CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022399Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Gabapentin Enacarbil
NDA:	22-399
PRODUCT (Brand Name):	SOLZIRA
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	600 mg
INDICATION:	Restless Legs Syndrome (RLS)
NDA TYPE:	505(b)(1)
SUBMISSION DATES:	1/8/2009, 1/14/2009, 2/20/2009, 2/25/2009, 3/23/2009, 3/25/2009, 4/7/2009, 4/24/2009, 5/1/2009, 5/8/2009, 5/29/2009, 6/2/2009, 6/5/2009, 6/8/2009, 7/15/2009, 7/22/2009, 7/23/2009, 7/24/2009, 7/28/2009
SPONSOR:	GlaxoSmithKline (GSK)
REVIEWER:	Ju-Ping Lai, Ph.D.
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OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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1.0 EXECUTIVE SUMMARY

This application for SOLZIRA™ (Gabapentin Enacarbil) Extended Release (ER) Tablets is being submitted as a 505(b)(1) submission for the treatment for moderate-to-severe primary Restless Legs Syndrome (RLS).

Oral gabapentin (Neurontin®) has been approved in the US for the treatment of post-herpetic neuralgia and as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in 2007 with the recommended dose of 1800 mg per day (600 mg TID). SOLZIRA™ (Gabapentin Enacarbil) is submitted as a new molecular entity, which is a transported prodrug of gabapentin designed and engineered to be stable in gastrointestinal contents and to be actively absorbed after oral dosing. Gabapentin Enacarbil converts to gabapentin rapidly by non-specific carboxylesterase primarily in enterocytes and to a lesser extent in the liver upon absorption. The concentration of intact prodrug in blood is transient and ≤ 2% of the corresponding gabapentin level. SOLZIRA™ is proposed to be marketed as 600 mg ER Tablets (b) (4)

The proposed starting dose is 600 mg QD (b) (4) given at 5 PM with food. The formulation has been constant throughout the clinical development of this product. The commercial formulation is identical to the clinical formulations that were used in Phase 1, 2, and 3 clinical studies.

The clinical development program for gabapentin enacarbil consists of 16 Phase I studies under IND 71,352 (b) (4). These studies include dose proportionality (SD 300-6000 mg and MD up to 4200 mg/day for IR formulation and 3600 mg/day for ER formulation for 11 days), drug interaction studies with cimetidine and naproxen, food effect studies, mass balance study and renal impairment study. An (b) (4) was also provided. Efficacy of SOLZIRA™ was evaluated in 4 Phase II (XP021, XP045, XP081, and XP083) and 4 Phase III (XP052, XP053, XP060, and XP055) studies. Among these studies, 3 adequate and well-controlled studies (XP052, XP053 and XP060) provided the primary efficacy data for RLS whereas 4 Phase II studies provided supportive data. Two population pharmacokinetic/ pharmacodynamic (PK/PD) analyses of efficacy and safety endpoints for RLS were also conducted (XP081, XP084) where XP084 used integrated data from Phase I, II and III studies for pharmacokinetic analysis and Phase II and Phase III studies for safety and efficacy analysis. Assessment of safety included data from all clinical studies. In addition, cardiac repolarization was investigated in a thorough QT study (XP078).

Across the SOLZIRA™ clinical development program, a total of 1566 unique subjects (365 subjects from the clinical pharmacology studies and 1201 subjects in Phase II and III studies) were exposed to at least one dose of SOLZIRA™ as of the 31 March 2008 submission cut-off date.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of the NDA 22-399. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Phase IV requirements and Agency's labeling recommendations.

Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review on page 39 ould be conveyed to the sponsor.

Comments to the sponsor:

For moderate and severe renal impairment patients, a 300 mg dose is recommended by the agency. To obtain this dose, a new 300 mg strength needs to be developed. Alternatively, the 600 mg tablet can be scored to allow splitting of the tablet. Depending upon the formulation of the new strength, in vivo or in vitro data will be necessary to demonstrate bioequivalence. If the 600 mg tablet is scored, in vitro dissolution comparisons between half and whole tablet is necessary.

1.2 PHASE IV REQUIREMENTS

The following Phase IV requirements should be conveyed to the sponsor:

1. In vitro study for evaluation of the potential of XP13512 and gabapentin to be an inhibitor of CYP2C8 and 2B6 should be conducted.
2. The sponsor should repeat the alcohol dose dumping study using their final dissolution method and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The overall findings from clinical pharmacology and biopharmaceutics section are as follows:

Gabapentin Enacarbil (XP13512) converts to gabapentin rapidly by non-specific carboxylesterase primarily in enterocytes and to a lesser extent in the liver upon absorption. Ester hydrolysis is the only significant metabolic pathway.Neither XP13512 nor gabapentin are substrates, inhibitors or inducers for CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 at clinically relevant concentrations. The concentration of intact prodrug in blood after absorption is transient and $\leq$ 2% of the corresponding gabapentin level. XP13512 mainly eliminates through urine with 94.1% radioactivity (89.6 % as gabapentin) and very little via feces (with 5 % radioactivity).

Dose proportionality:

The pharmacokinetic parameters, Cmax and AUC, of gabapentin after administration of XP13512 appears to be dose proportional within single dose of 300 mg to 6000 mg XP13512 ER and multiple doses up to 3600 mg/day for XP13512 ER formulation while administration of gabapentin (Neurontin®) exhibited saturation in absorption.

Proposed dose:

We recommend that the maintenance dose be 600 mg qd (and not 1200 mg) based on exposure-response. In addition, we are concerned about dosing (b) (4) due to high residual drug concentrations in the morning that could lead to sedation.

Intrinsic Factors:

Age: It is known that the renal clearance of gabapentin declines with age (Neurontin®). The decreases of apparent oral clearance (CL/F) of gabapentin after administration of XP13512 as age increases (in the current submission) can be explained by the decline of renal function. No additional effect of age on gabapentin CL/F was observed, after accounting for changes in renal function based on the population report (XP084). No dose adjustments are therefore recommended based on age.

Gender: A slight effect of gender was observed (15% higher exposure in females) in the population analysis (XP084). The differences are not considered clinically meaningful. No dose adjustments are therefore recommended based on gender.

Race: In the whole clinical program, the majority of the subjects were Caucasian (94%) while no other single race was greater than 4%. The effect of race therefore could not be studied.

PK in RLS patients: Based on study XP081, the PK of gabapentin following oral administration of XP13512 ER tablets were similar between subjects with RLS and healthy subjects.

Renal impairment patients:

Since gabapentin is mainly excreted through kidney, a PK study in subjects with severe renal impairment (creatinine clearance <30 mL/min) and in end-stage renal disease (ESRD) subjects undergoing hemodialysis and a population PK analysis were conducted to support the dose adjustment recommendations.

While the sponsor provided their proposed dosing regimens, the agency's analysis is not in agreement with the sponsor's recommendations. Below are the sponsor and the FDA's recommended dosing regimens, respectively.

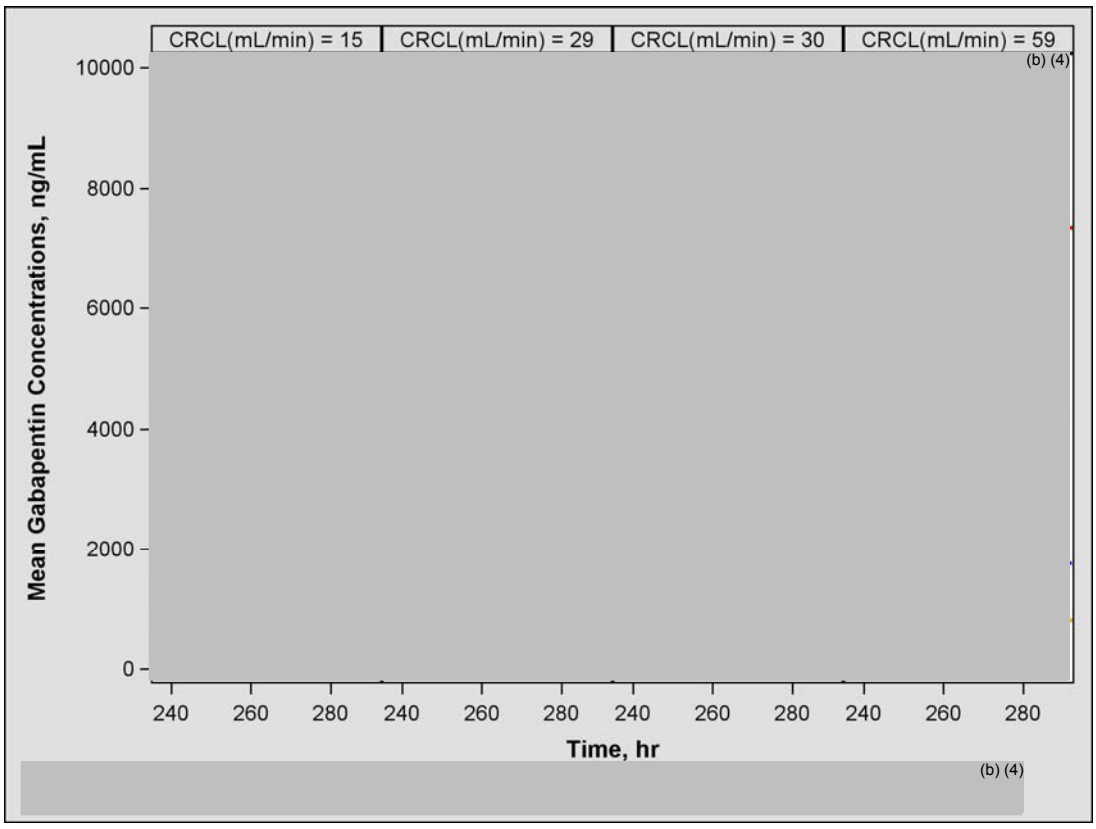
Sponsor proposed:

Table 37 XP13512 ER Tablets Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
		(b) (4)

FDA recommended:

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day



Extrinsic Factors:

Drug-drug Interactions:

Effect of other drugs on gabapentin pharmacokinetics after XP13512 ER administration:

- **Naproxen:** It is believed that XP13512 absorption involves active transport via monocarboxylate transporter (MCT1), which is aboundant in both small and large intestine. Naproxen is known to be a substrate of MCT1. Co-administration of naproxen didn't alter PK of gabapentin and XP13512 at steady state.
- **Cimetidine:** It is believed that after XP13512 absorption and conversion to gabapentin, gabapentin renal excretion involves active secretion via organic cation transporter (OCT2), which is present in the kidney. Cimetidine is known to be a substrate (inhibitor) of OCT2. Co-administration of cimetidine didn't alter Cmax of gabapentin at steady state as shown by 90 % confidence interval (CI) whereas AUCss was slightly increased by 24%. This slight increase is not considered clinical significant.

Effect of XP13512 on pharmacokinetics of other drugs:

- **Naproxen:** There was no change in steady-state pharmacokinetics of naproxen shown by 90 % confidence interval (CI) when co-administered with XP13512 indicating XP13512 has no effect on naproxen PK.
- **Cimetidine:** There was no change in steady-state pharmacokinetics of cimetidine shown by 90 % confidence interval (CI) when co-administered with XP13512 indicating XP13512 has no effect on cimetidine PK.

Biopharmaceutics:

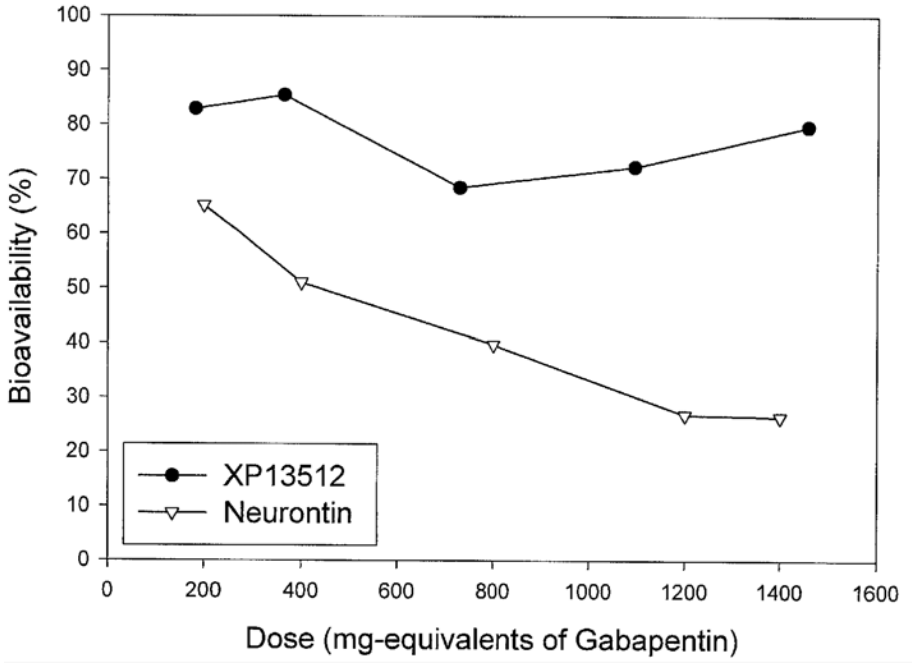
BCS Class:

Based on the sponsor, XP13512 is considered a highly permeable and low solubility compound (BCS Class II). The solubility of XP13512 is pH dependent, typical of a monoprotic weak acid. The lowest solubility it exhibits (0.46 mg/mL) is in acidic solution where the drug is present in the unionized form. As a result of this low solubility at gastric pH, XP13512 is considered to be poorly soluble for BCS Classification. The permeability class boundary is based indirectly on the extent of absorption of drug substance in humans. After oral administration of ^{14}C-XP13512 provided as a solution in gelatin capsules, mean recovery of the radioactive dose in urine was 94.1% (with 89.6% as the major metabolite, gabapentin), exceeding the minimum high permeability criteria set in the BCS guidance. However, the stability of the drug in GI fluids has not been evaluated, although XP13512 has been shown to be chemically stable for 1 hour at 37^{o}C at pH 2 to 8. Instability in pancreatin was also noted. Additionally, permeability data on parent and active metabolite are not available. Therefore, BCS class cannot be confirmed at this time.

Relative Bioavailability:

The formulation has been constant throughout the clinical development of this product. The commercial ER formulation is identical to that used in Phase I, Phase II, and Phase III clinical studies. There are therefore no relative bioavailability studies conducted for the purpose of linking the commercial and research formulations.

A study comparing XP13512 IR formulation (350 to 2800 mg) to Neurontin® (200 to 1400 mg) was conducted based on equivalent gabapentin dose under fasted condition. Bioavailability expressed by urinary recovery of gabapentin showed that the XP13512 administration demonstrated consistently high (> 68%) recovery of gabapentin over the dose range while Neurontin® administration showed recovery of gabapentin declined with increase of doses (65% to 27%).



XP13512 ER versus IR formulation were not formally evaluated at SD and steady state, since there is no approved IR XP13512 formulation available. However, in a single dose study XP019 where urinary recovery was measured for ER compared to an IR capsule, mean bioavailability of gabapentin (based on the urinary recovery of gabapentin) for XP13512 ER in fasted state is about 75% relative to XP13512 IR.

Food Effect:

Effect of food on gabapentin pharmacokinetics was evaluated with or without a high fat meal. The results showed that the exposure (AUC) of gabapentin increases by ~50% and Tmax delays by ~2 hours (from 5 hours to 7 hours) with high fat meal. Effect of fat content on gabapentin pharmacokinetics was also evaluated. Following co-administration of XP13512 ER tablets (1200 mg) with a low, moderate, and high fat/caloric meal, the

Cmax of gabapentin increases by ~30% to 50% regardless of fat content while AUC seems to increase with fat content by 24%, 34% and 44%, respectively. The sponsor recommended that XP13512 ER be taken with food at 5PM intended to reach the Tmax at around midnight to provide best efficacy during the evening and throughout the night as well.

Alcohol Dose Dumping:

Alcohol interaction study was conducted using 40% alcohol for 24 hours. The sponsor stated that a slight increase in the rate of release of XP13512 in presence of alcohol compared to buffer alone was observed. The sponsor therefore concluded that this result demonstrates that the formulation is resistant to dose dumping under these conditions. However, dissolution increased 20 to 30% within the first 2 hours with the presence of 40% alcohol. Although 40% alcohol is considered the worst scenario, the dissolution profile at lower percentage of alcohol is not known. Furthermore, the dissolution media and method used in this study is not the final dissolution method selected by the sponsor (as suggested in the draft guidance). These two methods are not comparable. Therefore, the sponsor should repeat this study using their final dissolution method and evaluate different concentrations of alcohol up to 40%.

(b) (4)

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2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dosage Form/Strengths: 600 mg ER tablets

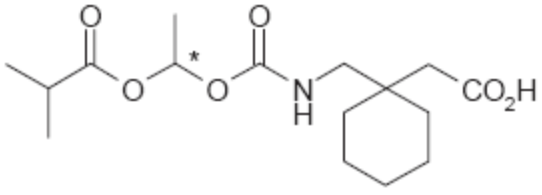
(b) (4)

Isomerism and Stereoisomerism: XP13512 contains one chiral center. The compound exists as a racemate of S-(XP17814) and R- (XP17815) enantiomers. The enantiomers of XP13512 (b) (4) Studies with the individual separated enantiomers indicate that there is no apparent stereoselectivity in the *in vivo* absorption or cleavage on the XP13512 isomers. Both isomers release the same active moiety and the prodrug fragments of isobutyric acid, acetaldehyde and carbon dioxide. XP13512 was developed as the racemate.

Indication: SOLZIRA (Gabapentin Enacarbil) is indicated for moderate to severe primary Restless Leg Symdrome (RLS).

Pharmacologic Class: Gabapentin Enacarbil (XP13512) is a prodrug of gabapentin which belongs to an evolving class of compounds known as gabapentinoids or alpha2delta ligands. These compounds bind with high affinity to the alpha2delta subunit of voltage-gated calcium channels in central nervous system.

Chemical Name: The chemical name of XP13512 is 1- {[isobutanoyloxyethoxy) carbonyl]-aminomethyl}- 1-cyclohexane acetic acid. The chemical name of gabapentin is 1-(aminomethyl) cyclohexaneacetic acid. The molecular formula of XP13512 is C16H27NO6. Its molecular weight is 329.4.



Physical Characteristics: XP13512 is a white to off-white crystalline solid. Its melting point is at 63.8ºC, and is soluble in water (0.51 mg/mL) and phosphate buffer (10.2 mg/mL at pH 6.3).

Formulation: XP13512 is formulated as an ER tablet. It is a white to off-white tablet containing 600 mg of XP13512. (b) (4) Excipients used in the formulation are standard ingredients. A summary of the components and quantitative composition of a 600 mg XP13512 ER Tablets is given in the table below.

Table 1 Composition of the 600 mg XP13512 ER

Component	Quantity (mg/tablet)	Function	Reference to Standard
(b) (4)			

1. Assuming 100% conversion of XP13512 to gabapentin in vivo, 600 mg of XP13512 (MW 329.39) is equivalent to 312 mg of gabapentin (MW 171.24) on a molecular weight basis. 2. GlaxoSmithKline Internal Specification. 3. Magnesium Stearate is (b) (4)

2.1.2 What is the mechanism of action and therapeutic indication?

The precise mechanism by which gabapentin is efficacious in RLS is unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but it does not modify GABAA or GABAB radioligand binding. It is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. XP13512 (up to 10 μM) and gabapentin (up to 100 μM), (Neurontin® Package Insert, 2007) have been tested in radioligand binding assays, and neither exhibited affinity to a number of other common receptor, ion channel, or transporter proteins. In vitro studies with radiolabelled gabapentin have revealed a gabapentin binding site in areas of rat brain, including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxillary

subunit of voltage-activated calcium channels; however its relationship to RLS is unknown.

The proposed indication for XP13512 ER tablets is the treatment of moderate to severe primary RLS.

2.1.3 What are the proposed dosages and route of administration?

Dosage and administration (Sponsor's Proposed):

The recommended initial dose is 600 mg XP13512 ER tablet once daily (b) (4) with food at about 5 PM. (b) (4) Tablets should be swallowed whole and should not be cut, crushed, or chewed.

Renal impairment patients: (creatinine clearance < 60 mL/min), a different dosing regimen should be applied as described below.

Table 37 XP13512 ER Tablets Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
(b) (4)		

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

The clinical development program for XP13512 in the treatment of RLS consists of 16 Phase I studies, conducted either under IND 71,352, filed with the Division of Neurology Products, (b) (4). The Phase I studies were designed to obtain initial safety and tolerability data, select the clinical and commercial formulations of XP13512, and define the dose regimen and treatment procedures for the Phase II and III studies in subjects with RLS. The initial two studies (XP006 and XP018) were conducted using an IR formulation of XP13512. Following this, an ER formulation was developed and compared to the IR formulation in Study XP019. All subsequent studies except the radiolabel study XP065 have used ER tablets. These Phase I studies include dose proportionality (SD 300-6000 mg and MD up to 4200 mg/day for IR formulation and

3600 mg/day for for ER formulation 11 days, drug interaction studies with cimetidine and naproxen, food effect studies, mass balance study and renal impairment study. An (b) (4)

There are four Phase III studies (XP052, XP053, XP055, and XP060) and four supporting Phase II studies (XP021, XP045, XP081 and XP083). All Phase II and III studies were conducted in the US using XP13512 ER tablets. Among these studies, 3 adequate and well-controlled studies (XP052, XP053 and XP060) provided the primary efficacy data for RLS whereas 4 Phase II studies provided supportive data. A population pharmacokinetic/ pharmacodynamic (PK/PD) analysis of efficacy and safety endpoints for RLS was also conducted (XP084) using integrated data from Phase I, Phase II and Phase III studies for pharmacokinetic analysis and Phase II and Phase III studies for safety and efficacy. In addition, cardiac repolarization was investigated in a thorough QT study (XP078).

As of the 31 March 2008 submission cut-off date, a total of 1566 unique subjects (365 subjects from the clinical pharmacology studies and 1201 subjects in Phase II and Phase III studies) were exposed to at least one dose of XP13512 in the XP13512 in RLS clinical development program.

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

The primary objective of the 2 pivotal studies (XP052 and XP053) was to compare the efficacy of XP13512 1200 mg given once daily at about 5PM versus placebo, for the treatment of subjects suffering from moderate-to-severe primary RLS. A secondary study objective for Study XP053 was to assess the efficacy of XP13512 600 mg versus placebo. Other secondary study objectives in both studies were to assess onset of treatment benefits, and improvement in sleep, RLS-associated pain, mood, quality of life, and safety and tolerability.

In both studies the co-primary efficacy endpoints, assessed at the end of treatment (Week 12), were: (i) the change from baseline in IRLS Rating Scale total score and (ii) the proportion of subjects who were rated as responders ("much improved" or "very much improved") on the investigator-rated CGI-I. Secondary efficacy endpoints included the change from baseline in the IRLS Rating Scale total score and the proportion of responders on the investigator-rated CGI-I at the end of Week 1, the proportion of responders on the patient-rated CGI-I at Week 1 and Week 12, the change from baseline in average daily total sleep time, and average daily wake time after sleep onset at the end of treatment as assessed by the Pittsburgh Sleep Diary (PghSD). Other secondary efficacy endpoints and analyses included the change from baseline to end of treatment on the Post-Sleep Questionnaire (PSQ), RLS pain assessment, Mood Assessment Question, Profile of Mood State (POMS), Medical Outcomes Study (MOS) Sleep Scale domains (sleep disturbance, sleep adequacy, sleep quantity, and somnolence), 24-hour RLS Symptom Record, and the Johns Hopkins RLS Quality of Life (QoL) instrument.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis of efficacy and safety endpoints for RLS was conducted (XP084) using integrated data from Phase I, Phase II and Phase III studies for pharmacokinetic analysis and Phase II and Phase III studies for safety and efficacy.

The population pharmacokinetic model was first developed to describe systemic gabapentin pharmacokinetics in subjects with RLS following oral administration of XP13512. This model determined the effects of covariates (age, weight, height, body mass index, sex, creatinine clearance) on selected PK parameters. The relationship between creatinine clearance and clearance of gabapentin after oral dosing of XP13512 in healthy subjects and subjects with renal impairment was also investigated. Steady state values for AUC and Cmax were predicted for all subjects in the Phase II and Phase III studies, based on the population PK model in order to perform the PK/PD analysis. The population PK/PD model was then developed to describe the relationship between XP13512 dose/ gabapentin systemic exposure and efficacy in subjects with RLS after administration of XP13512 (IRLS score, change from baseline IRLS score, percent change from baseline IRLS score, investigator rated CGI, patient rated CGI, change from baseline in average daily wake time after sleep onset, and average daily total sleep time).The second objective of the PK/PD model was to develop a population PK/PD model to describe the relationship between XP13512 dose/ gabapentin systemic exposure after administration of XP13512 and safety endpoints (dizziness, somnolence/sedation, and Brief Assessment of Cognition (BAC) composite score). Only data from the 12-week studies (XP052, XP053, and XP081) were used for the PK/PD efficacy analysis. Subjects were analyzed by the dose they were receiving at Week 12 LOCF, rather than the randomized dose. The PK/PD modelling was performed with XP13512 doses ranging from 600 mg to 2400 mg (a 4-fold range of doses). There was a wide range in subject weight and creatinine clearance values in these studies, and this resulted in a greater than 10-fold range of gabapentin exposures (AUC range 25 μg*h/mL to 339 μg*h/mL). Exposure-response relationships for the efficacy variables therefore may have greater potential to predict the outcomes for doses outside of the range evaluated in clinical studies.

For the PK/PD safety exposure-response analysis, the exposure on the day of the occurrence of the adverse event was used in the model. The change from baseline to week 12 was evaluated for the BAC.

The agency's analysis for the population PK/PD data for efficacy and safety is provided below and the whole review is provided in the Appendix 4.2.

2.2.4 Will 600 mg dose be equally efficacious with less safety concern (sedation)?

Yes, 600 mg dose seems to provide a better benefit/risk profile than 1200 mg.

Benefit: Figure 1 shows the relationship between dose and primary endpoints for efficacy (IRLS- International Restless Leg Syndrome rating scale, CGI-I-Clinical Global Impression-Improvement) in seven studies. It shows that 600 mg would provide similar benefit in comparison to 1200 mg. The reason for lack of effect after 600 mg dose in study XP045 was not explored.

Risk:
Sedation: The sedative effects of 1200 and 1800 mg dose were evaluated using lane position variability as the outcome measure. Figure 2, Figure 3 shows the relationship between mean and individual gabapentin concentrations collected on Day 14, 15 and 16 in Study XP083. The effects of 600 mg dose on lane position variability cannot be determined due to high variability in the data. However, both 1200 mg and 1800 mg dose groups were similar to active-control (Diphenhydramine) in terms of changes in LPV. The sponsor did not evaluate the changes in lane position variability (safety indicator for sedative effects) after 600 mg dose.
Dizziness, Somnolence: Figure 4 shows that 1200 mg dose has more adverse events (numerical) in comparison to 600 mg.

Figure 1. **(TOP)** Mean (95% CI) Change from Baseline in IRLS Rating Scale Total Score to End of Treatment (All Completed RLS Clinical Studies with Efficacy Outcomes). **(BOTTOM)** Proportion of Responders on the Investigator-Rated CGI-I Scale at End of Treatment (All Completed RLS Clinical Studies with Efficacy Outcomes)

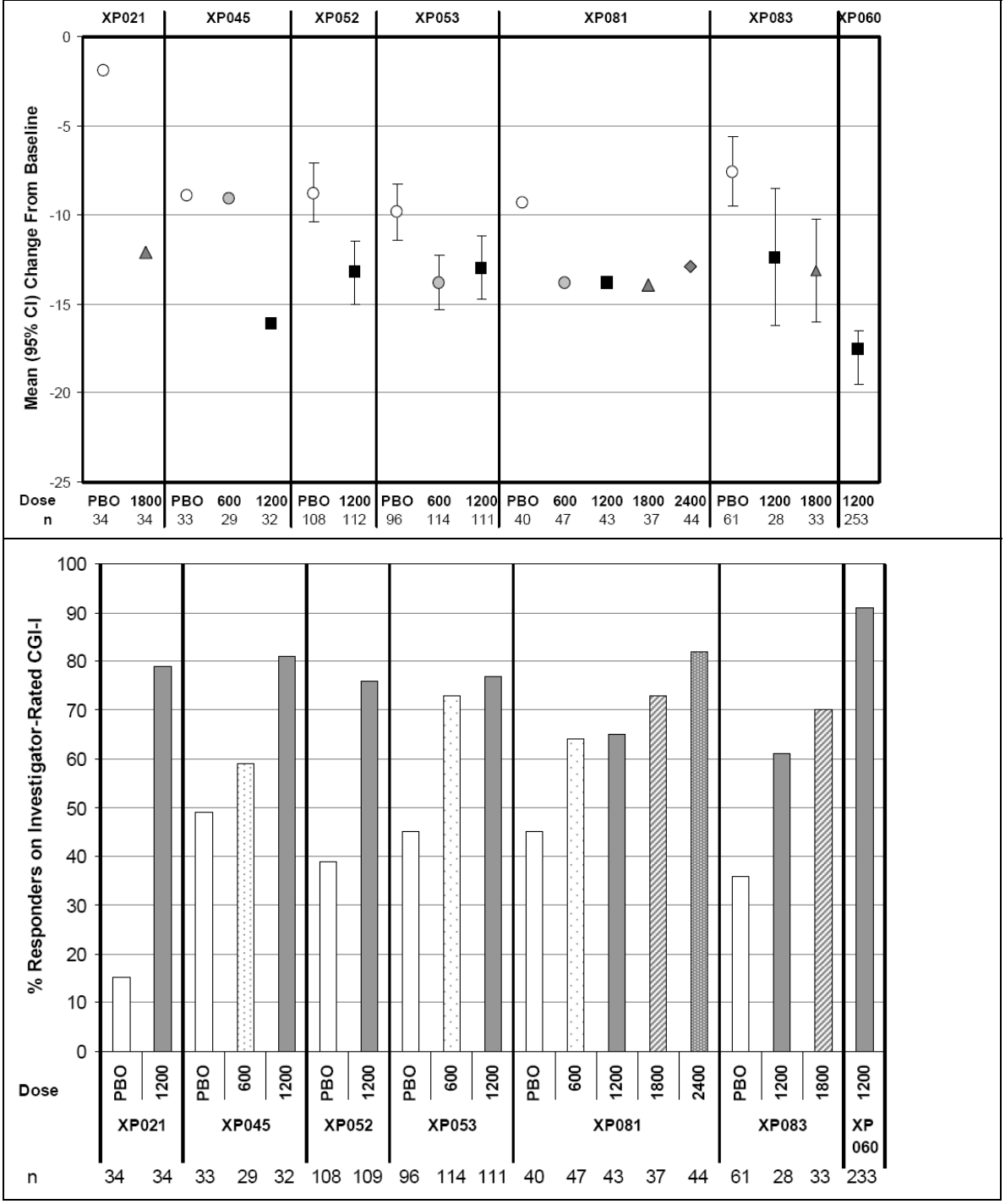


Figure 2. Relationship between mean concentrations of gabapentin (Day 14; 2h post-dose, Day 15; 14h post-dose on day 14, Day 16; 7h, Tmax) and baseline, placebo subtracted LPV (ft) in Study XP083. Shown in vertical lines are the observed mean steady state Cmax after 600, 1200 and 1800 mg in Study XP081 for reference purpose. Shown for reference (dotted line) is the change from baseline, placebo subtracted LPV for active control (Diphenhydramine; DPH)

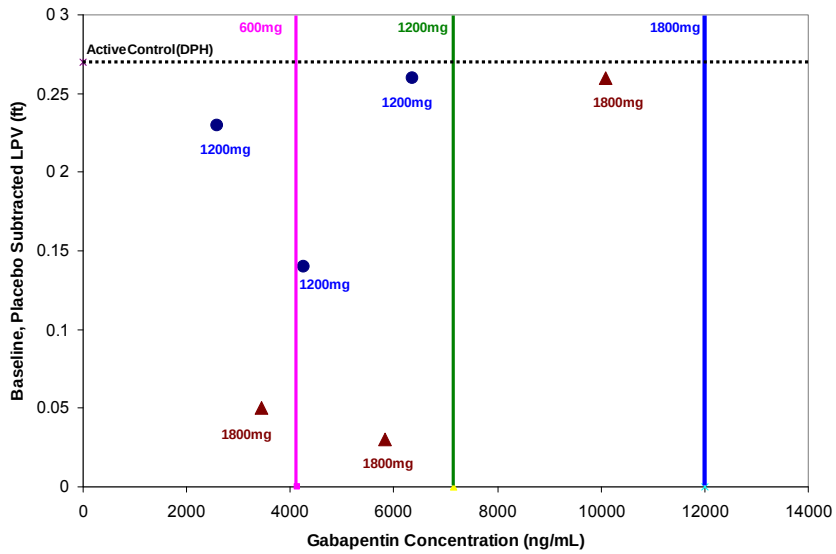


Figure 3. Relationship between change from baseline LPV and gabapentin concentrations after 1200 (LEFT) and 1800 (RIGHT) mg dose in study XP083. Shown for reference are the mean change from baseline LPV in placebo and diphenhydramine (DPH) groups.

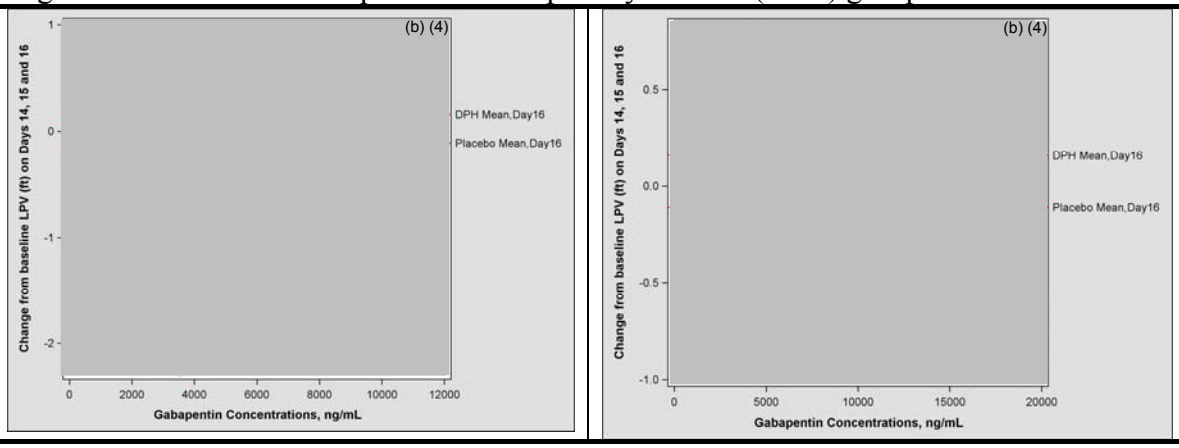
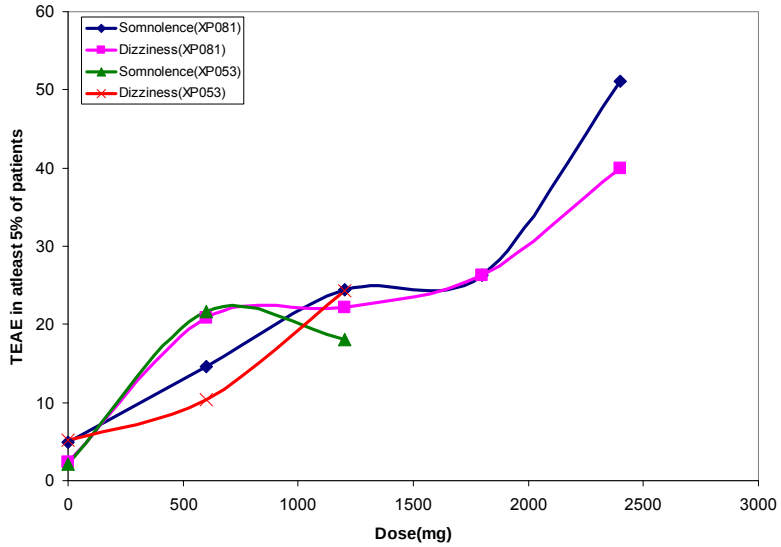
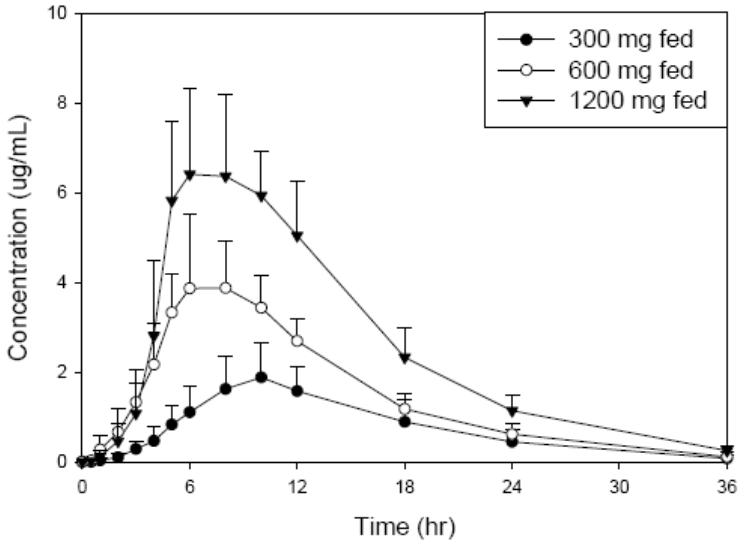


Figure 4. Relationship between dose and treatment emergent adverse events in atleast 5% of the patients. Shown are the data from two studies where various doses were studied.



2.2.5 Is the (b) (4) dose appropriate if 5PM dose is missed as proposed by the sponsor?

With the sponsor's proposal, the drug should be taken with food at 5 PM to receive best benefit during the evening and night while the Tmax would be approximately at 12 AM. By next morning the drug concentration should have gone lower. However, when the dose is given (b) (4) the Tmax appears to be at (b) (4) which raises the safety concern since the drug has the sedation effect. Therefore, the OCP would not agree with this alternative dosing regimen.



2.2.6 Does this drug prolong the QT or QTc interval?

The QT study conducted at 6000 mg dose of XP13512 has been reviewed and analyzed by IRT group. The study is found to be inconclusive. The sponsor is therefore recommended to conduct a repeat TQT study. The summary of the review is provided below.

The moxifloxacin response failed to meet our criteria for assay sensitivity. Our expectations for assay sensitivity are (1) the ΔΔQTc-time profile follows the expected moxifloxacin concentration-time profile (peak around Cmax and taper off over time) and (2) the mean effect on the QTc is greater than 5 ms as evidenced by the lower 90% confidence interval > 5 ms at least at one time point.

