CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
INTEGRATED REVIEW

NDA Number	212,102
Link to EDR	\\CDSESUB1\evsprod\NDA212102\0001
Submission Date	9/28/2019
Submission Type	Priority
Brand Name	FINTEPLA
Generic Name	Fenfluramine
Dosage Form and Strength	Solution, 2.5 mg/mL
Route of Administration	Oral
Proposed Indication	For the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older
Applicant	Zogenix, Inc.
Associated IND	125797
OCP Review Team	Jagan Parepally, Michael Bewernitz, Atul Bhattaram, Jianghong Fan, Xinyuan Zhang, Angela Men
OCP Final Signatory	Mehul Mehta, PhD., FAAPS Division Director Division of Neuropsychiatric Pharmacology (DNP)

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1. EXECUTIVE SUMMARY

Fenfluramine (ZX008) is a being developed by Zogenix, Inc. as an antiepileptic drug (AED). The applicant is seeking its approval for the treatment of seizures associated with Dravet syndrome in pediatric patients 2 years and above. Fenfluramine was previously approved in Europe in the 1960s, and in North America and other countries in the 1970s as an appetite suppressant for the treatment of obesity in adults. Fenfluramine for obesity was discontinued from the market due to a distinctive heart valvular abnormality. Fenfluramine and its active metabolite, norfenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor. The proposed dosing regimen includes the recommended starting dose 0.1 mg/kg twice daily (b) (4). The dose may be increased based on clinical efficacy and tolerability not less than every 4 days, to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg. When administered concomitantly with stiripentol and clobazam a maximum of 0.2 mg/kg twice daily (0.4 mg/kg/day) not to exceed a total daily dose of 17 mg.

The efficacy and safety of fenfluramine in DS patients were supported by two randomized, double-blind, placebo controlled, multicenter registration trials. The proposed titration and dosing were followed in confirmatory efficacy and safety studies. The Applicant reports statistically significant differences in the pivotal trials for seizure frequency in DS. The main safety concerns were potential for valvular heart disease, weight loss, somnolence and sedation. There were 4 clinical pharmacology studies and 12 in vitro studies in this submission. Stiripentol, with or without clobazam and valproate, increases fenfluramine exposure and decreases norfenfluramine exposure when administered concomitantly, which support the dose reduction while taking fenfluramine and stiripentol concomitantly.

The key review questions focus on acceptability of fenfluramine regard efficacy to safety and appropriateness of dosing recommendations for fenfluramine in patients taking concomitant medications.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Neuropsychiatric Pharmacology and Division of Pharmacometrics, have reviewed the information contained in NDA 212102. The review team recommends approval of this NDA from a clinical pharmacology perspective. The key review issues with specific recommendations /comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Two pivotal, adequate and well controlled (Study 1 and Study ZX008-1504) trials in Dravet Syndrome patients provide primary evidence of effectiveness.

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General dosing instructions	The proposed dosing regimen includes recommended starting dose 0.1 mg/kg twice daily (b) (4). The dose may be increased based on clinical efficacy and tolerability not less than every 4 days, to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg. The recommended titration and dosing were followed in confirmatory efficacy and safety studies. The proposed dosing regimen is acceptable from clinical pharmacology perspective (see Section 3.3.2). Fintepla may be taken with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Fintepla is not recommended in patients with moderate and severe renal impairment (see Section 3.3.3). • Fintepla is not recommended in patients with hepatic impairment (see Section 3.3.3). • The maximum maintenance of Fintepla should be reduced to 0.2 mg/kg twice a day, with a maximum of 17 mg/day, in patients taking stiripentol concomitantly with or without clobazam.
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed (TBM) formulation is the same as clinical trial formulation.

Note: The dose for fenfluramine listed in the individual study reports represents fenfluramine hydrochloride, which is 0.4 mg/kg twice daily (0.8 mg/kg/day) not to exceed a total daily dose of 30 mg. The base equivalent is 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg.

1.2 Post-Marketing Requirements

Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
Effect of hepatic impairment on PK of fenfluramine and norfenfluramine	Fenfluramine is primarily metabolized in liver.	A clinical study to evaluate the pharmacokinetics, safety, and tolerability of Fenfluramine and norfenfluramine in subjects with varying degrees of hepatic function.

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2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action (MOA): The exact mechanisms by which fenfluramine exerts its anticonvulsant effect in humans is unknown. Fenfluramine and norfenfluramine are selective serotonin releasing agent, stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine and norfenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor.

Absorption: Fenfluramine is well absorbed (the absolute bioavailability was 68% to 74%) following administration of oral solution. The median fenfluramine Tmax is 4 to 5 hours after multiple-dose administration. Co-administration with a high-fat meal showed no significant effect on the rate and the extent of absorption.

Distribution: Plasma protein binding of fenfluramine is moderate (50%). The estimated volume of distribution (Vz/F) of fenfluramine is 11.9 L/kg following oral administration in healthy subjects.

Metabolism: Fenfluramine is extensively metabolized in liver, more than 75% of fenfluramine is metabolized to norfenfluramine prior to elimination, primarily by CYP1A2 (32%), CYP2B6 (42%), and CYP2D6 (46%). Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19 and CYP3A4/5. Norfenfluramine is then deaminated and oxidized to form inactive metabolites.

Elimination: The mean elimination half-life was 20 hours. Following oral administration radiolabeled dose, fenfluramine (>90%) was eliminated in the urine as unchanged fenfluramine, norfenfluramine, or other metabolites. Fenfluramine and norfenfluramine accounted for less than 25% of the total in urine and less than 5% is found in feces.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant recommended starting dose 0.1 mg/kg twice daily (b) (4). The dose may be increased based on clinical efficacy and tolerability not less than every 4 days, to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg. The recommended titration and dosing were followed in confirmatory efficacy and safety studies. The proposed dosing regimen is acceptable from clinical pharmacology perspective (see Section 3.3.2). Fintepla may be taken with or without food.

2.2.2 Therapeutic individualization

<u>Dose Adjustments in Patients Receiving Stiripentol plus Clobazam</u>

Pharmacokinetic interactions have been observed when FINTEPLA is co-administered with

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stiripentol plus clobazam. The starting dose is 0.1 mg/kg twice daily, which can be increased based on efficacy and tolerability. The maximum daily maintenance dose of FINTEPLA for patients taking these medications is 0.2 mg/kg twice daily not to exceed a total daily dose of 17 mg.

No dose adjustments are needed for cannabidiol, stiripentol, clobazam and valproate when co-administered with Fintepla.

Renal Impairment: Few subjects with mild renal impairment were included in Phase 3 clinical trials. Fintepla is not recommended in patients with moderate and severe renal impairment and patients undergoing hemodialysis (refer to section 3.3.3 for details).

Hepatic Impairment: Fenfluramine is extensively metabolized. No studies on the effect of hepatic impairment on the PK of fenfluramine in adults or children were conducted. With hepatic metabolism of fenfluramine, plasma drug concentrations may be affected in patients with significant hepatic impairment. Subjects with hepatic impairment were excluded from the Phase 3 clinical trials. Fintepla is not recommended in patients with hepatic impairment (refer to section 3.3.3 for details).

2.3 Outstanding Issues

A PMR for a clinical trial is issued to evaluate the potential effects of hepatic impairment on the pharmacokinetics of Fintepla.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling recommendations to be included in the final package insert:

- Section 7: When administered with rifampin or strong CYP1A2 or CYP2B6 inducers include “which may lower the efficacy of FINTEPLA”.
- Section 8: Renal impairment section needs to be revised to be consistent with previous drugs (e.g. stiripentol and cannabidiol) indicated for DS.
- Section 12.3:
    - Elimination section needs to be revised to be consistent with previous drugs indicated for DS.
    - Specific Populations: Delete body weight from the list.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Fenfluramine solution for oral administration is colorless and cherry-flavored liquid containing 2.5 mg/mL fenfluramine hydrochloride (equivalent to 2.2 mg/mL fenfluramine free base) in aqueous vehicle. Fenfluramine is a racemic compound, (b) (4)

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(b) (4)

Fenfluramine was previously approved in Europe in the 1960s, and in North America and other countries in the 1970s where it was marketed under the trade names of Pondimin and Ponderax as an appetite suppressant for the treatment of obesity in adults. Fenfluramine for obesity was discontinued from the market due to a distinctive heart valvular abnormality. For the treatment of DS, the maximum dose administered was 0.7 mg/kg/day, maximum 26 mg/day fenfluramine hydrochloride (given in divided doses twice daily) which is four-fold lower than the maximum dose approved for weight loss.

3.2 General Pharmacological and Pharmacokinetic Characteristics

SUMMARY OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology	
Mechanism of Action	The exact mechanisms by which fenfluramine exerts its anticonvulsant effect in humans is unknown. Fenfluramine and norfenfluramine are selective serotonin releasing agent, stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine and norfenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor. Fenfluramine and norfenfluramine may also act through other mechanisms not yet identified in reducing seizures.
Active Moieties	Norfenfluramine is the major circulating active metabolite approximately similar AUC to that of the parent which inhibits serotonin uptake and may provoke release of serotonin. Norfenfluramine is then deaminated and oxidized to form inactive metabolites.
QT Change	Thorough QT study demonstrated that multiple fenfluramine therapeutic (15 mg BID) and supratherapeutic (60 mg BID) doses of ZX008 administered orally to healthy volunteers had no effect on the QT interval corrected for heart rate (QTc interval). No relationship between the plasma concentrations of fenfluramine or norfenfluramine on the QTc interval was found.
General Information	
Bioanalysis	A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical method was used to quantify plasma concentrations of fenfluramine and norfenfluramine in human plasma with a calibration range of 0.25 ng/mL to 100 ng/mL. A summary of the method validation report is included as an appendix.
Healthy Volunteers vs Patients	The PK of fenfluramine was comparable between healthy subjects and subjects with DS patients based on the population analysis.
Drug exposure at steady state following the therapeutic dosing regimen	The mean overall fenfluramine exposure at the steady state (AUC0-τ) of fenfluramine at 0.2 mg/kg/day was 375 ng.hr/mL and at 0.7 mg/kg/day was 1390 ng.hr/mL in children and young adults with Dravet Syndrome

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Dose Proportionality	The pharmacokinetics of ZX008 were essentially dose-proportional following multiple doses of 30 or 120 mg/day in Study 1603; 0.2 or 0.7 mg/kg/day in Study 1.
Variability	Inter-subject variability of fenfluramine in humans was up to 26.0% for Cmax and up to 26.8% for AUC0-τ and for norfenfluramine, Cmax was 31.7% and up to 33.1% for AUC0-τ at steady-state following 15 mg BID dose. The intrasubject variability was not reported.
ADME	
Absorption	The absolute bioavailability of fenfluramine was approximately 68-74%. There was no effect of food on the pharmacokinetics of fenfluramine or norfenfluramine
Tmax	The median fenfluramine Tmax 4 to 5 hours after multiple-dose administration. The median norfenfluramine Tmax was approximately 12 hours.
Distribution	Plasma protein binding of fenfluramine is moderate (50%) and independent of concentration. The estimated mean (CV%) volume of distribution (Vz/F) of fenfluramine is 11.9 (16.5%) L/kg following oral administration in healthy subjects.
Elimination	
Mean Clearance and Terminal Elimination half-life	The geometric mean (CV%) clearance (CL/F) of fenfluramine is 6.9 (29%) L/h the half-life is 20 hours.
Metabolism	
Primary metabolic pathway(s)	Fenfluramine is extensively metabolized in liver, more than 75% of fenfluramine is metabolized to norfenfluramine prior to elimination, primarily by CYP1A2 (32%), CYP2B6 (42%), and CYP2D6 (46%). Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19 and CYP3A4/5. Norfenfluramine is then deaminated and oxidized to form inactive metabolites.
Inhibitor/Inducer (in vitro)	Fenfluramine and norfenfluramine are not inhibitors or inducers of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations.
Transporter Systems (in vitro)	Fenfluramine and norfenfluramine are not substrates of the P-g, BCRP, OAT1, OAT3, OCT2, MATE1, and MATE2-K transporters and are not inhibitors of P-gp, BCRP, OAT1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters.
Excretion	Following oral administration radiolabeled dose, fenfluramine (>90%) was eliminated in the urine as unchanged fenfluramine, norfenfluramine, or other metabolites. Fenfluramine and norfenfluramine accounting for less than 25% of the total; less than 5% is found in feces.

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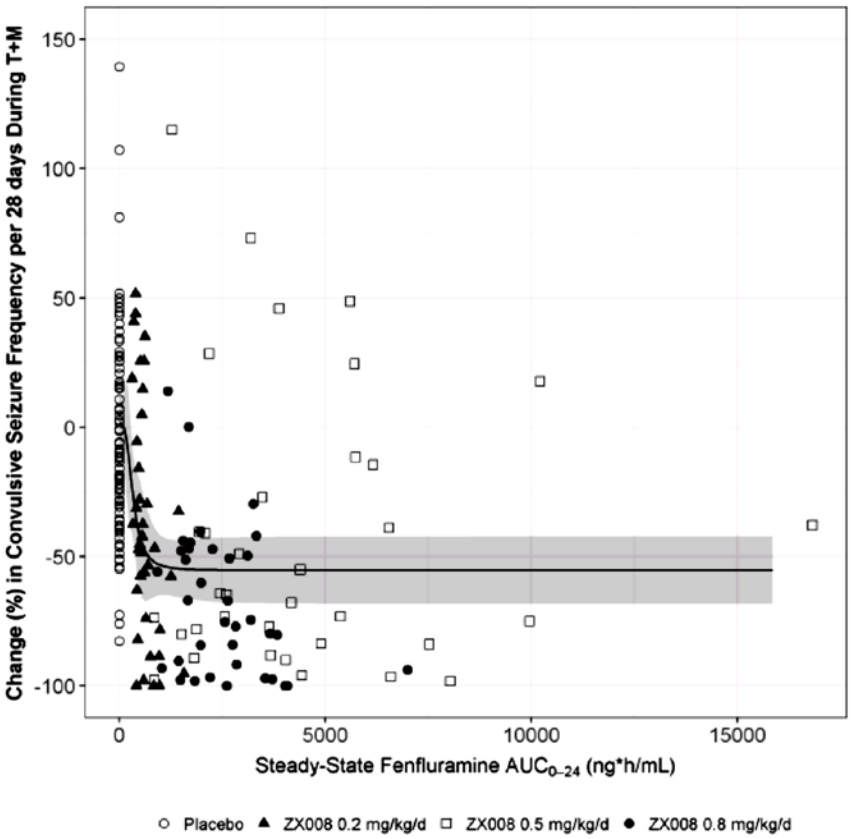
3.3 Clinical Pharmacology Questions

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

The exposure-response analyses of Phase 3 data from Study 1 and Study 1504 Cohort 2 indicate a trend of greater reduction in change from baseline seizure frequency with increasing exposure. The model predicts a maximum of 57% reduction from baseline seizure frequency. An AUC0-24 value of 342 ng*h/mL is predicted to achieve half of the maximum seizure reduction. The predicted AUC0-24 at steady state for 0.2 mg/kg/day dose (low maintenance dose in Phase 3 Study 1) is 375 ng*hr/mL in the absence of stiripentol and expected to achieve ~half of the maximum seizure reduction. The predicted AUC0-24 at steady state for 0.7 mg/kg/day dose (high maintenance dose in Phase 3 Study 1) is 1390 ng*hr/mL in the absence of stiripentol and expected to achieve near maximal seizure reduction.

Figure 1: percent change in convulsive seizure frequency per 28 days During Titration and Maintenance Period versus steady-state fenfluramine AUC0-24 with fit of Emax model overlaid



Exposure-response analyses were conducted by the Applicant to assess the relationship of fenfluramine exposure with platelet count, blood glucose levels, and mitral valve regurgitation. The data do not appear to support the existence of an E-R relationship for blood glucose or mitral value regurgitation. The exposure-response model for platelet count was statistically-significant but is shallow. As this drug was previously used as a weight-loss drug, the exposure-response relationship for weight loss is expected. Please refer to the medical officer's review for details on the weight-loss AE and whether it is to appear in the label

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

Yes, the proposed dosing regimen is appropriate for the general population for which the indication is being sought.

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

Yes. Fenfluramine is extensively metabolized in the liver and excreted as metabolites in urine. The average cumulative recovery in urine for all radioactive components was about 87.5% in human mass balance study.

Hepatic Impairment: The effect of hepatic impairment on PK of fenfluramine was not valuated. Subjects with hepatic impairment were excluded from the Phase 3 clinical trials. Fintepla is not recommended in patients with hepatic impairment. A PMR will be issued to the sponsor to conduct additional study evaluating the effect of hepatic impairment on PK of fenfluramine when compared to healthy subjects.

Renal Impairment: The effect renal impairment and hemodialysis on PK of fenfluramine was not valuated. The incidence of DS patients with end stage renal disease is very low. Few subjects with mild renal impairment were included in Phase 3 clinical trials. Fintepla is not recommended in patients with moderate and severe renal impairment.

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

Fenfluramine is extensively metabolized in the liver to norfenfluramine prior to elimination, primarily by CYP1A2, CYP2B6, and CYP2D6. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19 and CYP3A4/5. Norfenfluramine is then deaminated and oxidized to form inactive metabolites. There was no significant food effect observed. The effects of extrinsic factors on the dose-exposure and/or dose-response of fenfluramine was not assessed in dedicated studies. Since fenfluramine is metabolized by multiple enzyme pathways to norfenfluramine. There is a low risk for individual CYP1A2, CYP2B6, and CYP2D6 inhibitors having significant impact on the metabolism of fenfluramine. There is a potential for inducers of CYP1A2 and CYP2B6 (e.g., naficilin, modafinil) decreasing fenfluramine levels. The in vitro drug interaction potential, clinical drug-drug interactions between fenfluramine and valproate, stiripentol, clobazam and cannabidiol are further discussed in this section.

In Vitro Assessment of DDI Potential

In vitro studies indicate that fenfluramine and norfenfluramine are not inhibitors or inducers of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Fenfluramine and norfenfluramine are not substrates of the P-g, BCRP, OAT1, OAT3, OCT2, MATE1, and MATE2-K transporters and are not inhibitors of P-gp, BCRP, OAT1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K transporters.

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In Vivo Assessment of Drug-Drug Interactions

Effect of Other Drugs on Fenfluramine

Effect of Stiripentol, Clobazam, and Valproic Acid

The effect of STP regimen (stiripentol, clobazam and valproate) and its impact on fenfluramine and norfenfluramine PK was tested in 2 clinical studies, Study 1505 Part 1, in healthy volunteers, and Study 1504 Cohort 1, in subjects with Dravet syndrome.

Stiripentol regimen had a significant effect on the PK of fenfluramine and norfenfluramine, increased AUC0-t of fenfluramine by 66% and decreased norfenfluramine AUC0-t by 41% when compared to fenfluramine administered alone. Increased Cmax of fenfluramine by 18% and decreased norfenfluramine Cmax by 43% when compared to fenfluramine administered alone (table below).

Effect of Concomitant STP on PK of Fenfluramine from Study 1505 in healthy subjects

Drug PK Parameter	**Fenfluramine + STP versus Fenfluramine Alone Ratio**	**90% CI**
Fenfluramine (n=19)		
Cmax	118	109, 127
AUC0-t	166	152, 181
Norfenfluramine (n=19)		
Cmax	57	49, 68
AUC0-t	59	50, 68

The data from Study 1 (0.7 mg/kg/day, with a maximum of 26 mg/day) and the exposure evaluated in Study 1504 Cohort 2 (0.4 mg/kg/day, with a maximum of 17 mg/day), STP, with or without CLB and VPA, resulted in an increase of fenfluramine AUC by approximately 130% and decrease norfenfluramine exposure approximately 60%.

Based on the PPK-simulations, the Applicant concludes that a ~130% increase in FEN exposure and ~60% increase in NFEN exposures are likely in patients receiving ZX008 at the dose used in Study 1504 Cohort 2 (0.4 mg/kg/d with a max. of 17 mg/d) with concomitant STP/CLB/VPA compared to a ZX008 dose of 0.7 mg/kg/day with a max. of 26 mg/day without STP.

The 130% increase in fenfluramine exposures comes from a comparison of the simulated AUC0-24 values for 0.4 mg/kg/day arm in Study 1504 Cohort 2 (3150 ng*h/mL) versus the simulated AUC0-24 values 0.7 mg/kg/day arm from Study 1 (1390 ng*h/mL); 3150/1390 = 2.266, or ~130% increase. The Applicant intends to provide this comparison of the simulated fenfluramine AUC0-24 these two arms of the Phase 3 trials in the label as the description of the stiripentol effect on fenfluramine PK.

