPK analysis file	M:\Review\2022\NDA 212102 S_003 fenfluramine HCl\Rscript

---

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

/s/

JIE LIU
03/24/2022 09:29:11 AM

VENKATESH A BHATTARAM
03/24/2022 09:31:07 AM

GOPICHAND GOTTIPATI
03/24/2022 09:32:56 AM
In concurrence with primary clinical pharmacology reviewer Dr. Anantha Ram Nookala