In this study, the largest lower bound of the two-sided 90% CI of ΔΔQTcI for moxifloxacin 400 mg around Cmax (2 hours after dosing) was lower than 5 ms (4.2 ms) even before multiple endpoint adjustment, and the moxifloxacin profile over time is also not adequately demonstrated. A lack of PD profile for moxifloxacin can be further supported by the individual PK and PD plots. Therefore, lack of QTc effect of gabapentin enacarbil can not be reliably concluded. We found no problems with the PK of moxifloxacin or with the measurement of QT on ECGs so, we do not believe further analysis of existing data will be fruitful.

We recommend that the sponsor conducts a repeat TQT study to fulfill the requirements outlined in ICH E14 guidelines.

2.2.7 Are the active moieties in the biosamples appropriately identified and measured to assess pharmacokinetic parameters?

Yes. The assay validation and the biosample analysis for the prodrug, XP13512, and its metabolite, gabapentin, are acceptable. LC/MS/MS methods were developed and validated for measuring the XP13512 and gabapentin concentrations in human blood, plasma and urine. Quenched blood samples were initially analyzed knowing the instability of XP13512 in the plasma. Although almost linear correlation between blood and plasma was later revealed in study XP22, blood and plasma samples were still used for drug concentration analysis throughout different clinical pharmacology studies.

The LLOQ for XP13512 and gabapentin were 10 and 50 ng/mL, respectively, in blood and urine and LLOQ of gabapentin was 80 ng/mL in plasma. The validated concentrations range was from 10-2500 ng/mL for XP13512, 50-12500 ng/mL for gabapentin in blood and urine and 80-10000ng/mL for gabapentin in plasma.

A summary of all methods used is given in the individual study, analytical section of this review.

2.2.8 What are the general ADME characterstics of gabapentin?

The key ADME characteristics of gabapentin are summarized below:

Absorption:

In a mass balance study with ^{14}C-XP13512 immediate release formulation, mean recovery of total radioactivity in urine was 94.1%, with 5.2% of the radioactive dose recovered in faeces. Total recovery in urine and faeces combined was approximately 99.3% (XP065).

The absorption of gabapentin from XP13512 ER has been described as a zero-order process with a lag-time of around 0.5 hr, using population pharmacokinetic modeling (XP084).

In fed subjects, the maximum concentration of gabapentin in plasma occurred from 5.7 hr to 9.8 hr post dose. The corresponding mean bioavailability of gabapentin from XP13512 ER by urinary recovery ranged from 64.3% to 86.1%. Exposure to intact XP13512 in systemic blood after oral dosing of XP13512 was consistently low (≤2% of the corresponding gabapentin exposures based on AUC) at all dose levels examined.

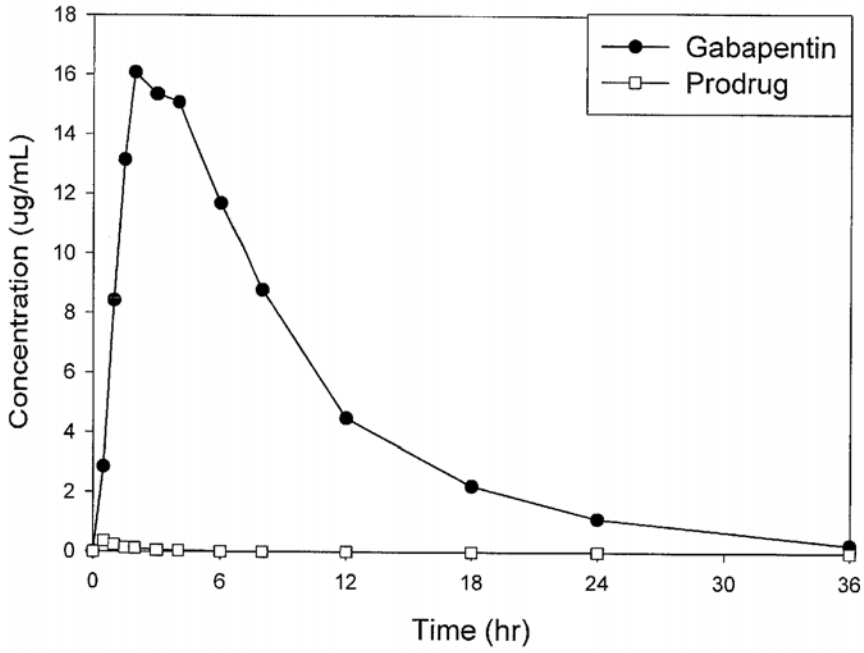


Figure 6.5. Mean concentrations of gabapentin and XP13512 in blood after oral administration of 2800 mg XP13512 in Study XP006. (Data are mean of 8 subjects.)

Steady state was achieved in 1 day after BID dosing of ER XP13512. Based on the PK, steady state with QD should be achieved within 2 days.

Distribution:

XP13512 was 78 to 87% bound to human serum albumin over the concentration range 5 to 100 μM (1.7 μg/mL -32.9 μg/mL). Protein binding of gabapentin has previously been reported to be <3.0% in plasma of rats, monkeys, and humans. Based on the population PK model, for typical male and female subjects weighing 79 kg and 51 years of age, the apparent volume of distribution values were 86.3 and 65.6 L, respectively.

Metabolism:

Following absorption from the intestinal tract, XP13512 undergoes extensive first-pass hydrolysis by non-specific carboxylesterases to form gabapentin, isobutyric acid, acetaldehyde, and carbon dioxide. There are no intermediates in this reaction. There are no other significant metabolites of XP13512.

Human liver and intestinal tissues have been shown to hydrolyze XP13512 to gabapentin extensively *in vitro* [Report PK-2003-002]. *In vitro* studies have shown that XP13512 is a substrate for human carboxylesterases including human carboxylesterase type 2 (hCE-2), an enzyme that is highly abundant in intestinal tissues. Gabapentin lactam, a potential metabolite, was not detected in the blood of healthy subjects at clinically relevant levels: concentrations of gabapentin lactam were close to the limit of detection (10 ng/mL) for all XP13512 doses up to 2800 mg (Study XP006). Therefore, this compound was not monitored in subsequent studies.

The formation of acetaldehyde from XP13512 occurs primarily in the intestinal epithelial cell layer. The acetaldehyde released from XP13512 at the anticipated clinical dose (1200 mg) is less than 2% of that produced from consumption of a single unit of alcohol.

It has been shown previously that gabapentin is not metabolized to any significant extent in humans, and the drug is cleared unchanged by renal elimination [Neurontin® Package Insert, 2007]. Neither XP13512 nor gabapentin are substrates, inducers or inhibitors of the major isoforms of human cytochrome P450, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [Report PK-2003-002]. However, the potential of XP13512 and gabapentin to be substrate or inhibitor of CYP2C8 and 2B6 were not evaluated. A study should be required as a PMR for the potential of XP13512 and gabapentin to be inhibitor of CYP2C8 and 2B6.

The results of the ^{14}C-XP13512 radiolabel study (XP065) indicated that ^{14}C-gabapentin was the only radioactive component detected in blood and the major metabolite in urine (accounting for a mean of 89.6% of the radioactive dose). The only significant metabolic pathway of ^{14}C-XP13512 in humans was ester hydrolysis of the prodrug to gabapentin.

Elimination:

Following hydrolysis of XP13512 to gabapentin, the released gabapentin is excreted by renal elimination. Recent evidence has shown that gabapentin is eliminated via an organic cation transporter (OCT2) present in the kidney. The elimination t1/2 is approximately 5-7 hours for gabapentin.

2.2.9 What is the variability in the PK data?

In the population PK analysis (XP084), a one-compartment model with linear elimination was fit to plasma concentrations of gabapentin. The absorption of gabapentin was modeled using a zero-order rate with duration (D) and a lag time (ALAG) of absorption. Sex, body weight, and creatinine clearance were identified as significant covariates on the apparent clearance (CL/F) and volume of distribution (V/F) of gabapentin. The bias and precision of the parameters of the final population PK model were examined using resampling strategies. Results of the final population PK analysis are presented in the table below. The final model, which included sex, weight and creatinine clearance as covariates, showed an inter-individual variability of 20.5% for CL/F and 33.9% for V/F.

Table 33 Population Pharmacokinetic Parameters for Gabapentin Following Oral Administration of XP13512.

PK Parameters	Estimate	IIV%
D (h)	6.86	22%
ALAG (h)	0.390	200%
CL/F (L/h)	$6.74 \times \left(\frac{\text{Weight(kg)}}{79}\right)^{0.228} \times \left(\frac{\text{CRCL}_{\text{TRUNC}}\text{(mL/min)}}{104}\right)^{0.675}$ for Men $5.74 \times \left(\frac{\text{Weight(kg)}}{79}\right)^{0.228} \times \left(\frac{\text{CRCL}_{\text{TRUNC}}\text{(mL/min)}}{104}\right)^{0.675}$ for Women	20.5%
V/F (L)	$86.3 \times \left(\frac{\text{Weight(kg)}}{79}\right)^{0.544} \times \left(\frac{\text{Age}}{51}\right)^{-0.239}$ for Men $65.6 \times \left(\frac{\text{Weight(kg)}}{79}\right)^{0.544} \times \left(\frac{\text{Age}}{51}\right)^{-0.239}$ for Women	33.9%

IIV%: inter-individual variability, $\text{CRCL}_{\text{TRUNC}}$: creatinine clearance truncated to 150 mL/min.

2.2.10 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

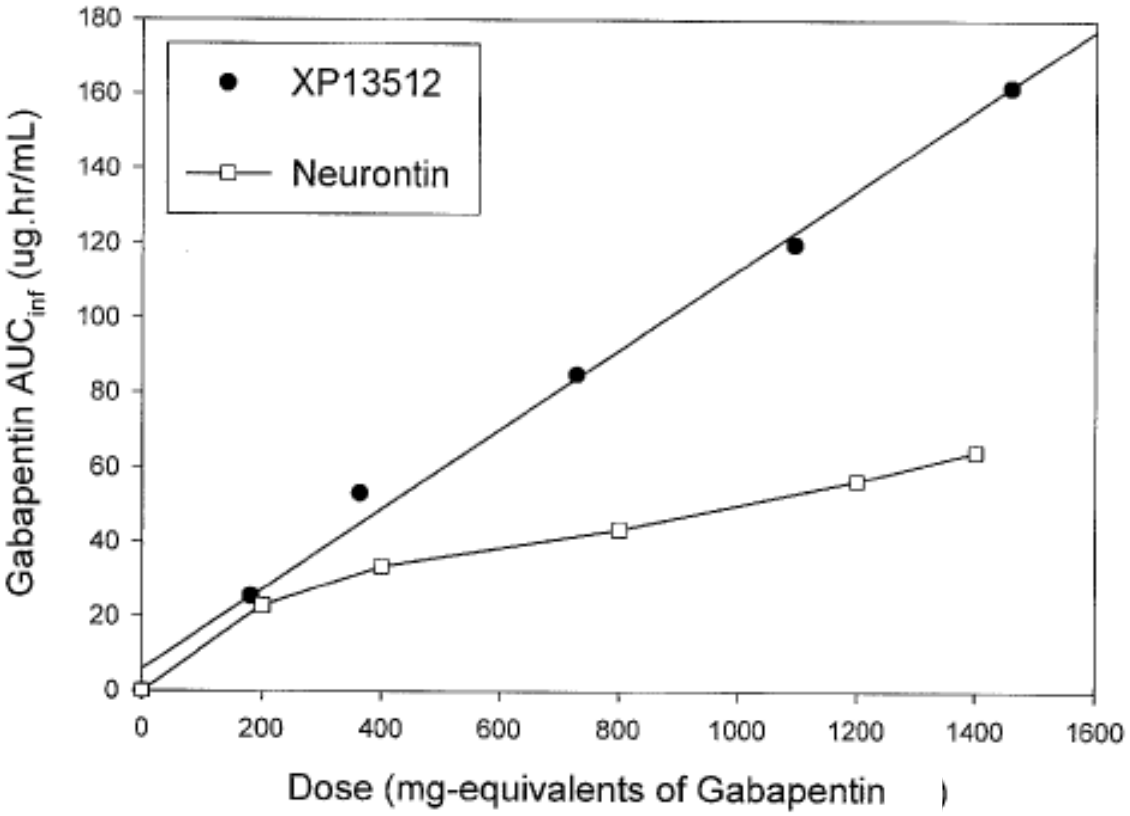
The pharmacokinetic parameters, Cmax and AUC, of gabapentin after administration of XP13512 appears to be dose proportional within single dose of 300 mg to 6000 mg XP13512 ER and multiple doses up to 4200 mg/day for XP13512 IR formulation and 3600 mg/day for XP13512 ER formulation while administration of gabapentin (Neurontin®) exhibited saturation in absorption. The linearity of gabapentin PK following administration of XP13512 was investigated in 3 Phase I studies (XP044, XP069, XP072) and in a Phase II study in RLS subjects (XP081). In studies XP069, XP072 and XP081,

dose proportionality of gabapentin exposure was examined by regression analysis of natural log transformed pharmacokinetic parameters. The slope of linear regression and the 95% confidence interval (CI) were estimated. The dose ranges used to assess the linearity of gabapentin exposure following oral administration of XP13512 ER are shown in the table below.

Table 25 Description of the Dose Linearity Assessment

Study	Population	Dosing regimen	Food
XP044	Healthy subjects	Single dose (300, 600, 1200 mg)	Fasted and High fat/calory
XP069	Healthy subjects	Single dose (2400, 3600, 4800, and 6000)	Standard fat/calory
XP072	Healthy subjects	Single dose (600, 1200, 1800 mg)	Fasted
XP081	RLS patients	Multiple dose for 12 weeks (600/day, 1200/day, 1800/day, 2400/day)	Standard fat/calory

The relationship of doses (mg-equivalents of gabapentin/kg) versus gabapentin exposure (AUC) after administration of XP13512 and Neurontin is shown below:



2.3 INTRINSIC FACTORS

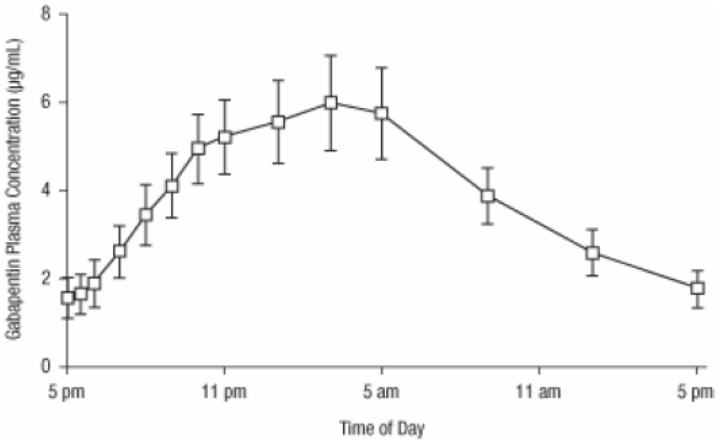
2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.1.1 PK in RLS patients:

Based on study XP081, the PK of gabapentin following oral administration of XP13512 ER tablets were similar between subjects with RLS and healthy subjects. The gabapentin plasma concentration-time profile of RLS patients is shown below.

Figure 1. Mean (±2 S.E.) Steady-State Plasma Concentrations of Gabapentin After Dosing 1,200 mg of SOLZIRA Once Daily With Food in RLS Patients



2.3.1.2 Effect of age:

It was known that the renal clearance of gabapentin declines with age (Neurontin®). The decreases of apparent oral clearance (CL/F) of gabapentin after administration of XP13512 as age increases in the current submission can be explained by the decline of renal function. Based on the population report (XP084), no additional effect of age on gabapentin CL/F was observed, after accounting for changes in renal function.

Dosage adjustment:
No dose adjustments are therefore recommended based on age.

2.3.1.3 Effect of Gender:

Based on the population analysis (XP084), a slight effect of gender was observed. Gabapentin CL/F after administration of XP13512 were 6.7 and 5.7 L/h for male and female (15% lower for females) weighing 79 kg with creatinine clearance of 104 mL/min, respectively, whereas the corresponding volumes of distribution were 86.3 L and 65.6 L, respectively for a subject weighing 79 kg and 51 years of age. These differences are not considered clinically meaningful.

Dosage adjustment:
No dosage adjustment is recommended based on gender.

2.3.1.4 Effect of Race:

In the whole clinical program, the majority of the subjects were Caucasian (94%) while no other single race was greater than 4%. The effect of race therefore could not be studied. Based on one study (XP072), pharmacokinetics of gabapentin released from XP13512 were similar in Caucasian and Japanese.

Dosage adjustment:
No dosage adjustment is recommended based on race.

2.3.1.5 Effect of Hepatic Impairment:

A specific study in subjects with hepatic impairment has not been conducted, since the gabapentin released by hydrolysis of XP13512 is not significantly metabolized by CYP enzymes. It does not inhibit nor induce these enzymes. Although hydrolysis of XP13512 to gabapentin could potentially be affected by alterations in the level of carboxylesterase activity, but given the abundance and wide distribution of hCE-2 in the body it is unlikely that concomitant medications would affect conversion of XP13512 to gabapentin. Further, the conversion of XP13512 to gabapentin occurs mainly in enterocytes and not liver.

Dosage adjustment:
No dosage adjustment is recommended based on hepatic function.

2.3.1.6 Effect of Renal Impairment:

Effect of renal impairment on gabapentin PK was evaluated and analyzed by the pharmacometrics reviewer. The review and recommendations for dose adjustments were described below.

Is the proposed dosing regimen of SOLZIRA® in patients with renal impairment acceptable?

No, if the benefit-risk is not acceptable at target doses of 1200 mg. The sponsor proposed dosing regimen in patients with renal impairment is shown in Table 1.

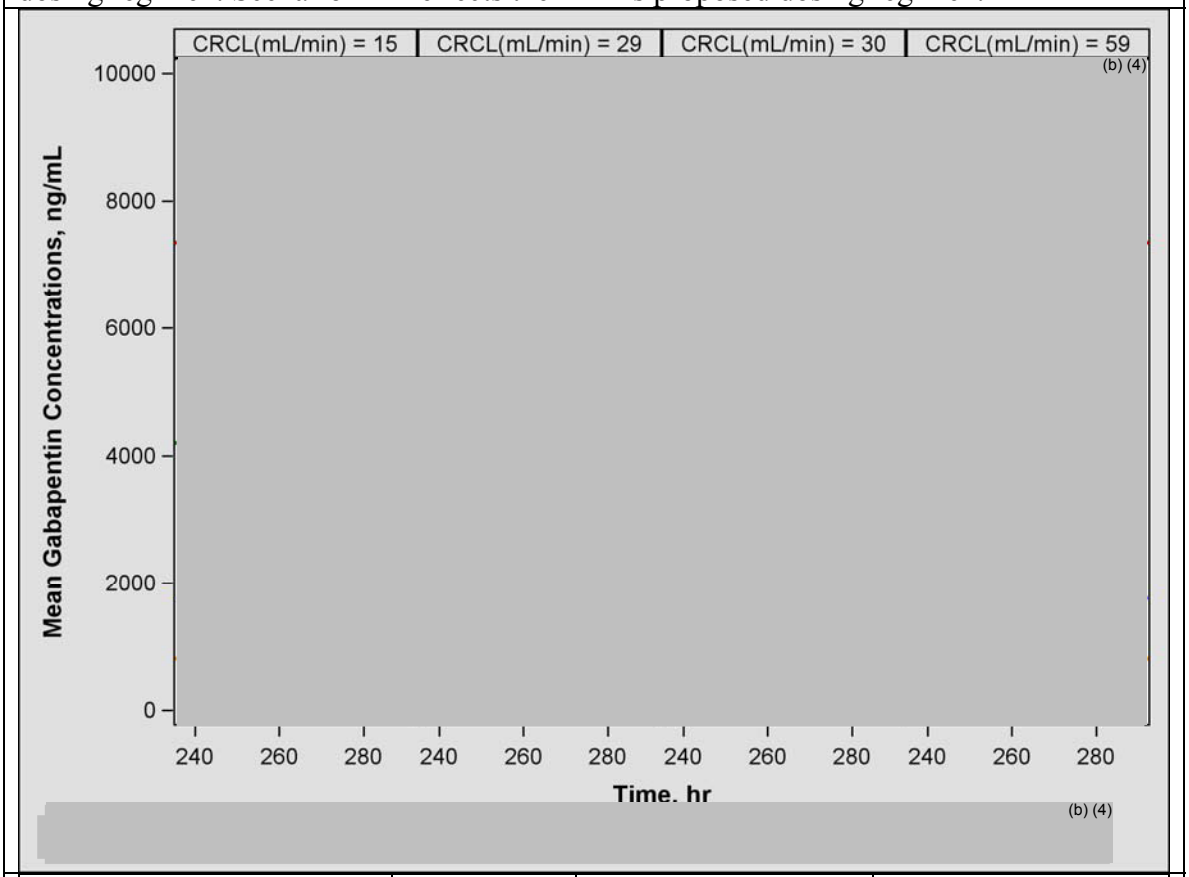
Table 1. Dosage of SOLZIRA® Tablets Based on Creatinine Clearance		
Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
[redacted] (b) (4)		

Table 2 shows the calculated Cmax, AUC at steady state ($C_{ss,max}$, AUC_{ss}) based on the dosing regimen proposed in Table 1. The sponsor concluded that simulated $C_{ss,max}$ and AUC_{ss} during steady state in subjects who require dosing adjustment are in the same range as those observed in subjects with normal renal function with the proposed dosage adjustment.

Table 2. Mean Pharmacokinetic Parameters for Gabapentin in Plasma at Steady State after Oral Dosing of 600 mg XP13512 Tablet in Subjects with Varying Renal Functions.		
CrCL (mL/min)	Steady State PK Parameters in plasma after administration of XP13512	
	AUCss (ug*h/mL)	Cmax,ss (ug/mL)
[redacted] (b) (4)		

Reviewer's Comments: The sponsor's proposed dosing regimen in patients with renal impairment is based on the relationship between gabapentin clearance and creatinine clearance (CrCL) derived from population pharmacokinetic analysis. The reviewer simulated the gabapentin concentration-time profile after administration of XP13512 tablets in patients with various degrees of renal function. The simulations were conducted using the dose/dosing regimen as proposed by the sponsor along with FDA's proposal as shown in Figure 5. The dosing regimen proposed by the sponsor and FDA are coded as D1 and D2 respectively. The reference lines show the observed Cmax, Ctrough at steady state after 600, 1200 mg dose in study XP081.

Figure 5. Mean steady-state simulated gabapentin concentrations based on zero order absorption model in a typical patient (Age=51, Weight=79 kg, Gender=Male) with creatinine clearance of 15, 29, 30 and 59 mL/min after administration of XP13512 using dosing regimens as shown in table below. Scenario=D1 reflects the sponsor's proposed dosing regimen. Scenario=D2 reflects the FDA's proposed dosing regimen.



Renal Function Creatinine Clearance (mL/min)	Scenario	Titration Dose Regimen	Target Dose Regimen
(b) (4)			
30-59	D2	300 mg per day for 3 days	600 mg per day starting day 4
(b) (4)			
15-29	D2	no titration	300 mg per day

Based on the simulations the following are the conclusions:

1. Patients with creatinine clearance 30-59 mL/min:
    - The sponsor's proposed dosing regimen [redacted] should be changed to 300 mg on Day 1, 2, 3 followed by 600 mg from Day 4 onwards. The FDA's proposal will avoid accidental dosing by patients on [redacted] as currently proposed by the sponsor.
    - Creatinine Clearance = 30 mL/min (Based on FDA's proposal)
        - The concentrations at steady-state in patients with creatinine clearance of 30 mL/min will be in the range of concentrations after 600 and 1200 mg dose in patients with normal renal function.
    - Creatinine Clearance=59 mL/min (Based on FDA's proposal)
        - The concentrations at steady-state will be in the range of concentrations after 600 mg dose in patients with normal renal function.
2. Patients with creatinine clearance 15-29 mL/min:
    - The sponsor's proposed dosing regimen [redacted]) should be changed to 300 mg per day. The FDA's proposal will avoid accidental dosing of [redacted] by patients as currently proposed by the sponsor.
    - Creatinine Clearance=15 mL/min (Based on FDA's proposal)
        - The concentrations at steady-state in patients with creatinine clearance of 15 mL/min will be in the range of concentrations after 600 mg dose in patients with normal renal function.
    - Creatinine Clearance=29 mL/min (Based on FDA's proposal)
        - The peak concentrations at steady-state will be slightly lower (after accounting for the observation that the model underpredicts the Cmax) than the Cmax after 600 mg dose in patients with normal renal function. The concentrations at steady-state in general will be in the range of concentrations after 600 mg dose in patients with normal renal function.

Based on observed data

In patients with creatinine clearance ≥ 60mL/min, the target titration dose of 1200 mg should be changed to 600 mg since both doses were equally efficacious in Study XP053 and XP081. Also the incidence of adverse events were higher (numerical) in 1200 mg dose in comparison to 600 mg.

The dosing regimen as proposed by FDA is shown below.

Table 3. FDA proposed dosing regimen for XP13512 in patients with various degrees of renal function

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day

2.4 EXTRINSIC FACTORS

2.4.1 Are XP13512 and gabapentin a substrate, inhibitor or inducer of CYP enzymes?

Substrate:

Neither XP13512 nor gabapentin are substrates for CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 at clinically relevant concentrations.

CYP2C8 and 2B6 were not evaluated; however, given that gabapentin is mostly eliminated unchanged, a study is not required.

Inhibitor:

Neither XP13512 nor gabapentin are inhibitors for CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 at clinically relevant concentrations

CYP2C8 and 2B6 were not evaluated and a study should be required as a PMR.

Inducer:

Neither XP13512 nor gabapentin are inducers for CYP1A2, 2C9, 2C19, 2D6, 2E1, 2B6 and 3A4 at clinically relevant concentrations.

CYP2C8 was not evaluated; however, it is known that CYP2C and CYP3A are co-induced. With a negative data in CYP3A4, a CYP2C induction study is therefore not required.

2.4.2 Are XP13512 and gabapentin a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

XP13512 is not a substrate or inhibitor of human P-gp. This conclusion is made by reviewing the respective reports and consulting with Dr. Lei Zhang in OCP.

In vitro studies have shown that XP13512 is a substrate for multiple high capacity nutrient transport pathways, including the monocarboxylate transporters Type 1 (MCT-1) and the sodium-dependent multivitamin transporters (SMVT), both of which are abundant throughout the intestinal tract.

Recent evidence has shown that gabapentin is eliminated via an organic cation transporter (OCT2) present in the kidney [XenoPort report BIO-2003-002]. It has previously been shown that coadministration of oral cimetidine, a known substrate for this same OCT2-mediated elimination pathway, produces a 14% decrease in mean apparent clearance of gabapentin, presumably by competition for the OCT2 transporter [Neurontin® Package Insert, 2007].

2.4.3 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.3.1 Influence of co-administration of XP13512 on other drugs:

Naproxen (MCT-1 substrate)

The pathway for absorption of XP13512 in animals and humans is believed to include active transport via a proton-linked monocarboxylate transporter (MCT1). MCT1 appears to be the primary monocarboxylate transporter localized on the apical surface of the intestinal tract and is abundant in both the small and large intestine. Naproxen has recently been shown to be a substrate for MCT1. Gabapentin has a pharmacokinetic drug interaction with naproxen shown previously that was not considered clinically significant; co-administration of naproxen led to a 12 to 15% increase in gabapentin exposure. [Neurontin® Package Insert, 2007].

The interaction of XP13512 ER tablets given once daily at a dose of 1200 mg with naproxen (500 mg B.I.D) has been investigated at steady state (Study XP067). The geometric mean ratios and 90% confidence intervals for naproxen PK parameters are presented in the table below. There was no change in steady state PK of naproxen (Css,max and AUCss) when co-administered with XP13512.

Naproxen PK Parameter	Geometric Mean Ratio [(XP13512 + Naproxen)/Naproxen]	
	Point Estimate	90% Confidence Interval
$C_{ss, max}$	0.99	(0.95, 1.03)
AUC_{ss}	0.98	(0.94, 1.03)

Cimetidine (OCT2 inhibitor)

Gabapentin renal excretion is believed to involve a component of active secretion and recent evidence has shown that gabapentin is a substrate for an organic cation transporter (OCT2) present in the kidney [XenoPort report BIO-2003-002]. Cimetidine is a known substrate for this same OCT2-mediated elimination pathway. It has previously been shown that coadministration of oral cimetidine produces a 14% decrease in mean apparent clearance of gabapentin, presumably by competition for the OCT2 transporter [Neurontin® Package Insert, 2007].

A pharmacokinetic drug-drug interaction study was conducted to examine the potential for an interaction of XP13512 with cimetidine at the level of renal secretion (Study XP068). Study XP068 investigated the interaction of XP13512 ER tablets given QD at a dose of 1200 mg with and without 400 mg of cimetidine. The geometric mean ratios and 90% confidence intervals for cimetidine PK parameters are presented in the table below. There was no change in steady state PK of cimetidine (Css,max and AUCss) when co-administered with XP13512.

Cimetidine PK Parameter	Geometric Mean Ratio [(XP13512 + Cimetidine)/Cimetidine]	
	Point Estimate	90% Confidence Interval
$C_{ss, max}$	0.96	(0.90, 1.02)
AUC_{ss}	0.99	(0.95, 1.03)

2.4.3.2 Influence of other drugs on gabapentin when co-administered with XP13512:

Gabapentin PK when co-administered XP13512 with naproxen (MCT-1 substrate)

Co-administration of XP13512 ER with naproxen produced an 8% and 13% increase in gabapentin Css,max and AUCss, respectively, and 13% and 17% decrease in XP13512 Css,max and AUCss, respectively, as compared to XP13512 ER administered alone, while XP13512 Css,max were ≤ 1.65% and AUCss were ≤ 0.34% of the corresponding Css,max and AUCss of gabapentin. However, these changes are not clinically significant. The geometric mean ratios and 90% confidence intervals for gabapentin PK parameters are presented in the table below.

Gabapentin PK Parameter	Geometric Mean Ratio [(XP13512 + Naproxen)/XP13512]	
	Point Estimate	90% Confidence Interval
$C_{ss, max}$	1.08	(1.00, 1.16)
AUCss	1.13	(1.08, 1.19)

Gabapentin PK when co-administered XP13512 with cimetidine (OCT2 inhibitor)

There was no statistically significant change in Css, max of gabapentin, while gabapentin AUCss was slightly increased, by 24%, consistent with a decrease in CLss/F of approximately 20% when XP13512 was dosed with cimetidine compared with XP13512 alone. This slight increase in gabapentin exposures associated with cimetidine co-administration is not considered clinically significant. The geometric mean ratios and 90% confidence intervals for gabapentin PK parameters are presented in the table below.

Gabapentin PK Parameter	Geometric Mean Ratio [(XP13512 + Cimetidine)/XP13512]	
	Point Estimate	90% Confidence Interval
$C_{ss, max}$	1.06	(0.98, 1.15)
AUCss	1.24	(1.17, 1.32)

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

XP13512 is considered a highly permeable and low solubility compound (BCS Class II). The solubility of XP13512 is pH dependent, typical of a monoprotic weak acid. The lowest solubility it exhibits (0.46 mg/mL) is in acidic solution where the drug is present in the unionized form. As a result of this low solubility at gastric pH, XP13512 is considered to be poorly soluble for BCS Classification. The permeability class boundary is based indirectly on the extent of absorption of drug substance in humans. After oral administration of 14C-XP13512 provided as a solution in gelatin capsules, mean recovery of the radioactive dose in urine was 94.1%, exceeding the minimum high permeability criteria set in the BCS guidance. However, the stability of the drug in GI fluids has not been evaluated, although XP13512 has been shown to be chemically stable for 1 hour at 37^{o}C at pH 2 to 8. Instability in pancreatin is also noted. Additionally, permeability data on parent and active metabolite are not available. Therefore, BCS class cannot be

confirmed at this time. Details of XP13512 solubility are reported in the Drug Product Section of the submission.

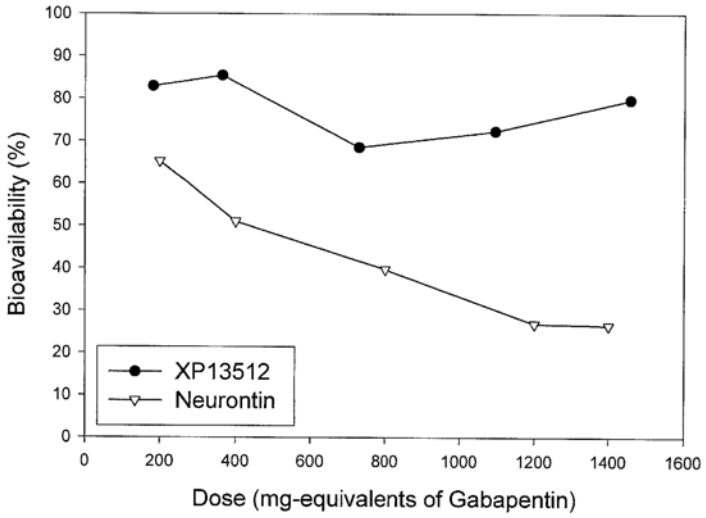
2.5.2 Is the proposed to-be-marketed formulation bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The formulation has been constant throughout the clinical development of this product. The commercial ER formulation is identical to that used in Phase I, Phase II, and Phase III clinical studies. There are therefore no relative bioavailability/ bioequivalence studies conducted for the purpose of linking the commercial and research formulations.

XP13512 ER vs IR: No formal studies were conducted comparing ER versus IR formulation of XP13512 at SD and steady state since no approved XP13512 IR formulation is available. In study XP019, mean bioavailability of gabapentin (based on the urinary recovery of gabapentin) for XP13512 ER in fasted state is about 75% relative to XP13512 IR (65 divided by 84).

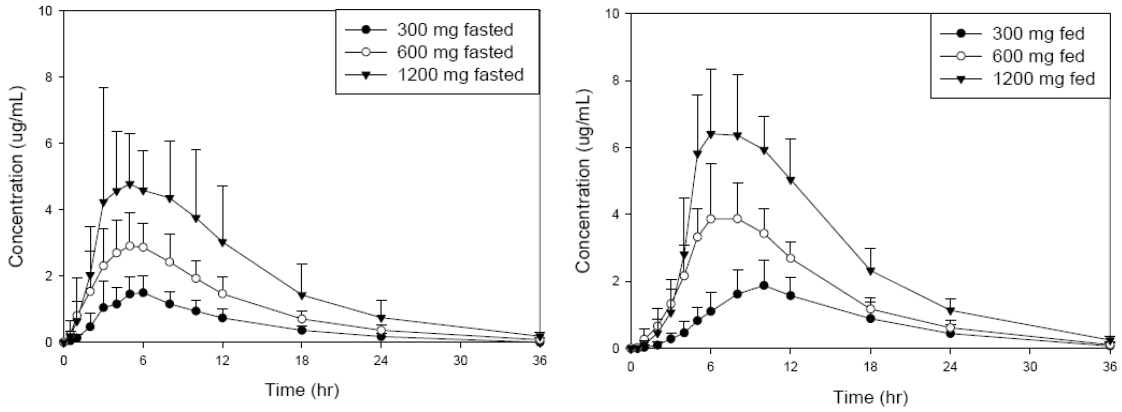
Group	Formulation	N	Dose (mg)	Dose (mg-equiv. gabapentin)	Mean Body Weight (kg)	Dose (mg-equiv. Gabapentin/kg)	F (%)
1	IR Capsules #030027	12	2 x 350	365	76.4	4.78	83.7
	(b) (4) Tablet #031124	12	1 x 600	313	76.4	4.10	52.1
	(b) (4) Tablet #031201	12	1 x 600	313	76.4	4.10	53.9
	(b) (4) Tablet #030040	12	1 x 600	313	76.4	4.10	71.1
2	(b) (4) Tablet #030040	12	1 x 600	313	78.9	3.97	65.2

Relative BA to Neurontin®: A study comparing XP13512 IR formulation (350 to 2800 mg) to Neurontin® (200 to 1400 mg) was conducted based on equivalent gabapentin dose under feasted condition. Bioavalibility expressed by urinary recovery of gabapentin showed that the XP13512 administration demonstrated consistently high (> 68%) recovery of gabapentin over the dose range while Neurontin® administration showed recovery of gabapentin declined with increase of doses (65% to 27%).



2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of gabapentin in relation to meals or meal types?

Effect of food on gabapentin pharmacokinetics was evaluated by comparing PK of gabapentin following a single oral dose of XP13512 ER with or without a high fat meal. The results showed that the high fat food increases gabapentin AUC by ~50% and Cmax by ~ 30% and delays Tmax from ~5 hours to ~7 hours postdose.



Parameter	XP13512 SR 300 mg Fasted (n=12)	XP13512 SR 300 mg Fed (n=12)	XP13512 SR 600 mg Fasted (n=12)	XP13512 SR 600 mg Fed (n=12)	XP13512 SR 1200 mg Fasted (n=11)	XP13512 SR 1200 mg Fed (n=12)
Dose (mg equivalent of gabapentin)	156		313		625	
C_{max} (µg/mL)	1.69 (±0.51)	2.26 (±0.55)	3.41 (±0.97)	4.41 (±1.26)	6.26 (±2.88)	7.59 (±1.65)
T_{max} (hr)	4.85 (±1.41)	9.83 (±2.76)	5.03 (±2.11)	7.27 (±1.68)	4.74 (±1.95)	7.92 (±2.19)
$T_{1/2}$ (hr)	5.92 (±0.77)	5.96 (±1.05)	5.86 (±1.00)	5.37 (±0.94)	6.18 (±0.86)	5.49 (±0.87)
$AUC_{(0\text{-inf})}$ (µg•hr/mL)	18.0 (±6.26)	27.4 (±6.29)	37.8 (±9.83)	54.1 (±11.8)	69.7 (±24.0)	92.4 (±13.0)

Effect of fat content on gabapentin pharmacokinetics was also evaluated. Following co-administration of XP13512 ER tablets (1200 mg) with a low, moderate, and high fat/caloric meal, the Cmax of gabapentin increases by ~30% to 50% regardless of fat content, while AUC seems to increase with fat content by 24%, 34% and 44%, respectively. The mean gabapentin AUCinf values were 72.1 ± 10.8, 77.2 ± 9.69 and 82.1 ± 7.43 µg*hr/mL, respectively, in comparison to 58.8 µg*hr/mL for fasted conditions. This corresponded to the urinary recovery as gabapentin of 64.3%, 64.9%, and 76.1% for low fat, moderate fat and high fat/caloric meals, respectively compared to 42.0% for fasted subjects. The Tmax values of gabapentin in plasma for the low, moderate, and high fat/caloric meals were 5.7, 7.0, and 7.3 hr, respectively. Pivotal clinical trials were conducted in fed state (however the caloric content or fat content were not controlled). It is recommended that XP13512 be taken with food by RLS subjects.