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OCP was concerned that the stiripentol drug interaction effect measured in the in-vivo drug interaction study 1505 appears differs from both the PPK-based interaction assessment. An IR was sent to the Applicant on May 20th, 2020 (archived in DARRTs on June 3rd, 2020) which included questions regarding the STP drug interaction assessment. One of the questions in the IR was whether the PPK-based STP interaction assessment is able to replicate the in-vivo STP drug interaction study result. In the IR response received on May 25th, 2020 (sequence 0057), the Applicant provided results of new PPK simulations which were able to approximate the results of the in-vivo drug interaction study 1505.

OCP agrees with the Applicant that the PPK-based assessment of the STP effect on FEN is the most clinically relevant as it is determined from the intended clinical population and takes into account the chronic administration of both agents.

The Applicant proposes labeling language to represent the STP interaction effect on FEN PK in terms of the dosing used in the Phase 3 Studies. However, there is a difference in dosing level between the two Phase 3 studies. The dose level in Study 1504 Cohort 2 is 0.4 mg/kg/day FEN with concomitant STP and the dose level in Study 1 is 0.7 mg/kg/day FEN without concomitant STP. However, in order to provide a clear understanding of the magnitude of the STP-mediated drug interaction, the FEN dose should not be a factor affecting the apparent DDI estimate. The available simulated PK information provides an estimate of the STP effect on steady-state FEN PK at the 0.2 mg/kg/day. OCP proposes adding the following label statements based on the simulated PK data:

a) STP is expected to increase FEN AUC_{0-24} by 166% while FEN is at steady-state.
b) STP is expected to increase FEN AUC_{0-24} by 42% a single FEN administration.

Please refer to **Table 5** in section 4.3.3 for additional details.

Note: Increase in fenfluramine AUC following concomitant administration with stiripentol could be due to time dependent inhibition of different CYPs by stiripentol. The increase in fenfluramine AUC at steady-state is more pronounced when compared to single dose administration as seen in dedicated DDI study compared to population PK analysis as described above.

Effect of Clobazam

Clobazam, an inhibitor of CYP2D6 is one of the CYP enzymes involved in fenfluramine metabolism. The potential impact of concomitant administration of CLB on the PK of fenfluramine and norfenfluramine was evaluated using the individual PK parameter estimates from Study 1 using the population PK model. Concomitant administration of CLB does not have a clinically relevant effect on the PK of fenfluramine or norfenfluramine in subjects with Dravet syndrome.

Effect of Valproic Acid

Valproic acid (VPA) is a weak inhibitor of some CYP450 isozymes (CYP2C9, CYP2A6, and CYP2C19), epoxide hydrase, and glucuronyltransferases. The data show that VPA does not have significant impact on the PK of fenfluramine and norfenfluramine.

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Effect of Cannabidiol

Cannabidiol (CBD), in vitro is a reversible competitive inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (IC50 < 10 μM) and a time-dependent inhibitor of CYP1A2 and CYP3A4. As fenfluramine is a substrate for some of these CYP450 enzymes, CBD could cause in an increase in fenfluramine concentrations due to the decreased metabolism of fenfluramine, and this interaction was tested in a clinical study in healthy volunteers.

The effect of coadministration of CBD on fenfluramine and norfenfluramine PK was evaluated in Study 1604. The study demonstrated that co-administration of CBD with ZX008 increased fenfluramine AUC0-t by approximately 59% and the Cmax was not changed significantly. However, norfenfluramine AUC0-t was lowered by approximately 22% and the Cmax was decreased by 33% (table below).

Effect of Concomitant CBD on PK of Fenfluramine

Drug PK Parameter	**Fenfluramine + CBD versus Fenfluramine Alone Ratio**	**90% CI**
Fenfluramine (n=14-24)		
Cmax	110	103, 117
AUC0-t	159	148, 170
Norfenfluramine (n=14-24)		
Cmax	67	61, 72
AUC0-t	78	70, 87

Effect of CYP450 Inducers

Fenfluramine is extensively metabolized in the liver to norfenfluramine prior to elimination, primarily by CYP1A2, CYP2B6, and CYP2D6. Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19 and CYP3A4/5. Moreover, norfenfluramine is an active metabolite which is equipotent compared to fenfluramine. CYP1A2 is mainly induced by smoking, which is less likely in most Dravet syndrome patient population. CYP2B6 can be induced by some antiepileptic drugs (eg, carbamazepine, phenobarbitaland phenytoin); these are contraindicated in Dravet syndrome, due to their sodium-channel blocking properties. Enzyme inducers such as naficilin and modafinil can also substantially increase CYP1A2 and CYP2B6 activity. Finally, CYP2D6 is not inducible.

Effect of Fenfluramine on Other Drugs

Effect of Fenfluramine on Concomitant AEDs

In vitro studies indicate that fenfluramine and norfenfluramine are not inhibitors or inducers of CYP enzymes at clinically relevant concentrations. Studies in vitro also indicate that fenfluramine and norfenfluramine are not substrates or inhibitors of major drug transporters. The dedicated drug-drug interaction studies (Study 1505, Study 1604) indicate that coadministration of fenfluramine and norfenfluramine does not alter the PK of stiripentol, clobazam, valproate or cannabidiol.

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Food Effect
Food Effect using oral solution was evaluated in Study 1505 (part 2). This study was an open-label, randomized, single dose 3-way crossover. The relative bioavailability following a single oral dose (0.7 mg/kg) of fenfluramine did not affect the Cmax, Tmax or AUC of fenfluramine or norfenfluramine by the consumption of a high-fat high-calorie breakfast taken within 30 minutes prior to administration of fenfluramine. All limits of the 90% CIs of the estimated geometric mean ratios for all of the comparisons (Cmax and AUC) fell within the 0.80 to 1.25 boundaries. See individual study review for further details.

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, the to-be-marketed (TBM) formulation will be oral solution of fenfluramine and it is the same as the clinical trial formulation.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

A validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical method was used to quantify plasma concentrations of fenfluramine and norfenfluramine using fenfluramine-d5, and norfenfluramine-d6 as internal standards in human plasma.

4.1.2 What bioanalytical methods are used to assess cannabidiol concentrations? Briefly describe the methods and summarize the assay performance.

Plasma fenfluramine and norfenfluramine was measured by a validated LC/MS/MS. The accuracy, precision, and other relevant parameters for the assay are described in Table below. This is sufficient to meet the requirements of the submitted studies.

Summary of Assay Validation Report

	Acceptance Criteria	**Method Performance**
Matrix – Human plasma		
Anticoagulant – K2EDTA, K3EDTA, Lithium Heparin		
Assay Volume	150 mcL	
Selectivity		
Analyte – Fenfluramine, Norfenfluramine	Interferences at <20% LLOQ (at least 5 of 6 screened)	Complies (16 lots interference –free)
Internal Standard – Fenfluramine- d5,	Interferences at < 5% mean IS (at least 5 of 6 screened)	Complies (16 lots interference –free)

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Matrix Effect (6 spiked matrix lots)	the % CV for IS Normalized MF must be < 15% over all 6 lots	Complies
Comedications (Valproic Acid, Stiripentol, Levetiracetam, Topiramate, Phenobarbital, Clonazepam, Phenytoin, Carbamazepine, Eslicarbazepine, Retigabine, Lamotrigine, Zonisamide, N-desmethylclobazam, Clobazam)	± 15.0% Bias; < 15.0% CV	Complies
Cannabidiol	± 15.0% Bias; < 15.0% CV	Complies
Hemolytic Effect Evaluation	± 15.0% Bias; < 15.0% CV	Complies.
Lipemic Effect Evaluation	± 15.0% Bias; < 15.0% CV	Complies
Carry-Over	< 20.0% LLOQ, < 5.0% mean IS	Complies
Fenfluramine		
Linearity		
Weighting		$1/x^2$
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
Precision		
Intra-assay	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	3.5 to 10.0% (LLOQ); 1.2 to 8.8% (above LLOQ)
Inter-assay	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	8.9 % (LLOQ); 3.5 to 6.2% (above LLOQ)
Accuracy		
Intra-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	4.3 to 7.1% (LLOQ); -3.8 to 6.6% (above LLOQ)
Inter-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	1.7% (LLOQ); -0.9 to 2.6% (above LLOQ)
Dilution (2x, 5x)		
Precision	≤ 15.0% CV	1.6%, 5.3%
Accuracy	± 15.0% Bias	0.6%, 1.3%
K3EDTA Human Plasma		
Precision	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	8.6 to 9.6% 1.5 to 8.0%
Accuracy	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	-9.6 to 0.7% -3.2 to 2.0%
Lithium Heparin Human Plasma		
Precision	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	5.7 to 17.7% 0.9 to 6.0%
Accuracy	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	-16.0 to 6.2% -4.6 to 1.6%

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Large Batch Size	In order for QC sample results to be accepted, at least one QC at each concentration level and two- thirds of the total number of QC samples were required to interpolate within ± 15.0% from nominal.	Acceptance criteria were met. (b) (4) samples
Precision	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	4.8% 1.2 to 4.1%
Accuracy	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	8.3% -2.8 to -1.2%
Norfenfluramine		
Linearity		
Weighting		$1/x^2$
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	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	4.8 to 5.9% (LLOQ); 1.2 to 6.4% (above LLOQ)
Inter-assay	< 20.0% CV (LLOQ); < 15.0% CV (above LLOQ)	5.3% (LLOQ); 3.4 to 4.0% (above LLOQ)

4.2 Population PK Analyses

The PK dataset included 2563 PK samples from n=183 subjects (1296 samples from n=25 subjects in Study 1505 part 1, 587 samples from n=75 subjects in Study 1, 177 samples from n=18 subjects in Study 1504 Cohort 1, and 504 samples from n=65 subjects in Study 1504 Cohort 2).The clinical studies which provided data for the PPK analyses are summarized below.

Study 1505 Part 1 (Phase 1): Part 1 of this two-part study is a randomized, three-way crossover study in n=26 healthy volunteers to assess the pharmacokinetic interaction between fenfluramine (ZX008 oral solution) and a stiripentol (STP)-based regimen of anti-epileptic drugs (AEDs). The STP-based regimen includes clobazam (CLB), STP, and valproic acid (VPA), or combinations thereof. Subjects were randomized to undergo each of three treatment regimens in a randomized order separated by ≥ 17 days washout period:

- Regimen A: A single dose of ZX008 0.7 mg/kg
- Regimen B: STP 3500 mg, CLB 20 mg, and VPA 25 mg/kg (maximum 1500 mg)
- Regimen C: ZX008 0.7 mg/kg plus STP 3500 mg, CLB 20 mg, and VPA 25 mg/kg (maximum 1500 mg)

Only data collected after regimens A and C were included in the population PK analysis.

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PK samples: pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after drug administration. |
Analytes: Fenfluramine, nor-fenfluramine

Part 2 of Study 1505 assessed the PK of fenfluramine in subjects who received ZX008 in a fed state as well as in a fasted state in a crossover manner. The Applicant did not include the data from Part 2 in the PPK analyses as a food effect was not apparent based on the Applicant's noncompartmental analyses of Part 2.

Study 1603 (Phase 1): Randomized, double-blind, double-dummy, placebo and positive-controlled, parallel study to assess the effect of fenfluramine (ZX008 oral solution) on heart-rate corrected QT interval using Fridericia's formula in healthy volunteers. Subjects were randomized one of four arms:

- Treatment A (therapeutic treatment): ZX008 30 mg/day (15 mg twice daily) on Days 1 - 6 and the morning of Day 7 followed by placebo on Day 8,
- Treatment B (supratherapeutic treatment): ZX008 120 mg/day (60 mg twice daily) on Days 1 through 6 and the morning of Day 7 followed by placebo on Day 8,
- Treatment C (moxifloxacin/placebo):
    - Moxifloxacin 400 mg on Days 1 through 6 followed by placebo on the morning of Day 7 and on Day 8,
    - Placebo on Days 1 through 6 and the morning of Day 7 followed by moxifloxacin 400 mg on Day 8.

Subjects randomized to Treatment A (n=59) or Treatment B (n=60) were included in the PPK analyses.

PK samples: On Day 7, pre-dose and at 0.5, 1, 2, 3, 4, 5.5, 6, 8, 10, 12, 15, and 23.5 hours after drug administration.
Analytes: Fenfluramine, nor-fenfluramine

Study 1504 Cohort 1 (Phase 1b): Open-label, single-dose, parallel study to assess drug interactions in n=18 patients with DS. Subjects were randomized to one of three arms:

- A single dose of ZX008 0.2 mg/kg + CLB+VPA (N = 3),
- A single dose of ZX008 0.4 mg/kg + CLB +VPA (N = 5), or
- A single dose of ZX008 0.2 mg/kg + CLB + VPA+ STP (N = 10)

Allocation to each group was stratified according to age (2 year to < 6 years; 6 year to 18 years).

[*Reviewer comment: The dose listed in the study report represents fenfluramine hydrochloride, which is 0.25 mg/kg twice daily (0.5 mg/kg/day) not to exceed a total daily dose of 20 mg/day. The fenfluramine base equivalent is 0.2 mg/kg twice daily (0.4 mg/kg/day) not to exceed 17 mg/day.*

The dose listed in the study report of 0.2 mg/kg fenfluramine hydrochloride is also expressed as 0.2 mg/kg fenfluramine base equivalent when the dose level is rounded to the nearest tenth of a mg/kg.]

PK samples: pre-dose, and at 2, 4, 8, 12, and 24 hours post-dose.
Analytes: Fenfluramine, nor-fenfluramine

Reference ID: 4630087

Study 1504 Cohort 2 (Phase 3): Double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of ZX008 as adjunctive therapy of seizures in pediatric and young adult patients with DS. N=87 subjects were randomized 1:1 to receive 0.4 mg/kg/day (max 17 mg/day) ZX008 or placebo in combination with STP/CLB/VPA (n=77 completed the study; n=65 subjects provided sufficient information to be included in the PPK analyses). Though only 40 were randomized to ZX008 treatment in this study, PK data are available from 65 subjects as some subjects in the placebo arm who were transitioned to fenfluramine in preparation for entry in the open-label extension provided PK data prior to exiting Study 1504 Cohort 2.

Allocation to each group was stratified according to age (2 year to < 6 years; 6 year to 18 years). Subjects were titrated over 21 days as follows: 0.2 mg/kg/day dose of ZX008 (or placebo equivalent) on Study Days 1 to 7, 0.4 mg/kg/day on Study Days 8 to 14, 0.4 mg/kg/day on Study Days 15 to 21. Upon completion of titration, subjects maintained their regimen of ZX008 or placebo for a 12-week maintenance period. Subjects who chose to enter the open-label extension, upon completion of the maintenance period, underwent a 14-day transition to a target of 0.2 mg/kg/day in a blinded manner. For patients randomized to ZX008, the dose transition involved a tapering as follows during the interval between Visit 12 and Visit 13 (Day 106 to 120 after first dose): 0.4 mg/kg/day on Day 1 to 7 of transition period and 0.2 mg/kg/day on Days 8 to 14 of transition period. For patients randomized to placebo, the dose transition during the interval between Visit 12 and Visit 13 was treatment with 0.2 mg/kg/day on Days 1 to 14 of transition period.

PK samples were collected during the 14-day transition period (Day 106 to 120 after first dose) in the subset of patients who chose to enter the open-label extension.

PK samples: pre-dose, and at 1,2, 4, and 6 hours post-dose.
Analytes: Fenfluramine, nor-fenfluramine

Study 1 (Phase 3): Study 1 is the designation for a prospectively-designed merged analysis of n=119 pediatric and young adult patients with DS that represent the first half (approximately) of subjects enrolled into two identical, partially-completed Phase 3 studies; Study 1501 and Study 1502. In each study, ~n=120 subjects are to be randomized. The design for these studies is double-blind, placebo-controlled, parallel study to assess the efficacy, safety, and PK of ZX008 (fenfluramine oral solution) as an adjunctive treatment in pediatric and young adult patients with DS. Study 1501 is being conducted at ~30 sites in North America and Study 1502 is being conducted at ~30 sites in Europe and Australia. After a 6-week baseline period, subjects were randomized 1:1:1 in a double-blind manner to receive placebo, ZX008 0.2 mg/kg/day or ZX008 0.7 mg/kg/day (maximum dose 26 mg/day). Randomization was stratified by age (< 6 years, ≥ 6 years) such that each arm contained at least 25% of each age group. PK data were provided from n=75 subjects enrolled in Study 1. PK samples were collected at Visit 8 (Day 43).

PK samples: pre-dose, and at 1,2, 4, and 6 hours post-dose .
Analytes: Fenfluramine, nor-fenfluramine

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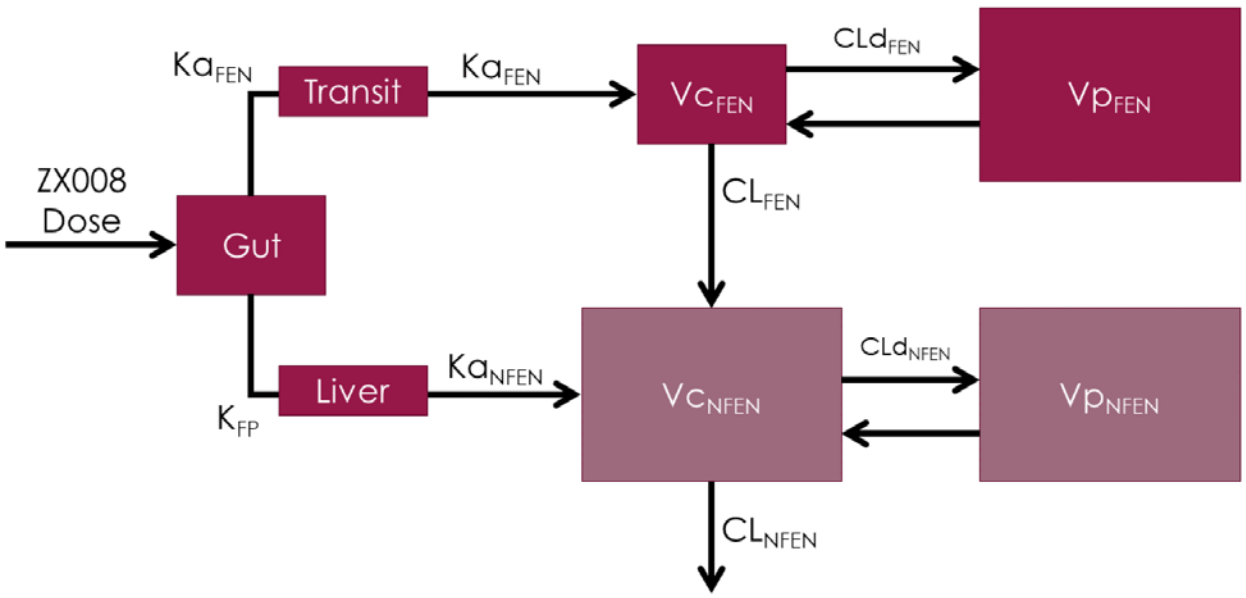
(b) (4)

4.3.2 Population PK Model

Structural Model: The final population PK model includes first-order absorption for FEN for a portion of administered 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. The model schematic for the final PPK model is shown in the figure below.

Figure 2: Model Schematic for the Final PPK Model (rfinal-ctl.txt)



K_{FP} = Presystemic (first-pass) metabolism;
K_{aFEN} = Absorption rate constant, fenfluramine;
K_{aNFEN} = Absorption rate constant, norfenfluramine;
CL_{FEN} = Apparent oral systemic clearance, fenfluramine;
CL_{NFEN} = Apparent oral systemic clearance, norfenfluramine;
$CL_{d,FEN}$ = Apparent oral distributional clearance, fenfluramine;
$CL_{d,NFEN}$ = Apparent oral distributional clearance, norfenfluramine;
V_{cFEN} = Apparent oral central volume of distribution, fenfluramine;
V_{cNFEN} = Apparent oral central volume of distribution, norfenfluramine;
V_{pFEN} = Apparent oral peripheral volume of distribution, fenfluramine;
V_{pNFEN} = Apparent oral peripheral volume of distribution, norfenfluramine;
K_{FP} was set equal to CL_{FEN}/Vc_{FEN}, the elimination rate constant of fenfluramine

Source: sequence 0002, icpd-00445-01.pdf, page 42 of 168

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Allometric Scaling: CL, CL_d (inter-compartmental clearance), V_c, and V_p for FEN and NFEN were scaled by body weight (normalized to the 70 kg) using a power model. The exponent was fixed to 1 for volume terms and fixed to 0.75 for clearance terms.

Inter-Individual Variability: Inter-individual variability (IIV) was estimated for the effect of concomitant STP on CL_{FEN}, CL_{FEN}, and CL_{NFEN}. No off-diagonal covariance terms were estimated. These parameters were implemented with an exponential model.

Residual Variability: Residual unexplained variability (RUV) was modelled for both FEN and NFEN using additive plus proportionate error models.

Covariates in final model: The effect of STP on CL_{FEN} was included in the final model. The effect of weight was included on all CL and V terms (see the "Allometric Scaling" heading above).

The parameter estimates for the final model (rfinal-ctl.txt) are presented in the table below.