Table 42 Geometric Mean Ratios (Fed/Fasting) and 90% Confidence Intervals for Gabapentin PK Parameters (XP087)

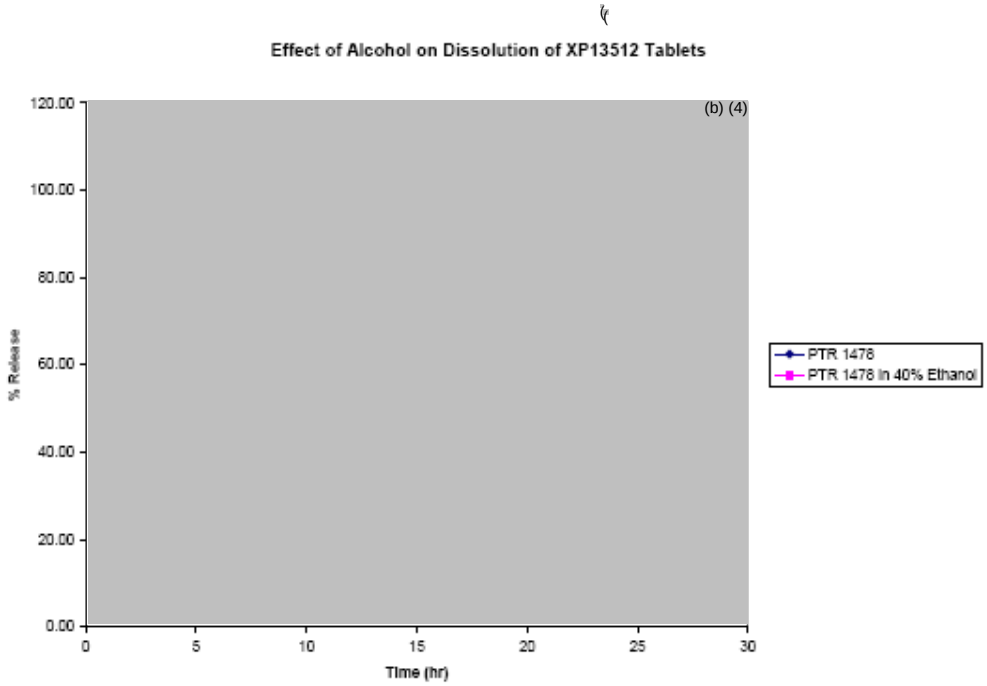
		Geometric Mean Ratio (Fed/Fasting)	
PK Parameter	Treatment	Point Estimate	90% Confidence Interval
C_{max}	Low fat vs. Fasted	1.48	(1.29, 1.69)
	Moderate fat vs. Fasted	1.33	(1.16, 1.52)
	High fat vs. Fasted	1.45	(1.27, 1.66)
AUC_{inf}	Low fat vs. Fasted	1.24	(1.13, 1.35)
	Moderate fat vs. Fasted	1.34	(1.23, 1.46)
	High fat vs. Fasted	1.44	(1.32, 1.57)

2.5.4 What is the effect of alcohol?

Dissolution testing of XP13512 ER Tablets, 600 mg, has been performed in alcoholic media. Dissolution data were generated using the following two dissolution media using (b) (4)

(b) (4)

The results were presented in the following figure. The sponsor stated that extended release of XP13512 is maintained in presence of alcohol. A slight increase in the rate of release of XP13512 in presence of alcohol compared to buffer alone was observed. However, less than (b) (4) of the dose was released within the first hour. The sponsor therefore concluded that this result demonstrates that the formulation is resistant to dose dumping under these conditions.



However, several points should be noted for this evaluation.

1. The dissolution medium and method used in this study is not the final dissolution method selected by the sponsor. The final medium is 75mM NaH_2PO_4 buffer, pH 6.8 with 0.1% SLS and the method used was USP type 2 apparatus at a speed of 100 rpm. As one can imagine, as (b) (4) SLS was used in the alcohol interaction study, 0.1% SLS in the final method should generate a much slower dissolution rate and (b) (4) was used in the alcohol interaction study, the 100 rpm in the final method should instead generate a faster dissolution theoretically, not to mention different buffers and concentrations used in the two methods. These two methods are not comparable. The sponsor should repeat this study using their final dissolution method and evaluate different concentrations of alcohol up to 40%.

2. The dissolution increased 20 to 30% within the first 2 hours with the presence of 40% alcohol. Although 40% alcohol is considered the worst scennario, the dissolution profile at lower percentage of alcohol is not known. However, if the 20 to 30% increase in dissolution translates into 20 to 30 % increase in exposure, this should not be considered a critical issue clinically since much higher doses have been evaluated in clinical trials. However, we do not have such data using the final method.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validation and the biosample analysis for the prodrug, XP13512, and its metabolite, gabapentin, are acceptable. LC/MS/MS methods were developed and validated for measuring the XP13512 and gabapentin concentrations in human blood, plasma and urine. Quenched blood samples were initially analyzed knowing the instability of XP13512 in the plasma. Although almost linear correlation between blood and plasma was later revealed in study XP22, both blood and plasma were used for drug concentration analysis throughout different clinical pharmacology studies.

The LLOQ for XP13512 and gabapentin were 10 and 50 ng/mL, respectively, in blood and urine and LLOQ of gabapentin was 80 ng/mL in plasma. The validated concentrations range was from (b) (4) ng/mL for XP13512, 50-12500 ng/mL for gabapentin in blood and urine and 80-10000ng/mL for gabapentin in plasma. Adequate concentrations of Quality Controls were used in these assay validations.

A summary of all methods used is given in the individual study, analytical section of this review.

3.0 DETAILED LABELING RECOMMENDATION

The reviewer's labeling recommendations are shown by track changes to the sponsor proposed label. These labeling changes should be incorporated in the revised label.

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.0 APPENDIX

4.1 INDIVIDUAL STUDY REVIEW

4.1.1 BIOPHARMACEUTIC STUDIES

Study XP-019: ***A Phase 1, Single dose, Randomized, Open-Label Crossover Study to Determine the Safety, Tolerance and Pharmacokinetics of Four Diferent Oral Formulations of XP13512 (IR vs ER) In Healthy Male Volunteers***

This study was conducted to evaluate 3 different SR formulations of XP13512 (b) (4) and compared with XP13512 IR formulation. The objective was to select a better SR formulation for later investigations.

A brief overview of some essential components of the study design is given below:

Study Design	Single-dose, randomized, open-label crossover
Study Population	N=24 Age: 18-52 years (mean 27.9 years) Gender: 24 males Weight: 63-99 kg (mean 77.4 kg) Race: White (91.7%), Asian (4.2%) and other (4.23%)
Dosage and Administration	Part I: 12 Subjects were randomized to receive 4 single doses with Treatment A, B, C or D in a designed treatment sequence. Part II: Additional 12 subjects received Treatment D. There was at least 4-day washout period between Treatment periods in Part I. Treatment A: A single dose of 700 mg(2x350mg) IR capsules Treatment B: A single dose of 600 mg (b) (4) SR(1) tablet Treatment C: A single dose of 600 mg (b) (4) SR(2) tablet Treatment D: A single dose of 600 mg (b) (4) SR tablet Lot no: 350 mg IR capsules: 030027A 600 mg (b) (4) SR(1) tablets: 031124 600 mg (b) (4) SR(2) tablets: 031201 600 mg (b) (4) SR tablets: 030040 Diet: Subjects were fasted overnight before dosing and up to 4 hours post-dose. Fluids were restricted from dosing to 2 hours postdose. At -2 and -1 hours prior to dosing, and at 2, 4, 6 and 12 hours post dosing, 250 ml of fluid was consumed. Poppy-containing food (e.g., poppy seed bagels, breads, or muffins) was not allowed during the 24 hours before any urine drug screen. Alcohol was prohibited for 24 hours before any study visit until 48 hours after dosing. Caffeine was prohibited for 24 hours before any study visit until 48 hours after dosing.

Sampling: Blood	At predose (0 hour), and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 24, 30 and 36 hours postdose. The samples were analyzed for blood concentrations of gabapentin and XP13512.
Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 hours postdose.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin Lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.7% Inter-day accuracy: < 8 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 7% Inter-day accuracy: < 10 % Long term Stability: 83 days at -80 ^{o}C Gabapentin Lactam: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 9% Inter-day accuracy: < 5 % Long term Stability: 83 days at -80 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin Lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 8% Inter-day accuracy: < 2 % Long term Stability: 236 days at -80 ^{o}C and 42 days at -20 ^{o}C XP13512: Linear range : 10-2500 ng/mL in urine Inter-day Precision

	(%CV for Quality Controls) : < 11.3% Inter-day accuracy: < 5 % Long term Stability: 231 days at -80 °C and 42 days at -20 °C Gabapentin Lactam: Linear range : 10-2500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 9.4% Inter-day accuracy: < 3 % Long term Stability: 231 days at -80 °C and 42 days at -20 °C
PK Assessment	Gabapentin and XP13512 in blood: Cmax, AUClast, tmax, λz, t½z and AUCinf Gabapentin in urine: Am, Am (0-36) and CLr
Safety Assessment	AEs, physical examinations, vital sign measurements (supine BP, pulse and oral temperature), 12-lead ECG (10mm/mV and at 25mm/sec) and Routine laboratory tests (hematology, biochemistry [including additional creatinine and urea assessments] and urinalysis)

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood (Part I):

No blood samples collected in Part I of the study were usable due to leakage of samples during shipment. No blood pharmacokinetic data was available in Part I.

Gabapentin recovery in urine (Part I and Part II):

Table 2.1 Mean Urinary Recovery of Gabapentin After Single Oral Doses of Various XP13512 Formulations in Study XP019

Group	Formulation	N	Dose (mg)	Dose (mg-equiv. gabapentin)	Mean Body Weight (kg)	Dose (mg-equiv. Gabapentin/kg)	F (%)
1	IR Capsules #030027	12	2 x 350	365	76.4	4.78	83.7
	(b) (4) Tablet #031124	12	1 x 600	313	76.4	4.10	52.1
	(b) (4) Tablet #031201	12	1 x 600	313	76.4	4.10	53.9
	(b) (4) Tablet #030040	12	1 x 600	313	76.4	4.10	71.1
2	(b) (4) Tablet #030040	12	1 x 600	313	78.9	3.97	65.2

- 83.7%, 52.1%, 53.9% and 71.1% of the urinary recovery were observed in IR capsule, (b) (4) SR tablet, respectively.
- Based on this data, the sponsor was able to choose the formulation (b) (4)) for further development.
- Due to the lack of the blood pharmacokinetic data (from Part I), the sponsor added an additional group (Part II) to assess PK using the selected formulation.

Gabapentin pharmacokinetics in blood (Part II):

Descriptive Statistics for Gabapentin PK Parameters are shown in the following table:

Table 2.2. Mean Pharmacokinetic Parameters for Gabapentin in Blood After a Single Oral Dose of (b) (4) Tablet #030040 (1 x 600 mg) in Study XP019 (Group 2)

	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	λ_z (hr^{-1})	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
Mean*	2.79	3.92	5.94	0.119	26.5	27.2	12.2	103	9.95
SD	0.83	1.92	0.87	0.015	6.27	6.4	3.19	25.2	1.65
Minimum	1.51	0.500	5.03	0.085	15.2	15.7	8.02	76.6	7.39
Median	3.03	3.50	5.72	0.121	26.0	27.0	11.7	101	9.76
Maximum	3.92	8.00	8.11	0.138	38.0	39.0	19.9	165	13.5
CV%	29.6	48.9	14.6	12.6	23.7	23.5	26.2	24.4	16.5
Geo. Mean	2.67	3.34	5.88	0.118	25.8	26.5	11.8	100	9.83

*Data are mean of 12 subjects.

Mean Gabapentin concentration-time plot is shown in the following figure:

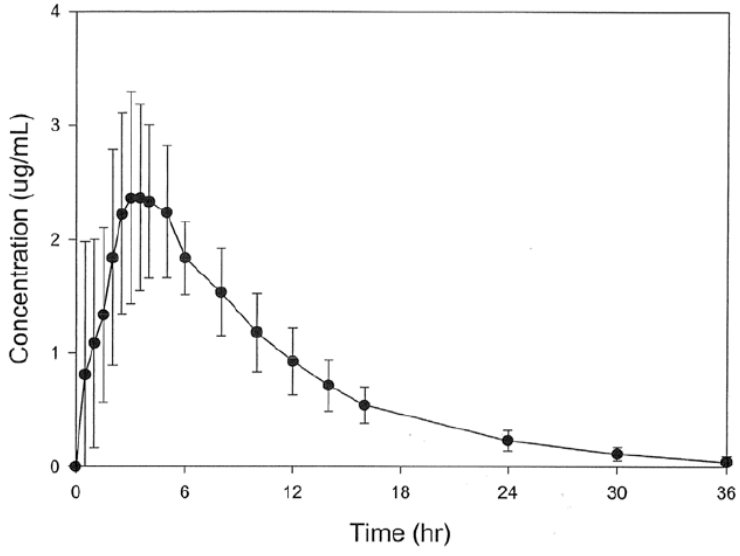


Figure 6.2. Mean concentrations of gabapentin in blood after oral administration of a single 600 mg (b) (4) XP13512 (b) (4) tablet (batch #030040) in Study XP019 (Group 2). Data are mean (SD) of 12 subjects.

- Cmax of gabapentin was 2.79 ± 0.83 µg/mL after Treatment D.
- Tmax was reached at 3.92 ± 1.92 hours.
- The apparent terminal half-life was 5.94 ± 0.87 hours

XP13512 pharmacokinetics in blood (Part II):

Descriptive Statistics for XP13512 PK Parameters are shown in the following table:

Table 2.3. Mean Pharmacokinetic Parameters for XP13512 in Blood After a Single Oral Dose of (b) (4) Tablet #030040 (1 x 600 mg) in Study XP019 (Group 2)

	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	λ_z (hr^{-1})	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
Mean*	0.044	3.18	1.67	0.578	0.104	0.191	3570	8110	3.24
SD	0.027	3.27	0.900	0.452	0.066	0.092	1340	5400	2.15
Minimum	0.017	0.500	0.630	0.310	0.025	0.136	2020	3910	1.16
Median	0.036	2.00	2.14	0.325	0.102	0.140	4300	6230	3.10
Maximum	0.103	10.0	2.24	1.10	0.213	0.297	4400	14200	5.45
CV%	60.9	103	54.0	78.2	63.4	48.0	37.6	66.6	66.4
Geo. Mean	0.038	1.87	1.44	0.480	0.081	0.178	3370	7020	2.70

*Data are mean of 12 subjects.

Mean XP13512 concentration-time plot is shown in the following figure:

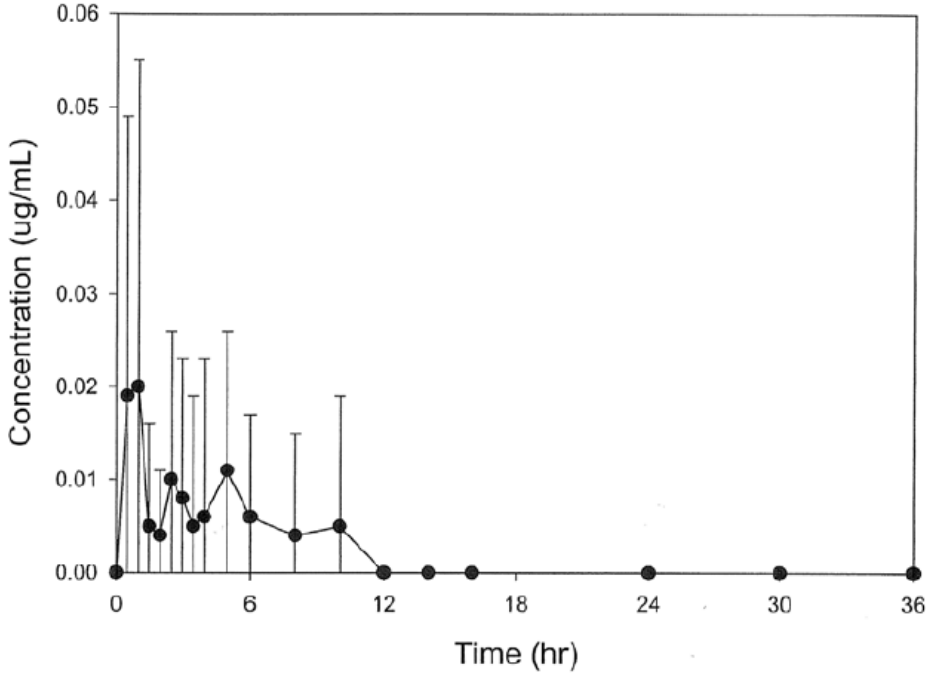


Figure 6.4. Mean concentrations of XP13512 in blood after oral administration of a single 600 mg (b) (4) XP13512 (b) (4) tablet (batch #030040) in Study XP019 (Group 2). Data are mean (SD) of 12 subjects.

- Cmax for XP13512 was 0.044 µg/mL, which is approximately 1.6 % of the corresponding peak gabapentin concentration.
- $AUC_{0-\infty}$ of XP13512 in blood was 0.7% of the corresponsing $AUC_{0-\infty}$ of gabapentin in blood.

Conclusions:

- The percent of the gabapentin dose recovered in urine was ranked as follows: IR capsule formulation > (b) (4) tablet formulation D> (b) (4) tablet formulation C> (b) (4) tablet formulation B.
- Based upon the results for the three extended release formulations, the (b) (4) tablet formulation was progressed to further clinical trials.

Study XP-022: ***A Phase 1, Randomized, Cross-Over, Fed/Fasted Single-dose Study of the Safety, Tolerability, and Pharmacokinetics of Oral XP13512 (ER vs Neurontin) in Healthy adult Subjects***

The primary objective of this study was to assess the pharmacokinetics of a single 1200 mg dose of the XP13512 ER formulation (a (b) (4) tablet formulation manufactured by (b) (4) under fed and fasted dosing conditions and compared with Neurontin®.

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Single-dose, randomized, open-label crossover</td></tr>
<tr><td>Study Population</td><td>N=12, (10 completed)
<u>Age:</u> 20-72 years (median 61.5 years)
<u>Gender:</u> 7 males (58%) and 5 females (42%)
<u>Weight</u>: 133-200 lbs (median 162.5 lbs)
<u>Race</u>: Caucasian (83.3%) and African American (16.7%)</td></tr>
<tr><td>Dosage and Administration</td><td>12 Subjects were enrolled and randomized to receive 3 single doses with Treatment A, B or C in a designed treatment sequence (ABC, BAC and CAB), 10 subjects completed the study.
<table>
<tr><th>Sequence</th><th>N</th><th colspan="3">Dosing Period</th></tr>
<tr><th></th><th></th><th>1</th><th>2</th><th>3</th></tr>
<tr><td>ABC</td><td>4</td><td>Treatment A</td><td>Treatment B</td><td>Treatment C</td></tr>
<tr><td>BCA</td><td>4</td><td>Treatment B</td><td>Treatment C</td><td>Treatment A</td></tr>
<tr><td>CAB</td><td>4</td><td>Treatment C</td><td>Treatment A</td><td>Treatment B</td></tr>
</table>
There was a 7-day washout period between Treatment periods.

Treatment A: A single dose of 1200 mg(2x600mg) (b) (4) SR tablets (fasted)
Treatment B: A single dose of 1200 mg(2x600mg) (b) (4) SR tablets (fed, high fat meal)
Treatment C: A single dose of 600 mg(2x300mg) Neurontin® IR capsules(fasted)

Lot no: 600 mg (b) (4) SR tablets: 040224
300 mg Neurontin® IR capsules: 01794V

<u>Diet:</u>
Subjects in fasted treatment were fasted 10 hours before dosing and up to 4 hours post-dose.

During the fast period, water or clear fluids were allowed *ad libitum*.

Alcohol was prohibited for 72 hours before any study visit until completion of the study.

Caffeine was prohibited for 72 hours before any study visit until completion of the study.</td></tr>
</table>

Sampling: Blood	At predose (0 hour), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 and 36 hours postdose. Aliquots of the blood samples were quenched for XP13512 concentrations. Plasma samples were analyzed for concentrations of gabapentin.
Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 hours postdose. Urine samples were analyzed for concentrations of gabapentin.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.7% Inter-day accuracy: < 8 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 7% Inter-day accuracy: < 10 % Long term Stability: 83 days at -80 ^{o}C
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 9.5% Inter-day accuracy: < 5.1 % Long term Stability: 163 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 8% Inter-day accuracy: < 2 %

	Long term Stability: 236 days at -80 °C and 42 days at -20 °C
PK Assessment	Gabapentin and XP13512 in blood and gabapentin in plasma: Cmax, Tmax, λz, t½, AUClast, AUCinf, CL/F, Vss and MRT Gabapentin in urine: Am(t1-t2), Am(0-36) and (%F)
Safety Assessment	AEs, ECGs, clinical laboratory measurements, vital signs, physical examinations and concomitant medications.

Pharmacokinetic Results:

Gabapentin in blood and urine:

Descriptive Statistics for gabapentin PK parameters are shown in the following table:

Table 5. Mean ± SD Gabapentin Pharmacokinetic Parameters from XP13512 SR or Neurontin® in Blood and Urine

Parameter	Treatment A XP13512 SR 1200mg fasted (N=12)	Treatment B XP13512 SR 1200mg fed (N=10)	Treatment C Neurontin® 600mg fasted (N=11)
Dose (mg equivalent of gabapentin)	625	625	600
C_{max} (µg/mL)	4.21 (±1.15)	6.24 (±1.55)	3.74 (±0.92)
T_{max} (hours)	5.08 (±1.62)	8.40 (±2.07)	2.73 (±1.33)
λ_z (hr^{-1})	0.108 (±0.012)	0.132 (±0.022)	0.103 (±0.025)
$T_{1/2}$ (hours)	6.47 (±0.77)	5.38 (±0.80)	7.12 (±1.91)
AUC_{last} (µg• hr/mL)	52.8 (±11.8)	81.0 (±20.9)	38.5 (±8.80)
AUC_{inf} (µg• hr/mL)	54.5 (±12.2)	83.0 (±21.8)	39.7 (±8.84)
CL/F (L/hr)	12.2 (±3.52)	7.97 (±1.96)	15.9 (±4.01)
V_{ss}/F (L)	114 (±35.7)	61.7 (±17.1)	163 (±58.5)
MRT (hr)	12.3 (±1.55)	13.4 (±1.59)	10.1 (±1.43)
Ae (mg)	291 (±98.9)	466 (±45.7)	219 (±54.3)
F (%)	46.5 (±15.8)	74.5 (±7.31)	36.6 (±9.04)

Source: Appendix 16.1.12

Mean gabapentin blood concentration-time plot for each of the treatments is shown in the following figures:

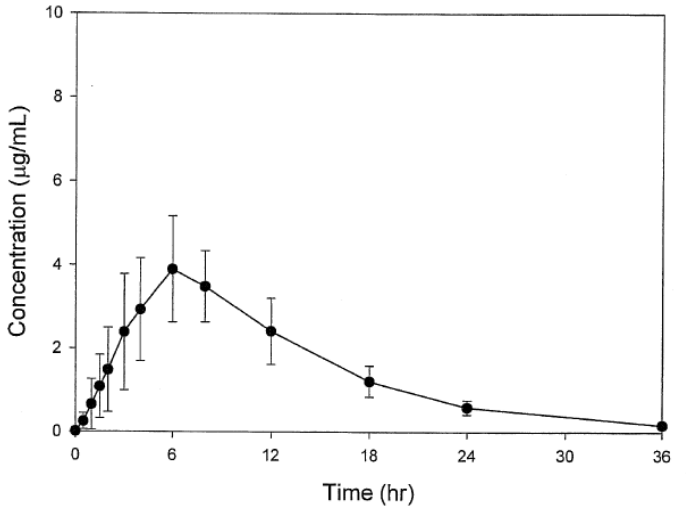


Figure 6.2. Mean concentrations of gabapentin in blood after oral administration of (b) (4) tablet (batch #040046) (2 x 600 mg) to fasted subjects in Study XP022 (Treatment A). Data are mean (SD) of 12 subjects.

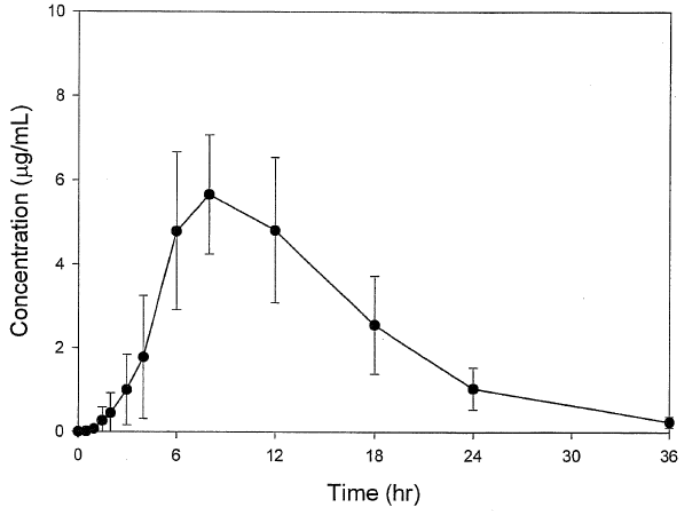


Figure 6.4. Mean concentrations of gabapentin in blood after oral administration of (b) (4) tablet (batch #040046) (2 x 600 mg) to fed subjects in Study XP022 (Treatment B). Data are mean (SD) of 10 subjects.

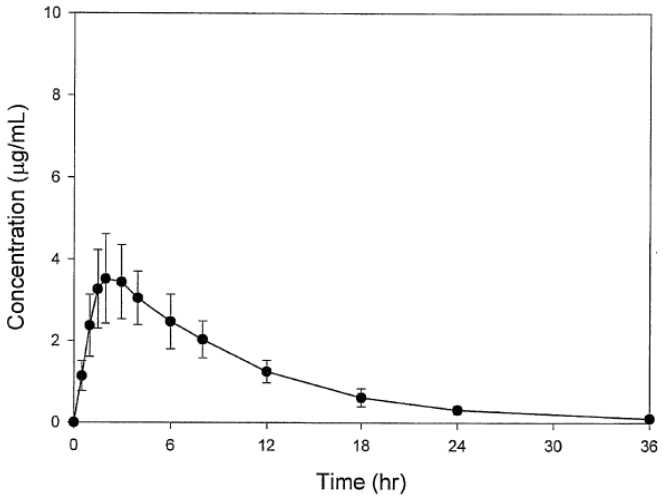


Figure 6.6. Mean concentrations of gabapentin in blood after oral administration of Neurontin Capsule (2 x 300 mg) to fasted subjects in Study XP022 (Treatment C). Data are mean (SD) of 11 subjects.

Overall gabapentin exposure in blood after different treatments for each individual by AUC normalized by dose and body weight is shown below:

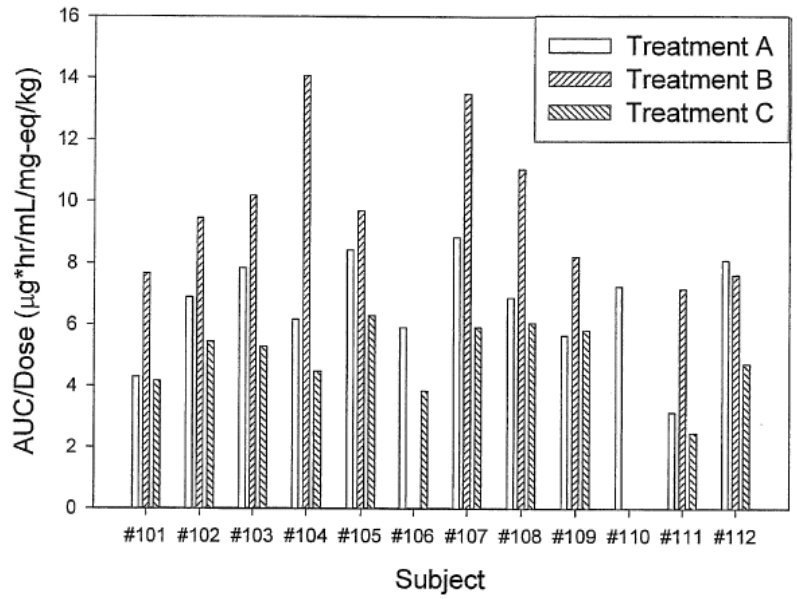


Figure 6.20. Effect of treatment on the resulting exposure to gabapentin in blood of individual subjects, expressed as AUC_{inf} normalized to dose in mg-equivalents of gabapentin per kg body weight.

- The mean Cmax for gabapentin in blood after XP13512 tablets (fasted), XP13512 tablets (fed) and Neurontin capsules were 4.21±1.15, 6.24±1.55 and 3.74±0.92 µg/mL, respectively.

- The mean AUCinf for gabapentin in blood after XP13512 tablets (fasted), XP13512 tablets (fed) and Neurontin capsules were 54.5±12.2, 83.0±21.8 and 39.7±8.84 µg*hr/mL, respectively.
- XP13512 tablets (fasted) produced a higher gabapentin exposure of 37% when compared to Neurontin capsules. In fed state, XP13512 produced a 52% increase in exposure when compared with XP13512 dosed in fasted state while it produced a 109% increase in exposure when compared with Neurontin capsules in fasted state.
- Tmax for gabapentin in blood were 5.08±1.62, 8.40±2.07 and 2.73±1.33 hours following administration of XP13512 (fasted), XP13512 (fed) and Neurontin, respectively.
- Elimination half-lives for gabapentin in blood were similar for all 3 treatments. The half-lives were 6.47±0.77, 5.38±0.80 and 7.12±1.91 hours following administration of XP13512 (fasted), XP13512 (fed) and Neurontin, respectively.
- The percentage of the gabapentin recovered in the urine was 46.5±15.8, 74.5±7.3 and 36.6±9.0 % following administration of XP13512 (fasted), XP13512 (fed) and Neurontin, respectively.

XP13512 (prodrug) in blood:

Descriptive Statistics for XP13512 blood PK parameters following treatment A and B are shown in the following tables:

PK PARAMETERS FOR XP13512 IN BLOOD:

Treatment		C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
XP13512 (b) (4) (b) (4) Tablet Batch #040046 (2 x 600 mg) Fasted Subjects	Mean	0.040	5.05	0.152	4.74	0.123	0.431	4207	25391	10.6
	SD	0.026	2.03	0.038	1.17	0.108	0.327	3102	13279	1.57
	Minimum	0.000	0.50	0.117	3.59	0.000	0.158	1513	12942	8.78
	Median	0.036	6.00	0.147	4.71	0.099	0.342	3510	23864	11.5
	Maximum	0.083	8.00	0.193	5.93	0.348	0.793	7598	39368	11.5
	CV%	63.6	40.2	25.2	24.6	88.1	75.8	73.7	52.3	14.8
	Geo. Mean	N/A	4.29	0.149	4.65	N/A	0.350	3430	22995	10.5

N/A – Not applicable.

PK PARAMETERS FOR XP13512 IN BLOOD:

Treatment		C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
XP13512 (b) (4) (b) (4) Tablet Batch #040046 (2 x 600 mg) Fed Subjects	Mean	0.018	6.38	N/A	N/A	0.026	N/A	N/A	N/A	N/A
	SD	0.014	1.69	N/A	N/A	0.033	N/A	N/A	N/A	N/A
	Minimum	0.000	3.00	N/A	N/A	0.000	N/A	N/A	N/A	N/A
	Median	0.014	6.00	N/A	N/A	0.011	N/A	N/A	N/A	N/A
	Maximum	0.047	8.00	N/A	N/A	0.088	N/A	N/A	N/A	N/A
	CV%	82.1	26.4	N/A	N/A	124	N/A	N/A	N/A	N/A
	Geo. Mean	N/A	6.13	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A – Not applicable.

Mean XP13512 blood concentration-time plot for treatment A and B are shown in the following figure:

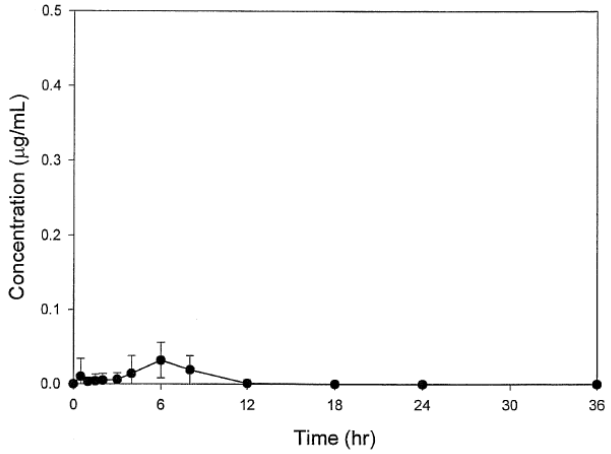


Figure 6.14. Mean concentrations of XP13512 in blood after oral administration of (b) (4) tablet (batch #040046) (2 x 600 mg) to fasted subjects in Study XP022 (Treatment A). Data are mean (SD) of 12 subjects.

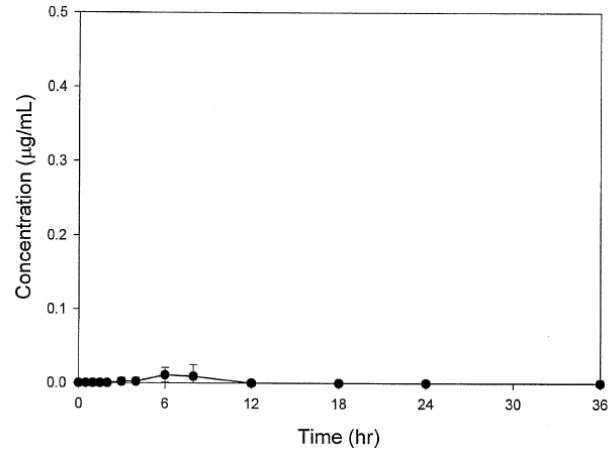


Figure 6.16. Mean concentrations of XP13512 in blood after oral administration of (b) (4) tablet (batch #040046) (2 x 600 mg) to fed subjects in Study XP022 (Treatment B). Data are mean (SD) of 10 subjects.

- Cmax of XP13512 in blood after administration of XP13512 tablets in fasted condition was 0.040 µg/mL, which is approximately 1 % of the corresponding peak gabapentin concentration.
- AUClast of XP13512 in blood after administration of XP13512 tablets in fasted condition was approximately 0.2 % of the corresponding AUCinf of gabapentin in blood.
- In fed condition, Cmax of XP13512 in blood after administration of XP13512 tablets was 0.018 µg/mL, which is approximately 0.3 % of the corresponding peak gabapentin concentration.

- In fed condition, AUClast of XP13512 in blood after administration of XP13512 tablets was < 0.1 % of the corresponding AUCinf of gabapentin in blood.

Gabapentin in plasma:

Descriptive Statistics for gabapentin plasma PK parameters are shown in the following tables:

Treatment A - XP13512 (b) (4) Tablets (Batch #040046) (2 x 600 mg) - FASTED

PK PARAMETERS FOR GABAPENTIN IN PLASMA:

Treatment		C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
XP13512 (b) (4) (b) (4) Tablet Batch #040046 (2 x 600 mg) Fasted Subjects	Mean	5.37	5.92	0.115	6.14	70.2	72.4	9.17	80.6	12.3
	SD	1.08	1.62	0.015	0.783	17.9	18.7	2.42	20.1	1.78
	Minimum	3.99	3.00	0.091	4.67	40.2	41.9	5.30	47.1	8.80
	Median	5.15	6.00	0.114	6.10	69.6	71.6	8.74	77.5	12.2
	Maximum	7.66	8.00	0.148	7.62	113	118	14.9	120	16.3
	CV%	20.1	27.4	13.3	12.7	25.5	25.8	26.4	24.9	14.5
	Geo. Mean	5.28	5.69	0.114	6.10	68.1	70.3	8.90	78.3	12.2

Treatment B - XP13512 (b) (4) Tablets (Batch #040046) (2 x 600 mg) - FED

PK PARAMETERS FOR GABAPENTIN IN PLASMA:

Treatment		C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
XP13512 (b) (4) (b) (4) Tablet Batch #040046 (2 x 600 mg) Fed Subjects	Mean	7.92	8.20	0.13	5.41	107	110	6.04	46.7	13.6
	SD	1.56	2.20	0.019	0.789	26.9	27.8	1.52	11.4	1.58
	Minimum	4.85	6.00	0.098	4.16	74.8	75.8	3.90	32.4	11.4
	Median	8.41	8.00	0.124	5.58	104	108	5.81	47.3	13.7
	Maximum	9.91	12.0	0.167	7.04	155	160	8.25	63.4	15.9
	CV%	19.7	26.8	14.4	14.6	25.2	25.4	25.1	24.4	11.6
	Geo. Mean	7.76	7.96	0.129	5.36	104	106	5.87	45.5	13.5

Treatment C - Neurontin Capsules (2 x 300 mg) - FASTED

PK PARAMETERS FOR GABAPENTIN IN PLASMA:

Treatment		C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)
Neurontin Capsules (2 x 300 mg) Fasted Subjects	Mean	5.06	3.05	0.108	6.59	51.3	52.8	12.0	112	10.1
	SD	0.94	0.91	0.018	0.923	10.9	11.1	3.33	24.1	1.27
	Minimum	3.15	1.50	0.087	4.41	28.5	29.4	9.07	81.0	7.02
	Median	5.22	3.00	0.107	6.47	54.6	56.4	10.6	106	10.5
	Maximum	6.32	4.00	0.157	7.92	64.8	66.1	20.4	154	11.6
	CV%	18.5	29.8	17.1	14.0	21.3	21.1	27.8	21.6	12.5
	Geo. Mean	4.97	2.91	0.106	6.52	50.0	51.6	11.6	109	10.1

Mean gabapentin plasma concentration-time plot for each of the treatments is shown in the following figures:

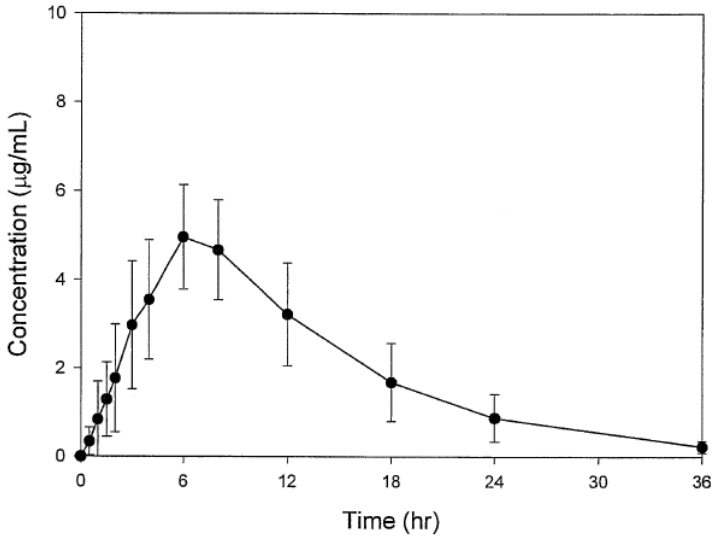


Figure 6.8. Mean concentrations of gabapentin in plasma after oral administration of (b) (4) tablet (batch #040046) (2 x 600 mg) to fasted subjects in Study XP022 (Treatment A). Data are mean (SD) of 12 subjects.