Table 1: Parameter Estimates for the Final Population PK Model (rfinal-ctl.txt)

Parameter[a]	Final estimate	%SEE	Shrinkage
CL_{FEN} (L/hr/70kg)	25.1	3.02	
Vc_{FEN} (L/70kg)	290	4.07	
CLd_{FEN} (L/hr/70kg)	130	5.28	
Vp_{FEN} (L/70kg)	500	—	
CL_{NFEN} (L/hr/70kg)	55.1	3.48	
Vc_{NFEN} (L/70kg)	829	4.09	
CLd_{NFEN} (L/hr/70kg)	49.5	14.4	
Vp_{NFEN} (L/70kg)	500	—	
Ka_{FEN} (hr^{-1})	0.690	1.97	
Ka_{NFEN} (hr^{-1})	1.88	7.93	
STP-CL_{FEN}	0.458	8.56	
$\omega^2_{CL, FEN}$	0.122 (34.9 %CV)	9.84	16.2
$\omega^2_{CL, NFEN}$	0.263 (51.3% CV)	6.96	5.12
$\omega^2_{STP-CL, FEN}$	0.460 (67.8% CV)	20.8	50.8
$\sigma^2_{FEN, Proportional}$	0.00359 (5.99 %CV)	8.11	4.91
$\sigma^2_{FEN, Additive}$	63.3 (7.96 ng/mL)	1.74	6.74
$\sigma^2_{NFEN, Proportional}$	0.00344 (5.87 %CV)	3.20	4.91
$\sigma^2_{NFEN, Additive}$	1.53 (1.24 ng/mL)	2.46	6.74

Source: sequence 0002, icpd-00445-01.pdf, page 69 of 168

Key diagnostic figures are presented in **Figure 3** and **Figure 4**.

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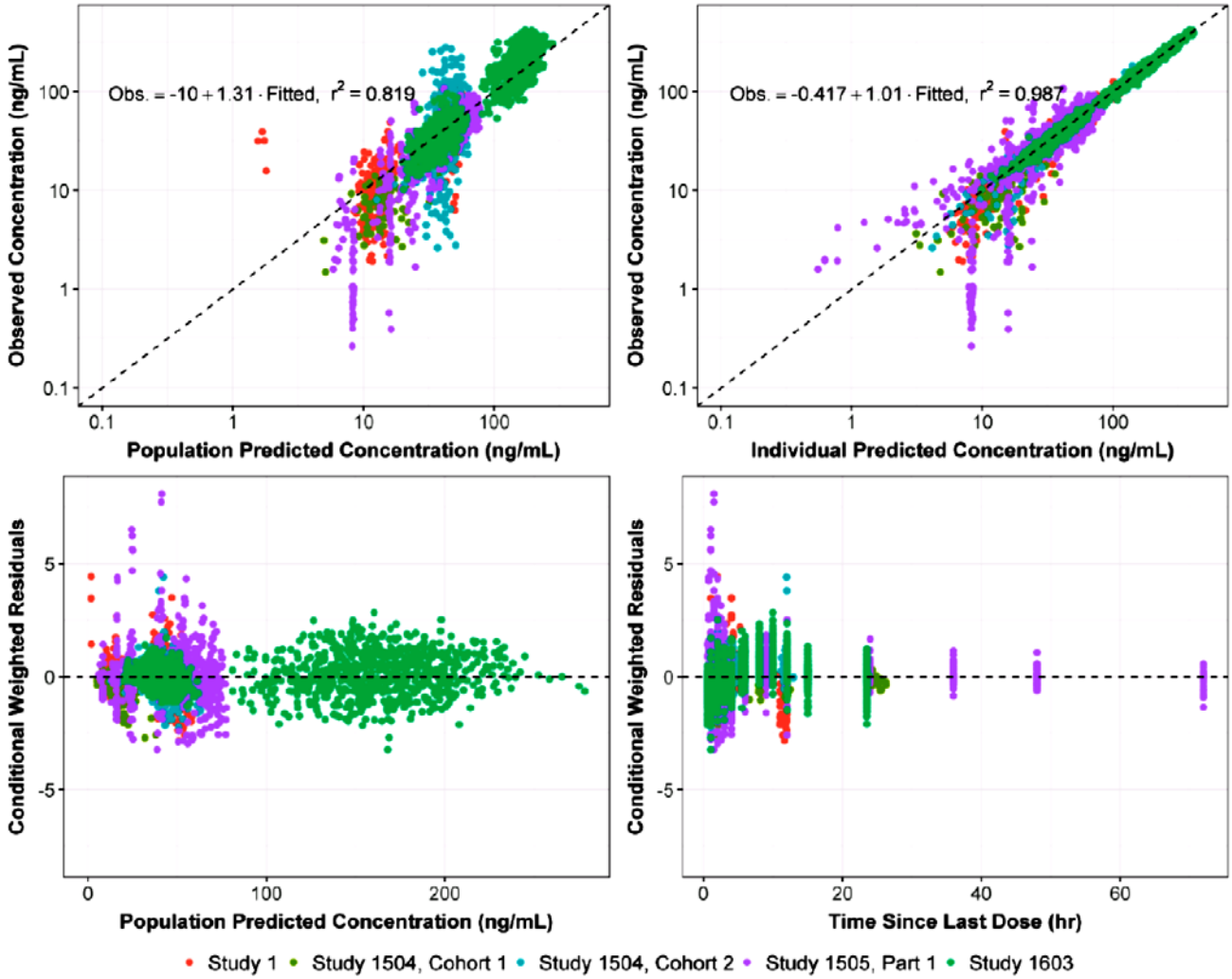
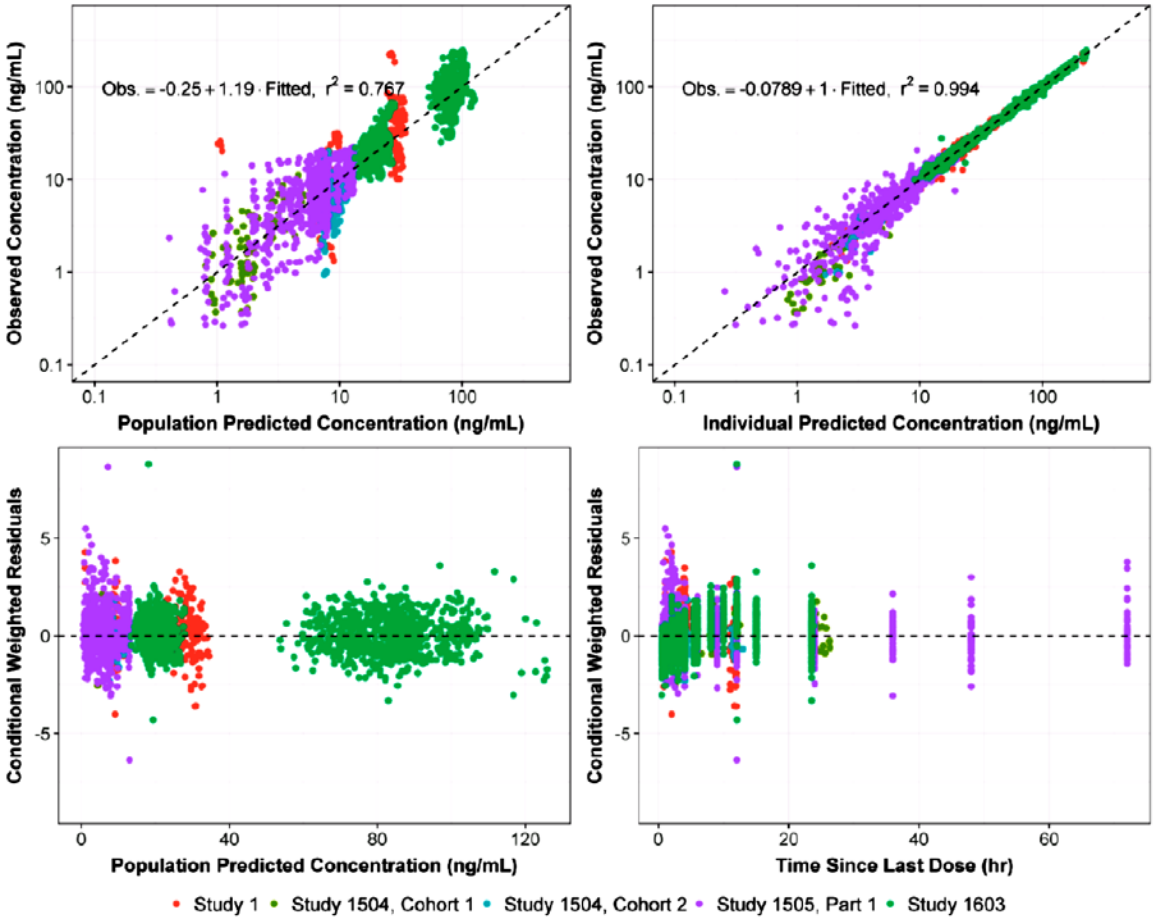
Figure 3: Diagnostic Plots for the Final PPK Model – <u>Fenfluramine</u> Analyte



Source: sequence 0002, icpd-00445-01.pdf, page 70 of 168

Reference ID: 4630085

Figure 4: Diagnostic Plots for the Final PPK Model – <u>Norfenfluramine</u> Analyte

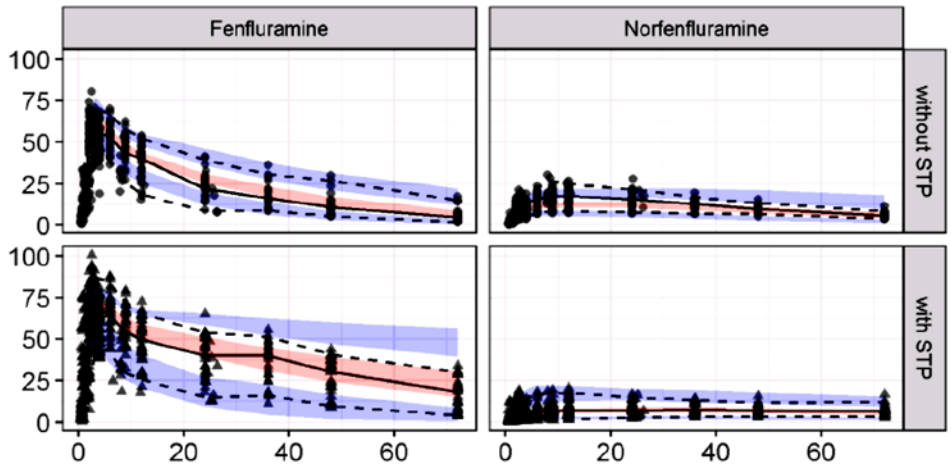


Source: sequence 0002, module 5335, icpd-00445-01.pdf, page 71 of 168

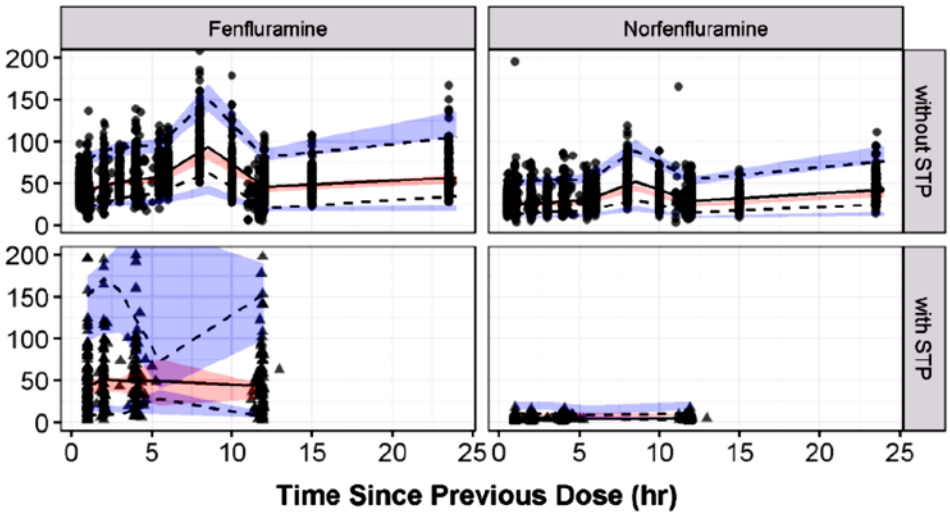
Reference ID: 4630085

Figure 5: Prediction-Corrected Visual Predictive Check for Plots for Fenfluramine and Norfenfluramine Using the Final PPK Model (rfinal.txt)

Single Administration



Multiple Administration



Black symbols 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: sequence 0002, module 5335, icpd-00445-01.pdf, page 73 to 75 of 168

The Applicant computed the individual post-hoc parameter estimates for fenfluramine as well as norfenfluramine and grouped the results by study and dose (see the table below).

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Table 2: Fenfluramine PK Parameters Obtained from Population PK Model

	N	AUC_{0-24} (ng•h/mL)[a]	CL/F (L/h)[b]	C_{max} (ng/mL)[a]	C_{min} (ng/mL)[a]	Vss/F (L/70 kg)[b]
Study 1505 (single dose)						
ZX008 Alone	20	851 (25.3)	31.9 (46.5)	60.7 (13.4)	—	799 (20.1)
ZX008 plus STP/CLB/VPA	25	1180 (21.9)	13.9 (64.7)	71.1 (10.2)	—	794 (19.2)
Study 1504, Cohort 1 (single dose)						
0.2 mg/kg (no STP)	3	244 (1.74)	17.0 (110)	19.5 (8.42)	—	354 (112)
0.2 mg/kg (plus STP)	10	310 (15.6)	6.59 (60.5)	20.2 (4.83)	—	271 (39.8)
0.4 mg/kg (no STP)	5	416 (16.3)	22.4 (64.6)	37.4 (4.63)	—	354 (52.3)
Study 1603 (steady state)						
15 mg BID	59	966 (26.2)	27.5 (24.4)	46.7 (23.9)	33.5 (29.3)	852 (15.8)
60 mg BID	60	5050 (34.1)	21.5 (31.9)	238 (31.3)	181 (37.8)	826 (17.4)
Study 1 (steady state)						
0.2 mg/kg/day	39	375 (32.9)	14.0 (36.5)	18.5 (29.2)	12.6 (38.1)	345 (49.9)
0.8 mg/kg/day	36	1390 (43.5)	12.3 (50.2)	68.0 (40.7)	46.9 (48.5)	331 (42.2)
Study 1504, Cohort 2 (steady state)						
0.2 mg/kg/day	65	999 (85.4)	5.92 (81.8)	48.1 (75.1)	35.5 (98.1)	334 (52.1)

a. AUC_{0-24}, C_{max}, and C_{min} calculated for first 24 hours after a single dose (Study 1505 and Study 1504, Cohort 1) or at steady-state (Study 1 and Study 1504, Cohort 2).

b. CL and V_{ss} calculated from individual post-hoc parameter estimates.

Source: sequence 0002, module 5335, icpd-00445-01.pdf, page 78 of 168

Table 3: Norfenfluramine PK Parameters Obtained from Population PK Model

	N	AUC_{0-24} (ng•h/mL)[a]	CL/F (L/h/70 kg)[b]	C_{max} (ng/mL)[a]	C_{min} (ng/mL)[a]	Vss/F (L/70 kg)[b]
Study 1505 (single dose)						
ZX008 Alone	20	305 (32.0)	54.9 (27.2)	12.1 (59.6)	—	1340 (20.1)
ZX008 plus STP/CLB/VPA	25	168 (49.0)	54.8 (26.7)	9.48 (60.0)	—	1340 (19.2)
Study 1504, Cohort 1 (single dose)						
0.2 mg/kg (no STP)	3	76.9 (25.4)	23.5 (51.2)	2.63 (42.1)	—	595 (112)
0.2 mg/kg (plus STP)	10	39.1 (38.8)	29.2 (29.1)	3.64 (81.2)	—	456 (39.8)
0.4 mg/kg (no STP)	5	189 (14.9)	20.9 (41.6)	10.7 (27.8)	—	595 (52.3)
Study 1603 (steady state)						
15 mg BID	59	565 (34.4)	53.1 (34.4)	24.1 (33.7)	22. 6(35.4)	1430 (15.8)
60 mg BID	60	2480 (42.6)	48.3 (42.6)	106 (41.7)	100 (44.0)	1390 (17.4)
Study 1 (steady state)						
0.2 mg/kg/day	39	220 (55.5)	27.7 (50.5)	9.60 (52.8)	8.56 (59.8)	581 (49.9)
0.8 mg/kg/day	36	872 (78.7)	22.6 (78.7)	37.8 (49.9)	34.1 (55.6)	557 (42.2)
Study 1504, Cohort 2 (steady state)						
0.2 mg/kg/day	65	135 (44.1)	43.7 (57.0)	5.78 (42.7)	5.42 (46.5)	562 (52.1)

a. AUC_{0-24}, C_{max}, and C_{min} calculated for first 24 hours after a single dose (Study 1505 and Study 1504, Cohort 1) or at steady-state (Study 1 and Study 1504, Cohort 2).

b. CL and V_{ss} calculated from individual post-hoc parameter estimates.

Source: sequence 0002, module 5335, icpd-00445-01.pdf, page 79 of 168

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[*Reviewer comment: The VPC plots in* ***Figure 5.*** *demonstrate that the PPK profiles are generally represented well for fenfluramine and norfenfluramine after single and multiple administrations.*

The Applicant points out that residual unexplained variability is relatively high (7.8 ng/mL). The Applicant states that "the exact timing of the ZX008 dose given on the day preceding the PK sampling day …. A general lack of details in the database around the timing of concomitant medications in the Phase 3 studies" (icpd-00445-01.pdf, page 82 of 162) may be factors that contribute to high residual unexplained variability. OCP considers this to be a plausible explanation.

The fenfluramine post-hoc parameter estimates for V_{ss} differ in patients vs. healthy volunteers (see ***Table 2****). The geometric mean fenfluramine V_{ss}/F estimates lower in patients with DS:*

- *Study 1504 Cohort 1: 271 – 345 L/70 kg,*
- *Study 1: 331 – 345 L/70 kg,*
- *Study 1504 Cohort 2: 334 L/70 kg,*

, and geometric mean fenfluramine Vss/F estimates are higher in healthy volunteers studies:

- *Study 1505: 794 – 799 L/70 kg,*
- *Study 1603: 826 - 852 L/70 kg.*

A similar trend was apparent for the norfenfluramine post-hoc parameter estimates of V_{ss}/F (see ***Table 3****). The geometric mean norfenfluramine V_{ss}/F estimates are lower in patients with DS:*

- *Study 1504 Cohort 1: 456 - 595 L/70 kg,*
- *Study 1: 557 - 581 L/70 kg,*
- *1504 Cohort 2: 562 L/70 kg,*

, and geometric mean norfenfluramine Vss/F estimates are higher in healthy volunteers studies:

- *Study 1505: 1340 L/70 kg,*
- *Study 1603: 1390 - 1430 L/70 kg.*

It is not clear why the apparent volume of distribution at steady-state for fenfluramine as well as norfenfluramine is 2-3 times higher in Study 1505/Study 1603 versus Study 1504 Cohort 1/Study 1/Study 1504 Cohort 2. One factor that may affect the be relevant is that the healthy volunteer studies generally more frequent PK sampling (10-11 samples over 12 hours) compared to the PK sampling in studies with DS patients (4 samples over 12 hours).

The reviewer generated additional diagnostic plots to look more closely at the PK data from Study 1504 Cohort 2, the study which provided the data used to estimate the STP interaction term (see ***Figure 6*** *and* ***Figure 7****).*

Reference ID: 4630085

Figure 6: Diagnostic Plot of Conditional Weighted Residual Versus Time Since Last Dose for Final PPK Model for Study 1504 Cohort 2

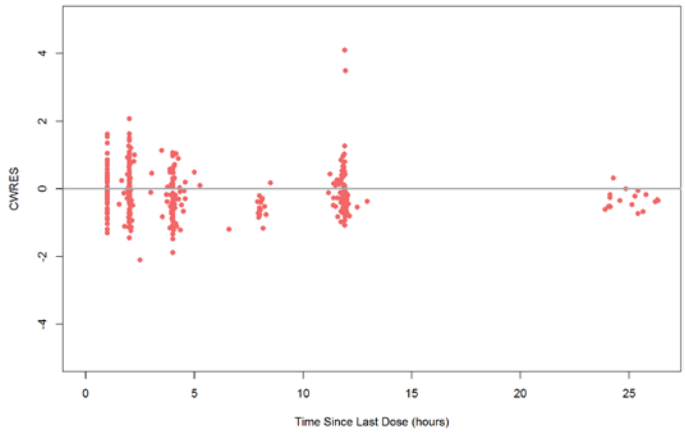
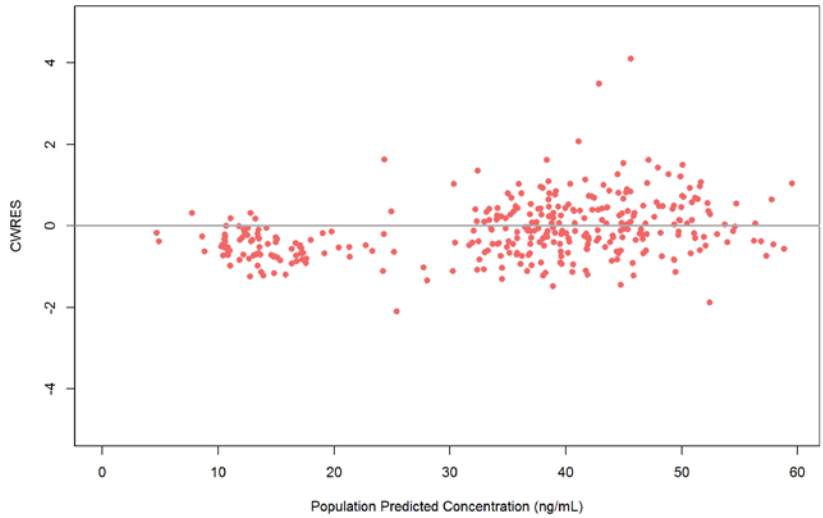


Figure 7: Diagnostic Plot of Conditional Weighted Residual Versus Population Predicted Concentration for Final PPK Model for Study 1504 Cohort 2



The diagnostic plots of Study 1504 Cohort 2 do not show signs of clear bias with respect to concentration magnitude nor time after administration.

Overall, the Applicant's PPK model appears to adequately characterize the PK profile.]

Key diagnostic plots are presented in **Figure 3** and **Figure 4**.

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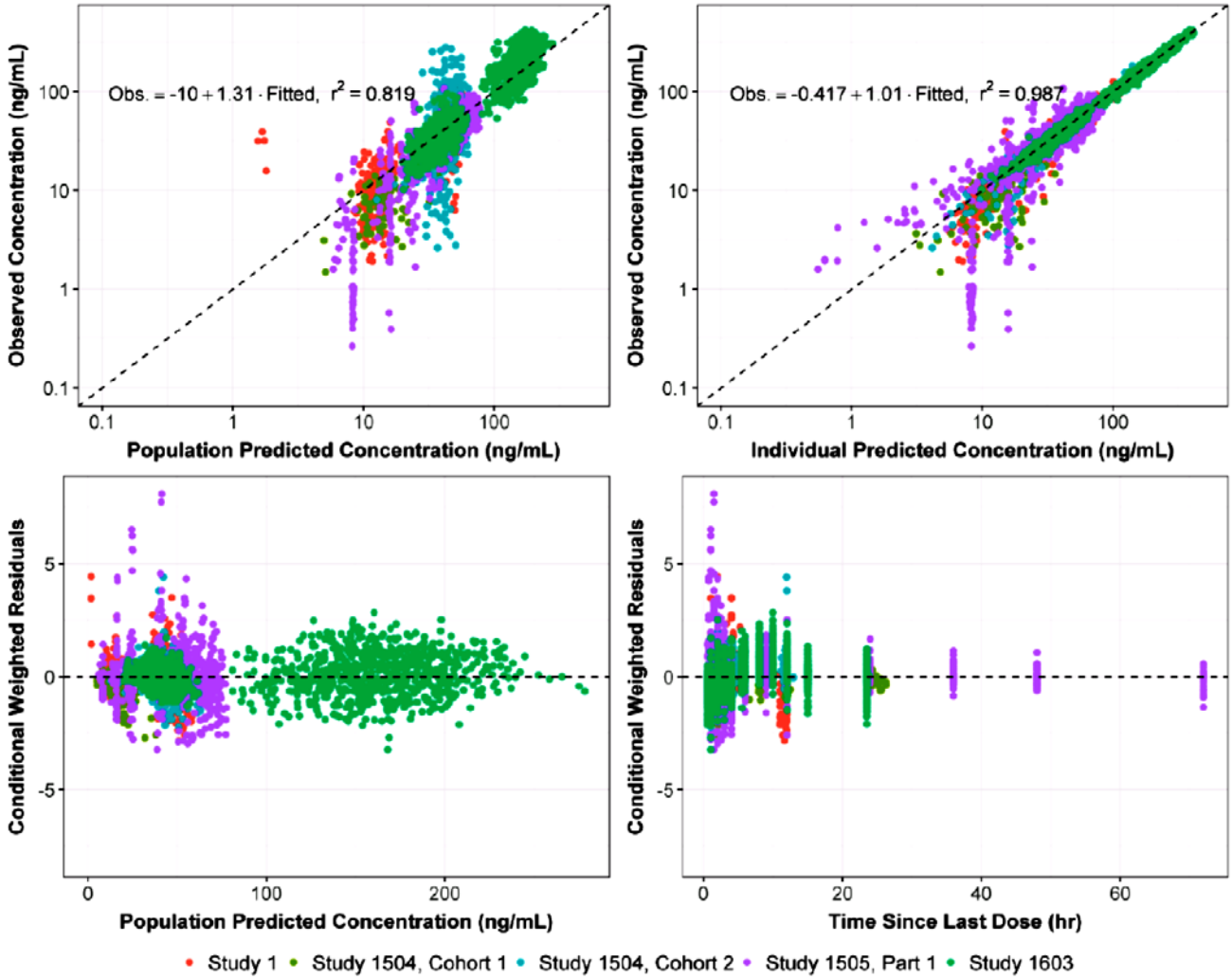
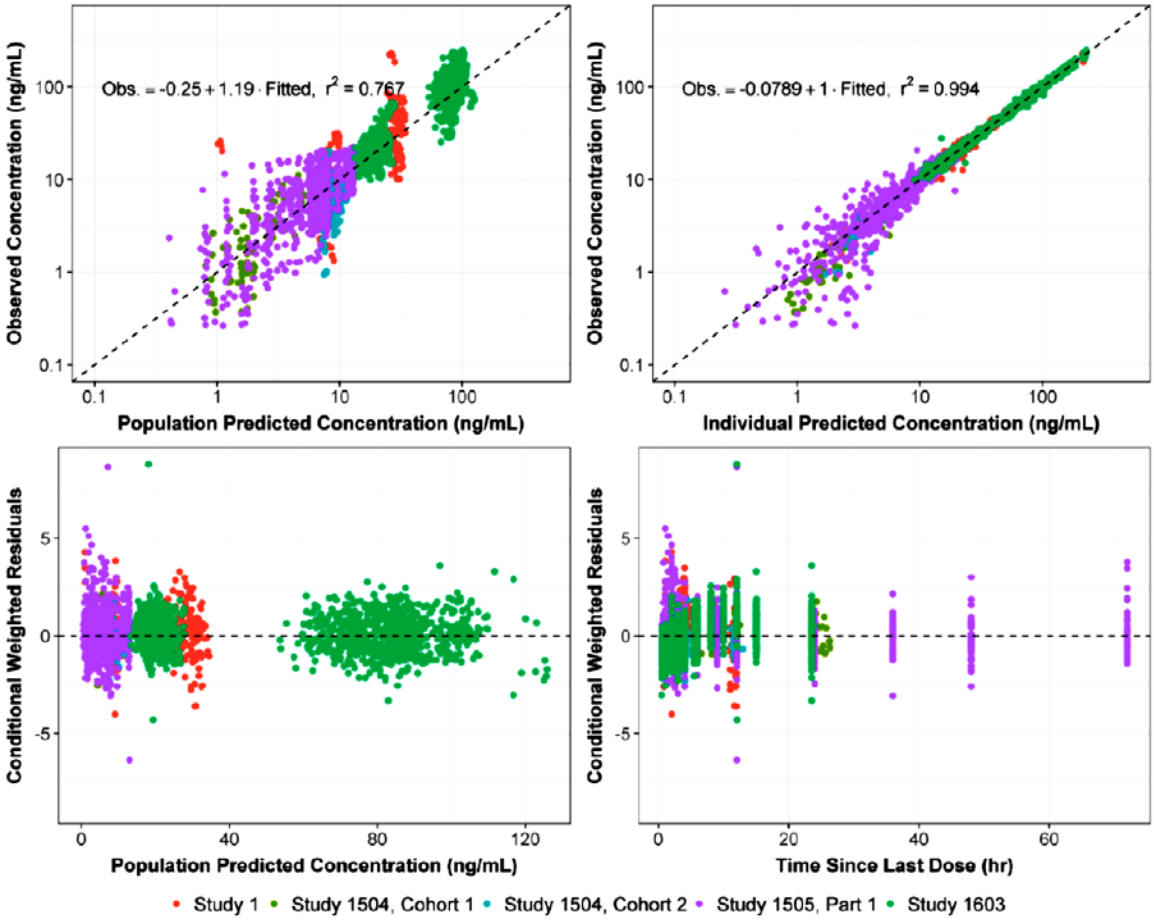
Figure 3: Diagnostic Plots for the Final PPK Model – Fenfluramine Analyte



Source: sequence 0002, icpd-00445-01.pdf, page 70 of 168

Reference ID: 4630085

Figure 4: Diagnostic Plots for the Final PPK Model – <u>Norfenfluramine</u> Analyte

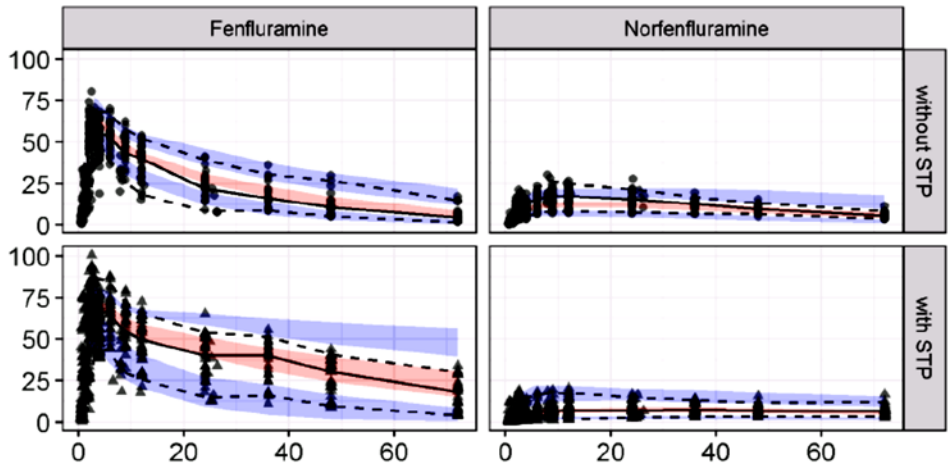


Source: sequence 0002, module 5335, icpd-00445-01.pdf, page 71 of 168

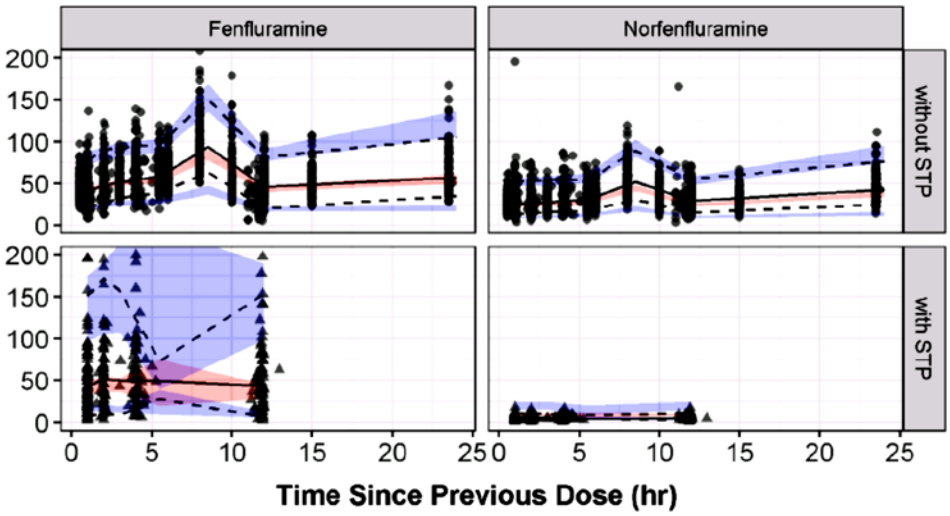
Reference ID: 4630085

Figure 5: Prediction-Corrected Visual Predictive Check for Plots for Fenfluramine and Norfenfluramine Using the Final PPK Model (rfinal.txt)

Single Administration



Multiple Administration



Black symbols 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: sequence 0002, module 5335, icpd-00445-01.pdf, page 73 to 75 of 168

The Applicant computed the individual post-hoc parameter estimates for fenfluramine as well as norfenfluramine and grouped the results by study and dose (see the table below).

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Table 2: Fenfluramine PK Parameters Obtained from Population PK Model

	N	AUC_{0-24} (ng•h/mL)[a]	CL/F (L/h)[b]	C_{max} (ng/mL)[a]	C_{min} (ng/mL)[a]	Vss/F (L/70 kg)[b]
Study 1505 (single dose)						
ZX008 Alone	20	851 (25.3)	31.9 (46.5)	60.7 (13.4)	—	799 (20.1)
ZX008 plus STP/CLB/VPA	25	1180 (21.9)	13.9 (64.7)	71.1 (10.2)	—	794 (19.2)
Study 1504, Cohort 1 (single dose)						
0.2 mg/kg (no STP)	3	244 (1.74)	17.0 (110)	19.5 (8.42)	—	354 (112)
0.2 mg/kg (plus STP)	10	310 (15.6)	6.59 (60.5)	20.2 (4.83)	—	271 (39.8)
0.4 mg/kg (no STP)	5	416 (16.3)	22.4 (64.6)	37.4 (4.63)	—	354 (52.3)
Study 1603 (steady state)						
15 mg BID	59	966 (26.2)	27.5 (24.4)	46.7 (23.9)	33.5 (29.3)	852 (15.8)
60 mg BID	60	5050 (34.1)	21.5 (31.9)	238 (31.3)	181 (37.8)	826 (17.4)
Study 1 (steady state)						
0.2 mg/kg/day	39	375 (32.9)	14.0 (36.5)	18.5 (29.2)	12.6 (38.1)	345 (49.9)
0.8 mg/kg/day	36	1390 (43.5)	12.3 (50.2)	68.0 (40.7)	46.9 (48.5)	331 (42.2)
Study 1504, Cohort 2 (steady state)						
0.2 mg/kg/day	65	999 (85.4)	5.92 (81.8)	48.1 (75.1)	35.5 (98.1)	334 (52.1)

a. AUC_{0-24}, C_{max}, and C_{min} calculated for first 24 hours after a single dose (Study 1505 and Study 1504, Cohort 1) or at steady-state (Study 1 and Study 1504, Cohort 2).

b. CL and V_{ss} calculated from individual post-hoc parameter estimates.

Source: sequence 0002, module 5335, icpd-00445-01.pdf, page 78 of 168

Table 3: Norfenfluramine PK Parameters Obtained from Population PK Model

	N	AUC_{0-24} (ng•h/mL)[a]	CL/F (L/h/70 kg)[b]	C_{max} (ng/mL)[a]	C_{min} (ng/mL)[a]	Vss/F (L/70 kg)[b]
Study 1505 (single dose)						
ZX008 Alone	20	305 (32.0)	54.9 (27.2)	12.1 (59.6)	—	1340 (20.1)
ZX008 plus STP/CLB/VPA	25	168 (49.0)	54.8 (26.7)	9.48 (60.0)	—	1340 (19.2)
Study 1504, Cohort 1 (single dose)						
0.2 mg/kg (no STP)	3	76.9 (25.4)	23.5 (51.2)	2.63 (42.1)	—	595 (112)
0.2 mg/kg (plus STP)	10	39.1 (38.8)	29.2 (29.1)	3.64 (81.2)	—	456 (39.8)
0.4 mg/kg (no STP)	5	189 (14.9)	20.9 (41.6)	10.7 (27.8)	—	595 (52.3)
Study 1603 (steady state)						
15 mg BID	59	565 (34.4)	53.1 (34.4)	24.1 (33.7)	22. 6(35.4)	1430 (15.8)
60 mg BID	60	2480 (42.6)	48.3 (42.6)	106 (41.7)	100 (44.0)	1390 (17.4)
Study 1 (steady state)						
0.2 mg/kg/day	39	220 (55.5)	27.7 (50.5)	9.60 (52.8)	8.56 (59.8)	581 (49.9)
0.8 mg/kg/day	36	872 (78.7)	22.6 (78.7)	37.8 (49.9)	34.1 (55.6)	557 (42.2)
Study 1504, Cohort 2 (steady state)						
0.2 mg/kg/day	65	135 (44.1)	43.7 (57.0)	5.78 (42.7)	5.42 (46.5)	562 (52.1)

a. AUC_{0-24}, C_{max}, and C_{min} calculated for first 24 hours after a single dose (Study 1505 and Study 1504, Cohort 1) or at steady-state (Study 1 and Study 1504, Cohort 2).

b. CL and V_{ss} calculated from individual post-hoc parameter estimates.

Source: sequence 0002, module 5335, icpd-00445-01.pdf, page 79 of 168

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[*Reviewer comment: The VPC plots in **Figure 5** demonstrate that the PPK profiles are generally represented well for fenfluramine and norfenfluramine after single and multiple administrations.*

The Applicant points out that residual unexplained variability is relatively high (7.8 ng/mL). The Applicant states that "the exact timing of the ZX008 dose given on the day preceding the PK sampling day …. A general lack of details in the database around the timing of concomitant medications in the Phase 3 studies" (icpd-00445-01.pdf, page 82 of 162) may be factors that contribute to high residual unexplained variability. OCP considers this to be a plausible explanation.

*The fenfluramine post-hoc parameter estimates for V_{ss} differ in patients vs. healthy volunteers (see **Table 2**). The geometric mean fenfluramine V_{ss}/F estimates lower in patients with DS:*

- *Study 1504 Cohort 1: 271 – 345 L/70 kg,*
- *Study 1: 331 – 345 L/70 kg,*
- *Study 1504 Cohort 2: 334 L/70 kg,*

, and geometric mean fenfluramine Vss/F estimates are higher in healthy volunteers studies:

- *Study 1505: 794 – 799 L/70 kg,*
- *Study 1603: 826 - 852 L/70 kg.*

*A similar trend was apparent for the norfenfluramine post-hoc parameter estimates of V_{ss}/F (see **Table 3**). The geometric mean norfenfluramine V_{ss}/F estimates are lower in patients with DS:*

- *Study 1504 Cohort 1: 456 - 595 L/70 kg,*
- *Study 1: 557 - 581 L/70 kg,*
- *1504 Cohort 2: 562 L/70 kg,*

, and geometric mean norfenfluramine Vss/F estimates are higher in healthy volunteers studies:

- *Study 1505: 1340 L/70 kg,*
- *Study 1603: 1390 - 1430 L/70 kg.*

It is not clear why the apparent volume of distribution at steady-state for fenfluramine as well as norfenfluramine is 2-3 times higher in Study 1505/Study 1603 versus Study 1504 Cohort 1/Study 1/Study 1504 Cohort 2. One factor that may affect the be relevant is that the healthy volunteer studies generally more frequent PK sampling (10-11 samples over 12 hours) compared to the PK sampling in studies with DS patients (4 samples over 12 hours).

*The reviewer generated additional diagnostic plots to look more closely at the PK data from Study 1504 Cohort 2, the study which provided the data used to estimate the STP interaction term (**Figure 6** and **Figure 7**).*

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Figure 6: Diagnostic Plot of Conditional Weighted Residual Versus Time Since Last Dose for Final PPK Model for Study 1504 Cohort 2

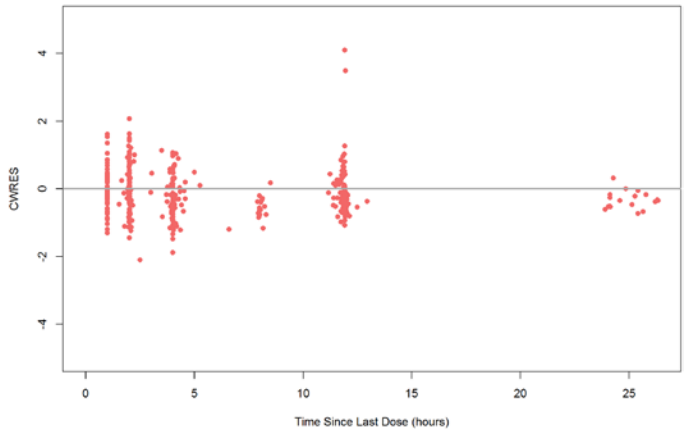
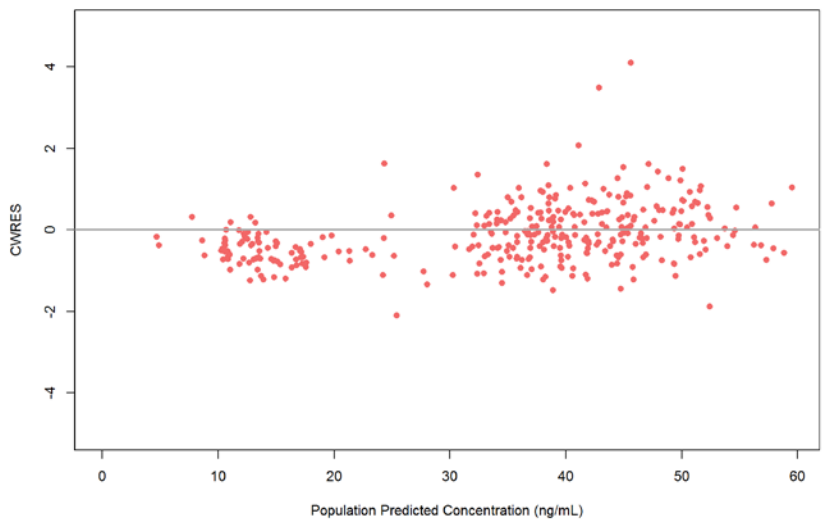


Figure 7: Diagnostic Plot of Conditional Weighted Residual Versus Population Predicted Concentration for Final PPK Model for Study 1504 Cohort 2



The diagnostic plots of Study 1504 Cohort 2 do not show signs of clear bias with respect to concentration magnitude nor time after administration.