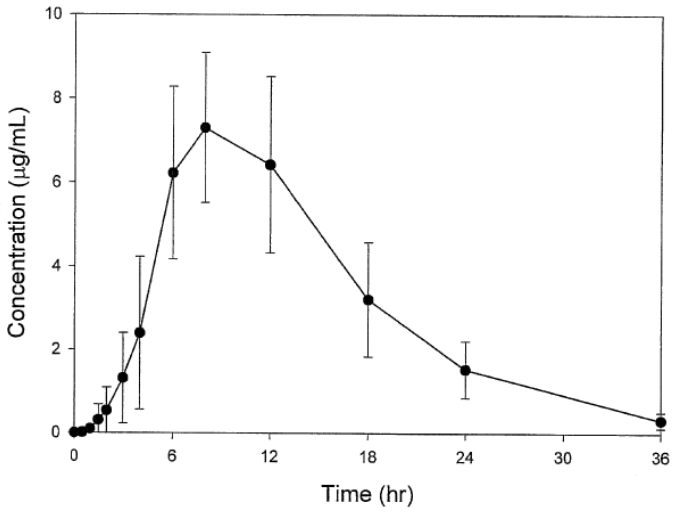


Figure 6.10. Mean concentrations of gabapentin in plasma after oral administration of (b) (4) tablet (batch #040046) (2 x 600 mg) to fed subjects in Study XP022 (Treatment B). Data are mean (SD) of 10 subjects.

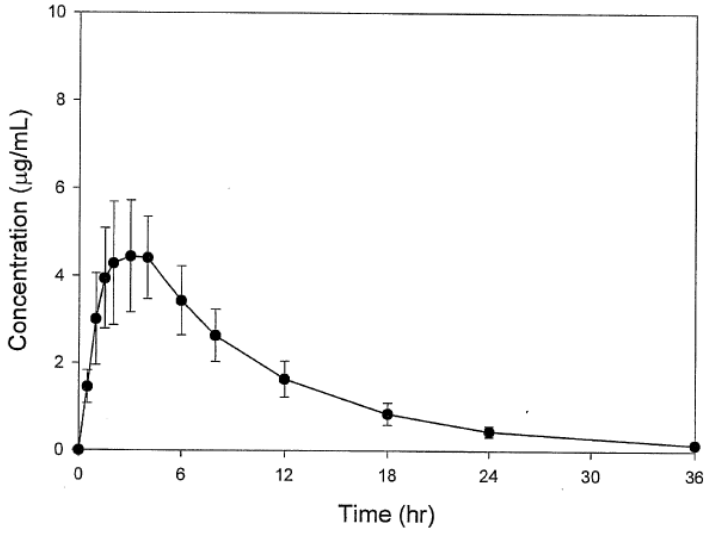


Figure 6.12. Mean concentrations of gabapentin in plasma after oral administration of Neurontin Capsule (2 x 300 mg) to fasted subjects in Study XP022 (Treatment C). Data are mean (SD) of 11 subjects.

- Plasma gabapentin concentrations were 23-26 % higher in the ER formulation and ~35% higher in the IR formulation than the corresponding blood gabapentin concentrations.

Relationship between plasma and blood gabapentin concentrations following administration of XP13512:

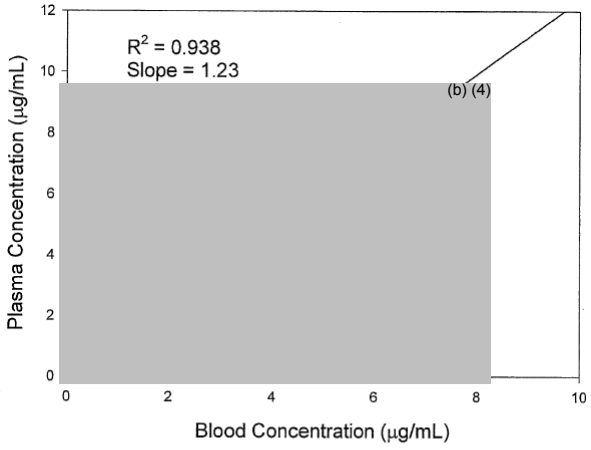


Figure 6.17. Relationship between blood and plasma concentrations of gabapentin after oral dosing of (b) (4) XP13512 Tablets (#040046) in fasted subjects (Treatment A).

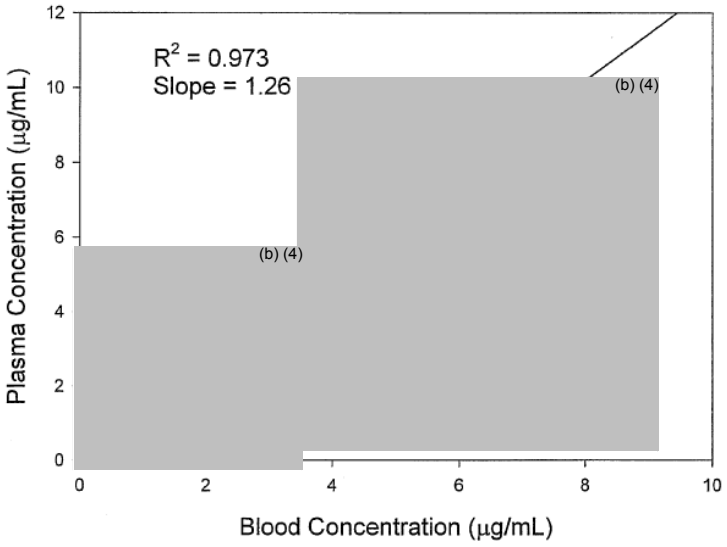


Figure 6.18. Relationship between blood and plasma concentrations of gabapentin after oral dosing of (b) (4) XP13512 Tablets (#040046) in fed subjects (Treatment B).

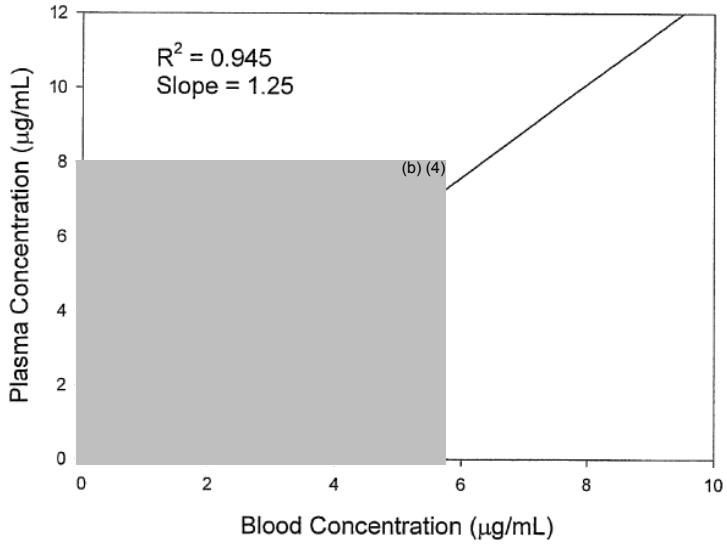


Figure 6.19. Relationship between blood and plasma concentrations of gabapentin after oral dosing of (b) (4) XP13512 Tablets (#040046) in fed subjects (Treatment C).

- A linear relationship was observed between plasma gabapentin concentrations and blood gabapentin concentrations regardless of the treatments.
- Same food effect (~ 50% ↑) was seen in plasma data as observed in blood.
- These results support the use of plasma concentrations as the primary source of the PK data in later XP13512 studies.

Gender effect on gabapentin:

MALES - PK PARAMETERS FOR GABAPENTIN IN BLOOD AND URINE:

Treatment		Body Wt. (kg)	C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)	Ae (mg)	F (%)
A	Mean	81.4	4.15	5.71	0.107	6.52	51.2	52.9	12.4	116	12.7	330	52.8
	SD	6.08	1.14	1.38	0.012	0.726	10.3	10.8	3.27	34.5	1.10	115	18.4
B	Mean	82.5	4.95	8.80	0.119	5.84	68.4	70.3	9.17	76.4	13.1	465	74.4
	SD	6.47	0.975	1.79	0.011	0.536	13.6	14.5	1.76	9.24	1.49	57.6	9.21
C	Mean	81.1	3.32	3.00	0.098	7.22	36.9	38.0	16.3	174	10.5	247	41.1
	SD	6.63	0.942	1.76	0.015	1.19	7.69	7.65	3.17	59.1	0.898	60.5	10.1

FEMALES - PK PARAMETERS FOR GABAPENTIN IN BLOOD AND URINE:

Treatment		Body Wt. (kg)	C_{max} (µg/mL)	T_{max} (hr)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)	Ae (mg)	F (%)
A	Mean	67.6	4.29	4.20	0.110	6.41	55.1	56.6	11.9	110	11.6	236	37.8
	SD	4.74	1.31	1.64	0.014	0.916	14.6	15.1	4.23	41.1	1.98	27.6	4.42
B	Mean	67.6	7.52	8.00	0.144	4.92	93.7	95.7	6.78	47.0	13.8	467	74.7
	SD	4.74	0.582	2.45	0.025	0.775	19.9	21.3	1.39	5.33	1.77	37.2	5.95
C	Mean	67.6	4.24	2.40	0.109	7.00	40.4	41.7	15.4	151	9.68	187	31.1
	SD	4.74	0.659	0.548	0.034	2.71	10.6	10.6	5.21	62.0	1.90	18.2	3.04

- Cmax of gabapentin in blood after XP13512 administration in fed state was significantly higher (52%) in females (7.52±0.582 µg/mL vs 4.95±0.975 µg/mL). Also, AUCinf of gabapentin in the same condition is 36% higher in females. This could be caused by the significantly lower body weight in females (67.6±4.7 kg in females vs 81.4±6.1 kg in males).
- Cmax and AUC of gabapentin in blood after XP13512 administration in fasted state, AUCinf, Tmax and half-life of gabapentin were not affected by gender.

Conclusions:

Bioavailability:

- Significant higher gabapentin exposure was observed following XP13512 administration compared to Neurontin, regardless of the presence of food. 37% and 109% higher exposure in fasted and fed state, respectively, after XP13512 dose were demonstrated when compared to Neurontin administration in fasted state.
- Similar results were observed in gabapentin urinary recovery (bioavailability) where 26% and 104% higher bioavailability in fasted and fed state, respectively, after XP13512 dose were demonstrated when compared to Neurontin administration in fasted state.
- Tmax of gabapentin in blood was delayed for ~2.5 hours and ~5.5 hours in fasted and fed state, respectively, after XP13512 dose were demonstrated when compared to Neurontin administration in fasted state.

Food effect:

- Gabapentin exposure (AUC and Cmax) was increased by 52 % following administration of XP13512 in fed condition when compared with fasted condition. Similarly, bioavailability (based on urine recovery) was increased by 60 % following administration of XP13512 in fed condition when compared with fasted condition.
- Tmax was delayed for ~3.5 hours when XP13512 was administered with high fat food.
- Elimination half-lives for gabapentin in blood were similar for all 3 treatments.
- The concentrations of intact prodrug (XP13512) in blood were < 1% of the corresponding gabapentin level, regardless of the presence of food.
- A linear relationship was found between plasma gabapentin concentrations and blood gabapentin concentrations regardless of the treatments.

Study XP-044: ***A Phase 1, Randomized, Cross-Over, Fed/Fasted Single-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Two Oral Sustained-Release Formulations of XP13512 in Healthy Adult Subjects***

This study was conducted to evaluate the dose proportionality (300 mg-1200 mg of XP13512 ER) and food effect of XP13512 using a same (b) (4) formulation as used in study XP022 but manufactured in a different site (b) (4).

A brief overview of some essential components of the study design is given below:

Study Design	Single-dose, randomized, open-label crossover
Study Population	N=36, (34 completed) For group A, B and C respectively: Age: 32-77, 18-72, 21-68 years (median 51.0, 49.9, 50.8 years) Gender: 9 M/3F (75%/25%), 5M/7F(41.7%/58.3%), 6M/6F(50%/50%) Weight: 147-192, 113-212, 125-212 lbs (median 158.5, 168, 168 lbs) Race: Caucasian/Black/Asian(100/0/0%, 91.7/8.3/0%, 75/16.7/8.3%)
Dosage and Administration	36 Subjects were enrolled and randomized to one of 3 cohorts (Group A, B or C). In each cohort, the subjects received single doses with a randomized treatment sequence of Fed/fasted or fasted /fed. 34 subjects completed the study.

Table 1. Dose Cohort and Treatment Periods

Group[a]	Dose	Treatment Period			
		1 (Fasted State)	n	2 (Fed State)	n
A	300 mg	One 300 mg tablet of XP13512 SR in a fasted state	6	One 300 mg tablet of XP13512 SR 5 minutes after test meal	6
B	600 mg	One 600 mg tablet of XP13512 SR in a fasted state	6	One 600 mg tablet of XP13512 SR 5 minutes after test meal	6
C	1200 mg	Two 600 mg tablets of XP13512 SR in a fasted state	6	Two 600 mg tablets of XP13512 SR 5 minutes after test meal	6

[a] The 600 mg and 1200 mg dose cohorts completed enrollment and treatment periods approximately a month before the 300 mg dose cohort started the study.

There was a 7-day washout period between Treatment periods.

Group A: a single dose of one 300 mg tablet (300 mg) of XP13512 SR in the fed and fasted state.
Group B: a single dose of one 600 mg tablet (600 mg) of XP13512 SR in the fed and fasted state.
Group C: a single dose of two 600 mg tablets (1200 mg) of XP13512 SR in the fed and fasted state.

Lot no: 300 mg (b) (4) SR tablets: 05JM-009
600 mg (b) (4) SR tablets: 05JM-010

Diet:
Subjects in fasted treatment were fasted 10 hours before dosing and up to 4 hours post-dose.

	During the fast period, water or clear fluids were allowed *ad libitum* and drinking liquid was encouraged. Alcohol was prohibited for 72 hours before any study visit until completion of the study. Caffeine was prohibited for 72 hours before any study visit until completion of the study.
Sampling: Plasma	Plasma samples were analyzed for concentrations of gabapentin. Plasma samples were collected at predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, and 36 hours postdose.
Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 hours postdose. Urine samples were analyzed for concentrations of gabapentin.
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 5.76% Inter-day accuracy: ranged from 97.7%-104% Long term Stability: 782 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.14% Inter-day accuracy: ranged from 98.1%-105% Long term Stability: 330 days at -80 ^{o}C and 791 days at -20 ^{o}C
PK Assessment	Gabapentin in plasma: Cmax, Tmax, t½, AUCinf, CL/F, Vss/F and MRT Gabapentin in urine: Am(t1-t2), Am(0-36) and (%F)
Safety Assessment	Adverse events, ECGs, clinical laboratory measurements, vital signs, physical examinations, and concomitant medications.

Pharmacokinetic Results:

Gabapentin in plasma and urine:

Descriptive Statistics for gabapentin PK parameters are shown in the following table:

Table 5. Mean ± SD Gabapentin Pharmacokinetic Parameters from XP13512 SR in Plasma and Urine

Parameter	XP13512 SR 300 mg Fasted (n=12)	XP13512 SR 300 mg Fed (n=12)	XP13512 SR 600 mg Fasted (n=12)	XP13512 SR 600 mg Fed (n=12)	XP13512 SR 1200 mg Fasted (n=11)	XP13512 SR 1200 mg Fed (n=12)
Dose (mg equivalent of gabapentin)	156		313		625	
C_{max} (µg/mL)	1.69 (±0.51)	2.26 (±0.55)	3.41 (±0.97)	4.41 (±1.26)	6.26 (±2.88)	7.59 (±1.65)
T_{max} (hr)	4.85 (±1.41)	9.83 (±2.76)	5.03 (±2.11)	7.27 (±1.68)	4.74 (±1.95)	7.92 (±2.19)
$T_{1/2}$ (hr)	5.92 (±0.77)	5.96 (±1.05)	5.86 (±1.00)	5.37 (±0.94)	6.18 (±0.86)	5.49 (±0.87)
$AUC_{(0\text{-inf})}$ (µg•hr/mL)	18.0 (±6.26)	27.4 (±6.29)	37.8 (±9.83)	54.1 (±11.8)	69.7 (±24.0)	92.4 (±13.0)
CL/F (L/hr)	9.57 (±3.07)	5.96 (±1.27)	8.78 (±2.18)	6.07 (±1.44)	9.77 (±2.65)	6.88 (±0.89)
V_{ss}/F (L)	80.5 (±22.7)	51.2 (±14.0)	73.6 (±20.3)	46.7 (±12.5)	86.9 (±26.0)	54.5 (±11.9)
MRT (hr)	11.4 (±1.28)	14.8 (±2.09)	11.0 (±1.85)	12.3 (±1.58)	11.6 (±1.93)	13.0 (±1.31)
Ae (mg)	93.5 (±19.7)	129 (±20.1)	191[a] (±60.9)	269 (±71.6)	395 (±92.5)	513[b] (±76.7)
F (%)	60.0 (±12.7)	82.4 (±12.9)	60.9[a] (±19.4)	86.1 (±22.9)	63.1 (±14.8)	82.1[b] (±12.2)

Source: Appendix 16.1.12

[a] Data are mean of 11 subjects.

[b] Data are mean of 10 subjects.

Mean gabapentin plasma concentration-time plot for each of the treatments is shown in the following figures:

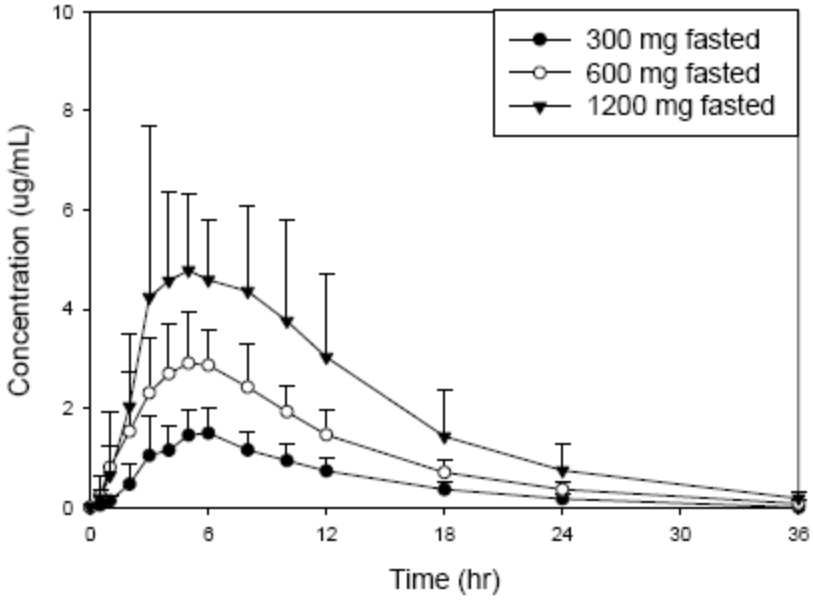


Figure 2. Mean (SD) Concentrations of Gabapentin in Plasma of Fasted Subjects After XP13512 SR 300 mg (N=12), 600 mg (N=12), and 1200 mg (N=11)

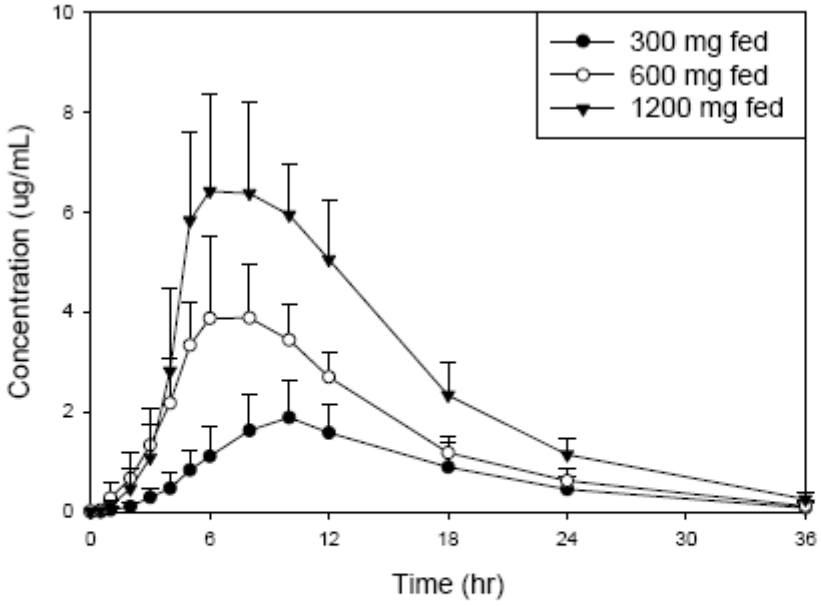


Figure 3. Mean (SD) Concentrations of Gabapentin in Plasma of Fed Subjects After XP13512 SR 300 mg (N=12), 600 mg (N=12), and 1200 mg (N=12)

- The Tmax values were 4.85, 5.03, and 4.74 hr at the 300, 600, and 1200 mg dose levels, respectively, in fasted state. The corresponding Tmax values were 9.83, 7.27, and 7.92 hr, respectively, in the fed state.
- The bioavailability observed from the urinary recovery data was 60%, 61%, and 63% at the 300, 600, and 1200 mg dose levels, respectively, in fasted state. The corresponding bioavailability was 82%, 86%, and 82%, respectively, in fed state.
- The presence of food increased the exposure (AUCinf) to gabapentin after oral XP13512 SR tablets by 52%, 43%, and 33%, at the 300 mg, 600 mg, and 1200 mg dose levels, respectively.
- The elimination half-lives were not changed over the studied dose range and regardless of the presence of food.

Dose proportionality:

Plots demonstrating the relationship of XP13512 doses versus Cmax and AUCinf are shown below:

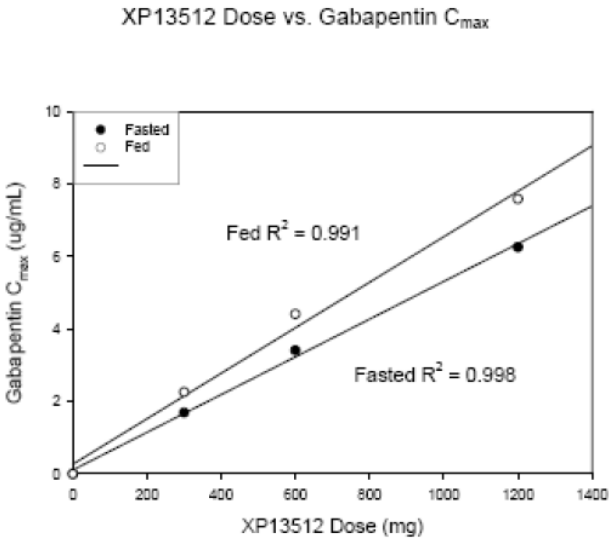


Figure 6.9. Relationship between XP13512 dose and gabapentin C_{max} in plasma after oral dosing of XP13512 SR Tablets.

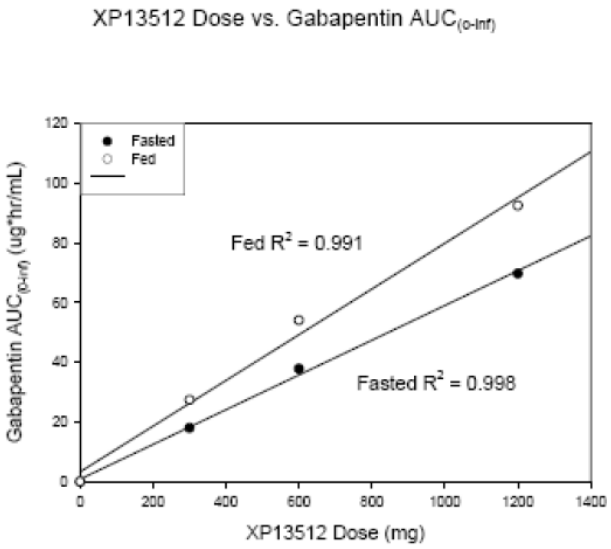


Figure 6.10. Relationship between XP13512 dose and gabapentin $AUC_{(0\text{-}inf)}$ in plasma after oral dosing of XP13512 SR Tablets.

- The mean Cmax values were 1.69, 3.41, and 6.26 µg/mL at the 300, 600, and 1200 mg dose levels, respectively, in fasted state. The corresponding Cmax values were 2.26, 4.41, and 7.59 µg/mL, respectively, in the fed state.
- The mean AUCinf values were 18.0, 37.8, and 69.7 µg*h/mL at the 300, 600, and 1200 mg dose levels, respectively, in fasted state. The corresponding AUC values were 27.4, 54.1, and 92.4 µg*h/mL, respectively, in the fed state.
- Exposure to gabapentin in plasma, expressed as both Cmax and AUC(0-inf), was proportional to the oral XP13512 dose over the dose range studied (300-1200mg).

<u>Comparison to XP13512 SR Formulation Used in Study XP022:</u>

While the composition of the formulations tested in both studies XP022 and XP044 were the same, the tablets tested in this study were manufactured at a different site (b) (4) and the manufacturing process differed in that a (b) (4) step was added.

Descriptive statistics for gabapentin plasma PK parameters following administration of 1200 mg XP13512 SR tablets with/without food in both studies are shown in the following table:

Table 6. Comparison of Mean Gabapentin Pharmacokinetic Parameters from XP13512 SR in Plasma After Single 1200 mg Doses of XP13512 SR in Studies XP044 and XP022

	XP13512 SR 1200 mg Fasted		XP13512 SR 1200 mg Fed	
Study →	XP022	XP044	XP022	XP044
Manufacturer →	[redacted] (b) (4)			
Parameter ↓	(n=12)	(n=11)	(n=10)	(n=12)
Dose (mg equivalent of gabapentin)	625		625	
C_{max} (µg/mL)	4.21	6.26	6.24	7.59
T_{max} (hr)	5.08	4.74	8.40	7.92
$T_{1/2}$ (hr)	6.47	6.18	5.38	5.49
$AUC_{(0\text{-inf})}$ (µg•hr/mL)	54.5	69.7	83.0	92.4
F (%)	46.5	63.1	74.5	82.1[a]

Source: Appendix 16.1.12
[a] Data for 10 subjects.

Mean gabapentin plasma concentration-time plot for both studies in the fasted condition is shown in the following figure:

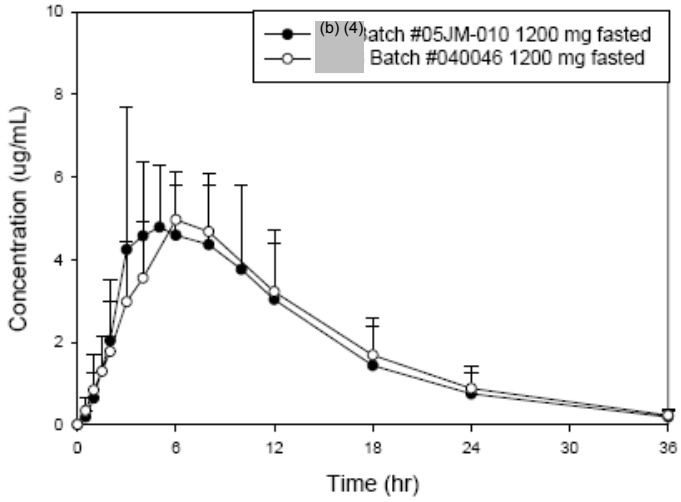


Figure 4. Comparison of Mean (SD) Concentrations of Gabapentin in Plasma of Fasted Subjects After XP13512 SR 1200 mg from [redacted] (b) (4) (N=12) and [redacted] (b) (4) (N=11)

Mean gabapentin plasma concentration-time plot for both studies in the fed condition is shown in the following figure:

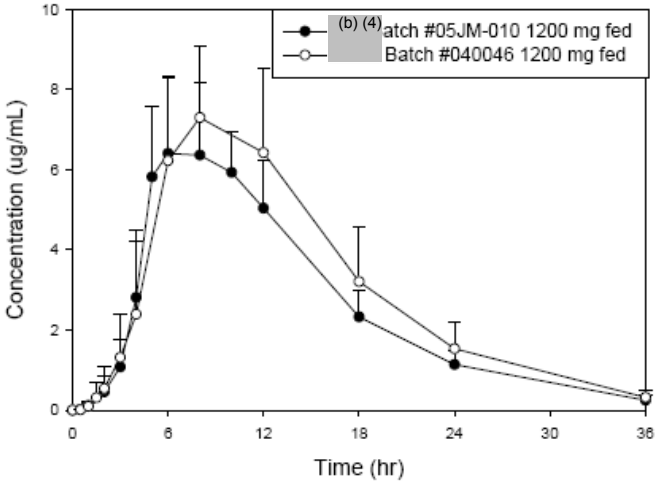


Figure 5. Comparison of Mean (SD) Concentrations of Gabapentin in Plasma of Fed Subjects After XP13512 SR 1200 mg from (b) (4) (N=10) and (b) (4) (N=12)

- Based on the sponsor, similar PK profiles were observed for both studies; therefore, the sponsor stated that manufacturing process involving (b) (4) didn't alter the release properties of the XP13512 SR tablets.

Reviewer's comment:

- *While the sponsor stated there were similar PK profiles for both studies, the conclusion was made by qualitative observation. No official statistical evaluation was conducted. Although statistical evaluation might not be required for the purpose of the comparison, more detail comparison for different PK parameters should be described.*
- *The half-life remain unchanged in both studies regardless of the presence of food, while Cmax, AUCinf and bioavailability appears to increase in the (b) (4) product when compared to (b) (4) product (from table). .*

Conclusions:

- Sustained-release XP13512 was well absorbed and converted to gabapentin.
- Exposure to gabapentin in plasma was proportional to the oral XP13512 dose over the dose range studied (300 to 1200 mg), expressed as both Cmax and AUC(0-inf).
- A sustained delivery of gabapentin was observed at all three dose levels. In fasted subjects, the Tmax values were 4.85, 5.03, and 4.74 hr at the 300, 600, and 1200 mg dose levels, respectively. In fed subjects, the corresponding Tmax values were 9.83, 7.27, and 7.92 hr, respectively.

- Bioavailability of gabapentin from the XP13512 SR tablets, determined from urinary recovery, was high at all three dose levels, with ~60% in fasted state and ~80% in fed state.
- Food increased the exposure (AUC) to gabapentin after oral XP13512 SR tablets by 52%, 43%, and 33%, at the 300 mg, 600 mg, and 1200 mg dose levels, respectively.
- Plasma pharmacokinetic data for the (b) (4) tablets showed similar pharmacokinetic profiles for gabapentin in plasma when compared to that for (b) (4) tablets in Study XP022 based on the sponsor. However, data in the table 6 showed that Cmax, AUCinf and bioavailability appears to increase in the (b) (4) product when compared to (b) (4) product.

Study XP-057: A Randomized, Cross-Over, Single-Dose Pharmacokinetic Study Assessing Two Oral Sustained Release Formulations of XP13512 in Healthy Adult Subjects

The study examined the pharmacokinetic profiles of 2 sustained release formulations of XP13512 under fed state in healthy subjects. One formulation was manufactured by (b) (4) and the other by Patheon. The only difference in the manufacturing process was the use (b) (4) compared to (b) (4) Patheon. (Patheon vs (b) (4) formulations, fed, BE study). Patheon ER product is made using the final formulation/process at the finalmanufacturing site.

A brief overview of some essential components of the study design is given below:

Study Design	Single-dose, randomized, open-label crossover
Study Population	N=12 Age: 19-70 years (median 40.5 years) Gender: 8 males (66.7%) and 4 females (33.3%) Weight: 61.8-99.0 kg (mean 79.2 kg) Race: Caucasian (91.7%) and Asian (8.3%)
Dosage and Administration	12 Subjects were randomized to receive 2 single doses with Treatment A and B in a designed treatment sequence (AB or BA) in fed condition. All subjects received high-fat breakfast before dosing. **Table 1. Treatment/Formulation Sequence** Sequence / Period 1 / n / Period 2 / n 1 / XP13512 1200 mg Formulation A Fed / 6 / XP13512 1200 mg Formulation B Fed / 6 2 / XP13512 1200 mg Formulation B Fed / 6 / XP13512 1200 mg Formulation A Fed / 6 Source: Section 14, Table 1; Appendix 16.2, Listing 1 There was a 7-day washout period between Treatment periods. Treatment A: A single dose of 1200 mg (2x600mg) XP13512 (b) (4) (b) (4) SR tablets Treatment B: A single dose of 1200 mg (2x600mg) XP13512 Patheon SR tablets Lot no: 600 mg (b) (4) SR tablets: 040046 600 mg Patheon SR tablets: 3049975R Diet: Subjects were fasted overnight before breakfast. Drinking water or clear fluids were allowed and was encouraged. Alcohol was prohibited for 72 hours before any study visit until

	completion of the study. Caffeine was prohibited for 72 hours before any study visit until completion of the study.
Sampling: Blood	At predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, and 36 hours postdose. The samples were analyzed for plasma concentrations of gabapentin.
Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 hours postdose. The samples were analyzed for urine concentrations of gabapentin.
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 5.76% Inter-day accuracy: 97.7-104 % Long term Stability: 782 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.14% Inter-day accuracy: 98.1-105 % Long term Stability: 330 days at -80 ^{o}C and 791 days at -20 ^{o}C
PK Assessment	Gabapentin in plasma: Cmax, Tmax, half-life, AUClast, AUCinf, CL/F, Vz/F and MRT Bioequivalence analysis: Cmax, AUC(0-tlast) and AUC(0-inf) of gabapentin in plasma Gabapentin in urine: Am, Am (0-36) and CLr
Safety Assessment	Adverse events (AEs), electrocardiograms (ECGs), clinical laboratory measurements, physical examinations, and vital signs

Pharmacokinetic Results:

Gabapentin pharmacokinetics in plasma and urine was shown in the table below:

Table 5. Mean ± SD Gabapentin Pharmacokinetic Parameters of Two XP13512 SR Formulations

Parameter	XP13512 SR (b) (4) 1200 mg (n=12)	XP13512 SR Patheon 1200 mg (n=12)
Dose (mg equivalent of gabapentin)	625	625
C_{max} (µg/mL)	6.93 (±1.47)	7.55 (±1.25)
T_{max} (hr)	8.42 (±1.88)	7.43 (±2.16)
$T_{1/2}$ (hr)	5.51 (±1.01)	5.57 (±1.04)
$AUC_{(0\text{-tlast})}$ (µg•hr/mL)	96.1 (±20.7)	96.3 (±17.6)
$AUC_{(0\text{-inf})}$ (µg•hr/mL)	98.7 (±22.1)	98.8 (±19.0)
CL/F (L/hr)	6.63 (±1.48)	6.52 (±1.13)
V_z/F (L)	52.2 (±13.0)	51.7 (±9.35)
$MRT_{(inf)}$ (hr)	13.5 (±1.46)	13.0 (±1.57)
Ae (mg)	504 (±102)	528 (±99.5)
CLr (L/hr)	5.45 (±1.57)	5.68 (±1.51)
F[a] (%)	80.2 (±15.4)	82.9 (±13.5)

Source: Appendix 16.1.13

[a] In the case that F >100%, the value was reported as 100%, which was used for the statistical calculation.

Mean Gabapentin concentration-time plot is shown in the following figure:

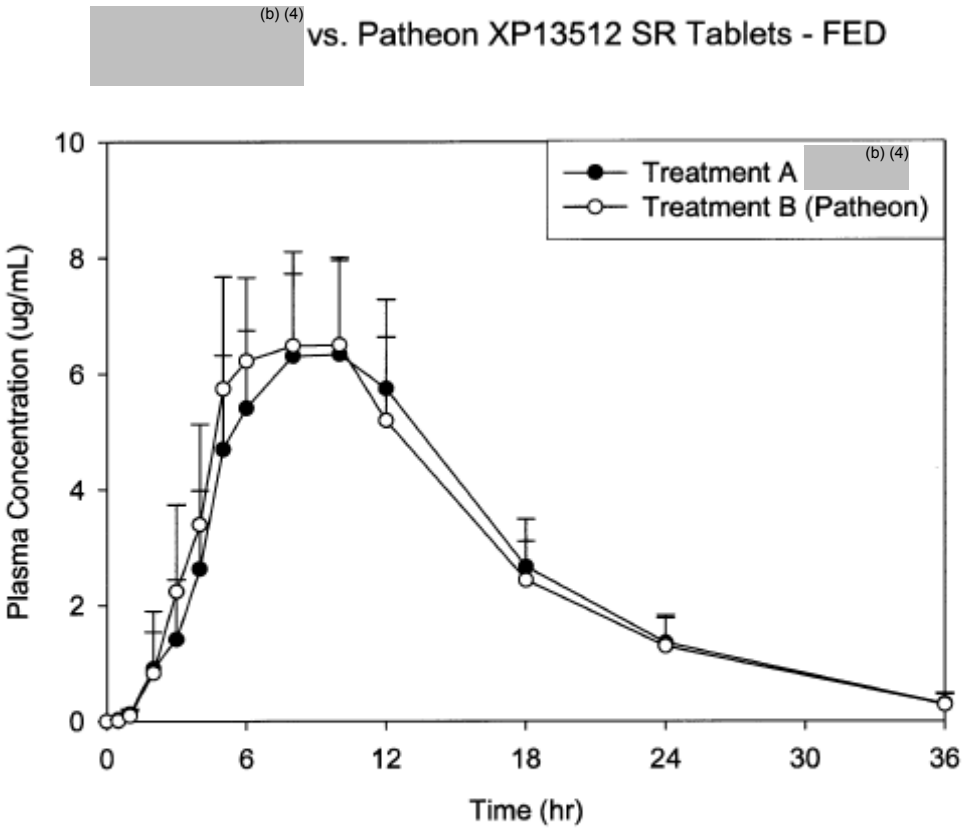


Figure 6.1. Comparison of mean (SD) concentrations of gabapentin in plasma of fed subjects after oral administration of 2 x 600 mg XP13512 Sustained Release Tablets either from (b) (4) (Batch #040046) or Patheon (Batch #3049975R) in Study XP057 (N = 12 per treatment)

- Cmax of gabapentin was 6.93 ± 1.47 µg/mL and 7.55 ± 1.25 µg/mL after administration of (b) (4) and Patheon formulation, respectively.
- Tmax of gabapentin was achieved at 8.42 ± 1.88 hours and 7.43 ± 2.16 hours after administration of (b) (4) and Patheon formulation, respectively.
- T1/2 of gabapentin was 5.51 ± 1.01 hours 5.57 ± 1.04 hours after administration of (b) (4) and Patheon formulation, respectively.
- Bioavailability of gabapentin from the XP13512 SR tablets, determined from urinary recovery, was high for both formulations: 80% for the (b) (4) SR tablets and 83% for the Patheon SR tablets.
- The estimated renal clearance of gabapentin was 5.45 L/hr for the (b) (4) SR tablets and 5.68 L/hr for the Patheon SR tablets.