Overall, the Applicant's PPK model appears to adequately characterize the PK profile.]

4.3.3 PK Simulations

Report icpd-00445-03.pdf (sequence 0002, module 5353) is titled "*Modelling and Simulation to Support the Development of ZX008 for the Treatment of Patients with Dravet Syndrome*" and describes population PK simulations. This review will focus on the simulation the effect of stiripentol on fenfluramine. The report describes PPK simulations as well as PBPK simulations. This section of the review will only discuss PPK-based simulations.

Methods: For the population PK model-based simulations, the patient demographic factors were used to calculate a population mean value for each PK parameter. A virtual population was selected by randomly

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re-sampling (with replacement) from the n=223 subjects in the pooled dataset of Study 1 and Study 1504 until a virtual population of n=1000 subjects was created. Random interindividual variability was applied to each relevant parameter based the final population PK model estimates.

Virtual subjects received the dosing regimens evaluated in the Phase 3 trials (ZX008 alone at 0.2 and 0.7 mg/kg/d and ZX008 in combination with STP at 0.4 mg/kg/d). Simulations were carried to 360 hours (15 days) to represent steady-state, with twice daily (BID) dosing occurring throughout. The dose of ZX008 administered to each hypothetical patient was calculated using their body weight (the exact mg dose was used for the simulation; no rounding for syringe volume).

PK predictions were made at 15-minute intervals throughout the simulation period. The simulation code allowed for calculation of cumulative AUC estimates for FEN and NFEN at 24-hour intervals. AUC_{0-24} was calculated by subtracting the cumulative AUC at 336 hours from that estimated at 360 hours. Cmax was calculated as the highest simulated concentration over that 24-hour window at steady state. The median, 25th, and 75th percentiles for the concentrations at each time point were then calculated, by analyte and dosing regimen.

Results:

Table 4: PPK-Predicted Fenfluramine and Norfenfluramine exposures With and Without STP Using Phase 3 Dosing Regimens

	N	AUC_{0-24} (ng•h/mL)[a]	C_{max} (ng/mL)[a]	T_{max} (h)	C_{min} (ng/mL)[a]
Fenfluramine					
Study 1					
0.2 mg/kg/day group[a]	39	375 (32.9)	18.5 (29.1)	3.00 (3.00 - 3.50)	12.6 (38.1)
0.8 mg/kg/day group	36	1390 (43.5)	68.0 (40.7)	3.00 (3.00 - 3.50)	46.9 (48.5)
Study 1504 Cohort 2					
0.2 mg/kg/day transition[b]	65	999 (85.4)	48.0 (75.1)	1.50 (1.50 - 2.00)	35.5 (98.1)
0.5 mg/kg/day group[c]	35	3150 (80.3)	146 (71.2)	2.00 (1.50 - 2.00)	116 (91.5)
Norfenfluramine					
Study 1					
0.2 mg/kg/day group	39	220 (55.5)	9.60 (52.8)	4.00 (3.50 - 5.00)	8.56 (59.8)
0.8 mg/kg/day group	36	872 (52.1)	37.8 (49.9)	4.50 (3.50 - 5.00)	34.1 (55.6)
Study 1504 Cohort 2					
0.2 mg/kg/day transition[b]	65	135 (44.1)	5.78 (42.7)	5.00 (4.00 - 5.50)	5.42 (46.5)
0.5 mg/kg/day group[c]	35	357 (42.9)	15.1 (42.4)	5.00 (4.50 - 5.50)	14.5 (43.7)

Values are expressed as geometric mean (%CV) for all parameters except Tmax (which is median, min, and max). Predicted exposures are calculated from individual post-hoc parameter estimates from the population PK model. The transition period refers to subjects who were randomized to placebo during the maintenance phase are transitioned to fenfluramine prior entry to the open-label extension. For the purposes of these PK simulations, the 0.2 mg/kg/day transition scenarios were simulated out to 360 hours after the first administration.

a. 0.2 mg/kg/day group and 0.7 mg/kg/day group had a maximum of 26 mg/day ZX008 without STP.
b. 0.2 mg/kg/day transition had a maximum of 17 mg/day fenfluramine and STP as a concomitant medication during the Transition period of Study 1504 when PK data were obtained.
c. 0.4 mg/kg/day group had a maximum of 17 mg/day and STP as a concomitant medication; the values used for these summary statistics are extrapolated based on PK parameter estimates derived from concentrations drawn during the transition phase.

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Source: sequence 0002, module 5335, icpd-00445-03.pdf, page 55 of 85

Conclusions: Based on the PPK-simulations, the Applicant concludes that a ~130% increase in FEN exposure and ~60% increase in NFEN exposures are likely in patients receiving ZX008 at the dose used in Study 1504 Cohort 2 (0.4 mg/kg/d with a max. of 17 mg/d) with concomitant STP/CLB/VPA compared to a ZX008 dose of 0.7 mg/kg/day with a max. of 26 mg/day without STP.

[*Reviewer comment: The 130% increase in fenfluramine exposures comes from a comparison of the simulated AUC_{0-24} values for 0.4 mg/kg/day arm in Study 1504 Cohort 2 (3150 ng*h/mL) versus the simulated AUC_{0-24} values 0.7 mg/kg/day arm from Study 1 (1390 ng*h/mL); 3150/1390 = 2.266, or ~130% increase. The Applicant intends to provide this comparison of the simulated fenfluramine AUC_{0-24} for each of these two arms of the Phase 3 trials in the label as the description of the stiripentol effect on fenfluramine PK. OCP has concerns about this comparison as well as other aspects of the stiripentol drug interaction assessment.*

One aspect of the stiripentol interaction that concerned OCP is that the stiripentol drug interaction effect measured in the in-vivo drug interaction study 1505 appears differs from both the PPK-based interaction assessment. An IR was sent to the Applicant on May 20th, 2020 (archived in DARRTs on June 3rd, 2020) which included questions regarding the STP drug interaction assessment. One question in the IR was whether the PPK-based STP interaction assessment is able to replicate the in-vivo STP drug interaction study result. In the IR response received on May 25th, 2020 (sequence 0057), the Applicant provided results of new PPK simulations which were able to approximate the results of the in-vivo drug interaction study 1505. The apparent difference between Study 1505 assessment of the stiripentol DDI effect and the PPK-based stiripentol DDI effect was due to the differing magnitude of the stiripentol effect after a single fenfluramine administration (such as in Study 1505) versus the stiripentol effect while fenfluramine is at steady-state (as was the scenario simulated with the population PK model). OCP agrees with the Applicant that the PPK-based assessment of the STP effect on FEN is the most clinically relevant as it is determined from the intended clinical population and takes into account the chronic administration of both agents.

However, the results of the IR response did not initially explain why the exposure for the 0.4 mg/kg/day fenfluramine HCl dose level, when combined with stiripentol, were higher than expected. Study 1504 Cohort 1 assessed the effect of stiripentol on a single dose of fenfluramine PK. The Applicant conducted PBPK modeling of the PK data from Study 1504 Cohort 1, conducted PBPK-based simulations, and using those simulations, predicted that the 0.4 mg/kg/day fenfluramine HCl dose level would, when combined with stiripentol, produce comparable exposures to 0.7 mg/kg/day fenfluramine HCl without STP (which is the regimen administered in Phase 3 Study 1). However, the PBPK reviewer determined that the PBPK model is inadequate (please refer to the "PBPK Analyses" section of this review for details). As the PBPK model was inadequate, then the PBPK simulations based off that model caused the incorrect dose level to be selected (0.4 mg/kg/day fenfluramine HCl) for use with stiripentol in Phase 3 Study 1504 Cohort 2. Thus, the inadequate PBPK model is the likely cause for why the exposure of 0.4 mg/kg/day fenfluramine HCl, when combined with stiripentol, produces exposure greater than 0.7 mg/kg/day fenfluramine without stiripentol.

The numerous assessments of the STP drug interaction, including the Applicant's IR response, are summarized in the table below.

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Table 5: Summary of Assessments of stiripentol effect on fenfluramine pharmacokinetics

Single Dose or Steady-State	***Study***	***FEN Dose Level for Simulation***	***PPK-Predicted FEN mean AUC_{0-24} (ng*h/mL)***		***% increase in FEN AUC_{0-24} due to STP***	***Source***
			Without STP	***With STP***		
Single dose	*1505 (adult HV)*	*0.7 mg/kg*	***954***	***1260***	***32% higher with STP*** *(1260-954)/954 = 0.3207547*	***1505 CSR*** *Table 11, page 55, of zx008-1505-body.pdf, sequence 0002*
			851	***1180***	***38% higher with STP*** *(1180-851)/851 = 0.386604*	***PPK Report #1*** *Table 9, page 78 of icpd-00445-01.pdf, sequence 0002*
			875.41	***1250***	***42% higher with STP*** *(1250.27-75.41)/875.41 = 0.4282108*	***IR Response*** *Table 1, page 3, of resp-fda-ir-20200520.pdf, sequence 0057*
	1504 Cohort 1 (pediatric DS patients)	*0.2 mg/kg*	***224***	***310***	***27% higher with STP*** *(310-244)/244 = 0.2704918*	***PPK report #1*** *Table 9, page 78 of icpd-00445-01.pdf, sequence 0002*
Steady-state	*Study 1 (pediatric DS patients) (merging of 1st half of subjects enrolled in Phase 3 study 1501 and 1502)*	*0.2 mg/kg/day*	***375***	***---***	***166% higher with STP*** *(999-375)/375 = 1.664 This is a cross study comparison of Applicant's simulated results.*	***PPK report #1*** *Table 9, page 78 of icpd-00445-01.pdf, sequence 0002*
	Study 1504 Cohort 2 (pediatric DS patients)		***---***	***999***		

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The Applicant proposes labeling language to represent the STP interaction effect on FEN PK in terms of the dosing used in the Phase 3 Studies. The dose level in Study 1504 Cohort 2 is 0.4 mg/kg/day FEN with concomitant STP and the dose level in Study 1 is 0.7 mg/kg/day FEN without concomitant STP. However, the comparison of these two arms may give an inaccurate estimate of the stiripentol effect on fenfluramine PK as the difference in fenfluramine dose level (0.4 mg/kg/day vs 0.7 mg/kg/day) affects the comparison as well as STP use. In order to provide a clear understanding of the magnitude of the STP-mediated drug interaction, the FEN dose should not be a factor affecting the apparent DDI estimate. Please refer to section 4.3.4 for discussion regarding labeling statements for the STP interaction.]

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4.3.4 Label Statements Based on PPK Modeling

This section provides discussion of the label statements which are supported by population pharmacokinetic modeling. OCP's proposed edits are indicated by red-colored text with a strikethrough effect for proposed deletion (e.g. ~~text proposed for deletion~~) and blue-color text with an underline effect for proposed addition (e.g. text proposed for addition).

The final label language will reflect ongoing internal discussions and external discussions with the Applicant that may occur after this review is archived.

12.3 Pharmacokinetics

Specific Populations

> *"Age* (b) (4) *sex, and race* (b) (4) *had no clinically meaningful effect on the pharmacokinetics of fenfluramine."*

[*Reviewer comment: The statement regarding age, sex, and race are supported by the population PK analyses. As dosing is administered on a mg/kg basis, OCP recommends removing* (b) (4).]

12.3 Pharmacokinetics

Drug Interaction Studies

(b) (4)

[*Reviewer comment: Please refer to section 4.3.3 for concerns regarding the conduct of the PPK simulations of the effect of STP on FEN PK.*

Use of simulations from the final population PK model to inform labeling statements regarding the STP interaction are acceptable. Please refer to section 4.3.3 regarding discussion of the PPK-based assessment of STP interaction potential and in-vivo-based assessment of STP interaction potential.

The current label language for the STP effect on FEN PK describes a comparison of two different FEN dose levels (0.4 mg/kg/day FEN + STP vs 0.7 mg/kg/day FEN without STP). As such, the difference in FEN dose level on FEN PK is confounded with the effect of STP on FEN PK. If PK simulations are to be used for informing STP interaction label statements, then OCP recommends use of a PK simulation scenario where the FEN dose level is not a factor affecting the resulting drug interaction estimate. The available simulated PK information provides an estimate of the STP effect on steady-state FEN PK at the 0.2 mg/kg/day. OCP proposes adding the following label statements based on the simulated PK data presented in ***Table 5*** *:*

a) *STP is expected to increase FEN $AUC_{0\text{-}24}$ by 166% while FEN is at steady-state.*

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b) STP is expected to increase FEN AUC_{0-24} by 42% a single FEN administration.

.]

4.3 Exposure-Response Analyses

Report icpd-00445-04.pdf was submitted under sequence 0002 and is titled "*Exposure-Response Analyses to Support the Development of ZX008 for the Treatment of Patients with Dravet Syndrome*". The Applicant conducted exposure-response analyses for efficacy and safety based on data collected from Phase 3 Study 1 (first 119 subjects from "twin" Phase 3 studies ZX008-1501 and ZX008-1502 combined) and Phase 3 Study 1504 Cohort 2. Only efficacy and safety data collected during the Titration and Maintenance periods were used.

Data

The exposure-response analyses utilized PK, efficacy, and safety data from Phase 3 Study 1 and Phase 3 Study 1504 Cohort 2. Information regarding Phase 3 "Study 1" can be found in section 4.3.1. This section provides details that are relevant to exposure-response analyses and not found in section 4.3.1.

Subjects in a placebo arm during the double-blind period were included in the analyses with PK exposure value set to zero.

Study 1 (Phase 3): There were n=115 subjects in Study 1 provided PK, efficacy, and safety data for exposure-response analyses. N=75 were in the treatment arm and n=40 were in the placebo arm.

Study 1504, Cohort 2 (Phase 3): There N=65 DS patients in Study 1504 Cohort 2 that provided PK, efficacy, and safety data for the exposure-response analyses. N=35 were in the treatment arm and n=30 were in the placebo arm during the double-blind period. Note that subjects randomized to placebo in Study 1504 Cohort 2 were transitioned to active drug after the maintenance period, at which time they provided PK measurements. For that reason, while they were included in the PPK analyses and have exposure measures during the transition period at 0.2 mg/kg/day. However, such subjects were in the placebo arm during the titration and maintenance period and as such were assigned exposure metric values of 0 for the exposure-response analyses.

PK Exposure Measures: Steady-state maximum plasma concentration (C_{max}), steady-state minimum plasma concentration (C_{min}), and steady-state daily area under the concentration-time curve (AUC_{0-24}) were computed. For each of these parameters, FEN, NFEN, and the sum of FEN plus NFEN were evaluated, for a total of nine possible exposure metrics of interest.

4.4.2 Exposure Response for Efficacy

Efficacy Endpoint: The percent change in convulsive seizure frequency normalized to 28 days during the titration and maintenance period was uses as the efficacy endpoint for exposure-response analyses.

Graphical Screening: The Applicant assembled plots to graphically assess the relationship between exposure and efficacy. If the plots indicated a potential for exposure-response relationships for a given outcome of interest, univariable statistical models were applied by the Applicant to quantify the potential relationships. For continuous endpoints, linear, log-linear, or non-linear regression techniques were used, as indicated by the exploratory graphical analyses. For categorical outcomes, analysis of variance

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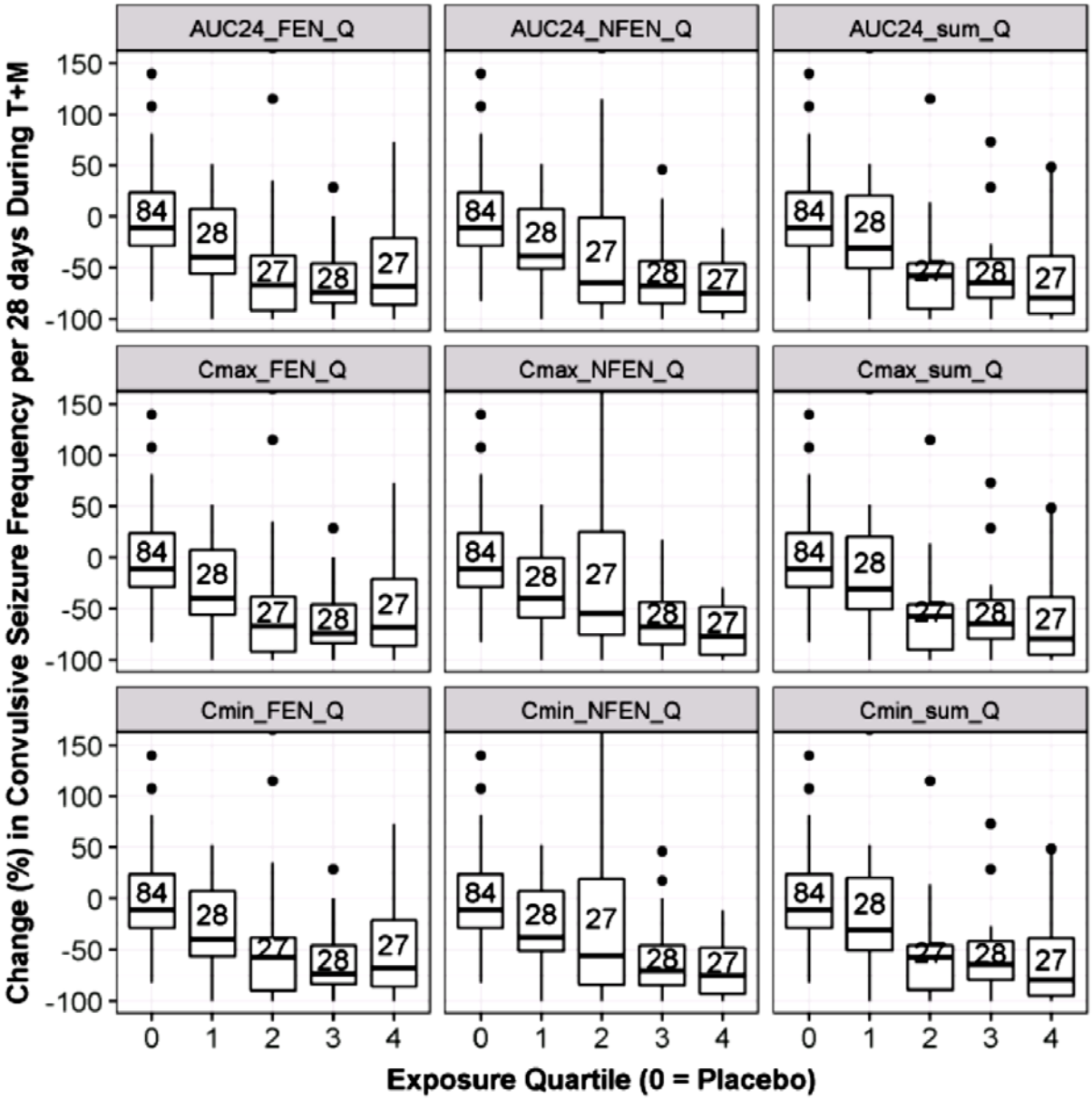
(ANOVA) models were applied. The figure below is an example of such a plot and lead to the Applicant pursuing analyses to characterize the relationship between fenfluramine exposure and efficacy.

Figure 8: Box plot of distribution of the percent change in convulsive seizure frequency per 28 days (stratified by exposure quartile)



Data for one subject who received placebo and had a percent change of +435% and two subjects receiving 0.2 mg/kg/day who had percent changes of 198% and 165% are excluded from the above plot for visualization purposes.

Source: sequence 0002, icpd-00445-04.pdf, page 32 of 63

Modeling: The graphical screening indicated that higher PK exposure was associated with improvements in seizure frequency. Based on the graphical screening, the Applicant determined that a sigmoidal maximum effect (Emax) model best described the relationship between exposure and efficacy. While all exposure metrics provided a consistent exposure-response relationship, none of the 9 metrics were

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substantially more predictive of efficacy and fenfluramine AUC_{0-24}. The model parameter estimates are found in the table below.

Table 6: Parameter Estimates for Emax Model Relating 9 Exposure Metrics to Percent Change from Baseline in Convulsive Seizure Frequency per 28 Days During Titration and Maintenance Period

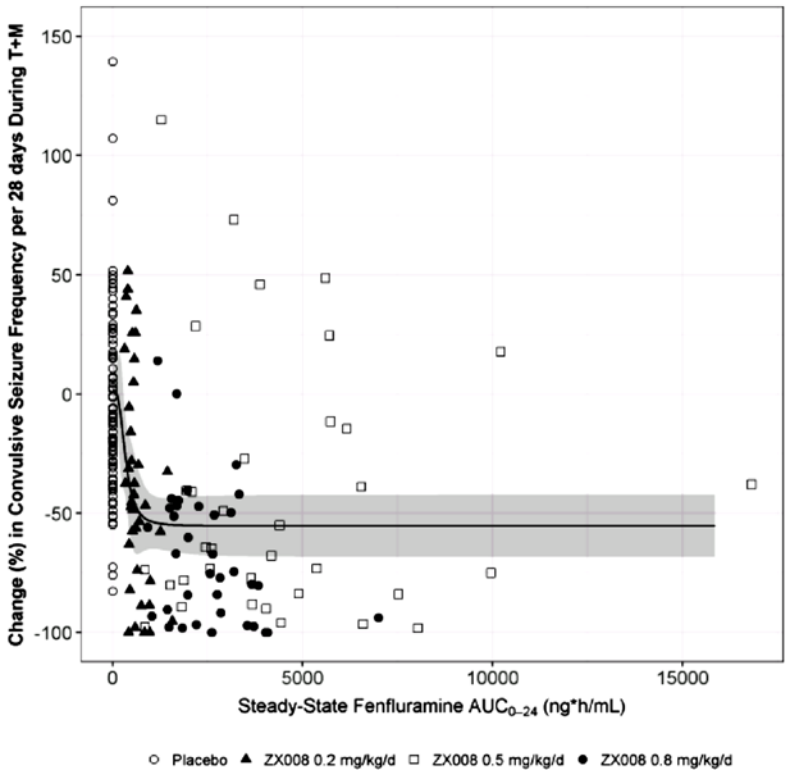
Variable	Analyte	E_0	EC_{50}	E_{max}[a]	Hill	AIC	r^2
Steady-State AUC_{0-24} (ng•h/mL)	Fenfluramine	1.56	342	-57.0	3.09	2126.7	0.410
	Norfenfluramine	0.804	309	-80.0	1.36	2122.9	0.429
	Sum (FEN + NFEN)	1.58	562	-58.2	2.44	2126.3	0.412
Steady-State C_{max} (ng/mL)	Fenfluramine	1.49	17.5	-57.1	3.21	2126.4	0.411
	Norfenfluramine	0.802	13.4	-80.0	1.38	2122.9	0.429
	Sum (FEN + NFEN)	1.57	26.8	-57.8	2.74	2126.2	0.413
Steady-State C_{min} (ng/mL)	Fenfluramine	1.55	11.0	-57.3	2.47	2127.3	0.407
	Norfenfluramine	0.803	12.2	-80.0	1.32	2123.0	0.429
	Sum (FEN + NFEN)	1.57	19.5	-58.7	2.12	2126.6	0.410

*Parameter units are as follows: E_0 and E_{max} are in units of the dependent variable (percent change in seizure frequency per 28 days during T+M), EC_{50} is in the units of the independent variable (ng*h/mL or ng/mL), and the Hill coefficient does not have units. AIC is a measure of goodness of fit (lower values indicate better fit). The r^2 is the correlation between observed and predicted percent change in convulsive seizure frequency per 28 days during titration and maintenance. All E_{max} values are negative indicating that the effect of FEN is to reduce convulsive seizure frequency.*

Source: sequence 0002, icpd-00445-04.pdf, page 34 of 63

The predictive performance of the model is presented in the figure below.

Figure 9: Scatterplot of percent change in convulsive seizure frequency per 28 days During Titration and Maintenance Period versus steady-state fenfluramine AUC_{0-24} with fit of E_{max} model overlaid



Data for one subject who received placebo and had a percent change of +435% and two subjects receiving 0.2 mg/kg/day who had percent changes of 198% and 165% are excluded from the above plot for visualization purposes.

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Points are observations, solid line and shaded region represent the mean (90% confidence interval) predicted values from the E_{max} model.

Source: sequence 0002, icpd-00445-04.pdf, page 35 of 63

Conclusion: The Applicant concluded that subjects with higher exposure are more likely to have a reduction in convulsive seizure frequency over 28 days. Applicant points out that a significant number of subjects who received the 0.2 mg/kg/day dose in Study 1 had substantial seizure reduction (including seizure freedom). As such, the Applicant believes this observation supports the proposed approach to have subjects started at the 0.2 mg/kg/day dose and be titrated to the maximum dose based on individual response.

[*Reviewer comment: The r^2 is low (~0.4) for all exposure metrics. This may be due the subjects that the Applicant mentioned who were in the 0.2 mg/kg/day arm, had low exposure, yet had substantial reduction from baselines seizure rate including seizure freedom (-100% change from baseline convulsive seizure frequency). Concomitant medication use is likely to be a covariate on change from baseline seizure use. However, the available data may only provide a limited understanding of the contribution of concomitant medications towards efficacy is. For example, 100% of subjects in Study 1504 Cohort 2 received at least 1 concomitant anti-epileptic drug and 99.2% of subjects in Study 1 received at least 1 anti-epileptic drug. In Study 1, 16%, 39.5%, 30.3%, 11.8%, and 1.7% of subjects received 1, 2, 3, 4, and 5 concomitant medications with fenfluramine. In addition, in Study 1504 Cohort 2, 2.3%, 51.7%, 36.8%, and 9.2% of subjects received 2, 3, 4, and 5 concomitant medications with fenfluramine. Finally, the Applicant did not collect PK data for the concomitant medications in Phase 3.*

The reviewer team discovered that the Applicant made retrospective edits efficacy database in Study 1 and Study 1504 Cohort 2 after the database lock. The relevant edits include changes in categorization of seizure types and determination of "no seizure" days. When the retrospective edits were un-applied, then 8.6% and 9.2% of the total seizure frequency data in Study 1 and Study 1504-c2, respectively, were reverted to the pre-edited state. In the resulting "revised miTT", 4 patients (two from each study) no longer met the randomization criterion of 6 convulsive seizures during the baseline period and were completely excluded from the analyses. The medical officer has determined, with concurrence from the biostatistics reviewer, that fenfluramine remains superior to placebo in the revised miTT dataset as was the case for the retrospectively-edited miTT dataset. As such, the exposure-response model for efficacy, which was built using the data edited after database lock, is expected to represent the pre-edited dataset. Please refer to the medical officer's review for details.

*The model estimates the EC_{50} of the seizure reduction to be at fenfluramine AUC_{0-24} of 342 ng*h/mL. This is comparable to the predicted AUC_{0-24} of 375 ng*h/mL for the 0.2 mg/kg/day dose in Study 1. For the 0.7 mg/kg/day dose in Study 1, the predicted AUC_{0-24} of 1390 ng*h/mL is expected to be close to the maximum seizure reduction (**Figure 9**). With concomitant stiripentol, the exposures for the 0.2 mg/kg/day are expected to increase due to stiripentol reducing fenfluramine clearance by ~60%.*

Overall, the Applicant's exposure-response analyses support a relationship between increasing fenfluramine exposure and increased efficacy in terms of % change from baselines convulsive seizure rate.]

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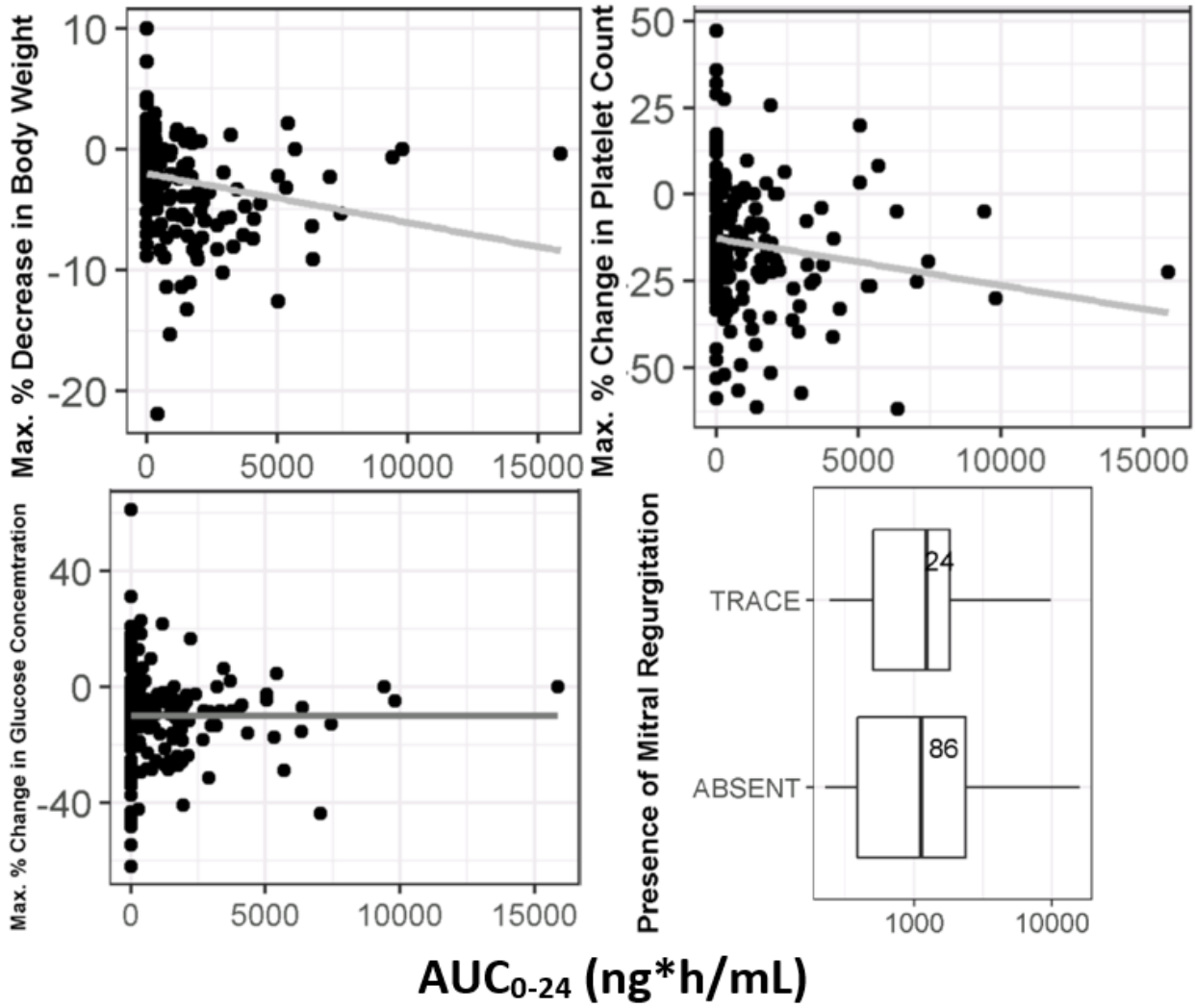
4.4.3 Exposure Response for Safety

Safety Endpoints: platelet counts, blood glucose measurement, body weight, and mitral regurgitation were included in exposure-safety analyses.

Graphical Screening: The Applicant assembled plots to graphically assess the relationship between exposure and safety for each adverse event. Only the fenfluramine $AUC_{0\text{-}24}$ metric will be shown.

Figure 10: Scatterplots of Maximum Percent Change in Blood Glucose Concentration, Platelet Count, Weight Loss, and Mitral Regurgitation versus $AUC_{0\text{-}24}$ during Titration and Maintenance in Phase 3



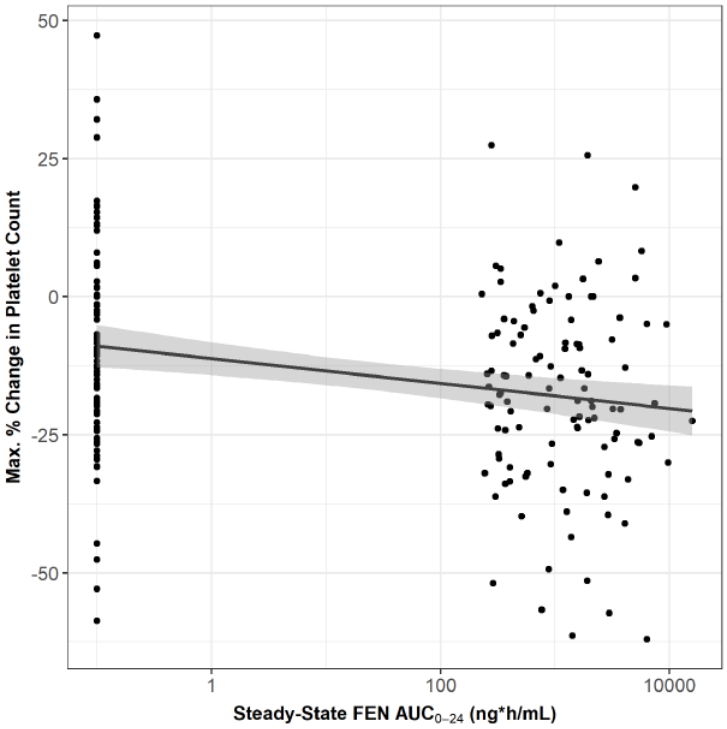
Grey lines represent linear regression smoothers through the data.

Source: sequence 0002, icpd-00445-04.pdf, page 38, 41, 47, and 55 of 63

Modeling: Based on graphical assessments, the Applicant conducted modeling to assess the exposure-response relationship for % change in body weight as well as % change in platelet count. For both adverse events, the Applicant utilized a log-linear regression model. The results of the analyses are found in the figures below.

Reference ID: 4630085

Figure 11: log-linear Regression Model Predictions Overlaid with Observed Maximum Percent Change in <u>Platelet Count</u> During Titration and Maintenance versus Steady-State Fenfluramine AUC_{0-24}



Dark grey line and shaded region represent the fit of the linear regression model to the data (mean and 90% confidence interval).

Source: sequence 0002, icpd-00445-04.pdf, page 44 of 63

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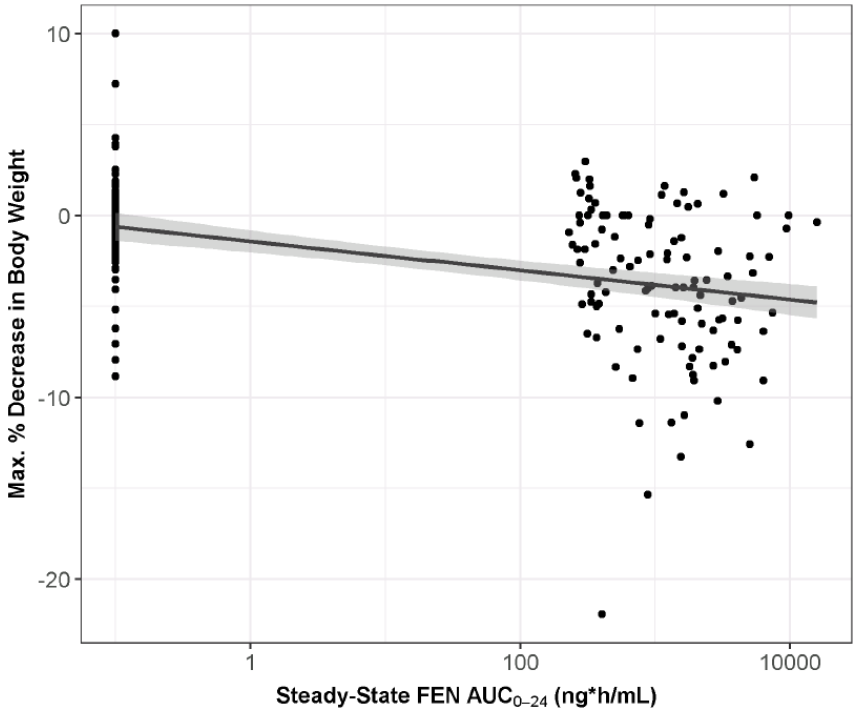
Figure 12: log-linear Regression Model Predictions Overlaid with Observed Maximum Percent Change in <u>Weight Loss</u> During Titration and Maintenance versus Steady-State Fenfluramine AUC_{0-24}



Dark grey line and shaded region represent the fit of the linear regression model to the data (mean and 90% confidence interval).

Source: sequence 0002, icpd-00445-04.pdf, page 50 of 63

<u>Conclusions</u>: The Applicant arrives at the following conclusions:

- Exploratory plots suggest there is no relationship between PK exposure and blood glucose concentrations
- Exploratory plots suggest there is no relationship between PK exposure mitral regurgitation
- Despite the statistically significant relationship between fenfluramine exposure and platelet count, that fenfluramine exposure only explains 6% of the variability in maximum % change in platelet count. Furthermore, the relationship weak (shallow) as only 11% decrease in platelet count is expected at the 90th percentile of fenfluramine AUC_{0-24} (5,047 ng*h/mL) compared to placebo.
- The statistically significant relationship between PK and body weight explains ~17% of the body weight variability. The mean predicted maximum percent decrease in body weight at the 90th percentile of FEN AUC0-24 (5,047 ng*h/mL) is a decrease of only 4% relative to placebo.
- There does not appear to be a relationship between weight loss over time and PK exposure.

[*Reviewer comment: The reviewer agrees that the E-R model for maximum % change in platelet count is shallow. The data do not appear to support the existence of an E-R relationship for blood glucose or mitral valve regurgitation.*

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As this drug was previously used as a weight-loss drug, the exposure-response relationship for weight loss is expected. Please refer to the medical officer's review for details on the weight-loss AE and whether it is to appear in the label.]

4.5 PBPK Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- ICPD-00445-02: Modeling and Simulation Support for the Development of ZX008 in Subjects with Dravet Syndrome: Development of a Physiologically-Based Pharmacokinetic Model System
- ICPD-00445-03: Modelling and Simulation to Support the Development of ZX008 for the Treatment of Patients with Dravet Syndrome

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and PBPK related regulatory history and concluded the current model is inadequate to evaluate,

- the PK of fenfluramine and its metabolite norfenfluramine in healthy subjects, adult and pediatric patients,
- the effect of stiripentol and clobazam on the PK of fenfluramine and its metabolite, norfenfluramine, in healthy subjects.
- the effect of strong inhibitors of CYP1A2, CYP2B6, or CYP2D6 on the PK of fenfluramine and its metabolite, norfenfluramine, in healthy subjects.
- The impact of renal impairment on the PK of fenfluramine and its metabolite, norfenfluramine, in healthy subjects.

PBPK related regulatory history

The interactions between the Sponsor/Applicant and the Agency related to PBPK specific questions are summarized below.

- On October 21, 2016 , the sponsor submitted a type C meeting request to indicate that the sponsor *will develop a physiologically-based PK (PBPK) model system to describe the PK of fenfluramine in Dravet syndrome (DS) patients with and without frequently-used concomitant AEDs (clobazam, valproic acid and stiripentol) that may interact with fenfluramine metabolism*, and ask if Agency agree that *the Sponsor's plan for development and use of a PBPK model is appropriate to support the NDA without any additional clinical PK data in the target population of children and young adults with Dravet syndrome*? In the response, FDA

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indicated that the age-related changes implemented in the pediatric system model should be verified using PK of drugs eliminated by major drug eliminating enzymes and the perpetrator models (stiripentol, clobazam and valproate) need to be verified with the clinical DDI data with probe substrates of relevant enzymes.

- On September 8, 2017, the sponsor submitted an interim PBPK report and Reviewer's guide for comment and advice. In the response, FDA indicated that the clobazam mediated inhibition effect on CYP2D6 was not properly validated and in vitro data supporting stiripentol as a time-dependent inhibitor for CYP1A2 should be included in the submission package. In addition, the sponsor needed to provide justification on how to assign the metabolism pathways for fenfluramine (hepatic and renal clearance).
- On September 24, 2018, the sponsor submitted a type B meeting request to indicate that "*In addition to the Physiologically Based Pharmacokinetic model system previously discussed with the Agency, Zogenix has also developed a Population PK model"* and ask *"if Agency agree that these two model systems combined with the results of clinical studies will be sufficient to support labeling regarding drug-drug interactions as well as the effects of age, sex, race and the need for dose adjustments based on intrinsic or extrinsic factors?"* In the response, FDA indicated that using population PK modeling to support labeling appears reasonable and emphasized 1) the contribution of individual enzymes to the metabolism of fenfluramine and norfenfluramine should be verified against clinical PK study data, 2) the need to describe and justify the systemic (drug-independent parameters) and drug components used in the PBPK analysis, and 3) the management of the dosing of fenfluramine when the drug is co-administered with CYP inducers needs to be discussed. In addition, FDA also indicated that per current practice, PBPK modeling and simulation cannot be used alone to prospectively support dose recommendations in subjects with renal impairment.