Determination of Bioequivalence

Table 6. Point Estimates and 90% Confidence Intervals for Assessing Bioequivalence for Gabapentin Pharmacokinetic Parameters

PK Parameter Evaluated	Estimate	90% Confidence Interval (Upper, Lower)
C_{max}	110%	(102% - 118%) [a]
$AUC_{(0\text{-tlast})}$	101%	(95.8% - 106%) [a]
$AUC_{(0\text{-inf})}$	101%	(95.6% - 106%) [a]

Source: Appendix 16.1.13

[a] Demonstrates equivalence based on FDA guidance.

- No statistical differences were observed for Cmax, AUClast and AUCinf of gabapentin between Patheon and (b) (4) tablets.
- The 90% confidence intervals for the mean PK parameters of Patheon were within 80-125% of (b) (4) formulation.

Conclusions:

- XP13512 was well absorbed and rapidly converted to gabapentin for both the (b) (4) and Patheon formulations.
- Sustained delivery of gabapentin after oral dosing of XP13512 was observed with both formulations.
- Gabapentin concentrations in plasma reached a maximum (Cmax) of 6.93 and 7.55 µg/mL for the (b) (4) and Patheon SR formulations, respectively.
- The corresponding Tmax values were 8.4 and 7.4 hours, respectively.
- The half-lives were similar for the two tablets (5.5 hours for the (b) (4) formulation and 5.6 hours for the Patheon formulation).
- Bioavailability of gabapentin from the 2 formulations, determined from urinary recovery, was high (80% for the (b) (4) SR tablets and 83% for the Patheon SR formulation).
- Renal clearance of gabapentin was 5.45 L/hr for the (b) (4) SR tablets and 5.68 L/hr for the Patheon SR tablets.
- The XP13512 SR tablet formulation manufactured by Patheon was found to be bioequivalent to the tablets manufactured by (b) (4) Pharma, under fed conditions.
- BE is not critical since the final product has been used in several PK and pivotal Phase 3 trials.

Study XP-087: ***A Phase 1, Randomized, Crossover, Open-label, Food Effect Comparison Study of the Pharmacokinetics, Safety, and Tolerability of XP13512 Sustained Release (SR) Tablet Formulation in Healthy Adult Subjects***

Pivotal food effect study
This study was conducted to evaluate the effect of fat content in the meals on gabapentin PK after administration of XP13512 ER.

A brief overview of some essential components of the study design is given below:

Study Design	4 period, single-dose, randomized, open-label crossover
Study Population	N=12 Age: 19-52 years (median 30 years) Gender: 8 males (66.7%) and 4 females (33.3%) Weight: 56.9-93.7 kg (mean 73.6 kg) Race: 7 Caucasian (58.3%) and 5 African-American (41.7%)
Dosage and Administration	12 Subjects were randomized to receive 4 single doses of 1200 mg (2x600 mg) with 4 different treatments in a designed treatment sequence. All subjects were fasted overnight. Treatment A: XP13512 1200 mg in the fasted state. Treatment B: XP13512 1200 mg immediately following a low fat meal. Treatment C: XP13512 1200 mg immediately following a moderate fat meal. Treatment D: XP13512 1200 mg immediately following a high fat (Food and Drug Administration, FDA,-compliant) meal. There was at least 5-day washout period between Treatment periods. Lot no: 600 mg Patheon SR tablets: 3051595R Diet: Subjects were fasted overnight before dosing or breakfast. Drinking water or clear fluids were allowed and was encouraged. All subjects were to drink 240 mL 2 h and 1 h prior to dosing, and 240 mL 2 h after dosing. Alcohol was prohibited for 72 hours before any study visit until completion of the study.
Sampling: Blood	At predose (0 hour), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 24, 30 and 36 hours postdose. The samples were analyzed for plasma concentrations of gabapentin.

Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 hours postdose. The samples were analyzed for urine concentrations of gabapentin.
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 5.76% Inter-day accuracy: 97.7-104 % Long term Stability: 782 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.14% Inter-day accuracy: 98.1-105 % Long term Stability: 330 days at -80 ^{o}C and 791 days at -20 ^{o}C
PK Assessment	Gabapentin in plasma: Cmax, Tmax, half-life, AUC and AUCinf Gabapentin in urine: Am, Am (0-36), F% and CLr
Safety Assessment	Adverse events (AEs), laboratory results, vital signs, electrocardiogram (ECG) assessments, and concomitant medications

Pharmacokinetic Results:

Gabapentin pharmacokinetics in plasma and urine was shown in the table below:

Table 5.1. Mean Pharmacokinetic Data for Gabapentin in Plasma and Urine After Oral Administration of XP13512 Sustained Release Tablets (2 x 600 mg) to Fasted and Fed Healthy Adult Volunteers in Study XP087

Treatment	N		C_{max} (µg/mL)	T_{max} (hr)	Kel (1/hr)	$T_{1/2}$ (hr)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (L/hr)	Vz/F (L)	MRT (hr)	$Ae_{(0\text{-}36)}$ (mg)	CLr (L/hr)	%F
Fasted	10	Mean	5.04	5.30	0.119	5.97	57.2	58.8	11.0	95.2	11.2	262 [a]	4.96 [a]	42.0 [a]
		SD	1.12	1.06	0.018	0.86	12.5	12.6	2.23	24.3	1.15	38.3	0.547	6.12
		Min	3.29	3.00	0.096	4.38	40.3	41.1	7.29	63.9	9.34	181	4.19	28.9
		Max	6.64	6.00	0.158	7.23	83.4	85.7	15.2	126	13.4	291	5.63	46.6
		CV%	22.1	20.0	15.5	14.4	21.9	21.4	20.2	25.5	10.2	14.6	11.0	14.6
Low Fat	10	Mean	7.34	5.70	0.129	5.49	70.9	72.1	8.87	70.4	11.1	402 [b]	5.80 [b]	64.3 [b]
		SD	1.10	1.16	0.020	0.82	10.8	10.8	1.52	16.1	0.84	82.6	1.25	13.2
		Min	6.24	4.00	0.108	4.32	50.1	50.7	7.30	46.0	10.0	284	3.83	45.4
		Max	9.42	8.00	0.161	6.41	85.0	85.6	12.3	89.8	12.6	510	7.46	81.7
		CV%	15.0	20.3	15.7	14.9	15.2	15.0	17.1	22.8	7.53	20.5	21.6	20.5
Moderate Fat	11	Mean	6.57	7.01	0.136	5.23	75.8	77.2	8.21	62.2	12.1	405 [c]	5.46 [c]	64.9 [c]
		SD	1.14	2.23	0.022	0.81	9.51	9.69	0.969	13.3	1.03	105	1.46	16.9
		Min	5.03	5.00	0.109	3.98	62.5	63.7	6.32	42.8	10.2	262	3.51	41.9
		Max	9.12	12.0	0.174	6.36	97.0	99.0	9.81	84.6	13.5	600	8.44	96.0
		CV%	17.4	31.8	16.2	15.5	12.5	12.6	11.8	21.4	8.50	26.0	26.7	26.0
High Fat	12	Mean	7.20	7.25	0.138	5.10	80.7	82.1	7.67	56.3	12.1	475	5.96	76.1
		SD	1.21	1.96	0.020	0.72	7.13	7.43	0.698	8.43	1.17	90.0	1.46	14.4
		Min	5.35	6.00	0.113	4.04	67.1	68.4	6.40	44.2	10.0	327	4.12	52.4
		Max	9.66	12.0	0.172	6.11	96.1	97.7	9.13	74.4	14.8	658	8.75	105
		CV%	16.8	27.0	14.5	14.0	8.83	9.04	9.10	15.0	9.65	18.9	24.4	18.9

Abbreviations: C_{max} = maximum concentration; T_{max} = time to C_{max}; Kel = terminal elimination rate constant; $T_{1/2}$ = half-life; AUC = area under the concentration-time curve; CL/F = apparent oral clearance; V_Z/F = volume of distribution; MRT = mean residence time; $Ae_{(0\text{-}36)}$ = amount excreted in 36 hr; CLr = renal clearance; F = bioavailability based on urinary recovery.
a N = 7; b N = 8; c N = 9.

Mean Gabapentin concentration-time plot is shown in the following figure:

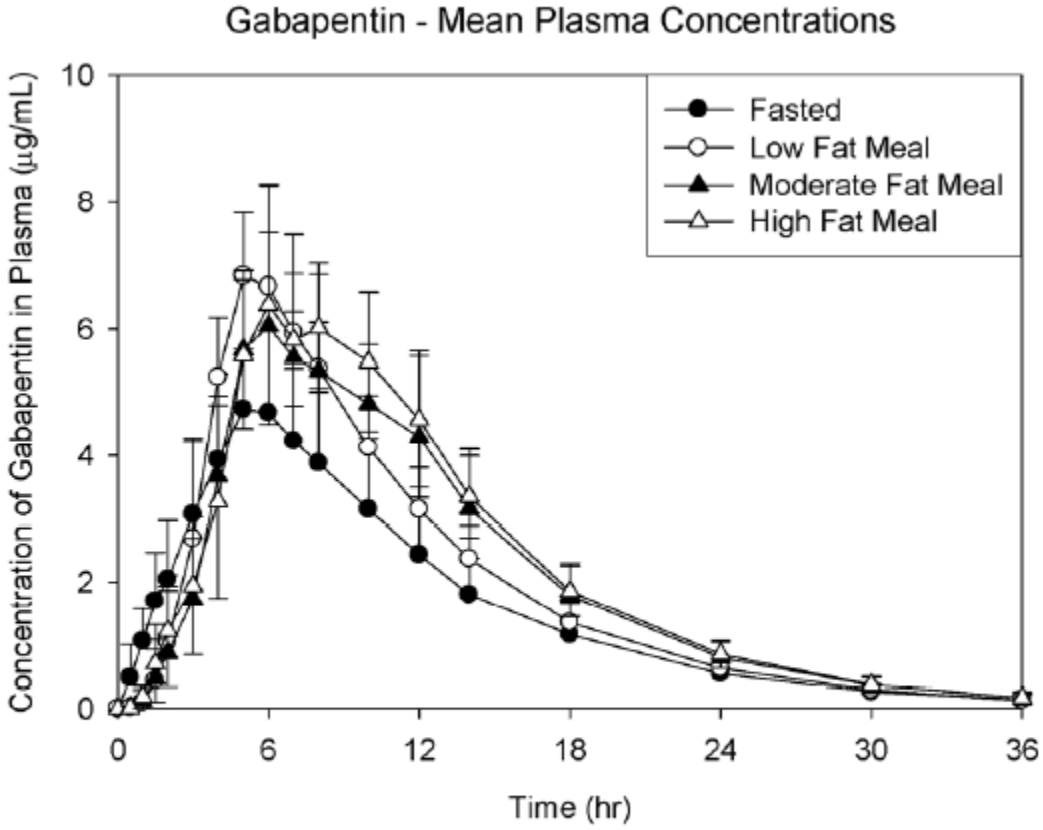


Figure 6.1. Mean (SD) concentrations of gabapentin in plasma of fasted and fed healthy subjects following oral dosing of 1200 mg XP13512 in Study XP087 (N = 10-12 subjects per treatment)

- Cmax of gabapentin was 5.04 ± 1.12 µg/mL, 7.34 ± 1.10 µg/mL, 6.57 ± 1.14 µg/mL and 7.20 ± 1.21 µg/mL after administration of 1200 mg XP13512 under fasted, low fat, medium fat and high fat meal, respectively. This suggests Cmax is increased by ~30-50% (46%, 30% and 42% increase under low, medium and high fat meal, respectively) under fed state regardless of fat content when compared with fasted condition.
- Tmax of gabapentin was achieved at 5.30 ± 1.06 hours, 5.70 ± 1.16 hours, 7.01 ± 2.23 hours and 7.25 ± 1.96 hours after administration of 1200 mg XP13512 under fasted, low fat, medium fat and high fat meal, respectively. This indicates that medium fat and high fat meal delay Tmax by ~2 hours.
- T1/2 of gabapentin was 5.97 ± 0.86 hours, 5.49 ± 0.82 hours, 5.23 ± 0.81 hours 5.10 ± 0.72 hours after administration of 1200 mg XP13512 under fasted, low fat, medium fat and high fat meal, respectively. T1/2 was not changed regardless of fed or fasted condition.
- AUCinf of gabapentin was 58.8 ± 12.6 µg*h/mL, 72.1 ± 10.8 µg*h/mL, 77.2 ± 9.69 µg*h/mL and 82.1 ± 7.43 µg*h/mL after administration of 1200 mg

XP13512 under fasted, low fat, medium fat and high fat meal, respectively. This represents an increase of 23, 31, and 40 % over the corresponding exposure in fasted subjects.

- Mean oral bioavailability of gabapentin from the XP13512 SR tablets, determined from urinary recovery was 42%, 64.3%, 64.9% and 76.1% for fasted, low fat, medium fat and high fat meal, respectively. This suggests that bioavailability was high and enhanced by the presence of food (a 50-80% increase).

Geometric mean ratios (fed/fasted) and 90% confidence intervals for gabapentin PK parameters:

Table 5.3 Geometric Mean Ratios (Fed/Fasting) and 90% Confidence Intervals for Gabapentin PK Parameters

		Geometric Mean Ratio (Fed/Fasting)	
PK Parameter	Treatment	Point Estimate	90% Confidence Interval
C_{max}	Low fat vs. Fasted	1.48	(1.29, 1.69)
	Moderate fat vs. Fasted	1.33	(1.16, 1.52)
	Fed fat vs. Fasted	1.45	(1.27, 1.66)
AUC_{inf}	Low fat vs. Fasted	1.24	(1.13, 1.35)
	Moderate fat vs. Fasted	1.34	(1.23, 1.46)
	Fed fat vs. Fasted	1.44	(1.32, 1.57)

- For both Cmax and AUCinf, all three meal types were statistically significant greater than fasted indicating significant increase in exposure with food.

<u>Conclusions:</u>

- Systemic exposure to gabapentin after oral dosing of XP13512 SR tablets was significantly enhanced relative to fasted conditions when administered with food.
- These data support dosing of XP13512 SR tablets with food in future clinical studies.

Reviewer's comments:

- *The sponsor concluded systemic exposure increased under fed condition regardless of fat content. However, while the increase in Cmax (46%, 30% and 42%) appeared to be similar over different meal types, the increase in AUC (23%, 31% and 40%) seemed to present a positive correlation with fat content.*
- *Phase 3 clinical trials were done in fed state (with no control on caloric or fat content of the meals).*

4.1.2 HEALTHY SUBJECT PHARMACOKINETIC STUDIES

Study XP-006: ***A Phase 1, Randomized, Placebo-Controlled, Ascending Single-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Oral XP13512 IR in Healthy Adult Subjects***

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Single-dose, randomized, double-blind, placebo-controlled (period 1) and single-dose, open-label (period 2)</td></tr>
<tr><td>Study Population</td><td>N=50 enrolled, 49 completed
<u>Age:</u> 18-55 years (mean 30 years)
<u>Gender:</u> 24 males, 26 females
<u>Weight</u>: 107.0-201.5 pounds (mean 149 pounds)
<u>Race</u>: 22 Caucasian (44%), 25 Hispanic (50%) and 3 Black (6%)</td></tr>
<tr><td>Dosage and Administration</td><td>Group 1: XP13512 350 mg capsule (n=8) or placebo (n=2), one week later, all received Neurontin® 200 mg (2 x 100 mg capsules)
Group 2: XP13512 700 mg capsule (n=8) or placebo (n=2), one week later, all received Neurontin® 400 mg capsules
Group 3: XP13512 1400 mg capsule (n=8) or placebo (n=2), one week later, all received Neurontin® 800 mg capsules
Group 4: XP13512 2100 mg capsule (n=8) or placebo (n=2), one week later, all received Neurontin® 1200 mg capsules
Group 5: XP13512 2800 mg capsule (n=8) or placebo (n=2), one week later, all received Neurontin® 1400 mg capsules

Study drugs were given under fasted state.

Table 3.2. Study Groups and Treatments
<table><tr><th>Group</th><th>Number of Males</th><th>Number of Females</th><th>First Dose Date</th><th>XP13512 Dose (mg)</th><th>Second Dose Date</th><th>Neurontin® Dose (mg)</th></tr><tr><td>1</td><td>4</td><td>4</td><td>11/8/03</td><td>350</td><td>11/15/03</td><td>200</td></tr><tr><td></td><td>1</td><td>1</td><td>11/8/03</td><td>0</td><td>11/15/03</td><td>200</td></tr><tr><td>2</td><td>4</td><td>4</td><td>11/15/03</td><td>700</td><td>11/22/03</td><td>400</td></tr><tr><td></td><td>1</td><td>1</td><td>11/15/03</td><td>0</td><td>11/22/03</td><td>400</td></tr><tr><td>3</td><td>4</td><td>4</td><td>11/22/03</td><td>1400</td><td>11/29/03</td><td>800</td></tr><tr><td></td><td>1</td><td>1</td><td>11/22/03</td><td>0</td><td>11/29/03</td><td>800</td></tr><tr><td>4</td><td>3</td><td>5</td><td>11/29/03</td><td>2100</td><td>12/6/03</td><td>1200</td></tr><tr><td></td><td>1</td><td>1</td><td>11/29/03</td><td>0</td><td>12/6/03</td><td>1200</td></tr><tr><td>5</td><td>4</td><td>4</td><td>12/6/03</td><td>2800</td><td>12/13/03</td><td>1400</td></tr><tr><td></td><td>1</td><td>1</td><td>12/6/03</td><td>0</td><td>12/13/03</td><td>1400</td></tr></table>
<u>Lot No.</u>
XP13512 350 mg capsules: 030027
Placebo capsules: 030026
Neurontin® (gabapentin) 100 mg capsules: 16343V
Neurontin® (gabapentin) 400 mg capsules: 11183V

<u>Diet:</u>
Subjects fasted for approximately 10 hours before dosing and 4 hours after dose.

All subjects drank 240 mL of water 2 h and 1 h prior to dosing and 240</td></tr>
</table>

	mL at 2, 4, 6 and 12 h post-dose. No fluids were allowed through 2 hours postdose. Alcohol was prohibited for 48 hours prior to dosing until study completion.
Sampling: Blood	At predose (0 hour), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24 and 36 hours. The samples were analyzed for blood concentrations of gabapentin, XP13512 and gabapentin lactam.
Sampling: Urine	At 0, 0-4, 4-8, 8-12, 12-24 and 24-36 hours.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.7% Inter-day accuracy: < 8 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 7.0% Inter-day accuracy: < 10 % Long term Stability: 83 days at -80 ^{o}C Gabapentin lactam: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 9.0% Inter-day accuracy: < 5 % Long term Stability: 83 days at -80 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin lactam 10 ng/mL Gabapentin:

	Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 8% Inter-day accuracy: < 2 % Long term Stability: 236 days at -80 °C and 42 days at -20 °C <u>XP13512:</u> Linear range : 10-2500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 11.3% Inter-day accuracy: < 5 % Long term Stability: 231 days at -80 °C and 42 days at -20 °C <u>Gabapentin lactam:</u> Linear range : 10-2500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 9.4% Inter-day accuracy: < 3 % Long term Stability: 231 days at -80 °C and 42 days at -20 °C
PK Assessment	Gabapentin, XP13512 and gabapentin lactam in blood: Cmax Tmax, T ½, AUC, and AUCinf Gabapentin, XP13512 and gabapentin-lactam in urine: Ae and %F
Safety Assessment	Assessment of physical examination findings, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs), hematology, serum chemistry, and urinalysis laboratory results.

<u>Pharmacokinetic Results:</u>

<u>Gabapentin pharmacokinetics in blood and urine:</u>

Mean gabapentin PK parameters after 350 mg to 2800 mg XP13512 single dose administration are shown in the following table:

Table 2.1. Mean Pharmacokinetic Parameters for Gabapentin in Blood After Single Oral Doses of XP13512 in Study XP006

Group	Dose (mg)	Dose (mg-equiv. gabapentin)	N	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{(0\text{-inf})}$ (µg*hr/mL)	F (%)
1	350	182	8	3.61	2.13	4.38	25.4	82.9*
2	700	365	8	6.55	2.06	5.38	53.0	85.4
3	1400	729	8	11.3	2.63	4.84	85.0	68.5
4	2100	1094	8	15.7	2.19	5.10	120	72.3
5	2800	1458	8	18.1	2.56	5.47	162	79.7

*One subject excluded due to an apparent error in urine volume measurement.

Mean gabapentin blood concentration-time plots after 350 mg to 2800 mg XP13512 single dose administration are shown in the following figure:

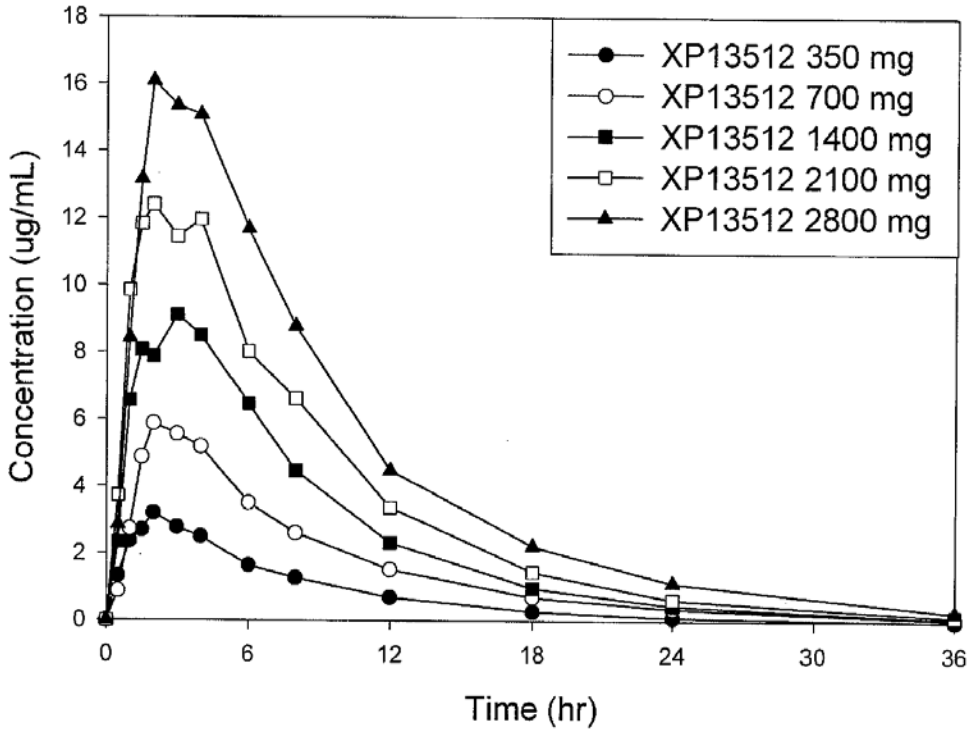


Figure 6.1. Mean concentrations of gabapentin in blood after oral administration of XP13512 in Study XP006. (Data are mean of 8 subjects.)

Mean gabapentin PK parameters after 200 mg to 1400 mg Neurontin® single dose administration are shown in the following table:

Table 2.2. Mean Pharmacokinetic Parameters for Gabapentin in Blood After Single Oral Doses of Neurontin® in Study XP006

Group	Dose (mg)	Dose (mg-equiv. gabapentin)	N	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{(0\text{-inf})}$ (µg*hr/mL)	F (%)
1	200	200	10	2.61	2.85	5.40	22.8	65.2
2	400	400	10	3.41	3.06	6.69	33.4	51.0
3	800	800	10	4.78	2.80	7.34	43.4	39.7
4	1200	1200	10	6.13	3.30	9.26	56.6	26.9
5	1400	1400	10	5.76	3.20	8.27	64.5	26.5

Mean gabapentin blood concentration-time plots after 200 mg to 1400 mg Neurontin® single dose administration are shown in the following figure:

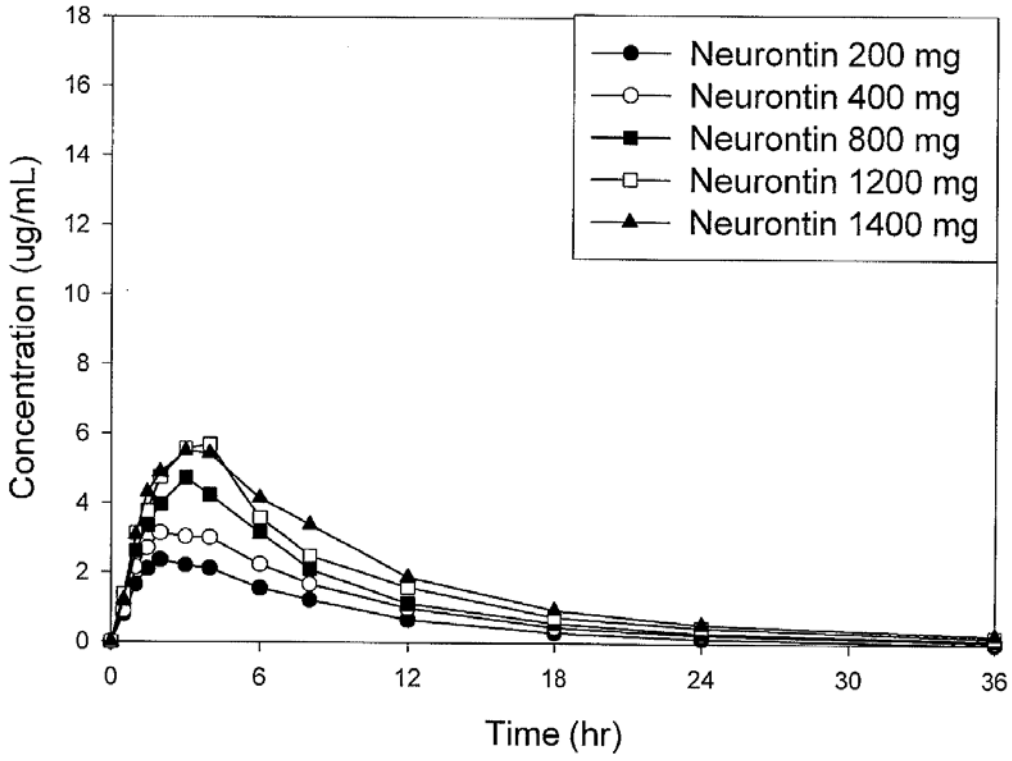
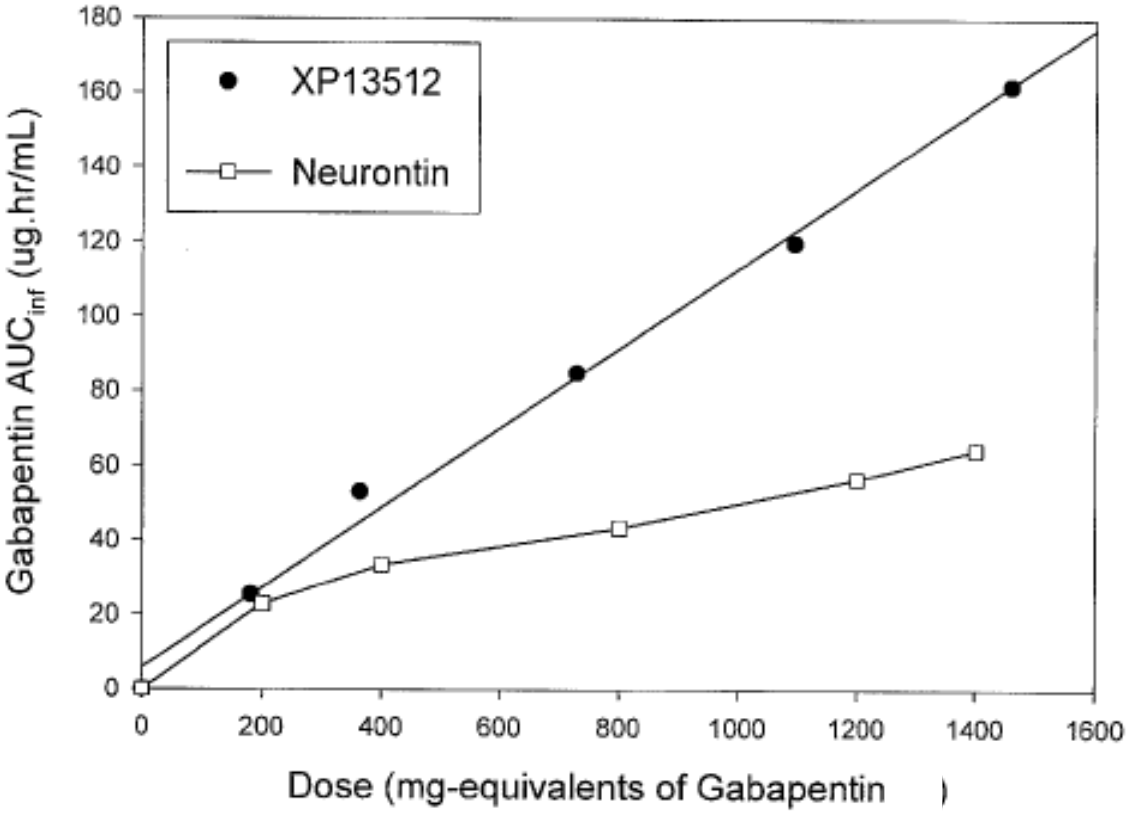


Figure 6.2. Mean concentrations of gabapentin in blood after oral administration of Neurontin® in Study XP006. (Data are mean of 10 subjects, except 9 subjects in the 400 mg dose group).

- The mean maximum concentration of gabapentin in blood (Cmax) after oral XP13512 ranged from 3.61 µg/L at the 350 mg dose level to 18.1 µg/mL at the 2800 mg dose level.
- Mean maximum gabapentin concentration in blood (Cmax) after oral Neurontin® ranged from 2.61 µg/mL at the 200 mg dose level to 5.76 µg/L at the 1400 mg dose level. This result is consistent with saturated extent of absorption for Neurontin®.
- At doses above 350 mg XP13512 provided higher gabapentin concentrations than near-equimolar doses of Neurontin®

Dose proportionality:

Relationship of XP13512 dose levels versus gabapentin AUCinf after administration of XP13512 and Neurontin® is shown in the figure below:



Relationship of XP13512 dose levels versus gabapentin Cmax after administration of XP13512 and Neurontin® is shown in the figure below:

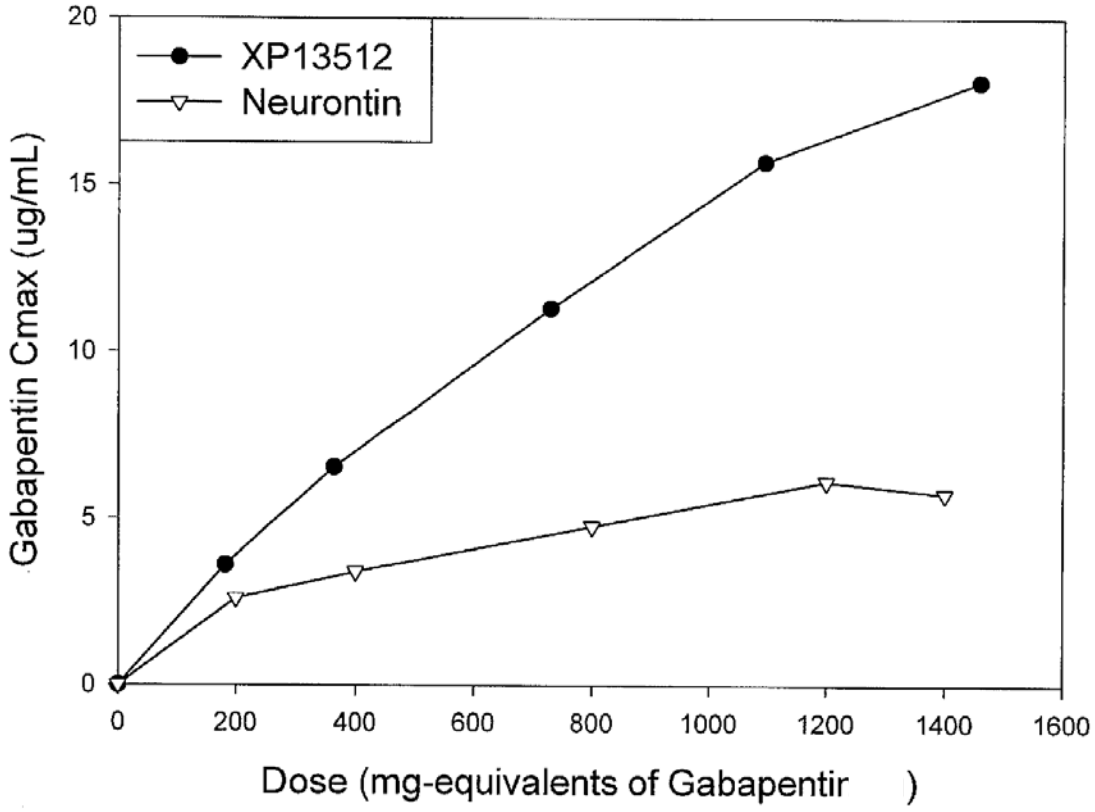


Figure 6.4. Dose proportionality of gabapentin C_{max} in blood after oral administration of XP13512 or Neurontin® in Study XP006. (Data are mean of 8 to 10 subjects per data point.)

Relationship of XP13512 dose levels (body weight corrected) versus gabapentin AUCinf after administration of XP13512 is shown in the figure below:

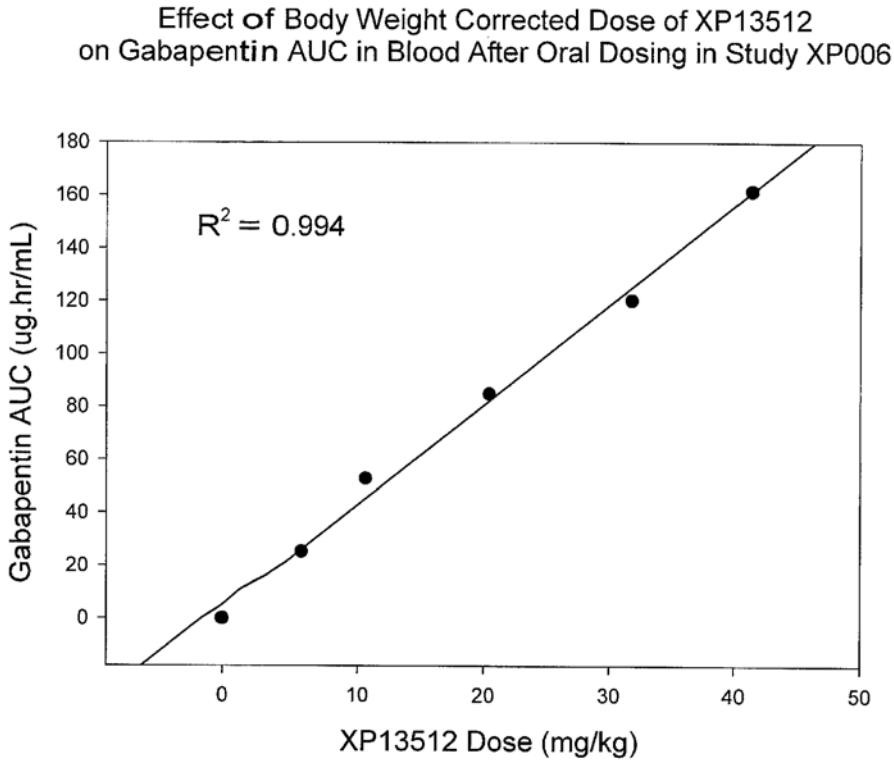


Figure 6.7. Relationship between body weight normalized dose of XP13512 (mg/kg) and gabapentin AUC_{inf} in blood after oral administration of XP13512 in Study XP006. (Data are mean of 8 to 10 subjects per data point.)

- Gabapentin exposure (AUCinf and Cmax) was proportional to dose after 350 mg to 2800 mg XP13512 administration.
- Neurontin® absorption was not dose proportional.

Bioavailability of gabapentin:

Plot of doses versus bioavailability is shown in the figure below:

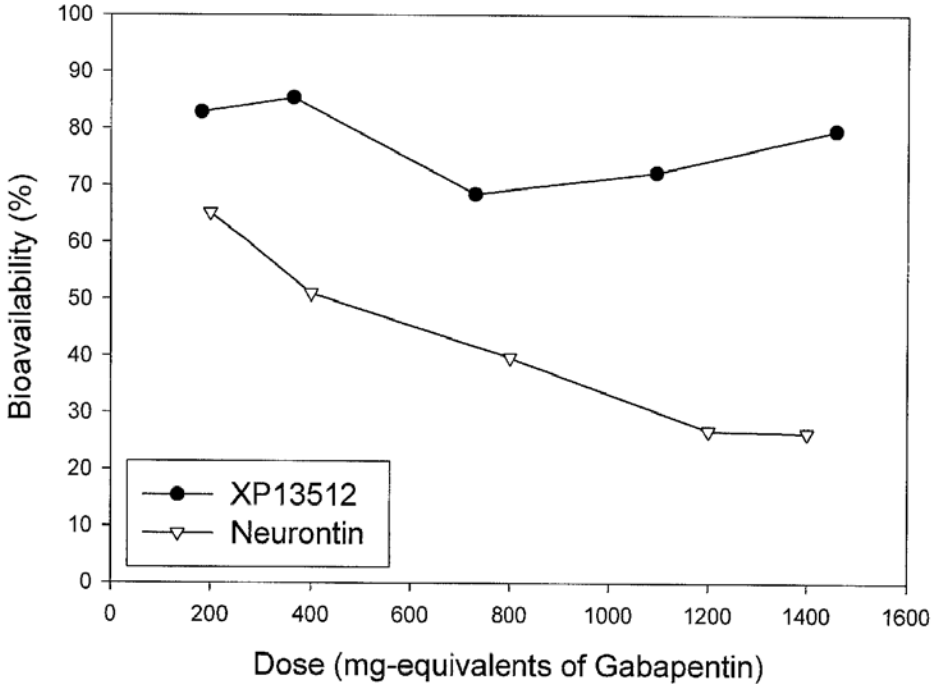


Figure 6.6. Bioavailability of gabapentin after oral administration of XP13512 or Neurontin® in Study XP006 based on urinary recovery of the administered dose. (Data are mean of 7 to 10 subjects per data point.)