  During the meeting, the sponsor asked if the studies of the contribution of individual enzymes to the metabolism of fenfluramine and norfenfluramine could be addressed as post-marketing requirements (PMRs). FDA stated that these studies of individual enzymes may not be required to determine approvability of the NDA submission and, if the NDA were approved, could be addressed as PMRs.
- In the current submission, the Applicant submitted two PBPK reports as mentioned in the executive summary section, to support the PK prediction of fenfluramine and its metabolite norfenfluramine in healthy subjects and adult and pediatric patients, the DDI potential evaluation of fenfluramine with concomitant administration of stiripentol and clobazam or the strong inhibitors of CYP1A2, CYP2B6, or CYP2D6, the evaluation of renal impairment on the PK of fenfluramine and its metabolite, norfenfluramine, and the evaluation of the dose proportionality of fenfluramine in patients with DS.

Reviewer's comments:

The initial adult PBPK model system was developed using Berkeley Madonna (Version 8.3.18) and then transitioned to R statistical software (Version 3.3.1) to conduct simulations. The reviewer

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reviewed the model structure, model equations, model assumption, and model parameter estimation and the following limitations in the Applicant's PBPK analyses are identified.

Parameter estimation and model validation/verification

1. The parameter optimization approach was not provided in the PBPK report. Parameter estimates may be biased because many parameters in the PBPK analysis, such as fenfluramine hepatic intrinsic clearance (CLint1), fenfluramine intestinal intrinsic clearance (CLint_ent), fraction absorbed for fenfluramine (fa), stiripentol mediated competitive inhibition of CYP2D6 (Ki_2D6), CYP1A2 (Ki_1A2), CYP3A4 (Ki_3A4), stiripentol mediated total competitive inhibition in intestine (Ki_ent), norfenfluramine hepatic intrinsic clearance (CLint_m), fraction of norfenfluramine hepatic clearance via CYP metabolism (fm_m), were acquired by optimization, the dedicated DDI study results available for model parameter verification are relatively limited, and there are potential correlations among parameters.
2. There is uncertainty regarding the fmCYP1A2, fmCYP2B6 and fmCYP2D6 values estimated for fenfluramine. The Applicant did not provide the approach or justification with respect to how to estimate these fm values for fenfluramine. There is no in vivo DDI study with strong inhibitors for those pathways currently available for verification of these fm values.
3. Stiripentol mediated time-dependent inhibition (TDI) parameter values (kinact_2B6, KI_2B6, kinact_2D6, KI_2D6 and kinact_1A2, KI_1A2) were obtained from in vitro study (QNT0803). There are no DDI studies between stiripentol and a sensitive CYP2B6, CYP2D6, or CYP1A2 substrate to validate the inhibition effect in vivo. In general, directly extrapolating in vitro TDI parameters does not lead to quantitative prediction of in vivo DDI magnitude. Therefore, the stiripentol mediated-TDI effects on the PK of fenfluramine and its metabolite norfenfluramine cannot be validated.
4. In the summary of clinical pharmacology studies, it was indicated that there were two components involved in the metabolism of fenfluramine by CYP2D6, one with a high affinity and low capacity (Km ~ 40 nM) and another with a low affinity and high capacity (Km ~ 2.5 μM). In the model, a Km value of 1.0 mg/L (4.3 μM) was selected, which is higher than both in vitro values. There is no justification provided for selecting the Km value in the model.
5. In the norfenfluramine final model, the fraction of norfenfluramine hepatic clearance dependent on CYP metabolism was optimized to be 0.45, the fractional contribution of each metabolizing enzyme to its overall metabolism clearance were assumed to be the same as those for fenfluramine. There is no justification provided for this assumption. As norfenfluramine is considered as an active moiety, quantifying and capturing the quantitative change in its exposure in DDI scenarios are important.
6. To account for the bioavailability discrepancy between the simulated results and the observed data in Study 1 (without stiripentol) and study 1504, cohort 2 (with stiripentol and clobazam and valproic acid), a much higher fenfluramine intestinal intrinsic clearance (8 L/hr) was introduced in the model. It appears not reasonable to have such higher intestinal intrinsic

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clearance compared to the hepatic intrinsic clearance (CLint1+CLint2= 3.6 L/hr), given CYP3A4 (fmCYP3A4=0.04) was not the major enzyme involved in the metabolism of fenfluramine.

Model structure

Based on the model structure (Figure 22 in PBPK report ICPD-00445-02) and the value assigned to the Qgut (54.6 L/hr), it appears that the Qgut represents the blood supply to the small intestine[1]. However, in the differential equations to describe the gut tissue fenfluramine concentration or liver concentration change with time, the two blood flow terms (Q_gut + Q_ent) or three blood flow terms (Q_gut + Q_ent +Q_ent) were added up together to represent the total blood flow to the small intestine, respectively. Due to this issue, the prediction might be inaccurate.

Differential equations

1. In vitro study ONT0801 results indicated that metabolism of fenfluramine by CYP2D6 appeared saturable. However, a linear kinetic equation was used to describe the inhibition effect of clobazam (CYP2D6 inhibitor) on CYP2D6 mediated metabolism pathway for fenfluramine.
2. Although unbound stiripentol concentrations were used in the equations to describe stiripentol mediated time-dependent inhibition effect on CYP2B6, CYP2D6 and CYP1A2, however, the total liver concentration of stiripentol and clobazam were used in the equations to describe the stiripentol and clobazam mediated competitive inhibition effect on CYP1A2 (stiripentol), CYP_others (stiripentol) and CYP2D6 (clobazam). The total stiripentol concentration in the enterocyte was used to describe the stiripentol mediated competitive inhibition effect. This may lead to overestimation of stiripentol and clobazam mediated competitive inhibition effect in both liver and intestine.
3. Unbound fraction in the plasma was used to calculate the unbound concentration of stiripentol and fenfluramine in the liver. Since the estimated Kp_liver values for stiripentol (3.60) and fenfluramine (37.0) are much greater than 1, the calculated unbound liver concentration of stiripentol and fenfluramine may be greater than the actual unbound stiripentol and fenfluramine concentration in the liver, leading to biased estimation of the change of liver concentration of fenfluramine with time.
4. A blood flow-rate-in term was missing in the differential equation used to describe the enterocyte fenfluramine concentration change with time.

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[1] Yang J, Jamei M, Yeo KR, Tucker GT, Rostami-Hodjegan A. Prediction of intestinal first-pass drug metabolism. Curr Drug Metab. 2007 Oct;8(7):676-84.

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Conclusions

Overall, there are many gaps in the Applicant's PBPK analyses including the major gaps that fenfluramine fm values were not validated with the in vivo DDI data, and the inhibition effect of stiripentol was not validated with the clinical DDI data with corresponding sensitive substrates of relevant enzymes. Based on the above model limitations, the current PBPK analysis is inadequate to evaluate

- the PK of fenfluramine and its metabolite norfenfluramine in healthy subjects, adult and pediatric patients,
- the effect of stiripentol and clobazam on the PK of fenfluramine and its metabolite norfenfluramine in healthy subjects,
- the effect of strong inhibitors of CYP1A2, CYP2B6, or CYP2D6 on the PK of fenfluramine and its metabolite norfenfluramine in healthy subjects, and
- the impact of renal impairment on the PK of fenfluramine and its metabolite norfenfluramine in healthy subjects.

4.6 Individual Study Reviews

Study ZX008-1604: An Open-label, 1-way Treatment Sequence, Drug-drug Interaction Study to Evaluate the Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) Oral Solution Administered as a Single Dose with and Without Cannabidiol BID for 18 Days in Recreational Drug Users

Study Rationale: Cannabidiol, in the form of the drug EPIDIOLEX® and as an ingredient in unapproved CBD containing products such as cannabis oils and other CBD artisanal products, may be used concomitantly with ZX008. In vitro, CBD is a reversible competitive inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (IC50 <10 μM) and a time-dependent inhibitor (TDI) of CYP1A2 and CYP3A4.

Study 1604 was a DDI study conducted in otherwise healthy, adult recreational drug users to evaluate the effect of the maximum feasible dosage of CBD on the PK parameters of fenfluramine and provide results to support the label instructions for co-administering ZX008 with CBD-containing products. CBD was administered with food, at the MTD, and dosed to steady state to maximize the DDI.

Objectives:

Primary Objective: The primary objective was to assess the pharmacokinetic (PK) profiles of fenfluramine and norfenfluramine following a single dose of ZX008 0.4 mg/kg oral solution

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administered with a meal, with and without co-administration of cannabidiol (CBD) at steady state, in otherwise healthy, adult recreational drug users.

Secondary Pharmacokinetic Objectives:

- To assess the PK profiles of CBD following up to 700 mg CBD administered twice daily (BID) with a meal, with and without co-administration of a single dose of ZX008 oral solution, in otherwise healthy, adult recreational drug users.
- To evaluate the safety and tolerability of single doses of ZX008 0.4 mg/kg oral solution, administered with and without CBD.
- To evaluate the safety and tolerability of up to 700 mg CBD administered BID with and without a single dose of ZX008 0.4 mg/kg oral solution.

Study Design	This study was a single-center, 1-sequence treatment, single-dose, drug-drug interaction (DDI) study of ZX008 (fenfluramine HCl) and CBD in otherwise healthy, adult recreational drug users.
Study Population	Healthy subjects (male or female) Age: 19-50 years BMI: 18 to 31 kg/m^2. A total of 24 subjects were planned and enrolled.
Test and Reference Products	ZX008; fenfluramine hydrochloride (HCl) oral solution Cannimed® Oil 1:20; cannabidiol oil 20:1 CBD: THC Cannabidiol (CBD) + 35 mg tetrahydrocannabinol (THC)
PK Sampling	Blood samples were collected for analysis of fenfluramine, norfenfluramine and CBD, THC, and 11-OH-THC at Predose, 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 on day 1 and on Day 22 additional time points 144, 168, 192, 216 and 240 hours were included to cover CBD and THC.
Pharmacokinetic Assessments	Venous blood samples were collected to determine the plasma concentrations of fenfluramine, norfenfluramine, and CBD, THC, and 11-OH-THC. Samples were collected, processed, and shipped according to the site's Standard Operating Procedures (SOPs) and instructions from the Sponsor and/or bioanalytical laboratories. Further details are provided in the bioanalytical laboratory manuals.
Safety Assessments	Recorded medical history, recreational drug use history, physical examination, electrocardiogram (ECG), vital signs, C-SSRS, clinical laboratory parameters (standard clinical chemistry, hematology and urinalysis, pregnancy, follicle-stimulating hormone [FSH], viral screen, breath alcohol, and drugs of abuse screen).
Determination of Sample Size	Assuming a percent coefficient of variation (CV) of 18.647, based on the variability of the Cmax of l-fenfluramine, a sample size of 16 completers was determined to be required for 90% power. This calculation was for a crossover bioequivalence study with the criteria that the 90% CI on the paired GMR comparing the 2 treatments would fall between the interval of 80% to 125%. Assuming a 30% drop-out rate, 24 subjects were to have been randomized, with the intention of completing at least 16 subjects.

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Statistical Methods	Statistical analysis was performed on the log-transformed PK parameters, Cmax, AUClast, and AUCinf for fenfluramine and norfenfluramine, to assess the effect of CBD co-administration on the PK parameters of ZX008. The analysis was performed using an analysis of variance (ANOVA) model. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the comparisons of PK parameters between ZX008 dosed with and without CBD are provided, where the ratio was defined as Test (with CBD)/Reference (without CBD). Similar statistical analysis was performed to assess the effect ZX008 co-administration on CBD PK exposure parameters.

Note: Cannimed oil was administered with a meal to maximize exposure. The higher doses resulted in an unacceptable rate of AEs and dropouts. Group 2 (n=7) titrated to a dose of 500 mg BID on Day 18 and received the morning dose of 500 mg on Day 19. After a review of the tolerability in this group, a decision was made to decrease the dose to 400 mg BID and amend the protocol.

Note: The dose for fenfluramine listed in this study reports represents fenfluramine hydrochloride, which is 0.4 mg/kg twice daily (0.8 mg/kg/day) not to exceed a total daily dose of 30 mg. The base equivalent is 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg.

RESULTS:

Disposition of Subjects

Thirty-two (32) subjects were enrolled, received study drug (ZX008 or CBD), and were included in the Safety Population. Eight (8) subjects from the Safety Population were excluded from the PK Population: 1 subject due to a positive drug screen (Subject (b) (6)), 1 subject withdrew consent (Subject (b) (6)), 1 subject due to an adverse event (Subject (b) (6)) and 5 subjects in Group 1 due to stopping the study to amend the Protocol for Protocol Amendment 03. Fourteen (14) subjects received all study treatments and completed all treatment days in the Treatment Phase and comprise the Completers Population.

Pharmacokinetics:

Mean (±SD) Fenfluramine and Norfenfluramine Plasma Concentrations (ng/mL)

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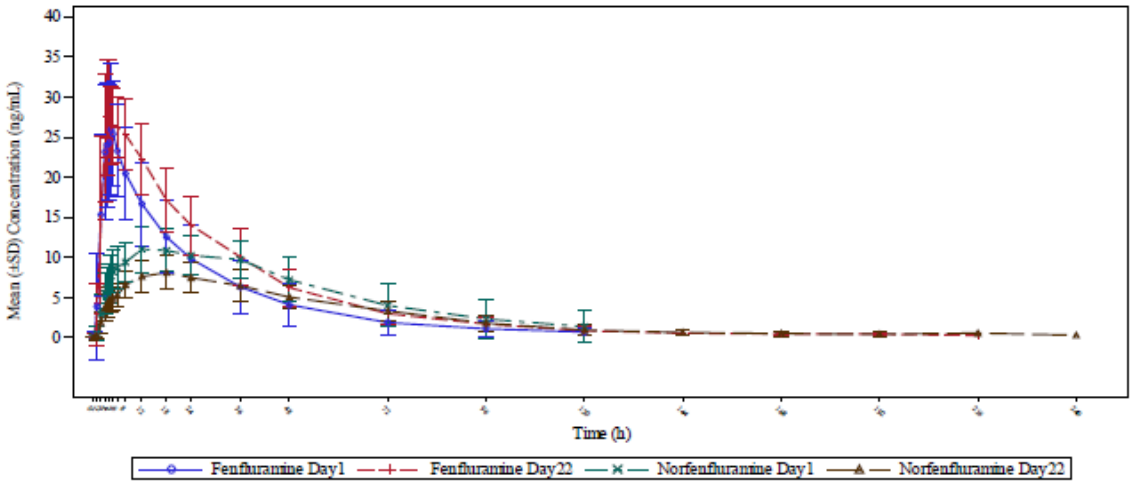

Fenfluramine PK Parameters Following Single Dose of ZX008 Alone and in Combination with CBD (Geometric Meana Ratio [%CV])

PK Parameters	N	ZX008 0.4 mg/kg Day 1	N	ZX008 0.4 mg/kg + 400 mg CBD Day 22
Median T_{max} (hr) (Range)	24	4.5 (2.0, 50)	14	4.0 (2.0, 8.0)
Mean C_{max} (ng/mL) (%CV)	24	28.59 (29.9)	14	30.84 (21.3)
Mean AUC_{0-12} (ng*h/mL) (%CV)	24	221.6 (27.1)	14	256.3 (17.4)
Mean AUC_{inf} (ng*h/mL) (%CV)	24	673.1 (44.7)	14	934.5 (29.2)
$t_{1/2}$ (h) (Range)	24	19.35 (9.42, 36.9)	14	24.62 (14.1, 36.5)
GMR C_{max} (90% CI)	14	NC		109.592 (102.961, 116.651)
GMR AUC_{0-t} (90% CI)	14	NC		158.754 (147.907, 170.395)

Sources: End-of-Text Table 14.2.2.1 and Table 14.2.4.1.
Abbreviations: AUC_{0-t}=area under the curve from time 0 to time t; AUC_{inf}=area under the curve from time of dosing (time 0) extrapolated to infinity; CBD=cannabidiol; CI=confidence interval; C_{max}=maximum observed concentration in plasma; %CV=percent coefficient of variation; GMR=geometric mean ratio; Max=maximum; Min=minimum; NC=not calculated; PK=pharmacokinetic; $t_{1/2}$=elimination half-life; T_{max}=time to maximum observed concentration in plasma.
[a] Geometric mean ratio for CBD/ZX008.

Norfenfluramine PK Parameters Following Single Dose of ZX008 Alone and in Combination with CBD (Geometric Meana Ratio [%CV])

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PK Parameters	N	ZX008 0.4 mg/kg Day 1	N	ZX008 0.4 mg/kg + 400 mg CBD Day 22
Median T_{max} (hr) (Range)	24	18.0 (12.0, 36.0)	14	18.0 (11.9, 35.9)
Mean C_{max} (ng/mL) (%CV)	24	11.72 (24.7)	14	8.277 (24.9)
Mean AUC_{0-12} (ng*h/mL) (%CV)	24	87.22 (30.3)	14	58.33 (26.9)
Mean AUC_{inf} (ng*h/mL) (%CV)	24	798.4 (60.1)	14	542.3 (32.3)
Mean $t_{1/2}$ (h)[b] (Range)	24	28.98 (17.8, 97.5)	14	29.32 (16.2, 48.1)
GMR C_{max} (90% CI[c])	14	NC[d]		66.657 (61.503, 72.243)
GMR AUC_{0-t} (90% CI)	14	NC		78.278 (70.341, 87.112)

Note: Co-administration of CBD increased fenfluramine concentrations, resulting in fenfluramine Cmax and AUC0-t geometric mean ratios (GMRs) of approximately 1.1-fold and 1.6-fold, respectively.

For norfenfluramine, mean AUC0-t and Cmax values were ~22% and ~33% lower following CBD administration.

The CBD product (CanniMed® Oil 1:20) used in this study contains CBD and a low amount of THC at concentrations of 20 mg/mL and 1 mg/mL, respectively. The maximum dose of 700 mg CBD per dose requires that 35 mL of the CBD product (700 mg CBD and 35 mg THC) be dispensed at each dosing.

At the time of initiation of this study, purified CBD for human use was not FDA-approved or available in the US, CBD products obtained by purification of oils from the cannabis plant were available commercially in Canada. These oils contained a small amount of tetrahydrocannabinol (THC); more purified CBD was not available. The inhibitory potencies of THC toward CYP450 enzymes are lower than those of CBD, ie, higher IC50 values for THC than CBD as shown in the table below.

CYP450 Inhibitory Potency (Stout 2014) and Plasma Cmax of CBD and THC in Study 1604.

	IC_{50} (µM)		Study 1604 C_{max} (ng/mL)	
CYP450 Enzyme	CBD	THC	CBD	THC
CYP1A1	0.155	4.78		
CYP1A2*	2.69	7.54		
CYP1B1	3.63	2.47		
CYP2A6	55	28.9		
CYP2B6*	0.694	2.81	446	23.2
CYP2C9	0.95 to 9.88	0.94 to 1.5		
CYP2D6*	1.16 to 2.69	17.1 to 22.9		
CYP3A4	1	>50		
CYP3A5	0.195	35.6		
CYP3A5	12.3	30.3		

* Over 75% of fenfluramine is metabolized to norfenfluramine prior to elimination, primarily by CYP1A2, CYP2B6, and CYP2D6.

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Reviewer's Comment: Based on the cytochrome P450 (CYP450) inhibitory potency of CBD and THC in vitro, this interaction could be attributed to the CBD component.

CBD PK Parameters Following CBD Alone and in Combination with a Single Dose of ZX008 (Geometric Mean Ratio [%CV])

PK Parameters	N	400 mg CBD	N	400 mg CBD + 0.4 mg/kg ZX008
Median T_{max} (hr) (Range)	14	3.0 (2.0, 6.0)	14	4.3 (3.0, 6.0)
Mean C_{trough} (ng/mL) (%CV)	14	48.25 (37.0)	14	79.40 (79.4)
Mean C_{max} (ng/mL) (%CV)	14	391.6 (35.0)	14	445.6 (38.3)
Mean AUC_{0-12} (ng*h/mL) (%CV)	12	1733 (27.9)	12	1865 (31.4)
GMR C_{max} (90% CI[c])	14	NC		113.444 (94.043, 136.847)
GMR AUC_{0-12} (90% CI)	14	NC		102.609 (91.335, 115.274)

THC PK Parameters Following CBD Alone and in Combination with a Single Dose of ZX008 (Geometric Meana Ratios [%CV])

PK Parameter	N	400 mg CBD	N	400 mg CBD + 0.4 mg/kg ZX008
Median T_{max} (hr) (Range)	14	3.0 (2.0, 6.0)	14	4.2 (2.0, 6.0)
Mean C_{trough} (ng/mL) (%CV)	0	NC[d]	1	10.92 (N/A)
Mean C_{max} (ng/mL)(%CV)	14	20.84 (36.4)	14	23.21 (43.4)
Mean AUC_{0-12} (ng*h/mL) (%CV)	10	87.09 (24.4)	7	88.39 (35.4)
GMR C_{max} (90% CI)	14	NC		108.697 (90.542, 130.494)
GMR AUC_{0-12} (90% CI)	14	NC		NC

11-OH-THC PK Parameters Following CBD Alone and in Combination with a Single Dose of ZX008 (Geometric Meana Ratios [%CV])

PK Parameters	N	400 mg CBD	N	400 mg CBD + 0.4 mg/kg ZX008
Median T_{max} (hr) (Range)	14	3.5 (2.0, 6.0)	14	4.5 (3.0, 6.0)
Mean C_{trough} (ng./mL) (%CV)	14	3.663 (43.2)	1	4.182 (50.1)
Mean C_{max} (ng/mL) (%CV)	14	15.87 (19.8)	14	16.12 (27.7)
Mean AUC_{0-12} (ng*h/mL) (%CV)	11	97.63 (22.4)	12	91.38 (29.7)
GMR C_{max} (90% CI)	14	NC		100.018 (89.928, 111.240)
GMR AUC_{0-t} (90% CI)	14	NC		93.720 (87.556, 100.318)

Fenfluramine had no significant effect on the PK parameters of CBD, THC, or 11-OH-THC.

CONCLUSIONS:

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- Co-administration of CBD increased fenfluramine concentrations, resulting in fenfluramine Cmax and AUC0-t ratios of approximately 1.1-fold and 1.6-fold, respectively. Norfenfluramine, mean AUC0-t and Cmax values were ~22% and ~33% lower following CBD administration.
- Fenfluramine had no significant effect on the PK parameters of CBD, THC, or 11-OH-THC.

Note: The proposed labeling indicates a starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). The dose may be increased based on clinical efficacy and tolerability not less than every 4 days, to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg. Clinical studies support efficacy of range of treatment regimens from 0.2 mg/kg/day to 0.7 mg/kg/day.

Labeling Recommendations

The clinical relevance of 60% increase in fenfluramine and 33% decrease in norfenfluramine AUC is unknown. No ZX008 dose adjustment is required when co-administering ZX008 with CBD.

Study ZX008-1505: A Two Part, Randomized, Open-label, Single-dose, 3-way Crossover Study to Evaluate the Drug-drug Interaction Between ZX008 (Fenfluramine Hydrochloride) Oral Solution and Stiripentol Regimen (Stiripentol/Clobazam/Valproate) (Part 1) and Single-dose, 2-way Crossover Food Effect of ZX008 (Part 2) in Healthy Volunteers

Study Rationale: Fenfluramine is partially metabolized by CYP1A2, CYP2B6, and CYP2D6, with the possibility of additional metabolism by CYP2C9, CYP2C19, and CYP3A4, and, as such, its PK could be affected by stiripentol, clobazam and valproate. Stiripentol is reported to be a strong inhibitor of CYP2C19 and CYP3A4, and also CYP1A2, CYP2C9, and CYP2D6. Studies in human liver microsomes confirmed that STP is a time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6. CLB is reported to inhibit CYP2D6, increasing the AUC of the CYP2D6 substrate dextromethorphan by 90%. Valproic acid is a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyltransferases.

Objectives:

Primary Objective: To assess the pharmacokinetic (PK) profile of ZX008 administered as a single oral dose with and without stiripentol regimen (stiripentol/clobazam[CLB]/ valproate[VPA]), and in the fed and fasted state

Secondary Objectives:

- To assess the PK profile of the stiripentol regimen (stiripentol/CLB/VPA) administered as a single oral dose with and without ZX008
- To evaluate the safety and tolerability of ZX008, stiripentol regimen (stiripentol/CLB/VPA) and ZX008 administered as a single oral dose in the fed and fasted state

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Study Design	This study was an open-label, single dose, 3-way crossover trial
Study Population	Healthy subjects (male or female) Age: 18-50 years BMI: 19 to 31 kg/m^2.
Number of Subjects	Part 1 Planned: 24; Randomized: 26; Dosed: 26; Completed: 17; Withdrawn: 9. 26 subjects were included in the safety population, 25 subjects were included in the PK population, 19 subjects were included in PK Analysis Dataset 1, and 18 subjects were included in PK Analysis Dataset 2. Part 2 Planned: 14; Randomized: 14; Dosed: 14; Completed: 13; Withdrawn: 1. 14 subjects were included in the safety and PK populations, and 13 subjects were included in the PK analysis dataset.
Methodology	Part 1 Part 1 of this study was conducted using an open-label, randomized, single-dose, 3-period crossover design to evaluate the drug-drug interaction between ZX008 and a stiripentol regimen (stiripentol/CLB/VPA). It was planned to enroll 24 healthy subjects to ensure data in 16 evaluable subjects for the primary objectives. Each period followed the same study design. Subjects were screened for inclusion in the study up to 28 days before dosing and were admitted to the clinical unit on the evening before dosing (Day -1). Subjects were randomized on Day 1 of Period 1 to receive each of the following oral doses over 3 study periods, separated by at least a 17-day washout period: □ Regimen A: 0.8 mg/kg ZX008 (5 mg/mL solution) □ Regimen B: 3500 mg stiripentol capsules (7 × 500 mg capsules), plus 20 mg CLB tablet and 25 mg/kg VPA (40 mg/mL solution; maximum 1500 mg) □ Regimen C: 0.8 mg/kg ZX008 (5 mg/mL solution) plus 3500 mg stiripentol (7 × 500 mg capsules), 20 mg CLB tablet and 25 mg/kg VPA (40 mg/mL solution; maximum 1500 mg) Following an overnight fast of at least 10 h, each subject received study medication in the morning of Day 1 of each of the 3 treatment periods, based on the randomization code. All subjects remained fasted until approximately 4 h post-dosing, when lunch was provided. Water was not restricted. Part 2 Part 2 of this study was conducted using an open-label, randomized, single-dose, 2-period crossover design to evaluate the effect of food on the PK of ZX008 and its metabolite, norfenfluramine. It was planned to enroll 14 healthy subjects to ensure data in 12 evaluable subjects for the primary objectives. Each period followed the same study design. Subjects were screened for inclusion in the study up to 28 days before dosing, and were admitted to the clinical unit on the evening before dosing (Day -1). Subjects were randomized on Day 1 of Period 1 to receive each of the

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	following oral doses over 2 study periods, separated by at least a 9-day washout period: □ Regimen D: 0.8 mg/kg ZX008 (5 mg/mL solution) following an overnight fast □ Regimen E: 0.8 mg/kg ZX008 (5 mg/mL solution) following a high-fat breakfast
Test/Reference Product, Dose and Mode of Administration	Part 1 Subjects received oral doses of ZX008 following an overnight fast of at least 10 h: □ Regimen A: 0.8 mg/kg ZX008 (5 mg/mL solution) □ Regimen C: 0.8 mg/kg ZX008 (5 mg/mL solution), plus reference therapy Part 2 Subjects received an oral dose of ZX008 in the fasted and fed states: Regimen D: 0.8 mg/kg ZX008 (5 mg/mL solution) following an overnight fast Regimen E: 0.8 mg/kg ZX008 (5 mg/mL solution) following a high-fat breakfast Regimen B: − 3500 mg stiripentol capsules (7 × 500 mg capsules) − 20 mg CLB tablet, batch number 117731-02 − 25 mg/kg VPA (40 mg/mL solution; maximum 1500 mg Regimen C: test product plus − 3500 mg stiripentol (7 × 500 mg capsules), batch number 117731-01 − 20 mg CLB tablet − 25 mg/kg VPA (40 mg/mL solution; maximum 1500 mg)
Duration of Treatment:	Part 1 Single oral doses of test and/or reference product were administered on 3 occasions separated by a minimum washout period of 17 days. Subjects had a follow-up call on Day 17 (± 1 day) of the third treatment period (16 days post-final dose). Part 2 Single oral doses of test and/or reference product were administered on 2 occasions separated by a minimum washout period of 9 days. Subjects had a follow-up call on Day 9 (± 1 day) of the second treatment period (8 days post-final dose).
Pharmacokinetic Assessments	The following plasma PK parameter estimates for concentrations of fenfluramine and its metabolite (norfenfluramine; both in Parts 1 and 2) and stiripentol, CLB and its metabolite (norclobazam), and VPA (all in Part 1 only) were estimated where possible for each subject and relevant

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	regimen estimated (using non-compartmental analysis methods in Phoenix WinNonlin PK software. Tlag the elapsed time from dosing at which analyte was first quantifiable in a concentration vs time profile Tmax the time from dosing at which Cmax was apparent Tlast the time from dosing at which the last measurable concentration was apparent Cmax maximum observed concentration AUC(0-24) area under the curve from 0 time to 24 h post dose (Part 1 only) AUC(0-t) area under the curve from 0 time to last measurable concentration AUC(0-inf) area under the curve from 0 time extrapolated to infinity AUC%extrap percentage of AUC(0–inf) extrapolated beyond last measured time point T½ the apparent elimination half-life Kel the slope of the apparent elimination phase Kel Lower lower limit on time for values to be included in the calculation of Kel Kel Upper upper limit on time for values to be included in the calculation of Kel CL/F clearance, the apparent volume cleared of parent drug per unit time after extravascular administration Vz/F the apparent volume of distribution after extravascular administration (for parent drug in plasma only) Frel relative bioavailability MPR metabolite to parent ratios for AUC (for fenfluramine and metabolite in Parts 1 and 2; for clobazam and metabolite in Part 1 only)
PK Sampling	Blood samples were collected for analysis of fenfluramine and its metabolite, stiripentol, CLB and its metabolite (norclobazam), and VPA were obtained up to 72 h after the administration of the last capsule/solution/tablet, at Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48 and 42 hours postdose.Validated liquid chromatographic-tandem mass spectrometric bioanalytical methods were used to quantify plasma concentrations of the above analytes.
Safety Assessments	Adverse events, physical examination, vital signs, ECG, clinical laboratory parameters (standard hematology, clinical chemistry and urinalysis), assessment of suicidality using the Columbia-Suicide Severity Rating Scale (Part 1 only).
Statistical Methods	Part 1 Formal statistical analysis was performed on the log transformed PK parameters AUC(0-inf), AUC(0-t) (analyzed due to multiple AUC(0-inf) values being unreliable), AUC(0-24) and Cmax for each of fenfluramine and its metabolite (norfenfluramine) unless specified otherwise, to assess the effect of the stiripentol regimen on the PK of ZX008. The analysis was performed using a mixed effects model with treatment, sequence and period as fixed effects and subject nested with sequence as a random effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals for the adjusted GMRs for the comparisons between ZX008 dosed with and without the stiripentol regimen were provided, where the ratio was defined as ZX008 plus the stiripentol regimen/ ZX008 alone. Part 2 Formal statistical analysis was performed on the log transformed PK parameters Cmax and AUC(0-inf) for fenfluramine, and Cmax and AUC(0-t) (analyzed due to multiple AUC(0-inf) values being unreliable) for its metabolite (norfenfluramine) to assess the effect of food on the PK of

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	ZX008. The analysis was performed using a mixed effects model with treatment, sequence and period as fixed effects and subject nested with sequence as a random effect. Adjusted GMRs and 90% confidence intervals for the adjusted GMRs for the comparisons between ZX008 dosed with and without food were provided, where the ratio was defined as ZX008 Fed/ ZX008 Fasted. For fenfluramine only, formal criteria were used to determine an absence of a food effect on bioavailability. An absence of food effect was indicated when the 90% CI for the GMR for the fed and fasted treatment comparison, based on log-transformed Cmax and AUC(0-inf) values, was contained within the equivalence limits of 80.00%-125.00%.

RESULTS:

Part 1
Fenfluramine and Norfenfluramine

Fenfluramine
The geometric mean (CV%) key PK parameters for fenfluramine following single oral doses of ZX008 alone and in combination with the stiripentol regimen are presented below:

Regimen **Dose level** **No. of Subjects**	**A** **0.8 mg/kg ZX008** **N = 19**	**C** **0.8 mg/kg ZX008 +** **3500 mg Stiripentol, 20 mg CLB,** **25 mg/kg VPA** **N = 24**
Tmax (h)[a]	3.00 (2.00 – 12.00)	3.00 (1.00 – 9.00)
Cmax (ng/mL)	61.9 (14.1)	74.3 (20.2)
AUC(0-t) (ng.h/mL)	1600 (29.7)	2570 (33.6)
AUC(0-inf) (ng.h/mL)	1660 (28.9) [n=17]	2310 (35.8) [n=12]
T½ (h)	19.842 (16.1) [n=17]	22.258 (17.3) [n=12]
GMR (90% CI) Cmax	NC	118.10 (109.43, 127.46) [n=19]
GMR (90% CI) AUC(0-t)	NC	166.19 (152.00, 181.71) [n=19]

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen C/Regimen A; CI = confidence interval

The geometric mean (CV%) key PK parameters for norfenfluramine following single oral doses of ZX008 alone and in combination with the stiripentol regimen are presented below:

Norfenfluramine

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Regimen Dose level No. of Subjects	A 0.8 mg/kg ZX008 N = 19	C 0.8 mg/kg ZX008 + 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA N = 24
Tmax (h)[a]	12.05 (9.02 – 36.00)	24.015 (2.00 – 72.15)
Cmax (ng/mL)	15.8 (31.1)	9.39 (44.2)
AUC(0-t) (ng.h/mL)	779 (26.9)	483 (42.9)
AUC(0-inf) (ng.h/mL)	836 (9.5) [n=4]	NC
T½ (h)	23.414 (9.9) [n=4]	NC
MPR(AUC(0-t)	0.553 (49.0)	0.214 (69.6)
GMR (90% CI) Cmax	NC	57.51 (48.80, 67.77) [n=19]
GMR (90% CI) AUC(0-t)	NC	58.71 (50.40, 68.40) [n=19]

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen C/Regimen A; CI = confidence interval

Stiripentol

The geometric mean (CV%) key PK parameters for stiripentol following single oral doses of the stiripentol regimen alone and in combination with ZX008 are presented below.

Regimen Dose level No. of Subjects	B 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA N = 20	C 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA + 0.8 mg/kg ZX008 N = 24
Tmax (h)[a]	6.00 (1.05 – 48.05) [n=19]	6.00 (1.50 – 36.00)
Cmax (ng/mL)	3020 (43.8) [n=19]	3510 (33.3)
AUC(0-t) (ng.h/mL)	76400 (39.8) [n=17]	69800 (49.4)
AUC(0-inf) (ng.h/mL)	92100 (25.6) [n=9]	70700 (50.3) [n=12]
T½ (h)	15.577 (26.1) [n=9]	14.798 (61.1) [n=12]
GMR (90% CI) Cmax	NC	115.60 (97.93, 136.46) [n=18]
GMR (90% CI) AUC(0-t)	NC	86.73 (67.99, 110.64) [n=16]

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen C/Regimen B; CI = confidence interval

Clobazam and Norclobazam

Clobazam

The geometric mean (CV%) key PK parameters for CLB following single oral doses of the stiripentol regimen alone and in combination with ZX008 are presented below:

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Regimen Dose level No. of Subjects	B 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA N = 20	C 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA + 0.8 mg/kg ZX008 N = 24
Tmax (h)[a]	3.00 (1.50 – 6.00) [n=19]	3.00 (1.50 – 6.03)
Cmax (ng/mL)	228 (16.8) [n=19]	209 (25.1)
AUC(0-t) (ng.h/mL)	7880 (14.6) [n=17]	7610 (19.0)
AUC(0-inf) (ng.h/mL)	11800 (NC) [n=1]	8430 (17.5) [n=4]
T½ (h)	28.926 (NC) [n=1]	25.503 (8.4) [n=4]
GMR (90% CI) Cmax	NC	95.29 (88.02, 103.17) [n=18]
GMR (90% CI) AUC(0-t)	NC	94.82 (90.25, 99.63) [n=16]

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen C/Regimen B; CI = confidence interval

Norclobazam

The geometric mean (CV%) key PK parameters for norclobazam following single oral doses of the stiripentol regimen alone and in combination with ZX008 are presented below:

Regimen Dose level No. of Subjects	B 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA N = 20	C 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA + 0.8 mg/kg ZX008 N = 24
Tmax (h)[a]	72.00 (48.02 – 72.23) [n=19]	72.000 (71.55 – 72.15)
Cmax (ng/mL)	92.2 (36.4) [n=19]	90.1 (34.9)
AUC(0-t) (ng.h/mL)	4110 (38.8) [n=17]	4120 (41.6)
MPR(AUC(0-t)	0.548 (29.3) [n=17]	0.567 (35.7)
GMR (90% CI) Cmax	NC	100.54 (96.45, 104.80) [n=18]
GMR (90% CI) AUC(0-t)	NC	101.60 (95.03, 108.62) [n=16]

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen C/Regimen B; CI = confidence interval

Valproate

The geometric mean (CV%) key PK parameters for VPA following single oral doses of the stiripentol regimen alone and in combination with ZX008 are presented below:

Regimen Dose level No. of Subjects	B 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA N = 20	C 3500 mg Stiripentol, 20 mg CLB, 25 mg/kg VPA + 0.8 mg/kg ZX008 N = 24
Tmax (h)[a]	0.750 (0.50 – 3.00) [n=18]	1.000 (0.50 – 3.00)
Cmax (ng/mL)	100000 (8.9) [n=19]	105000 (16.7)
AUC(0-t) (ng.h/mL)	1680000 (22.1) [n=17]	1850000 (21.1)
AUC(0-inf) (ng.h/mL)	1740000 (23.0) [n=17]	1910000 (21.8)
T½ (h)	14.754 (19.9) [n=17]	14.612 (16.9)
GMR (90% CI) Cmax	NC	101.29 (96.58, 106.23) [n=18]
GMR (90% CI) AUC(0-t)	NC	99.57 (94.14, 105.32) [n=16]

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen C/Regimen B; CI = confidence interval

Part 2

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The geometric mean (CV%) key PK parameters for fenfluramine following single oral doses of ZX008 in the fasted and fed state are presented below:

Fenfluramine

Regimen Dose level No. of Subjects	D 0.8 mg/kg ZX008, Fasted N = 14	E 0.8 mg/kg ZX008, Fed N = 13
Tmax (h)[a]	3.00 (1.50 – 4.00)	3.00 (0.75 – 6.02)
Cmax (ng/mL)	56.6 (17.5)	58.8 (22.8)
AUC(0-t) (ng.h/mL)	1430 (20.8)	1470 (24.7)
AUC(0-inf) (ng.h/mL)	1580 (23.2)	1630 (28.2)
T½ (h)	20.948 (17.5)	21.076 (15.9)
GMR (90% CI) Cmax	NC	104.23 (97.85, 111.02)
GMR (90% CI) AUC(0-inf)	NC	102.74 (98.91, 106.71)

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen E/Regimen D; CI = confidence interval

The geometric mean (CV%) key PK parameters for norfenfluramine following single oral doses of ZX008 in the fasted and fed state are presented below:

Norfenfluramine

Regimen Dose level No. of Subjects	D 0.8 mg/kg ZX008, Fasted N = 14	E 0.8 mg/kg ZX008, Fed N = 13
Tmax (h)[a]	12.000 (9.00 – 36.00)	12.000 (6.00 – 36.03)
Cmax (ng/mL)	16.4 (14.0)	16.0 (15.3)
AUC(0-t) (ng.h/mL)	838 (19.0)	828 (19.5)
AUC(0-inf) (ng.h/mL)	776 (8.0) [n=2]	846 (22.2) [n=2]
T½ (h)	39.693 (29.1) [n=13]	44.856 (38.8) [n=12]
MPR (AUC(0-t)	0.668 (22.5)	0.640 (25.5)
GMR (90% CI) Cmax	NC	97.41 (92.12, 103.00)
GMR (90% CI) AUC(0-t)	NC	98.10 (92.99, 103.50)

[a] Median (range); NC = Not Calculated; GMR = geometric mean ratio for Regimen E/Regimen D; CI = confidence interval

Note: This study is designed to evaluate the effect of concomitant administration of stiripentol, clobazam and valproate cocktail on the PK of fenfluramine and norfenfluramine.

CONCLUSIONS:

- Concomitant administration of ZX008 did not affect PK of stiripentol, clobazam or valproate.
- Stiripentol regimen had a significant effect on the PK of fenfluramine and norfenfluramine, increased AUC0-t of fenfluramine by 66% and decreased norfenfluramine AUC0-t by 41% when compared to fenfluramine administered alone. Increased Cmax of fenfluramine by 18% and decreased norfenfluramine Cmax by 43% when compared to fenfluramine administered alone.
- Food had no effect on the rate or extent of absorption of fenfluramine and the systemic exposure of fenfluramine and norfenfluramine after a single dose of 0.8 mg/kg of ZX008.

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