- Bioavailability of gabapentin from XP13512 was consistently high (>68%) across the entire dose range (350 - 2800 mg, 182 to 1458 mg-equivalents of gabapentin).
- Bioavailability of gabapentin from Neurontin® declined from 65% at 200 mg to 27% at 1400 mg.
- Higher gabapentin concentrations were achieved after dosing of XP13512 than with Neurontin® at equimolar doses.

XP13512 exposure in blood:

Mean XP13512 blood concentration-time plot (versus gabapentin blood concentrations) after the highest dose 2800 mg XP13512 single dose administration is shown in the following figure:

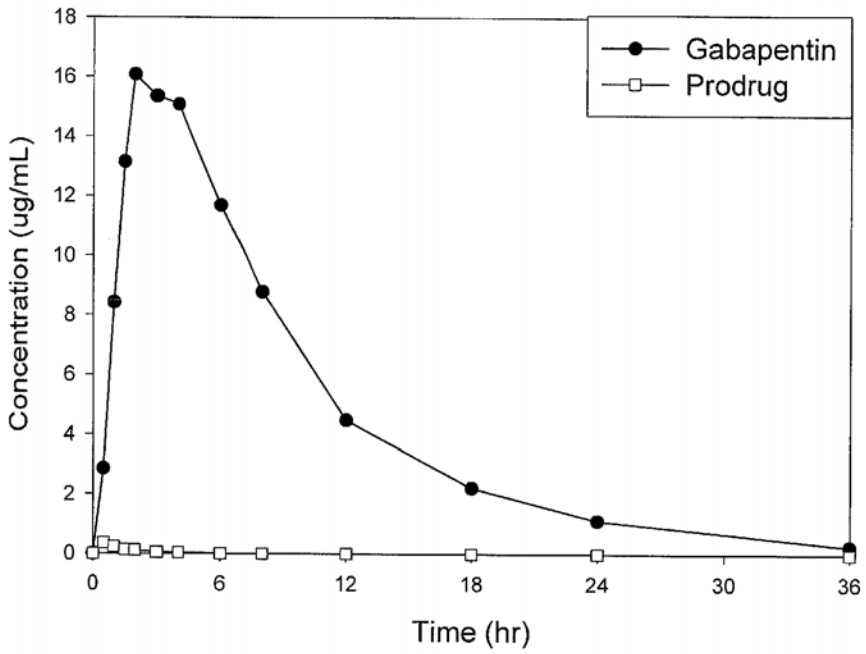


Figure 6.5. Mean concentrations of gabapentin and XP13512 in blood after oral administration of 2800 mg XP13512 in Study XP006. (Data are mean of 8 subjects.)

- Concentrations of intact prodrug in blood after oral dosing of XP13512 were low and transient.
- The prodrug Cmax in blood was 2.0% (1/50th) of the corresponding Cmax for released gabapentin at the highest XP13512 dose.
- Similarly, prodrug AUCinf was <1% of the corresponding AUCinf for released gabapentin at the highest XP13512 dose.

Gender:

Mean gabapentin PK parameters after XP13512 administrations are shown in the following table:

Table 5.11. Effect of Gender on Mean Pharmacokinetic Parameters for Gabapentin in Blood and Urine After Oral Administration of XP13512 to Healthy Adults in Study XP006

MEAN PK PARAMETERS FOR GABAPENTIN IN BLOOD AND URINE:

Treatment	Dose (mg)	Gender	N	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	λ_z (hr^{-1})	AUC_{last} (µg.hr/mL)	AUC_{inf} (µg.hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)	$Ae_{(0-36)}$ (mg)	% Dose Excreted
XP13512	350	Male	4	2.93	2.75	4.63	0.151	21.9	22.6	8.12	54.1	7.84	148	81.0
		Female	4	4.30	1.50	4.13	0.174	27.4	28.1	6.68	38.9	6.51	155	85.3
	700	Male	4	5.86	2.25	5.91	0.119	48.8	50.0	7.58	63.5	9.21	314	86.2
		Female	4	7.24	1.88	4.86	0.143	54.9	56.0	6.60	46.0	7.84	308	84.6
	1400	Male	4	11.4	2.38	5.71	0.123	83.6	84.7	8.74	72.4	8.29	475	65.2
		Female	4	11.2	2.88	3.96	0.176	84.1	85.5	8.54	48.8	7.45	524	71.9
	2100	Male	3	13.0	1.33	5.64	0.125	108	110	10.2	82.6	8.69	919	84.0
		Female	5	17.3	2.70	4.77	0.145	126	127	8.71	59.9	7.66	714	65.3
	2800	Male	4	16.9	2.13	6.02	0.120	153	157	9.33	80.4	9.45	1147	78.7
		Female	4	19.3	3.00	4.91	0.143	165	167	9.05	63.4	8.12	1176	80.7

- No significant PK differences were observed between females and males over the dose range.

Race:

Mean gabapentin PK parameters after XP13512 administrations are shown in the following table:

Table 5.12. Effect of Race on Mean Pharmacokinetic Parameters for Gabapentin in Blood and Urine After Oral Administration of XP13512 to Healthy Adults in Study XP006

MEAN PK PARAMETERS FOR GABAPENTIN IN BLOOD AND URINE:

Treatment	Dose (mg)	Race	N	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	λ_z (hr^{-1})	AUC_{last} (µg.hr/mL)	AUC_{inf} (µg.hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	MRT (hr)	$Ae_{(0-36)}$ (mg)	% Dose Excreted
XP13512	350	C	3	3.21	2.33	4.22	0.166	22.4	23.0	8.02	49.1	7.12	148	81.1
		H	4	3.72	2.25	4.24	0.168	25.1	25.9	7.28	44.4	7.09	149	82.0
		AA	1	4.43	1.00	5.47	0.127	29.1	30.4	5.98	47.2	7.68	165	90.7
	700	C	5	6.05	2.40	5.62	0.126	50.6	52.0	7.15	57.6	8.86	319	87.7
		H	3	7.37	1.50	4.98	0.139	53.9	54.7	6.98	50.1	7.96	297	81.7
		AA	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1400	C	2	15.0	1.25	4.97	0.150	80.0	81.2	9.00	65.2	7.30	468	64.2
		H	6	10.0	3.08	4.79	0.149	85.2	86.4	8.52	59.1	8.06	510	70.0
		AA	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2100	C	2	13.5	3.00	5.30	0.132	123	124	8.87	67.3	9.15	892	81.5
		H	5	17.6	2.10	4.75	0.146	122	123	9.08	62.2	7.30	718	65.7
		AA	1	10.5	1.00	6.44	0.108	97.0	100	11.0	102	9.60	952	87.0
	2800	C	5	19.1	2.10	5.25	0.134	167	169	8.78	66.4	8.63	1140	78.2
		H	2	17.8	3.00	4.76	0.146	140	141	10.5	71.7	7.28	1162	79.7
		AA	1	13.8	4.00	7.99	0.087	160	168	8.68	100	12.6	1266	86.9

C – Caucasian.
H – Hispanic.
AA – African-American.
N/A – Not applicable.

- No significant PK differences were observed between Caucasians and Hispanics over the dose range.

Reviewer's comments:

- *Although the PK data between Caucasians and Hispanics shown above seem to be similar, however, a conclusive statement can not be made based on this data due to the relatively small numbers in each population.*

Conclusions:

- XP13512 was rapidly absorbed and converted to gabapentin following oral administration to healthy adults, producing dose proportional exposure.
- The percent of gabapentin absorbed following oral administration of Neurontin® to healthy adults decreased with increasing dosage, consistent with saturable absorption.
- The bioavailability of gabapentin from Neurontin® declined from 65% at 200 mg to 27% at 1400 mg consistent with saturated absorption.
- The bioavailability of gabapentin from XP13512, measured from urinary excretion, was > 68% over the 350 to 2800 mg dose range.
- Higher gabapentin concentrations were obtained after dosing with XP13512 than after equimolar doses of Neurontin®.
- The Tmax was shorter after XP13512 administration compared with Neurontin®.
- XP13512 at doses of 350 to 2800 mg and Neurontin® at doses of 200 to 1400 mg were generally well tolerated by healthy male and female subjects in this study.

Reviewer's Comment:

- *Five of the subjects who received placebo have low gabapentin urine levels up to 605 ng/mL. The sponsor stated that this suggested possible low level interference which was considered not significant and conclusion was not affected. Although the levels were low and not significant, the finding also indicated some degree of deficiencies either in study conduct or in biosample analysis.*

Study XP-018: ***A Phase 1, Randomized, Placebo-Controlled, Ascending Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Oral XP13512 IR in Healthy Adult Subjects***

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Multiple-dose, randomized, double-blind, placebo-controlled</td></tr>
<tr><td>Study Population</td><td>N=38 enrolled, 37 completed
<u>Age:</u> 19-49 years (mean 31 years)
<u>Gender:</u> 24 males, 14 females
<u>Weight</u>: 123.5-197.5 pounds (mean 148.3 pounds)
<u>Race</u>: 14 Caucasian (36.8%), 22 Hispanic (57.9 %) and 2 Black (5.3 %)</td></tr>
<tr><td>Dosage and Administration</td><td>Group 1: XP13512 350 mg capsule (n=6) or placebo (n=2) BID for 7 days
Group 2: XP13512 700 mg capsule (n=8) or placebo (n=2) BID for 7 days
Group 3: XP13512 1400 mg capsule (n=8) or placebo (n=2) BID for 7 days
Group 4: XP13512 2100 mg capsule (n=8) or placebo (n=2) BID for 7 days

Study drugs were given 2 hours prior to meal for the first 6 days and under fasted state for day 7.

<table>
<tr><th>Group</th><th colspan="10">XP13512 Dose (mg) Administered Twice Per Day</th></tr>
<tr><th></th><th>Day -3</th><th>Day -2</th><th>Day -1</th><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th><th>Day 5</th><th>Day 6</th><th>Day 7*</th></tr>
<tr><td>1</td><td>-</td><td>-</td><td>-</td><td>350</td><td>350</td><td>350</td><td>350</td><td>350</td><td>350</td><td>350</td></tr>
<tr><td>2</td><td>-</td><td>-</td><td>350</td><td>700</td><td>700</td><td>700</td><td>700</td><td>700</td><td>700</td><td>700</td></tr>
<tr><td>3</td><td>-</td><td>350</td><td>700</td><td>1400</td><td>1400</td><td>1400</td><td>1400</td><td>1400</td><td>1400</td><td>1400</td></tr>
<tr><td>4</td><td>350</td><td>700</td><td>1400</td><td>2100</td><td>2100</td><td>2100</td><td>2100</td><td>2100</td><td>2100</td><td>2100</td></tr>
</table>
*One dose was administered on the Day 7 of the study.

<u>Lot No.</u>
XP13512 350 mg capsules: 030027
Placebo capsules: 030026

<u>Diet:</u>
Drinking water and other caffeine-free clear liquids was allowed and encouraged throughout the study, except within 2 hours postdose.

At the last dose (day 7), all subjects drank 240 mL of water 2 h and 1 h prior to dosing and 240 mL at 2, 4, 6, 12 and 24 h post-dose.

Alcohol was prohibited for 48 hours prior to dosing until study completion.</td></tr>
<tr><td>Sampling: Blood</td><td>At predose (0 hour) each morning, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours following the Day 7 dose. The samples were analyzed for blood concentrations of gabapentin and XP13512.</td></tr>
</table>

Sampling: Urine	At 0, 0-4, 4-8, 8-12 and 12-24 hours following the Day 7 dose.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.7% Inter-day accuracy: < 8 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 7.0% Inter-day accuracy: < 10 % Long term Stability: 83 days at -80 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 8% Inter-day accuracy: < 2 % Long term Stability: 236 days at -80 ^{o}C and 42 days at -20 ^{o}C XP13512: Linear range : 10-2500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 11.3% Inter-day accuracy: < 5 % Long term Stability: 231 days at -80 ^{o}C and 42 days at -20 ^{o}C
PK Assessment	Gabapentin and XP13512 in blood: Cmax, Cmin, Tmax, T ½, Kel, CL/F, Vd/F and AUC0-tau Gabapentin and XP13512 in urine: Ae and %F

Safety Assessment	Assessment of physical examination findings, vital sign measurements, 12-lead electrocardiogram (ECG) results, adverse events (AEs), hematology values, serum chemistry values, and urinalysis findings.

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood and urine:

Mean gabapentin PK parameters after 350 mg to 2100 mg XP13512 BID for 7 days are shown in the following table:

Table 2.1. Mean Pharmacokinetic Parameters for Gabapentin in Blood at Steady State After Twice Daily Oral Administration of XP13512 in Study XP018

Group	Dose (mg) b.i.d.	Dose (mg-equiv. gabapentin)	N	$C_{ss,max}$ (μg/mL)	$C_{ss,min}$ (μg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{ss} (μg*hr/mL)	F (%)
1	350	182	6	3.24	0.997	1.92	5.17	20.0	79.1
2	700	365	8	8.04	2.24	1.56	4.96	51.2	93.2
3	1400	729	8	14.0	4.49	1.69	4.57	89.6	88.0
4	2100	1094	7	20.7	7.24	1.86	4.83	128	73.1

Mean gabapentin blood concentration-time plots after 350 mg to 2100 mg XP13512 BID for 7 days are shown in the following figure:

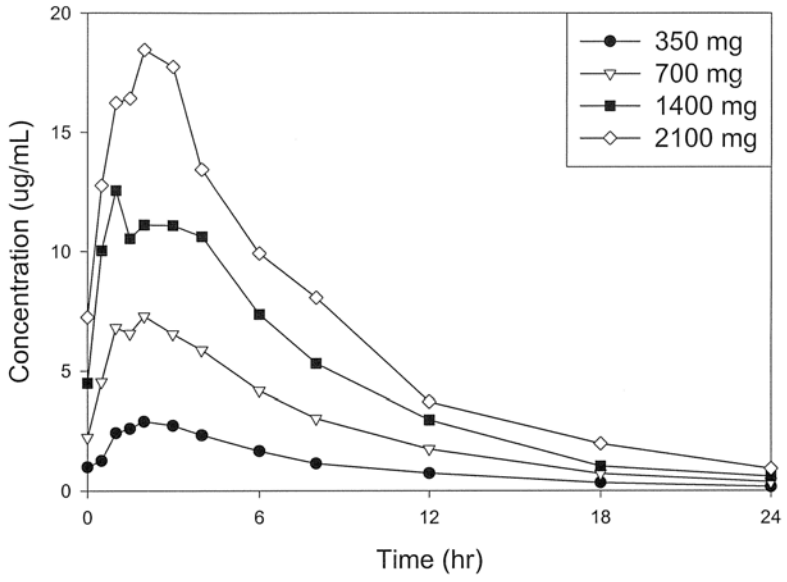


Figure 6.1. Mean concentrations of gabapentin in blood at steady state after twice daily oral administration of XP13512 in Study XP018. (Data are mean of 6 to 8 subjects per group.)

- Tmax were achieved within 1 to 2 hours after dosing.
- Mean maximum gabapentin concentration in blood at steady-state (Css, max) ranged from 3.24 µg/mL at the 350 mg BID dose level to 20.7 µg/mL at the 2100 mg BID dose level.
- Mean minimum gabapentin concentration in blood at steady-state (Css, min) ranged from 0.997 µg/mL at the 350 mg BID dose level to 7.24 µg/mL at the 2100 mg BID dose level.
- T1/2 was 4.6 to 5.2 hours after XP13512 administration.

Dose proportionality:

Relationship of XP13512 dose levels versus gabapentin AUCss after administration of XP13512 is shown in the figure below:

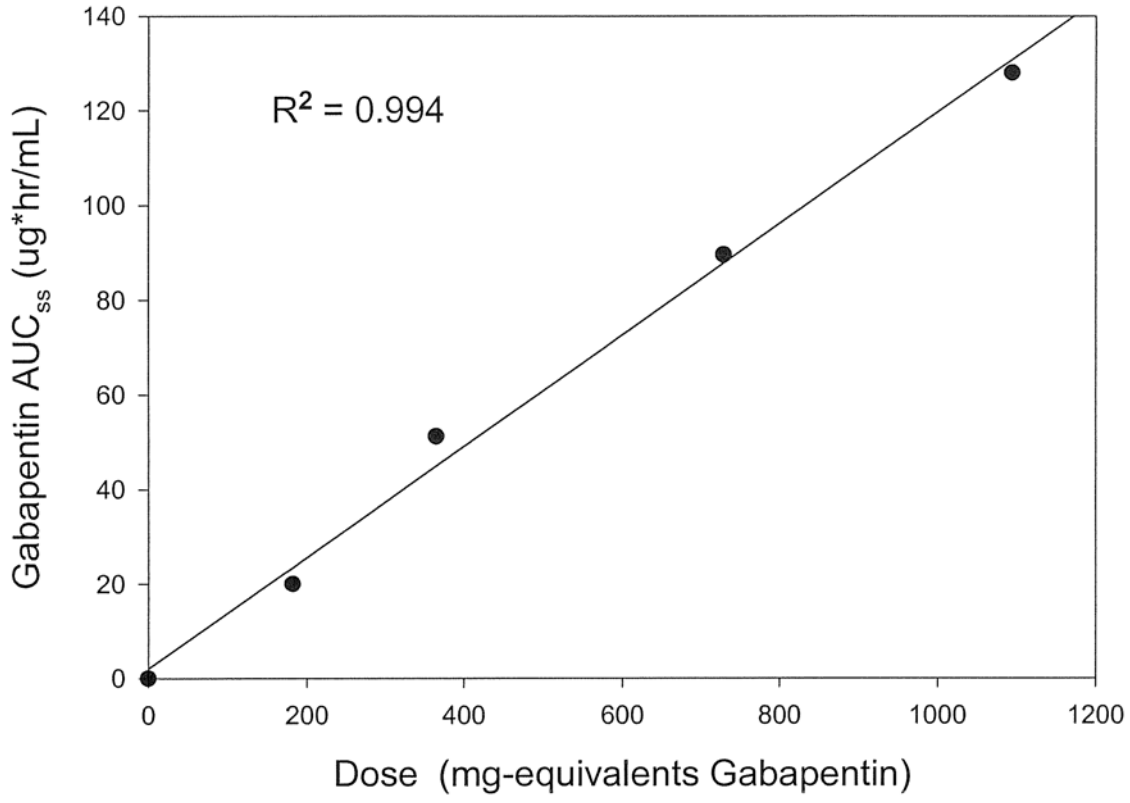


Figure 6.2. Dose proportionality of gabapentin AUC_{ss} in blood at steady state after twice daily oral administration of XP13512 in Study XP018. (Data are mean of 6 to 8 subjects per data point.)

Relationship of XP13512 dose levels (body weight normalized) versus gabapentin AUCss after administration of XP13512 is shown in the figure below:

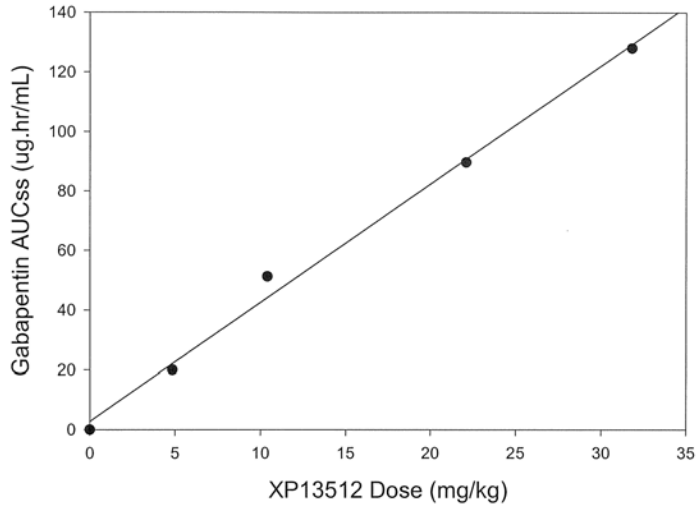


Figure 6.8. Relationship between body weight normalized dose (mg/kg) and gabapentin AUC_{ss} in blood at steady state after twice daily oral administration of XP13512 in Study XP018. (Data are mean of 6 to 8 subjects per data point.)

Relationship of XP13512 dose levels versus gabapentin Css,max after administration of XP13512 is shown in the figure below:

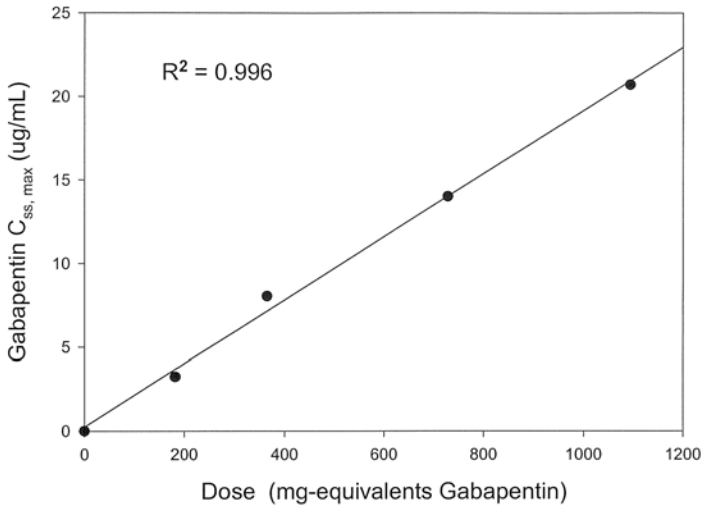


Figure 6.3. Dose proportionality of gabapentin $C_{ss,max}$ in blood at steady state after twice daily oral administration of XP13512 in Study XP018. (Data are mean of 6 to 8 subjects per data point.)

Relationship of XP13512 dose levels versus gabapentin Css,min after administration of XP13512 is shown in the figure below:

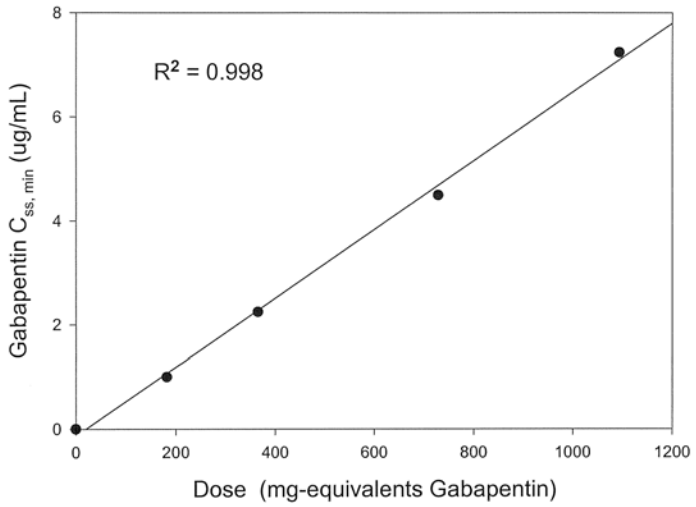


Figure 6.4. Dose proportionality of gabapentin $C_{ss,\ min}$ in blood at steady state after twice daily oral administration of XP13512 in Study XP018. (Data are mean of 6 to 8 subjects per data point.)

- Gabapentin exposure (AUCss, Css,max and Cmax) was proportional to dose after 350 mg to 2100 mg XP13512 administration based on linear regression.

Bioavailability of gabapentin:

Plot of doses versus bioavailability is shown in the figure below:

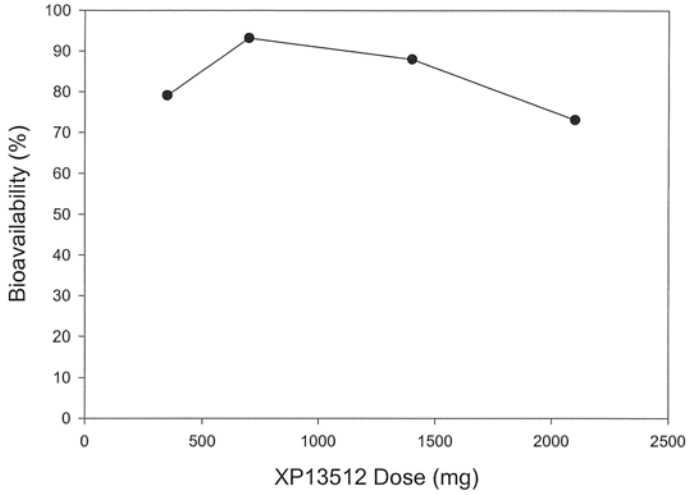


Figure 6.7. Bioavailability of gabapentin at steady state after twice daily oral administration of XP13512 in Study XP018, based on urinary recovery of the administered dose. (Data are mean of 5 to 8 subjects per data point.)

- Bioavailability of gabapentin from XP13512 at steady-state was consistently high (>70%) across the entire dose range (350 - 2100 mg, BID).

XP13512 exposure in blood:

Mean XP13512 blood concentration-time plot (versus gabapentin blood concentrations) after the highest dose 2100 mg XP13512 BID for 7 days is shown in the following figure:

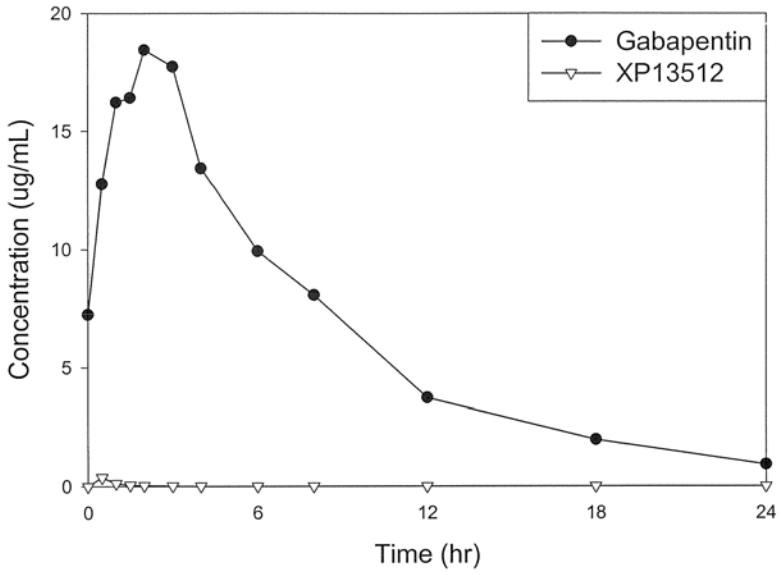


Figure 6.5. Mean concentrations of gabapentin and XP13512 in blood at steady state after twice daily oral administration of 2100 mg XP13512 in Study XP018. (Data are mean of 7 subjects.)

- Concentrations of intact prodrug in blood after oral dosing of XP13512 were low and transient at all dose levels.
- The AUCss of gabapentin in blood was > 380 times higher than the AUCss of intact prodrug at the highest XP13512 dose (2100 mg BID).
- The Css,max of gabapentin in blood was > 54 times higher than the Css, max of intact prodrug at the highest dose.

Gender:

Mean gabapentin PK parameters by gender after XP13512 administrations are shown in the following table:

Table 5.5. Effect of Gender on Mean Pharmacokinetic Parameters for Gabapentin and XP13512 in Blood and Urine at Steady State After Twice Daily Oral Administration of XP13512 to Healthy Adults in Study XP018

Dose Level	Gender	N	$C_{ss,max}$ (μg/mL)	$C_{ss,min}$ (μg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{ss} (μg*hr/mL)	F (%)
350 mg b.i.d.	Male	6	3.24	0.997	1.92	5.17	20.0	79.1[a]
	Female	0	N/A	N/A	N/A	N/A	N/A	N/A
700 mg b.i.d.	Male	4	7.35	2.30	1.75	5.72	49.9	91.7
	Female	4	8.72	2.18	1.38	4.20	52.5	94.7
1400 mg b.i.d.	Male	5	14.6	5.06	1.80	5.12	95.6	90.6[b]
	Female	3	13.0	3.54	1.50	3.66	79.5	84.5
2100 mg b.i.d.	Male	4	18.2	6.73	2.13	5.11	123	65.4
	Female	3	24.1	7.92	1.50	4.45	135	83.4

[a]Urine data for 5 subjects – one subject excluded because a urine sample was not received at the 4-8 hr interval.
[b]Urine data for 4 subjects – one subject excluded because the urine data were considered erroneous.
N/A – Not applicable.

- No significant PK differences were observed between females and males over the dose range.

Race:

Mean gabapentin PK parameters by race after XP13512 administrations are shown in the following table:

Table 5.6. Effect of Race on Mean Pharmacokinetic Parameters for Gabapentin and XP13512 in Blood and Urine at Steady State After Twice Daily Oral Administration of XP13512 to Healthy Adults in Study XP018

Dose Level	Race	N	$C_{ss,max}$ (μg/mL)	$C_{ss,min}$ (μg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{ss} (μg*hr/mL)	F (%)
350 mg b.i.d.	Caucasian	3	3.27	1.10	2.50	5.42	22.0	66.6
	Hispanic	2	2.82	0.77	1.50	4.32	16.2	86.3[a]
	African-American	1	3.99	1.14	1.00	6.11	21.7	109
700 mg b.i.d.	Caucasian	2	8.06	2.81	1.50	6.40	58.0	102
	Hispanic	6	8.03	2.05	1.58	4.48	48.9	90.5
	African-American	0	N/A	N/A	N/A	N/A	N/A	N/A
1400 mg b.i.d.	Caucasian	2	11.6	5.07	1.50	5.11	90.1	92.6
	Hispanic	5	15.4	4.21	2.00	4.69	91.7	85.0[b]
	African-American	1	10.3	4.70	1.50	4.22	81.3	90.7
2100 mg b.i.d.	Caucasian	3	19.3	8.00	2.17	4.92	132	75.5
	Hispanic	4	21.8	6.67	1.63	4.75	125	71.4
	African-American	0	N/A	N/A	N/A	N/A	N/A	N/A

[a]Urine data for 5 subjects – one subject excluded because a urine sample was not received at the 4-8 hr interval.
[b]Urine data for 4 subjects – one subject excluded because the urine data were considered erroneous.
N/A – Not applicable.

- No significant PK differences were observed between Caucasians and Hispanics over the dose range.

Reviewer's comments:

- *Although the PK data between Caucasians and Hispanics shown above seem to be similar, however, a conclusive statement can not be made based on this data due to the relatively small numbers in each population.*

Trough levels:

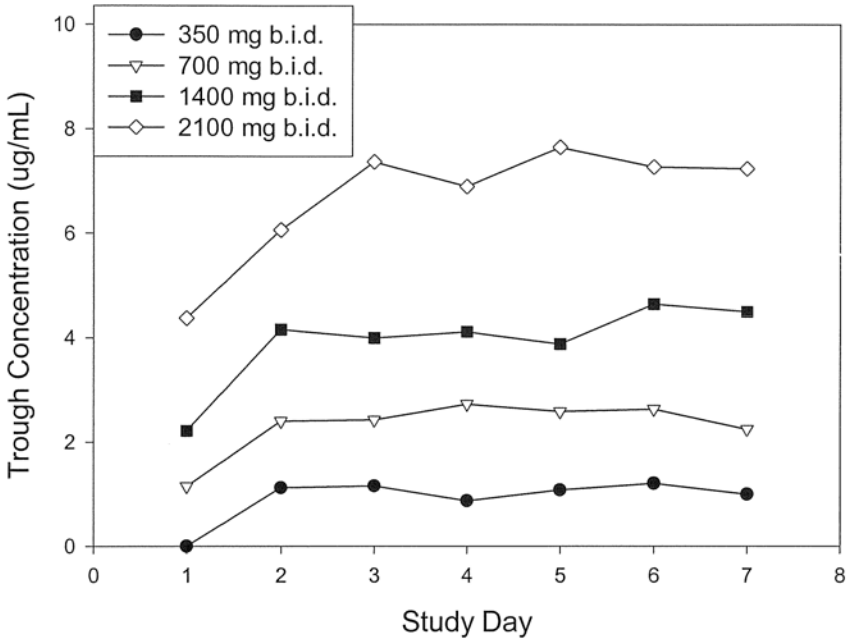


Figure 6.6. Mean trough concentrations of gabapentin in blood prior to the morning dose after twice daily oral administration of XP13512 in Study XP018. (Data are mean of 6 to 8 subjects.)

- The steady-state was achieved within 2 days of the target dose.

Conclusions:

- After repeated doses of XP13512 twice a day, on Day 7 a dose proportional increase in peak and total exposure (i.e., Cmax and AUC[0-tau]) was observed for gabapentin across the dose range 350 mg to 2100 mg.

Study XP-065: ***A PHASE 1, SINGLE-DOSE STUDY OF THE DISPOSITION OF ^{14}C RADIOLABELED XP13512 IR IN HEALTHY MALE VOLUNTEERS***

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Single-dose, open-label</td></tr>
<tr><td>Study Population</td><td>N=6
Age: 24-46 years (mean 37 years)
Gender: 6 males
Weight: Male 66.8-92.7 kg
Race: 5 White (83.33%), 1 black or African American (16.67%)</td></tr>
<tr><td>Dosage and Administration</td><td>All 6 healthy subjects received a single dose of 600 mg XP13512 (100 μCi) after a standard breakfast.

<table><tr><th>Number of Subjects</th><th>Treatment</th><th>Condition</th></tr><tr><td>6 (male)</td><td>600 mg of ^{14}C-XP13512 (100 μCi) administered as 2 capsules</td><td>Fed</td></tr></table>
14C-XP13512 (600 mg, approximately100 μCi), oral capsule
Lot Number: 60080JUL07-01

Diet:
Standard breakfast (30% calories from fat) was provided before dosing. Drinking water and other caffeine-free clear liquids was allowed and encouraged throughout the study, except within 2 hours postdose.

All subjects drank 240 mL of water 2 h and 1 h prior to dosing and 240 mL at 2, 4, 6, 12 and 24 h post-dose.

Alcohol was prohibited for 72 hours prior to dosing until study completion.</td></tr>
<tr><td>Sampling: Blood</td><td>At predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, and 168 (192, 216, 240 if not discharged) hours post-dose. The samples were analyzed for blood and plasma concentrations of gabapentin.</td></tr>
<tr><td>Sampling: Urine</td><td>At 0, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, (168-192, 192-216 and 216-240 if not discharged) hours post-dose.</td></tr>
<tr><td>Sampling: Feces</td><td>At 0, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, (168-192, 192-216 and 216-240 if not discharged) hours post-dose.</td></tr>
<tr><td>Analysis
(Plasma, blood, urine and feces)</td><td>Method

Sample combustions and liquid scintillation counting (LSC)</td></tr>
<tr><td>PK Assessment</td><td>Gabapentin in blood and plasma:
Cmax, Tmax, AUC(0-t), AUC(0-∞), AUCb:AUCp, Kel, T ½, CL/F, and Vd/F</td></tr>
</table>

	Gabapentin in urine: Ae, %R, and CLr Gabapentin in feces: Ae and %R
Safety Assessment	Adverse event (AE) monitoring, 12-lead electrocardiograms (ECGs), clinical laboratory tests, vital signs and physical examinations.

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood and plasma:

Descriptive statistics for gabapentin blood PK parameters after single dose of 600 mg XP13512 administration are shown in the following table:

Table 14.2.2.-1a (Page 1 of 1)
Individual Subject and Mean Blood Pharmacokinetic Parameter Data for [^{14}C]-XP13512 - Derived Total Radioactivity Final 17APR2008
Study Population: Pharmacokinetic Set XP065

Subject Number	T_{max} (hr)	C_{max} (ng equivalents/mL)	K_{el} (1/hr)	$T_{1/2}$ (hr)	$AUC_{(0-t)}$ (ng equivalents*hr/mL)	$AUC_{(0-\infty)}$ (ng equivalents*hr/mL)	CL/F (L/hr)	Vd/F (L)	AUC_b:AUC_p
001									(b) (4)
002									
003									
004									
005									
006									
N	6	6	6	6	6	6	6	6	6
MEAN	3.84	9887	0.114	6.10	73020	80750	7.48	65.9	0.914
GEO. MEAN	3.67	9711	0.114	6.09	72828	80503	7.45	65.5	0.913
SD	1.16	2002	0.00848	0.451	5754	6792	0.664	7.95	0.0262
MIN	2.00	7070	0.102	5.44	64399	70477	6.87	55.1	0.878
MEDIAN	4.00	10300	0.115	6.03	73866	83521	7.18	64.9	0.913
MAX	5.00	12700	0.128	6.77	80264	87380	8.51	78.6	0.943
%CV	30	20	7	7	8	8	9	12	3

NOTE: T_{last} was reported as 24 for all subjects except for Subject 003, which was reported as 18.
Reference:Listing 16.2.8-1a

Descriptive statistics for gabapentin plasma PK parameters after single dose of 600 mg XP13512 administration are shown in the following table:

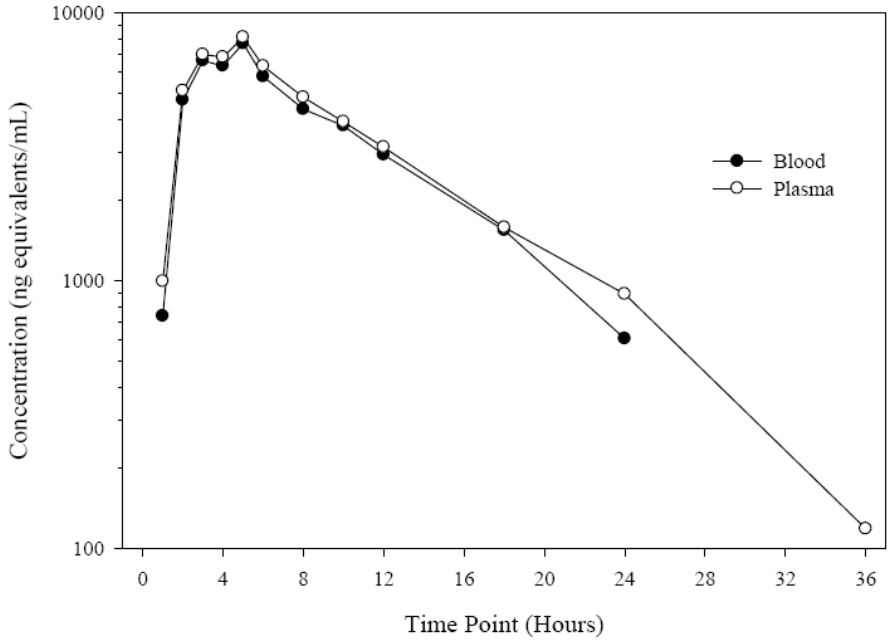
Table 14.2.2.-1b (Page 1 of 1)
Individual Subject and Mean Plasma Pharmacokinetic Parameter Data for [^{14}C]-XP13512 - Derived Total Radioactivity Final 17APR2008
Study Population: Pharmacokinetic Set XP065

Subject Number	T_{max} (hr)	C_{max} (ng equivalents/mL)	K_{el} (1/hr)	$T_{1/2}$ (hr)	$AUC_{(0-t)}$ (ng equivalents*hr/mL)	$AUC_{(0-\infty)}$ (ng equivalents*hr/mL)	CL/F (L/hr)	Vd/F (L)
001	[redacted]							(b) (4)
002								
003								
004								
005								
006								
N	6	6	6	6	6	6	6	6
MEAN	3.84	10195	0.107	6.56	82502	88451	6.83	64.9
GEO. MEAN	3.67	9994	0.106	6.53	82013	88130	6.81	64.1
SD	1.16	2202	0.0119	0.703	9503	8025	0.676	11.1
MIN	2.00	7120	0.0939	5.55	66384	74766	6.35	52.2
MEDIAN	4.00	10400	0.104	6.67	85700	92600	6.48	62.9
MAX	5.00	13600	0.125	7.38	91170	94469	8.03	85.5
%CV	30	22	11	11	12	9	10	17

NOTE: T_{last} was reported as 24 for all subjects except for Subjects 005 and 006 which was reported as 36.
Reference: Listing 16.2.8-1b

Mean gabapentin concentration-time plot after single dose of 600 mg XP13512 administration is shown in the following figure:

Figure 1
Mean concentrations of radioactivity in blood and plasma at specified times after a single 600-mg (100-μCi) oral dose of ^{14}C-XP13512 to healthy male subjects



- Mean Tmax was observed at 3.84 hours postdose in blood and plasma.
- T1/2 values were 6.56 and 6.10 hours in plasma and blood, respectively.
- Mean Cmax was 9887 and 10195 ng equivalents/mL in blood and plasma, respectively.
- Mean AUCinf was 80750 and 88451 ng equivalents x h/mL in blood and plasma, respectively.
- AUCb:AUCp was 0.91 indicating the total radioactivity in plasma is similar to blood and suggesting the total radioactivity was not highly associated with red blood cells.
- Mean Vd/F (64.9 L) and CL/F (6.83 L/hr) values for total radioactivity in plasma suggest that total radioactivity is distributed to tissues and is not highly extracted by the liver.

Gabapentin pharmacokinetics in urine and feces:

Gabapentin urine PK parameters in individual subjects after single dose of 600 mg XP13512 administration are shown in the following table:

Table 14.2.2-2 (Page 1 of 1)
Individual Subject Urine Excretion Data for [^{14}C]-XP13512 - Derived Total Radioactivity Final 17APR2008
Study Population: Pharmacokinetic Set XP065

Subject Number	$A_{e(0-t)}$ (mg equivalents)	CL_R (L/hr)	% Excreted (%)
001	[redacted] (b) (4)		
002			
003			
004			
005			
006			
N	6	6	6
MEAN	579	6.58	94.1
GEO. MEAN	576	6.54	93.8
SD	58.7	0.744	9.17
MIN	541	5.85	88.1
MEDIAN	560	6.47	91.2
MAX	696	7.56	112
%CV	10	11	10

NOTE: Upper range for time of last measurable concentration in urine.
$Ae_{(0-t)}$ reported as $Ae_{(0-72)}$ for all subjects except for Subject 006, which was reported as $Ae_{(0-120)}$.
Reference: Listing 16.2.8-2

Gabapentin feces PK parameters in individual subjects after single dose of 600 mg XP13512 administration are shown in the following table:

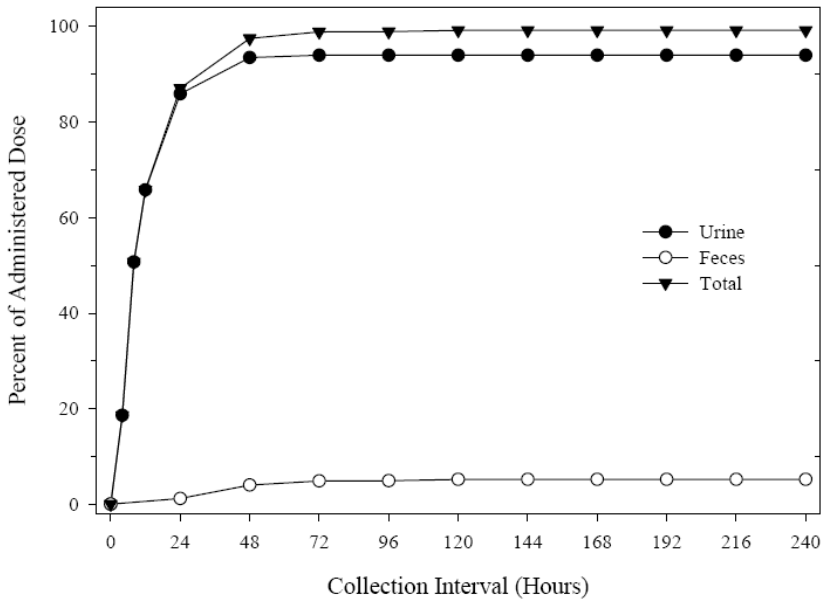
Table 14.2.2-3
Individual Subject Fecal Excretion Data for [^{14}C]-XP13512 - Derived Total Radioactivity
Study Population: Pharmacokinetic Set

Subject Number	$A_{e(0-t)}$ (mg equivalents)	% Excreted (%)
001	(b) (4)	
002		
003		
004		
005		
006		
N	6	6
MEAN	32.0	5.20
GEO. MEAN	29.2	4.76
SD	11.8	1.92
MIN	10.5	1.71
MEDIAN	34.3	5.56
MAX	42.3	6.89
%CV	37	37

NOTE: Upper range for time of last measurable concentration in feces.
$Ae_{(0-t)}$ reported as $Ae_{(0-72)}$ for all subjects except for Subject 006, which was reported as $Ae_{(0-120)}$.
Reference: Listing 16.2.8-3

Mean cumulative percent of radioactive dose recovered in urine and feces after single dose of 600 mg XP13512 (100 µCi) administration is shown in the following figure:

Figure 2
Mean cumulative percent of radioactive dose recovered in urine and feces at specified intervals after a single 600-mg (100-µCi) oral dose of ^{14}C-XP13512 to healthy male subjects



- Mean recovery of total radioactivity in urine was 94.1%, with 5.20% of the radioactive dose recovered in feces. Total recovery in urine and feces combined was approximately 99.3%.
- More than 85% of the radioactive dose was recovered in urine within 24 hours of dosing.
- Mean CLR values of 6.58 L/hr approached the typical glomerular filtration rate in the kidney (approximately 7.5 L/hr) suggesting that renal excretion represents the main clearance pathway for total radioactivity.

Metabolites in urine:

The individual data of gabapentin and metabolites recovered in urine are shown below:

Subject	Gabapentin	Unknown 1	Unknown 2
M 1	(b) (4)		
M 2			
M 3			
M 4			
M 5			
M 6			
Mean	89.6	1.69	0.91
SD	5.73	0.68	0.41

- Two unknown metabolites were observed in urine in all subjects, accounting for less than 3% of the total radioactivity.

Conclusions:

- The maximum mean concentrations of drug-derived radioactivity in blood and plasma were observed at 3.84 hours postdose, with values of 9887 and 10195 ng equivalents/mL, respectively. These data are consistent with minimal sequestration of radioactivity within red blood cells.
- A mean of 94.0% of the dose was excreted in urine and 5.20% was excreted in feces through the last collection interval. Elimination of radioactivity was rapid, with the majority of the dose (>85%) recovered within 24 hours postdose.
- Most of the administered radioactivity was recovered in the first 48 hours postdose (97.5%). The overall mean recovery of radioactivity in urine and feces samples was 99.3% over the 240-hour study, with recovery in six individual subjects ranging from 93.8 to 117%.
- ^{14}C-Gabapentin was the only radioactive species detected in blood and accounted for >89% of the administered dose in urine. Two minor unidentified metabolites accounted for <3% of the administered radioactivity in urine. The only significant metabolic pathway of ^{14}C-XP13512 was ester-hydrolysis of the parent drug to yield gabapentin.

Study XP-069: ***A Phase I, Double-Blind, Randomized, Placebo-Controlled, Dose Escalation, Crossover Study of the Safety, Tolerability, and Pharmacokinetics of Oral XP13512 ER in Healthy Adult Subjects***

This study was conducted to assess the safety, tolerability and pharmacokinetics of supra-therapeutic doses of XP13512 to allow the design of clinical studies including a thorough QT/QTc study.

A brief overview of some essential components of the study design is given below:

Study Design	Single-dose, randomized, double-blind, placebo-controlled, crossover
Study Population	N=32 Age: 18-50 years (mean 31 years) Gender: 14 males, 18 females Weight: 48.9-102 kg (mean 72.0 kg) Race: 24 Caucasian (75%), 5 African-American (15.6%), 2 Native Hawaiian (6.25 %) and 1 Asian (3.1%)
Dosage and Administration	Group 1: XP13512 2400 mg XP13512 ER tablet (n=4) (Treatment A) or placebo (n=4) (Treatment B) as a sequence of AB or BA, one week washout in between Treatments Group 2: XP13512 3600 mg XP13512 ER tablet (n=4) (Treatment A) or placebo (n=4) (Treatment B) as a sequence of AB or BA, one week washout in between Treatments Group 3: XP13512 4800 mg XP13512 ER tablet (n=4) (Treatment A) or placebo (n=4) (Treatment B) as a sequence of AB or BA, one week washout in between Treatments Group 4: XP13512 6000 mg XP13512 ER tablet (n=4) (Treatment A) or placebo (n=4) (Treatment B) as a sequence of AB or BA, one week washout in between Treatments All treatments were given after a standard-fat breakfast. Lot No. XP13512 600 mg ER tablets: 3051595R Placebo tablets: 3049685R Diet: Before morning dose, subjects fasted for approximately 10 hours until breakfast and 4 hours after dose. Drinking water and other caffeine-free clear liquids was allowed. All subjects drank 240 mL of water 1 h prior to dosing and 240 mL for dose administration. Alcohol and caffeine-containing foods and beverages were prohibited for 72 hours prior to dosing until study completion.

Sampling: Blood	At predose (0 hour), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 18, 21, 22.5, 24 and 36 hours. The samples were analyzed for blood concentrations of gabapentin and XP13512.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 10.1% Inter-day accuracy: 91.7-102 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.77% Inter-day accuracy: 95.8-101 % Long term Stability: 83 days at -80 ^{o}C
PK Assessment	Gabapentin, XP13512 and gabapentin lactam in blood: Cmax Tmax, T ½, AUC, and AUCinf
Safety Assessment	Assessment of physical examination findings, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs), hematology, serum chemistry, and urinalysis laboratory results.

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood:

Mean gabapentin PK parameters after 2400 mg to 6000 mg XP13512 single dose administration are shown in the following table:

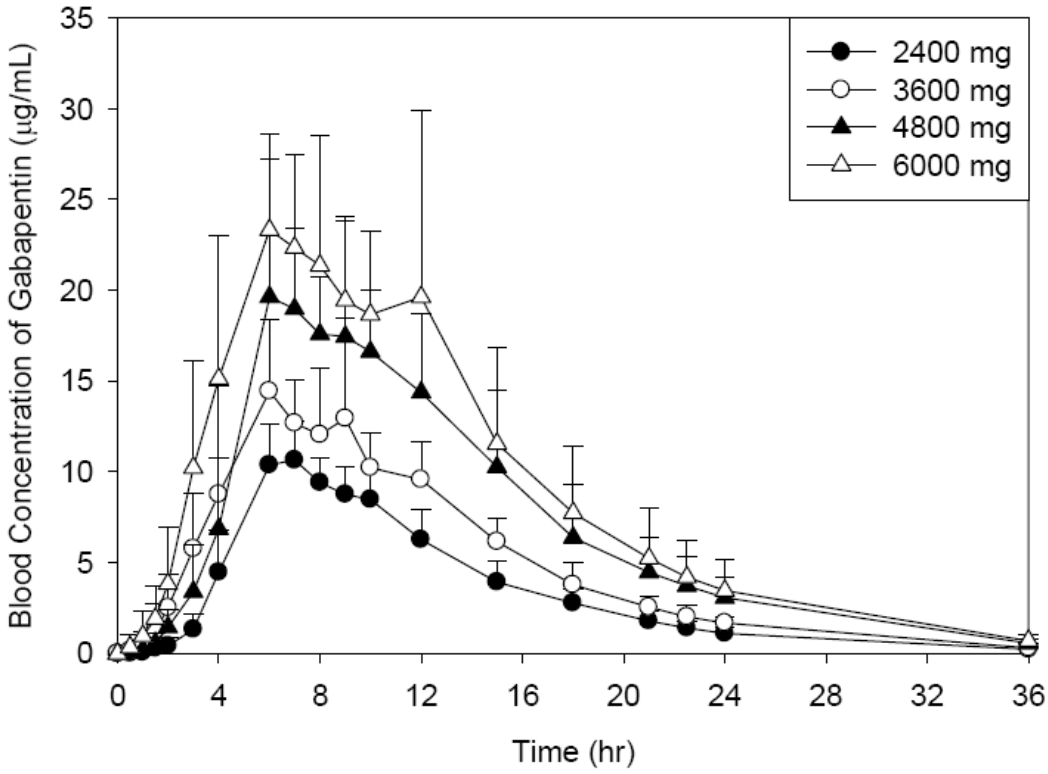
Table 13 Mean (standard deviation) Pharmacokinetic Data for Gabapentin in Blood following Oral Administration of XP13512

Gabapentin PK Parameters	Dose level of XP13512			
	2400 mg	3600 mg	4800 mg	6000 mg
N	8	8	8	8
C_{max} (µg/mL)	11.4 (1.72)	16.2 (4.24)	22.7 (4.88)	28.9 (6.06)
$AUC_{(0\text{-}inf)}$ (µg.h/mL)	118 (21.0)	175 (18.6)	254 (62.2)	322 (55.8)
T_{max} (h)	6.88 (0.84)	7.51 (2.51)	6.63 (1.06)	8.63 (3.89)
$T_{½}$ (h)	5.07 (0.66)	5.06 (1.06)	5.06 (0.81)	5.19 (0.60)

Data Source: PK Table 5.1

Mean gabapentin blood concentration-time plots after 2400 mg to 6000 mg XP13512 single dose administration are shown in the following figure:

Figure 2 Mean (standard deviation) Concentrations of Gabapentin in Blood following Oral Administration of XP13512 at 2400, 3600, 4800 or 6000 mg doses in Study XP069 (N = 8 per dose level)



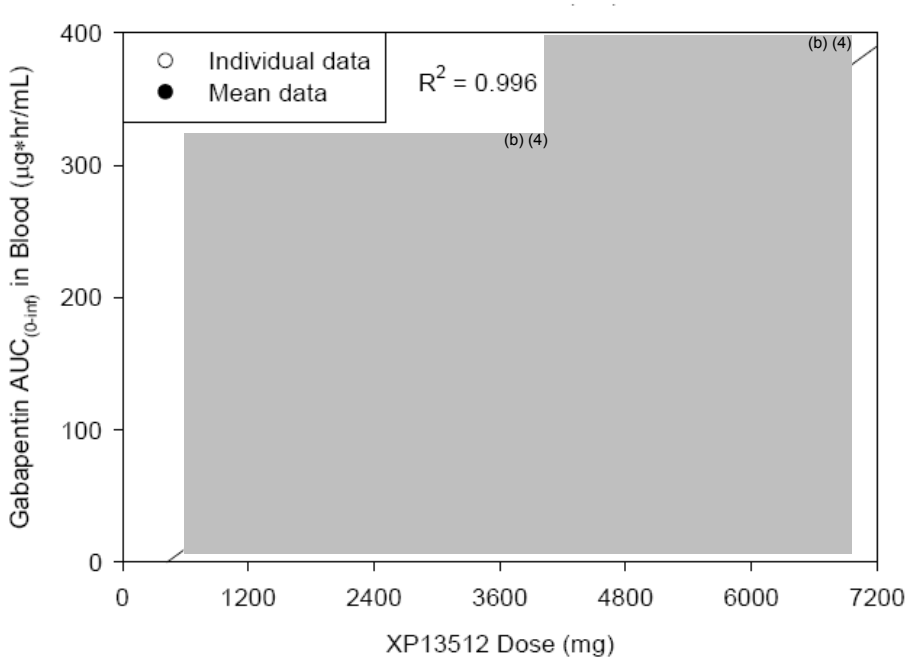
Data Source: PK Figure 6.1

- Following oral administration of XP13512 SR tablets at 2400, 3600, 4800 and 6000 mg under fed conditions, the mean maximum blood concentration (Cmax) values of gabapentin were 11.4, 16.2, 22.7 and 28.9 µg/mL at 6.9, 7.5, 6.6 and 8.6 h post-dose, respectively.
- The corresponding AUC(0-inf) values were 118, 175, 254 and 322 µg.h/mL, respectively.
- The mean apparent terminal half-life of gabapentin in blood was 5.1 to 5.2 h.

Dose proportionality:

Relationship of XP13512 dose levels versus gabapentin AUCinf after administration of XP13512 is shown in the figure below:

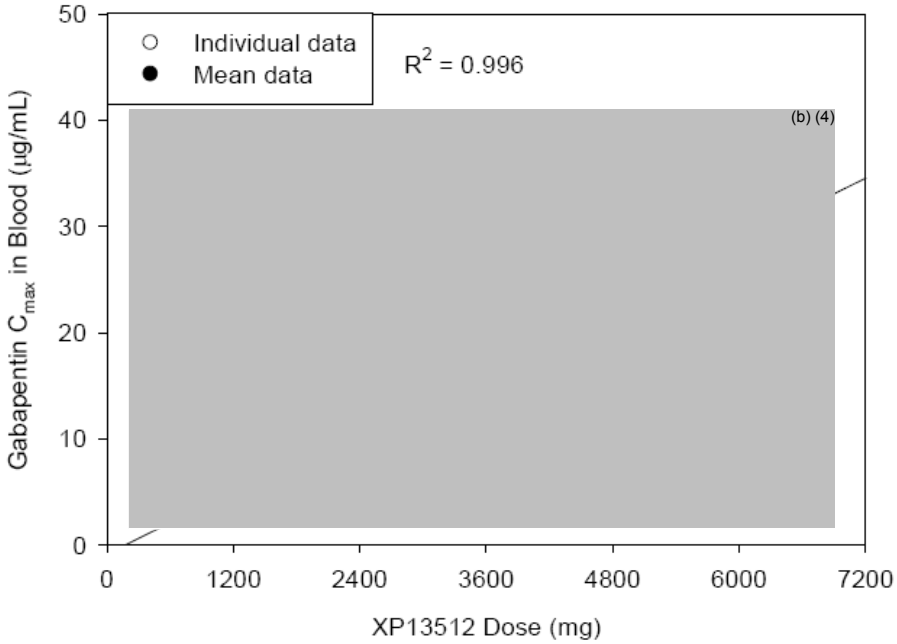
Figure 3 Relationship between XP13512 dose and Area under the Concentration- time curve of Gabapentin in Blood following Oral Administration of XP13512



Data Source: PK Figure 6.7

Relationship of XP13512 dose levels versus gabapentin Cmax after administration of XP13512 is shown in the figure below:

Figure 4 Relationship between XP13512 dose and Peak Concentration of Gabapentin in Blood following Oral Administration of XP13512



Data Source: PK Figure 6.6

- Gabapentin exposure in blood (AUCinf and Cmax) was proportional to dose after 2400 mg to 6000 mg XP13512 administration.

XP13512 exposure in blood:

Mean XP13512 PK parameters after 2400 mg to 6000 mg XP13512 single dose administration are shown in the following table:

Table 14 Mean (standard deviation) Pharmacokinetic Data for XP13512 in Blood following Oral Administration of XP13512

	Dose level of XP13512			
	2400 mg	3600 mg	4800 mg	6000 mg
N	8	8	8	8
C_{max} (µg/mL)	0.028 (0.008)	0.050 (0.019)	0.083 (0.029)	0.136 (0.129)
$AUC_{(0\text{-tlast})}$ (µg.h/mL)	0.094 (0.068)	0.177 (0.083)	0.365 (0.184)	0.553 (0.381)
Tmax (h)	5.25 (1.49)	5.31 (2.05)	5.00 (1.51)	5.87 (3.36)

Data Source: PK Table 5.2

Mean XP13512 blood concentration-time plot after 2400 mg to 6000 mg XP13512 single dose administration is shown in the following figure:

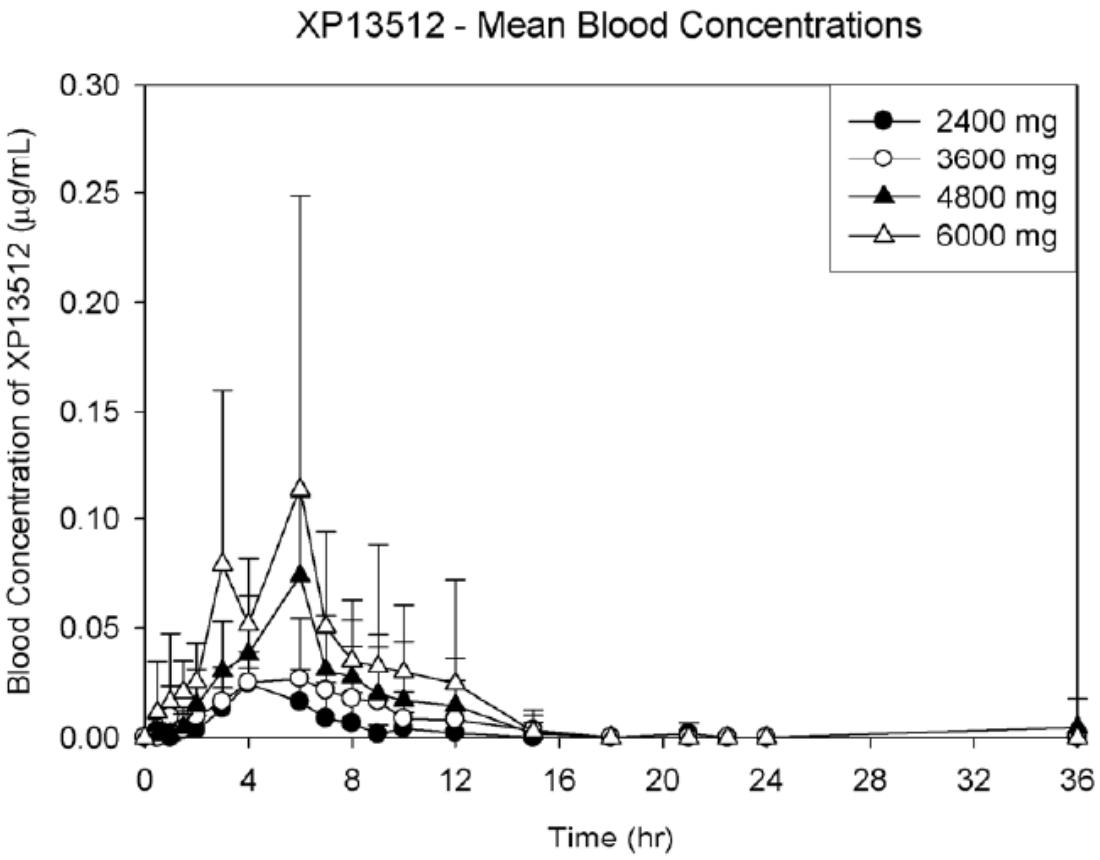


Figure 6.8. Mean (SD) concentrations of XP13512 in blood of fed subjects following oral dosing of XP13512 at 2400, 3600, 4800, or 6000 mg doses in Study XP069 (N = 8 per dose level)

- Concentrations of intact prodrug in blood after oral dosing of XP13512 were low and variable.
- The prodrug Cmax in blood was ≤ 0.5 % of the corresponding Cmax for released gabapentin at all dose levels.
- Similarly, prodrug AUCinf was ≤ 0.2 % of the corresponding AUCinf for released gabapentin at all dose levels.

Gender:

Mean gabapentin PK parameters by gender after XP13512 administrations are shown in the following table:

Table 5.3. Effect of Gender on Mean Pharmacokinetic Parameters for Gabapentin in Blood After Oral Dosing of XP13512 Sustained Release Tablets to Fed Healthy Adult Volunteers in Study XP069

XP13512 Dose	Gender		Gabapentin PK Parameter												
			C_{max} (µg/mL)	T_{max} (hr)	Kel (1/hr)	$T_{1/2}$ (hr)	C_{last} (µg/mL)	T_{last} (hr)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	$AUC_{(0\text{-}inf)}$ (µg*hr/mL)	$AUC_{(0\text{-}tlast)}$/ $AUC_{(0\text{-}inf)}$	AUC% Extrapolated	CL/F (L/hr)	Vz/F (L)	MRT (hr)
2400 mg (4 × 600 mg SR Tablets)	Female	N	4	4	4	4	4	4	4	4	4	4	4	4	4
		Mean	11.1	7.25	0.148	4.74	0.212	36.0	120	121	0.988	1.18	10.8	72.0	12.1
		SD	2.57	0.96	0.021	0.59	0.090	0.06	27.9	28.5	0.005	0.47	2.77	9.32	0.76
	Male	N	4	4	4	4	4	4	4	4	4	4	4	4	4
		Mean	11.7	6.50	0.130	5.39	0.245	36.0	113	115	0.983	1.72	11.0	86.3	12.1
		SD	0.252	0.58	0.015	0.61	0.046	0.00	14.2	13.8	0.007	0.65	1.23	19.0	0.73
3600 mg (6 × 600 mg SR Tablets)	Female	N	5	5	5	5	5	5	5	5	5	5	5	5	5
		Mean	18.2	7.61	0.159	4.38	0.435	33.6	178	181	0.985	1.53	10.5	66.2	11.0
		SD	4.11	1.51	0.015	0.39	0.557	5.39	17.5	18.5	0.020	1.92	1.16	10.0	0.83
	Male	N	3	3	3	3	3	3	3	3	3	3	3	3	3
		Mean	12.8	7.33	0.113	6.20	0.574	36.0	160	165	0.969	3.13	11.5	103	13.7
		SD	1.08	4.16	0.014	0.74	0.125	0.02	16.8	17.1	0.008	0.83	1.24	20.7	1.24
4800 mg (8 × 600 mg SR Tablets)	Female	N	5	5	5	5	5	5	5	5	5	5	5	5	5
		Mean	24.7	6.80	0.147	4.79	0.602	36.0	284	288	0.986	1.43	8.82	60.4	13.0
		SD	4.45	1.30	0.020	0.61	0.247	0.00	40.8	42.8	0.005	0.51	1.20	7.37	1.32
	Male	N	3	3	3	3	3	3	3	3	3	3	3	3	3
		Mean	19.3	6.34	0.129	5.51	0.530	36.0	192	197	0.978	2.22	13.1	104	12.7
		SD	4.00	0.59	0.026	1.02	0.289	0.00	43.3	45.1	0.013	1.28	2.66	26.3	0.84
6000 mg (10 × 600 mg SR Tablets)	Female	N	4	4	4	4	4	4	4	4	4	4	4	4	4
		Mean	28.7	8.25	0.138	5.04	0.675	36.0	327	332	0.986	1.43	9.70	69.9	11.8
		SD	6.09	4.79	0.011	0.39	0.408	0.03	59.1	61.4	0.008	0.81	2.16	11.0	2.79
	Male	N	4	4	4	4	4	4	4	4	4	4	4	4	4
		Mean	29.0	9.00	0.132	5.34	0.734	36.0	305	311	0.982	1.81	10.3	79.5	12.5
		SD	6.97	3.46	0.021	0.80	0.381	0.00	54.3	56.7	0.009	0.96	2.20	18.4	1.55

- No consistent PK differences were observed between females and males over the dose range.

Race:

Mean gabapentin PK parameters by race after XP13512 administrations are shown in the following table:

Table 5.4. Effect of Race on Mean Pharmacokinetic Parameters for Gabapentin in Blood After Oral Dosing of XP13512 Sustained Release Tablets to Fed Healthy Adult Volunteers in Study XP069

XP13512 Dose	Race		Gabapentin PK Parameter												
			C_{max} (µg/mL)	T_{max} (hr)	Kel (1/hr)	$T_{1/2}$ (hr)	C_{last} (µg/mL)	T_{last} (hr)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	$AUC_{(0\text{-}inf)}$ (µg*hr/mL)	$AUC_{(0\text{-}tlast)}$/ $AUC_{(0\text{-}inf)}$	AUC% Extrapolated	CL/F (L/hr)	Vz/F (L)	MRT (hr)
2400 mg (4 × 600 mg SR Tablets)	African American	N	2	2	2	2	2	2	2	2	2	2	2	2	2
		Mean	10.3	7.50	0.134	5.17	0.264	36.1	111	113	0.983	1.75	11.1	82.9	12.7
		SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Caucasian	N	5	5	5	5	5	5	5	5	5	5	5	5	5
		Mean	11.7	6.60	0.143	4.97	0.222	36.0	120	121	0.986	1.37	10.7	76.4	12.0
		SD	1.97	0.89	0.024	0.83	0.085	0.00	26.8	27.1	0.008	0.75	2.61	19.8	0.59
	Native Hawaiian	N	1	1	1	1	1	1	1	1	1	1	1	1	1
		Mean	11.7	7.00	0.130	5.32	0.191	36.0	111	112	0.987	1.31	11.1	85.5	11.1
		SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
3600 mg (6 × 600 mg SR Tablets)	African American	N	1	1	1	1	1	1	1	1	1	1	1	1	1
		Mean	12.0	6.00	0.104	6.69	0.707	36.0	163	169	0.960	4.03	11.1	107	14.7
		SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Asian	N	1	1	1	1	1	1	1	1	1	1	1	1	1
		Mean	16.5	9.02	0.163	4.25	0.196	36.0	187	188	0.994	0.64	9.98	61.1	10.7
		SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Caucasian	N	5	5	5	5	5	5	5	5	5	5	5	5	5
		Mean	17.1	7.41	0.137	5.16	0.569	33.6	169	174	0.976	2.38	11.0	82.6	11.7
		SD	5.09	3.13	0.020	0.85	0.507	5.38	22.8	23.5	0.018	1.74	1.53	23.8	1.58
	Native Hawaiian	N	1	1	1	1	1	1	1	1	1	1	1	1	1
		Mean	15.5	8.00	0.184	3.77	0.149	36.0	172	173	0.995	0.47	10.9	59.0	11.8
		SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

ND – Not determined.

Table 5.4 (continued). Effect of Race on Mean Pharmacokinetic Parameters for Gabapentin in Blood After Oral Dosing of XP13512 Sustained Release Tablets to Fed Healthy Adult Volunteers in Study XP069

XP13512 Dose	Race		Gabapentin PK Parameter												
			C_{max} (µg/mL)	T_{max} (hr)	Kel (1/hr)	$T_{1/2}$ (hr)	C_{last} (µg/mL)	T_{last} (hr)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	$AUC_{(0\text{-}inf)}$ (µg*hr/mL)	$AUC_{(0\text{-}tlast)}/AUC_{(0\text{-}inf)}$	AUC% Extrapolated	CL/F (L/hr)	Vz/F (L)	MRT (hr)
4800 mg (8 × 600 mg SR Tablets)	African American	N	2	2	2	2	2	2	2	2	2	2	2	2	2
		Mean	17.3	6.00	0.114	6.09	0.690	36.0	203	209	0.971	2.93	12.4	109	13.2
		SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Caucasian	N	6	6	6	6	6	6	6	6	6	6	6	6	6
		Mean	24.5	6.84	0.149	4.72	0.537	36.0	265	268	0.987	1.32	9.79	65.7	12.8
		SD	4.03	1.17	0.019	0.57	0.273	0.00	59.3	61.3	0.005	0.52	2.61	14.5	1.28
6000 mg (10 × 600 mg SR Tablets)	Caucasian	N	8	8	8	8	8	8	8	8	8	8	8	8	8
		Mean	28.9	8.63	0.135	5.19	0.704	36.0	316	322	0.984	1.62	10.0	74.7	12.2
		SD	6.06	3.89	0.016	0.60	0.367	0.02	53.8	55.8	0.009	0.85	2.05	15.0	2.12

ND – Not determined.

- No obvious influence of race on the PK of gabapentin was observed over the dose range.

Reviewer's comments:

- *No conclusive statement can be made based on this data due to the relatively small numbers in each population.*

Age

Relationship of gabapentin Cmax/dose versus age was shown below.

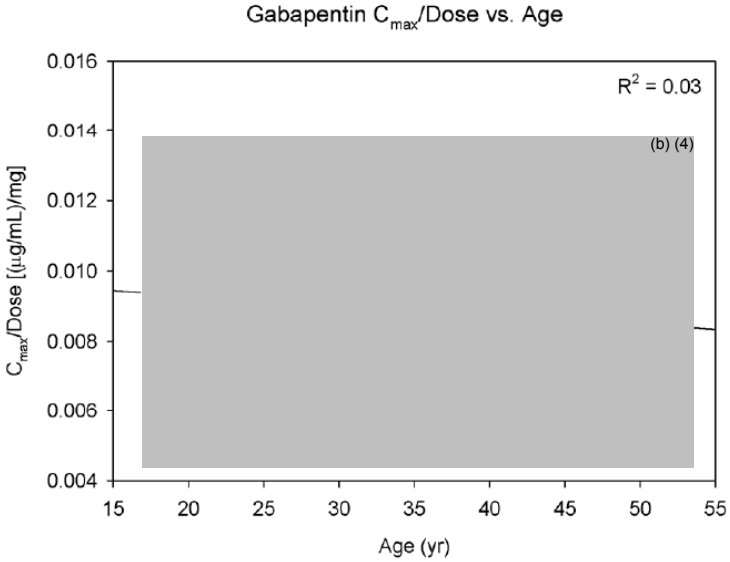


Figure 6.14. Relationship between age and dose-normalized C_{max} of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin AUCinf/dose versus age was shown below.

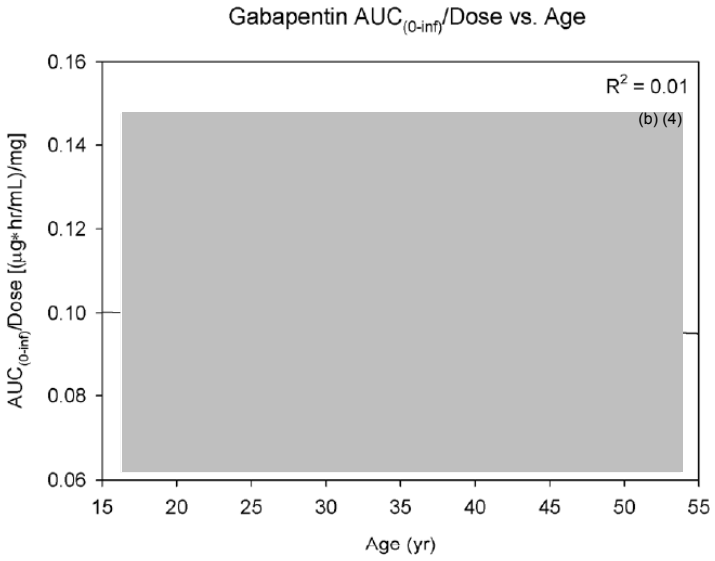


Figure 6.15. Relationship between age and dose-normalized $AUC_{(0\text{-}inf)}$ of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

- The correlation between dose-normalized Cmax or dose-normalized AUCinf of gabapentin is 0.03 and 0.01, respectively.
- No apparent effect of subject age on the gabapentin PK was observed after XP13512 administration.

Weight

Relationship of gabapentin Cmax/dose versus weight was shown below.

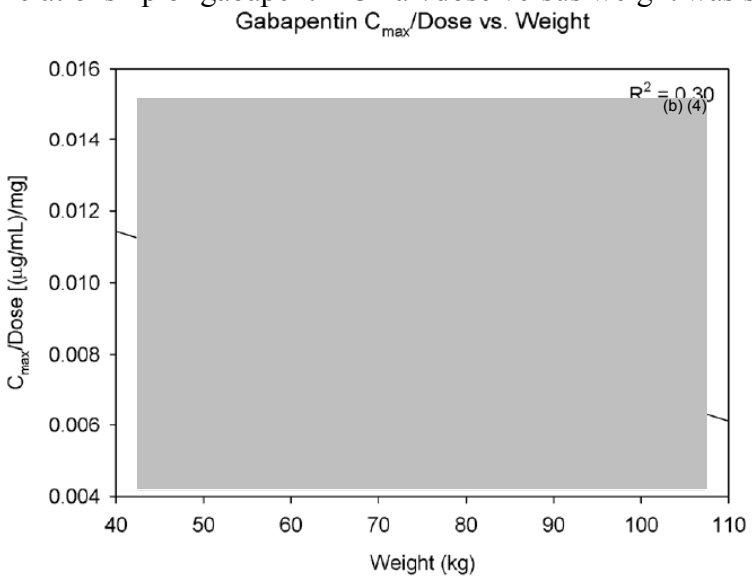


Figure 6.16. Relationship between weight and dose-normalized C_{max} of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin AUCinf/dose versus weight was shown below.

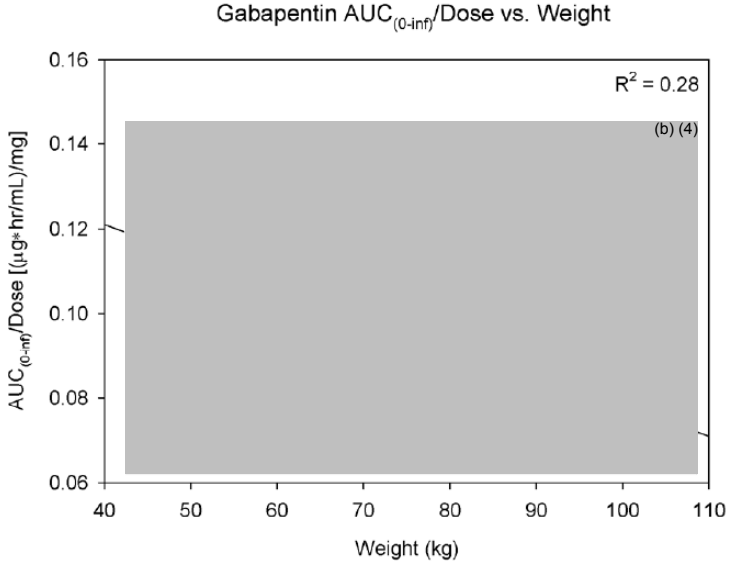


Figure 6.17. Relationship between weight and dose-normalized $AUC_{(0\text{-}inf)}$ of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

- The correlation between dose-normalized Cmax or dose-normalized AUCinf of gabapentin is 0.30 and 0.28, respectively.
- No apparent effect of body weight on the gabapentin PK was seen after XP13512 administration.

Height

Relationship of gabapentin Cmax/dose versus height was shown below.

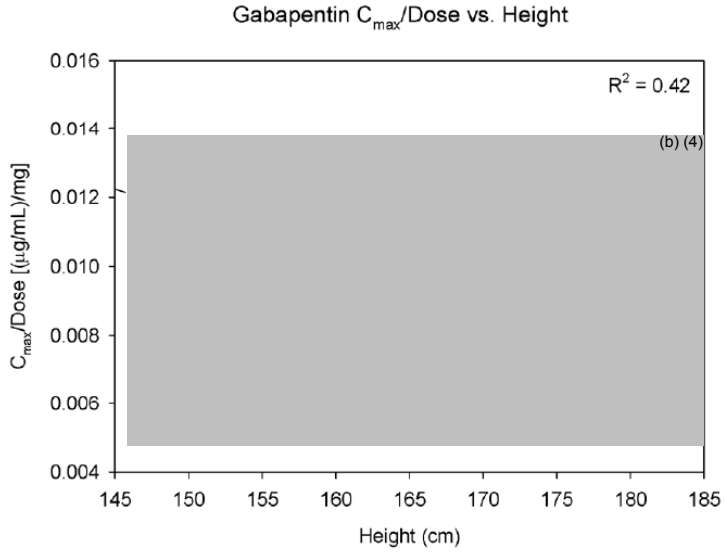


Figure 6.18. Relationship between height and dose-normalized C_{max} of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin AUCinf/dose versus weight was shown below.

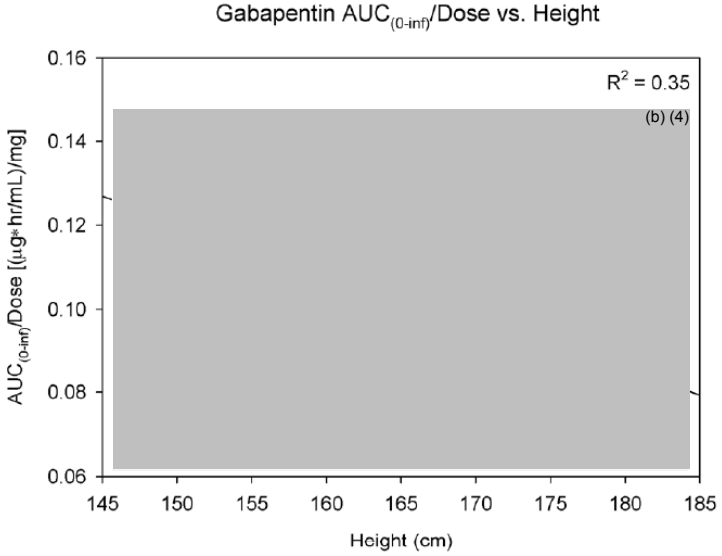


Figure 6.19. Relationship between height and dose-normalized $AUC_{(0-inf)}$ of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

- The correlation between dose-normalized Cmax or dose-normalized AUCinf of gabapentin is 0.42 and 0.35, respectively.
- No apparent effect of height on the gabapentin PK was seen after XP13512 administration.

BMI

Relationship of gabapentin Cmax/dose versus BMI was shown below.

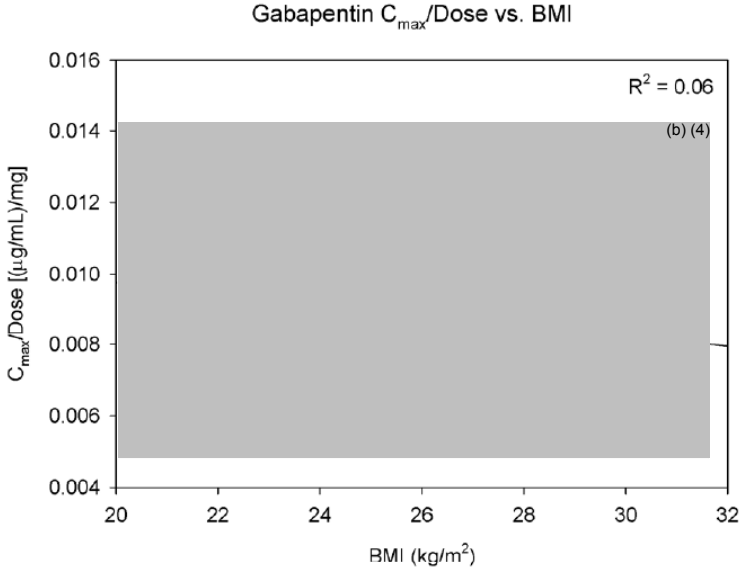


Figure 6.20. Relationship between BMI and dose-normalized C_{max} of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin AUCinf/dose versus BMI was shown below.

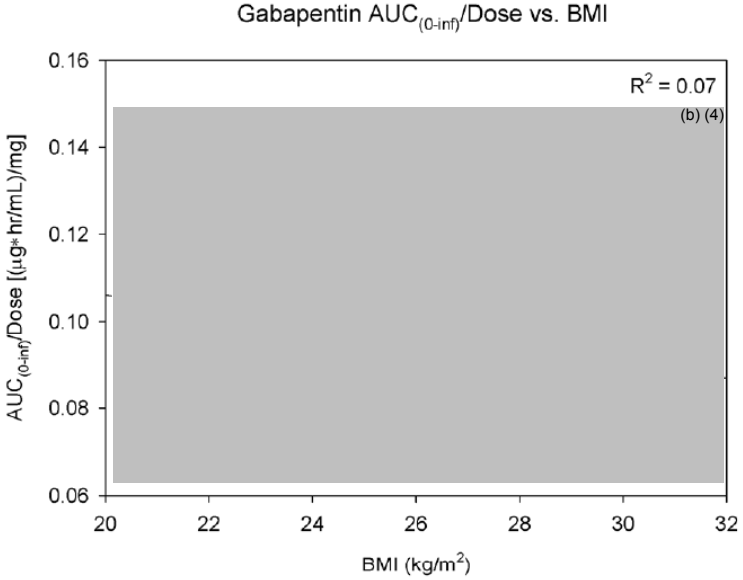


Figure 6.21. Relationship between BMI and dose-normalized $AUC_{(0\text{-}inf)}$ of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

- The correlation between dose-normalized Cmax or dose-normalized AUCinf of gabapentin is 0.06 and 0.07, respectively.
- No apparent effect of BMI on the gabapentin PK was seen after XP13512 administration.

CLcr

Relationship of gabapentin Cmax/dose versus CLcr was shown below.

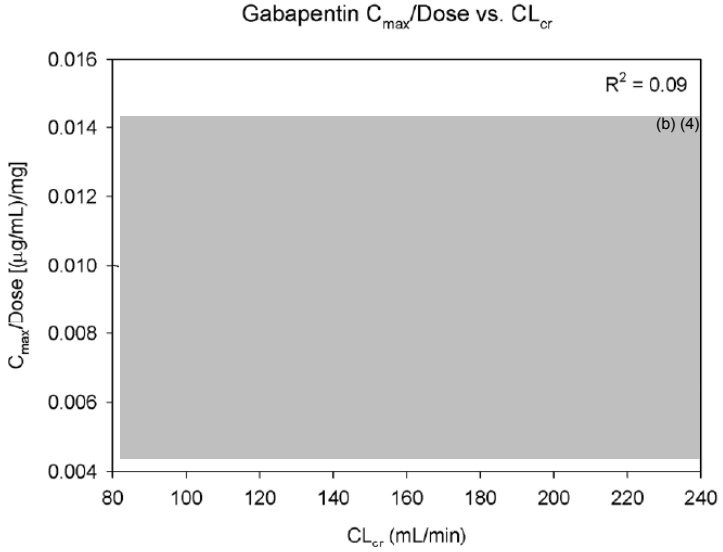


Figure 6.22. Relationship between creatinine clearance (CLcr) and dose-normalized C_{max} of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin CL/F versus CLcr was shown below.

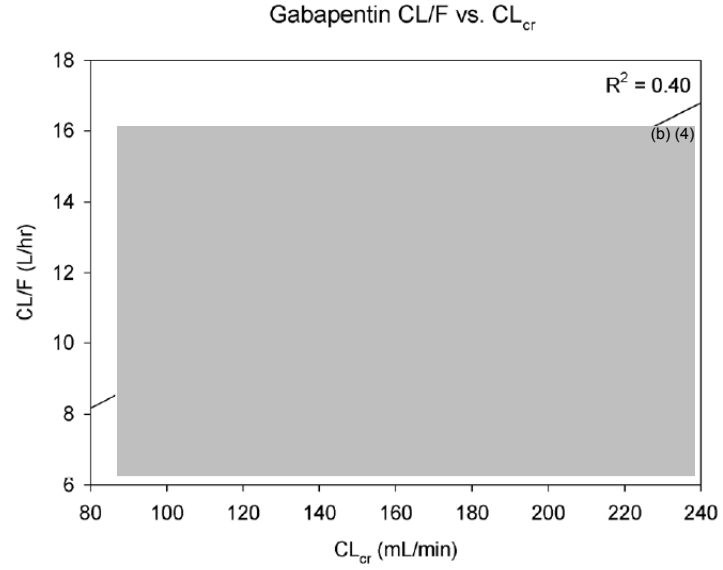


Figure 6.23. Relationship between creatinine clearance (CLcr) and CL/F of gabapentin in blood after oral administration of XP13512 SR tablets in fed subjects in Study XP069

- The correlation coefficient between dose-normalized Cmax or CL/F of gabapentin and CLcr is 0.09 and 0.40, respectively.
- No apparent effect of CLcr on the gabapentin PK was observed (this study enrolled subjects with normal renal function).

Relationship between gabapentin exposure and adverse events:

Relationship of gabapentin Cmax versus XP13512 dose and the occurrence of light-headedness/dizziness was shown below.

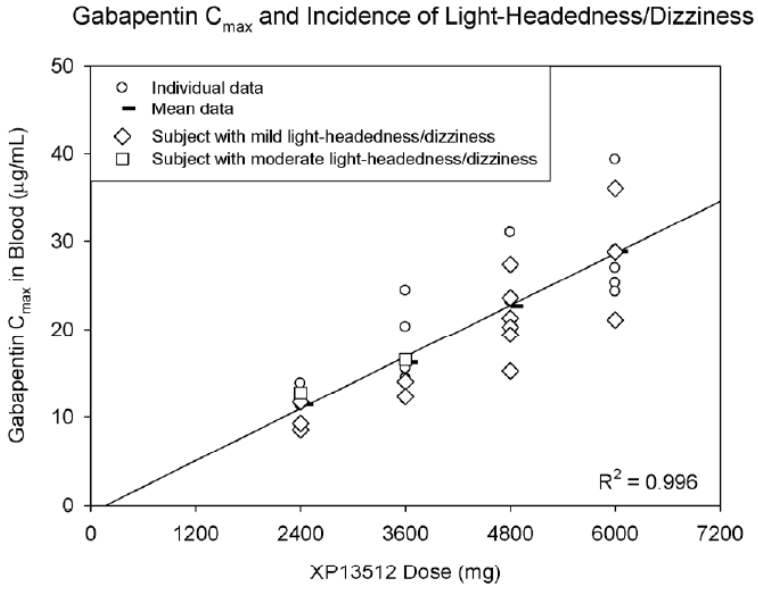


Figure 6.24. Relationship between XP13512 dose, gabapentin C_{max}, and incidence of light-headedness/dizziness following oral dosing of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin AUCinf versus XP13512 dose and the occurrence of light-headedness/dizziness was shown below.

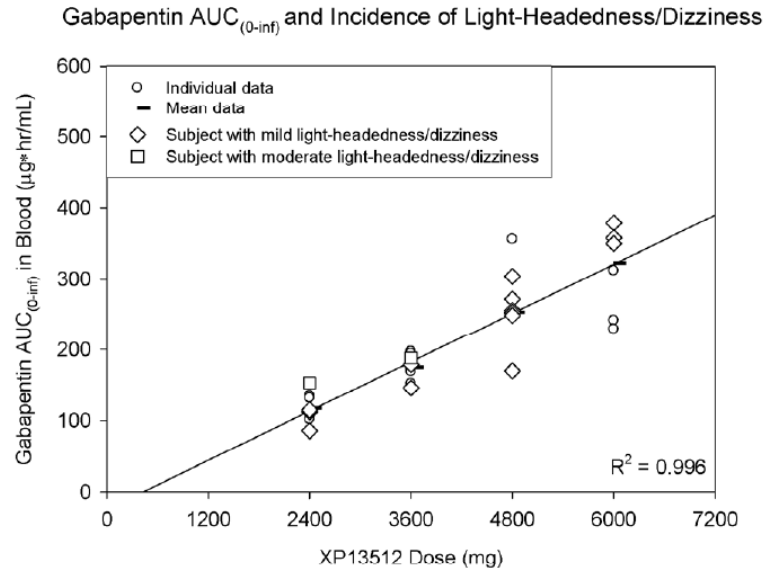


Figure 6.25. Relationship between XP13512 dose, gabapentin $AUC_{(0-inf)}$, and incidence of light-headedness/dizziness following oral dosing of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin Cmax versus XP13512 dose and the incidence of somnolence/sedation were shown below.

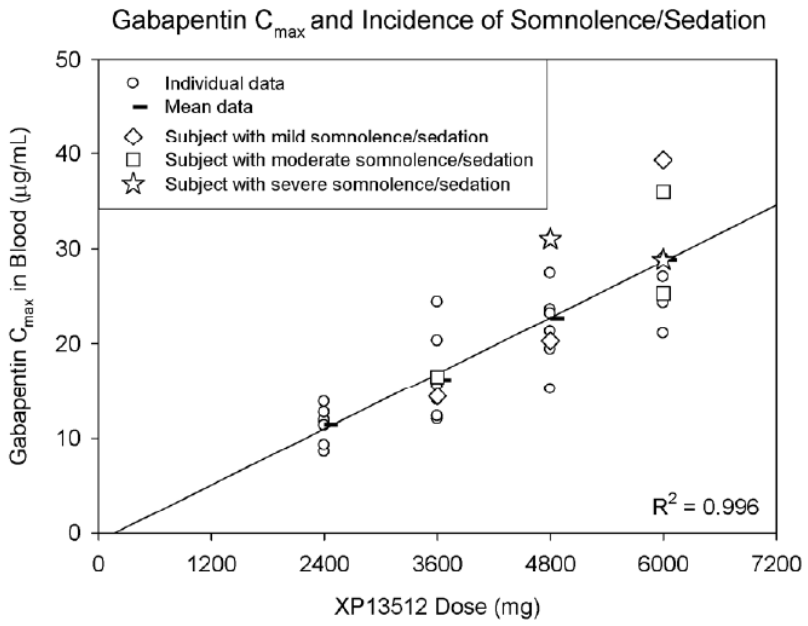


Figure 6.26. Relationship between XP13512 dose, gabapentin C_{max}, and incidence of somnolence/sedation following oral dosing of XP13512 SR tablets in fed subjects in Study XP069

Relationship of gabapentin AUCinf versus XP13512 dose and the incidence of somnolence/sedation was shown below.

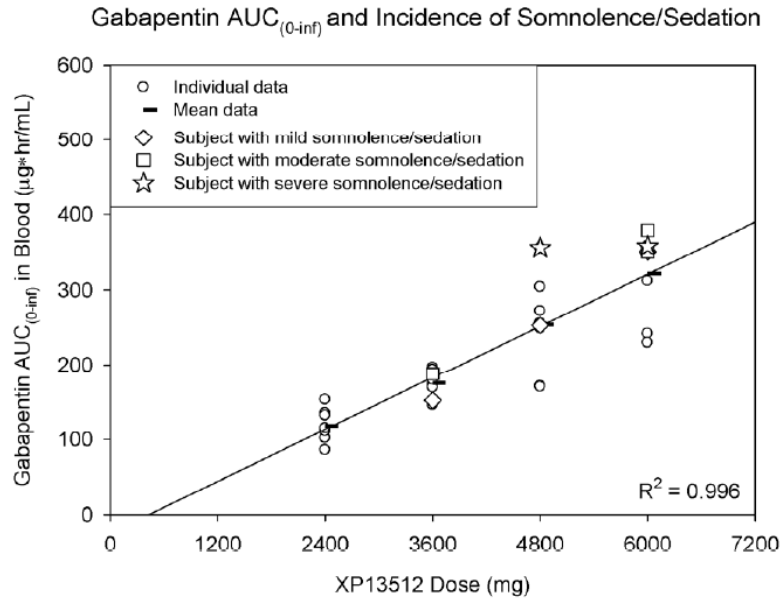


Figure 6.27. Relationship between XP13512 dose, gabapentin $AUC_{(0\text{-inf})}$, and incidence of somnolence/sedation following oral dosing of XP13512 SR tablets in fed subjects in Study XP069

- Light-headedness/dizziness and somnolence/sedation are known adverse events with gabapentin.
- These AEs observed in this study are generally mild to moderate, except that 2 female subjects at higher dose levels experienced severe adverse events which are associated with high gabapentin exposure (one at 4800 mg had severe sedation, vertigo and psychomotor retardation and the other at 6000 mg had severe somnolence).
- A tendency toward increase in frequency of dizziness and somnolence/sedation was noted at 4800 mg and 6000 mg doses.

Conclusions:

- XP13512 was rapidly absorbed and converted to gabapentin following oral administration to healthy adults.
- Gabapentin exposure in blood (Cmax and AUC) was dose proportional over the range of 2400 mg to 6000 mg XP13512.
- Exposure to prodrug was low and variable.
- There were no apparent differences in gabapentin PK between males and females.
- There were no obvious influences of race, age, body weight, height, BMI or CLcr on gabapentin PK within this normal healthy subject group.

Reviewer's Comment:

- *The correlation coefficient (r) for exposure versus weight and height were around 0.54 and 0.64. Although this was not sufficient to conclude any correlation, a decreased trend of exposure was observed as the weight and height increased.*

4.1.3 INTRINSIC FACTORS

Study XP-066: ***A Phase 1, Single-Dose Study of the Safety, Tolerability, and Pharmacokinetics of XP13512 Sustained Release (SR) Tablets in Subjects with Moderate or Severe Renal Impairment and End Stage Renal Disease (ESRD) Subjects on Hemodialysis***

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Single-dose, open-label</td></tr>
<tr><td>Study Population</td><td>N=15
Age: 28.2-75.5 years (mean 55.1 years)
Gender: 11 males, 4 females
Weight: Male 61.5-134 kg (mean 85.6 kg)
Race: 10 Caucasian (66.7%), 4 African-American (26.7%) and 1 Alaskan Native (6.6%)</td></tr>
<tr><td>Dosage and Administration</td><td>All 15 patients received single dose of 600 mg XP13512 after a standard breakfast.

Group A: XP13512 600 mg SR tablet in severe renal impairment patients (n=7)
Group B: XP13512 600 mg SR tablet in ESRD on hemodialysis patients (n=7)
Group C: XP13512 600 mg SR tablet in moderate renal impairment patients (n=1)

<table>
<tr><th>Group</th><th>Number of Subjects</th><th>CLcr (mL/min)</th><th>Treatment</th><th>Condition</th></tr>
<tr><td>Severe renal impairment Group A</td><td>6 (male or female)</td><td><30 mL/min</td><td>600 mg XP13512</td><td>Fed</td></tr>
<tr><td>ESRD on hemodialysis Group B</td><td>6 (male or female)</td><td><15 mL/min</td><td>600 mg XP13512</td><td>Fed</td></tr>
<tr><td>Moderate renal impairment Group C</td><td>Up to 6 (male or female)</td><td>30-59 mL/min</td><td>600 mg XP13512</td><td>Fed</td></tr>
</table>

XP13512 600 mg SR tablets
Batch number: 3051091

Diet:
Standard breakfast (30% calories from fat) was provided before dosing. Drinking water and other caffeine-free clear liquids were allowed and encouraged throughout the study, except within 2 hours postdose.

At the last dose (day 6), all subjects drank 240 mL of water 2 h and 1 h prior to dosing and 240 mL at 2, 4, 6, 12 and 24 h post-dose.

Alcohol was prohibited for 72 hours prior to dosing until study completion.</td></tr>
<tr><td>Sampling: Blood</td><td>Moderate and severe renally impaired patients: at predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-dose.</td></tr>
</table>

	ESRD: at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 27, 30, 36 and 48 hours post-dose. Pre- and post-dialyzer blood samples were collected at one hour interval throughout the hemodialysis session (Pre-dialysis, 24, 25, 26, 27, and 28 hours). The samples were analyzed for plasma concentrations of gabapentin.
Sampling: Urine	Moderate and severe renally impaired patients: at pre-dosing, and at 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours post-dose. ESRD: for anuric patients, pre-dosing, 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 hours when possible.
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 5.76% Inter-day accuracy: 97.7-104 % Long term Stability: 782 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.14% Inter-day accuracy: 98.1-105 % Long term Stability: 562 days at -80 ^{o}C, 42 days at -20 ^{o}C
Analysis (Dialysate)	Method LC/MS/MS Lower Limits of Quantitation Dialysate Gabapentin 50 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in dialysate Inter-day Precision (%CV for Quality Controls) : < 3.66% Inter-day accuracy: 98.0-104 % Long term Stability: in progress to cover 278 days

PK Assessment	Gabapentin in plasma: Cmax Tmax, T ½, AUC, and AUCinf Gabapentin in urine: Ae, %R, and CLr
Safety Assessment	Adverse event (AE) monitoring, electrocardiograms (ECGs), clinical laboratory tests, vital signs, and review of concomitant medications.

Pharmacokinetic Results:

Gabapentin pharmacokinetics in plasma:

Descriptive statistics for gabapentin PK parameters after XP13512 administration in moderate or severe renal impairment patients are shown in the following table:

Table 5.1. Mean Pharmacokinetic Parameters for Gabapentin in Plasma after Oral Administration of 600 mg XP13512 SR Tablet in Moderate or Severe Renal Impairment Subjects in Study XP066

Group Description		PK Parameter for Gabapentin in Plasma										CL_{cr} (mL/min)	
		C_{max} (µg/mL)	T_{max} (hr)	K_{el} (1/hr)	$T_{1/2}$ (hr)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	$AUC_{(0\text{-}168)}$ (µg*hr/mL)	$AUC_{(0\text{-}inf)}$ (µg*hr/mL)	CL/F (L/hr)	V_d/F (L)	MRT (hr)	Using GFR	Using Cockroft-Gault
Moderate Renal Impairment (N = 1)		4.71	6.00	0.074	9.40	71.6	74.1	74.4	4.20	56.9	17.9	73.0	48.0
Severe Renal Impairment (N =7)	Mean	5.92	9.29	0.033	23.2	189	191	195	1.74	54.9	37.0	21.0	31.9
	SD	1.31	4.27	0.011	7.39	67.2	66.4	71.7	0.484	12.0	13.8	8.66	12.5
	Min	3.87	5.00	0.020	13.3	119	121	123	0.894	36.7	24.2	8.00	15.6
	Median	5.55	8.00	0.032	21.7	174	177	181	1.73	54.2	31.0	26.0	27.5
	Max	7.92	18.0	0.052	35.3	332	332	350	2.54	70.3	62.6	28.0	54.7
	CV%	22.1	46.0	32.9	31.8	35.5	34.9	36.7	27.8	21.8	37.3	41.2	39.2
	Geo. Mean	5.79	8.59	0.031	22.2	181	183	186	1.68	53.7	35.2	19.0	29.9

Abbreviations: C_{max} = maximum concentration; T_{max} = time to C_{max}; K_{el} = apparent elimination constant; $T_{1/2}$ = apparent terminal half-life; $AUC_{(0\text{-}tlast)}$ = area under the concentration-time curve from time zero to the time of last quantifiable concentration; $AUC_{(0\text{-}168)}$ = area under the concentration-time curve from time zero to 168 hr post-dose; AUC_{inf} = area under the concentration-time curve extrapolated to infinity; CL/F = apparent clearance after oral dosing; V_d/F = apparent volume of distribution; MRT = mean residence time; CL_{cr} = creatinine clearance.

- The T1/2 was observed to be 23.2 hr (13.3-35.3 hr) for severe renal impairment patients and 9.40 hr for the moderate renal impairment patient.
- The mean CL/F of gabapentin was 1.74 L/hr (0.894-2.54 L/hr) for severe renal impairment patients and 4.20 L/hr for the moderate renal impairment patient.
- The mean CLr of gabapentin was 0.962 L/hr (0.450-1.73 L/hr) for severe renal impairment patients and 3.11 L/hr for the moderate renal impairment patient.
- The mean Vd/F of gabapentin was 54.9 L (36.7-70.3 L) for severe renal impairment patients and 56.9 L for the moderate renal impairment patient.
- The mean percentage of gabapentin dose recovered in urine (R) was 54.9 % (26.2-78.7 %) for severe renal impairment patients and 73.6 % for the moderate renal impairment patient.

Gabapentin pharmacokinetics in urine:

Descriptive statistics for gabapentin urine PK parameters after XP13512 administration in moderate or severe renal impairment patients are shown in the following table:

Table 5.2. Mean Pharmacokinetic Parameters for Gabapentin in Urine after Oral Administration of 600 mg XP13512 SR Tablet in Moderate or Severe Renal Impairment Subjects in Study XP066

Group Description		PK Parameter for Gabapentin in Urine			CL_{cr} (mL/min)	
		$Ae_{(0\text{-}168)}$ (mg)	CL_r (L/hr)	R (%)	Using GFR	Using Cockroft-Gault
Moderate Renal Impairment (N = 1)		230	3.11	73.6	73.0	48.0
Severe Renal Impairment (N = 7)	Mean	171	0.962	54.9	21.0	31.9
	SD	55.3	0.414	17.7	8.66	12.5
	Min	81.7	0.450	26.2	8.00	15.6
	Median	185	0.983	59.3	26.0	27.5
	Max	246	1.73	78.7	28.0	54.7
	CV%	32.2	43.0	32.2	41.2	39.2
	Geo. Mean	162	0.889	51.9	19.0	29.9

Abbreviations: $Ae_{(0\text{-}168)}$ = amount excreted in 168 hr; CL_r = renal clearance; R(%) = Percent of gabapentin dose (mg-eq) recovered in urine in 168 hr post-dose; CL_{cr} = creatinine clearance.

- The mean estimated creatinine clearance was 21.0 mL/min (8-28 mL/min) for severe renal impairment patients and 73.0 mL/min for moderate renal impairment patients based on GFR.
- The mean estimated creatinine clearance was 31.9 mL/min (15.6-54.7 mL/min) for severe renal impairment patients and 48.0 mL/min for moderate renal impairment patients based on Cockroft-Gault calculation.

Gabapentin pharmacokinetics in dialysate:

Descriptive statistics for gabapentin dialysate PK parameters after XP13512 administration in ESRD patients on hemodialysis are shown in the following table:

APPENDIX H. Pharmacokinetics of Gabapentin in Dialysate of Individual Subjects with End Stage Renal Disease after Oral Dosing of 600 mg XP13512 SR Tablet in Study XP066

End State Renal Disease (ESRD) Subjects – Dialysate

Group Description	Site Number	Subject Number	PK Parameter for Gabapentin				
			A_d (mg)	R_d (%)	AUC_{HD} (µg*hr/mL)	$CL_{HD,1}$ (mL/min)	$CL_{HD,2}$ (mL/min)
End Stage Renal Disease	001	003 [a]	134	43.0	11.9	188	261
	001	004 [a]	87.7	28.1	8.69	168	279
	237	001	79.7	25.5	11.4	116	239
	237	002	76.1	24.4	11.9	106	193 [b]
	237	003	106	33.9	11.6	153	266
	237	004	55.8	17.9	8.49	110	178
	237	005	85.0	27.2	13.1	108	156
		N	7	7	7	7	7
		Mean	89.3	28.6	11.0	136	225
		SD	24.9	7.97	1.75	33.5	48.8
		Min	55.8	17.9	8.49	106	156
		Median	85.0	27.2	11.6	116	239
		Max	134	43.0	13.1	188	279
		CV%	27.9	27.9	15.9	24.7	21.7
		Geo. Mean	86.4	27.7	10.9	132	220

Abbreviations: A_d = Amount of gabapentin recovered in dialysate in 4-hr collection interval (24 to 28 hours post-dose); R_d = Amount of gabapentin recovered in dialysate as a percentage of the dose (mg-eq) administered; AUC_{HD} = area under the predialyzer plasma concentration time curve during dialysis period; $CL_{HD,1}$ = hemodialysis clearance calculated from A_d/AUC_{HD}; $CL_{HD,2}$ = hemodialysis clearance calculated from [(Qa*Ca) – (Qv*Cv)]/Ca.

a For Subjects 001003 and 001004, the dialysate collection interval was 3 hr (24 to 27 hours post-dose).

b The hemodialysis clearance at 25 hr post-dose was excluded from the calculations due to clotted arterial line.

Mean gabapentin plasma concentration-time plots pre- and post-dialysis after single 600 mg XP13512 administration in ESRD patients on hemodialysis are shown in the following figures:

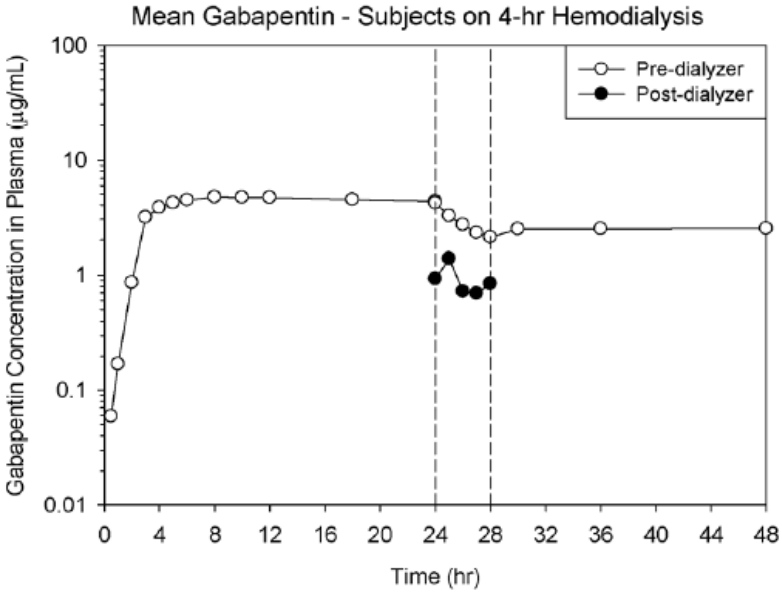


Figure J-2. Mean concentrations of gabapentin in plasma following oral dosing of 600 mg XP13512 SR tablet in ESRD Subjects on 4-hour hemodialysis between 24 to 28 hours post-dose in Study XP066 (N = 5).

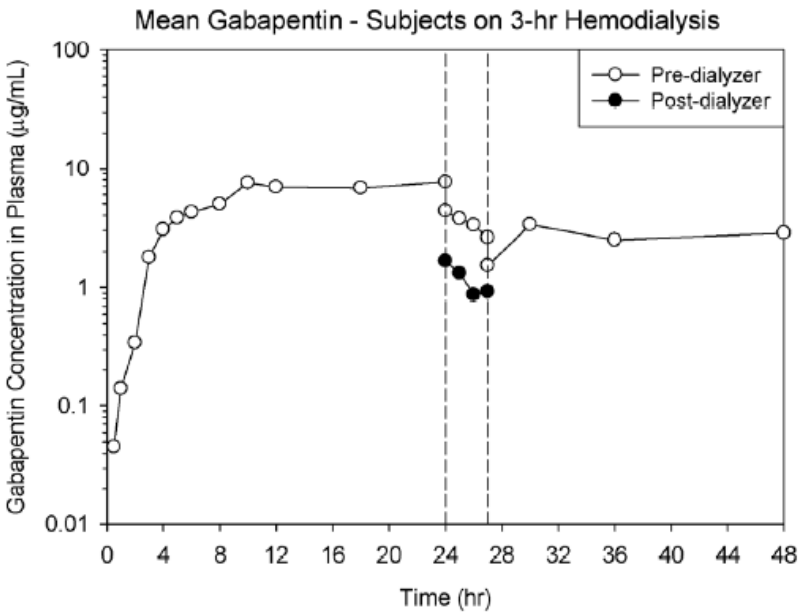


Figure J-3. Mean concentrations of gabapentin in plasma following oral dosing of 600 mg XP13512 SR tablet in ESRD Subjects on 3-hour hemodialysis between 24 to 27 hours post-dose in Study XP066 (N = 2).

- The T1/2, EFF (prior to hemodialysis) was 74.6 hours.
- The mean Cmax was 5.59 µg/mL at 9.18 hours post-dose.
- The mean percentage of gabapentin dose revovered in 3 or 4 hour hemodialysis was 28.6%.
- The mean clearance of gabapentin during hemodialysis was 136 mL/min (dialysate data) and 225 mL/min (arterial and venous plasma data).

Conclusions:

- Clearance of gabapentin in renal impairment patients was low and is consistent with reduced creatinine clearance.
- The data in this report was to be used with Phase I studies and the Population PK study (XP084) to establish the recommended doses of XP13512 for renal impairment patients with varying degrees.

Study XP-072: ***A Double-Blind, Placebo-Controlled, Ascending Single Dose Study of XP13512 ER in Caucasian and Japanese Healthy Subjects***

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Single-dose, sequential parallel, double-blind, placebo-controlled</td></tr>
<tr><td>Study Population</td><td>N=48
<u>Age:</u> Caucasian 20-44 years (mean 31 years)
Japanese 21-45 years (mean 30 years)
<u>Gender:</u> 48 males
<u>Weight</u>: Caucasian 60.0-102 kg (mean 79.3 kg)
Japanese 53.5-90.4 kg (mean 68.6 kg)
<u>Race</u>: 24 Caucasian (50%) and 24 Japanese (50%)</td></tr>
<tr><td>Dosage and Administration</td><td>16 Subjects per group with 8 Caucasians and 8 Japanese. 6 of them received XP13512 and 2 of them received placebo.

Group A: XP13512 600 mg SR tablet in the morning (fasted)
Group B: XP13512 1200 mg SR tablet in the morning (fasted)
Group C: Period 1-XP13512 1800 mg SR tablet in the morning (fasted)
Period 2-XP13512 1800 mg SR tablet in the morning (fed)
<table><tr><th>Group</th><th>Number of Subjects</th><th>Treatment</th><th>Condition</th></tr><tr><td>Group A</td><td>8 Japanese; 8 Caucasian</td><td>600 mg or placebo</td><td>Fasted</td></tr><tr><td>Group B</td><td>8 Japanese; 8 Caucasian</td><td>1200 mg or placebo</td><td>Fasted</td></tr><tr><td>Group C</td><td>8 Japanese; 8 Caucasian</td><td>1800 mg or placebo</td><td>Fasted and Fed (crossover)</td></tr></table>There was a 6-day washout period between treatments in Group C.

Meal: high fat content (50% calories from fat)

<table><tr><th>Study Drug</th><th>Drug Batch Numbers</th></tr><tr><td>XP13512 600 mg tablet</td><td>3049975R</td></tr><tr><td>Identical Placebo tablet</td><td>3049685R</td></tr></table><u>Diet:</u>
For fasted condition, subjects were fasted at least 10 hours prior to and 4 hours post-dose. For fed condition, subjects fasted for approximately 10 hours until breakfast and 4 hours after dose.

All subjects drank 8 ounces of water 2 h and 1 h prior to dosing and 8 ounces at 2, 4, 6, 12 and 24 h post-dose.

Alcohol was prohibited for 72 hours prior to dosing until study completion.</td></tr>
<tr><td>Sampling: Blood</td><td>At predose (0 hour), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hours after morning dosing. The samples were analyzed for blood concentrations of gabapentin, XP13512 and gabapentin lactam.</td></tr>
</table>

Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 hours after morning dosing.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 10.1% Inter-day accuracy: 91.7-102 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.77% Inter-day accuracy: 95.8-101 % Long term Stability: 83 days at -80 ^{o}C Gabapentin lactam: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.94% Inter-day accuracy: 94.7-98.3 % Long term Stability: 83 days at -80 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : 4.57% Inter-day accuracy: 101-104 % Long term Stability: 236 days at -80 ^{o}C and 42 days at -20 ^{o}C Gabapentin lactam: Linear range : 10-2500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.60% Inter-day accuracy: 102-104 % Long term Stability: 231 days at -80 ^{o}C and 42 days at -20 ^{o}C

PK Assessment	Gabapentin, XP13512 and gabapentin lactam in blood: Cmax, Tmax, T 1/2, Tlast, Clast, AUClast, AUC0-48, AUC 0-inf, CL/F, Vz/F and MRTinf Gabapentin or gabapentin-lactam in urine: Ae0-48 (gabapentin and gabapentin-lactam only), CLr, and %F (based on urinary recovery of gabapentin).
Safety Assessment	Treatment-emergent adverse events (TEAEs), clinical laboratory test values (hematology, chemistry, and urinalysis), vital signs (blood pressure, pulse rate, and oral body temperature), electrocardiograms (ECGs), physical examinations, and concomitant medication.

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood:

Descriptive statistics for gabapentin PK parameters after XP13512 administration in Japanese and Caucasians are shown in the following table:

Table 2.1. Mean Pharmacokinetic Parameters for Gabapentin in Blood and Urine After Oral Dosing of XP13512 Sustained Release Tablet Formulation in Japanese and Caucasian Subjects (Study XP072/8825-CL-0001)

Population	Group	XP13512 Dose (mg)	Food	N	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{inf} (µg.hr/mL)	CL_r (L/hr)	F (%)
Japanese	A	600	Fasted	6	2.47	4.35	4.89	21.3	7.56	49.5
	B	1200	Fasted	6	5.08	5.67	5.31	47.1	9.91	74.0
	C	1800	Fasted	6	8.59	4.52	5.68	83.3	6.95	60.2
			Fed	6	9.28	6.33	5.43	99.4	6.95	73.0
Caucasian	A	600	Fasted	6	1.94	5.33	6.10	21.0	7.43	49.3
	B	1200	Fasted	6	4.09	4.67	6.91	46.6	7.37	54.7
	C	1800	Fasted	6	7.51	5.67	6.79	70.9	9.38 [a]	68.9 [a]
				5 [b]	7.04	5.60	7.08	67.6	9.50 [c]	65.4 [c]
			Fed	5 [b]	7.24	6.40	6.14	89.5	6.95	64.1
				5 [b]	7.24	6.40	6.14	89.5	7.08 [c]	60.7 [c]

Abbreviations: C_{max} = maximum concentration; T_{max} = time to C_{max}; $T_{1/2}$ = half-life; AUC = area under the concentration-time curve; CL_r = renal clearance; F = Bioavailability based on urinary recovery;

a Excluded urine data for Subject 001160 due to incomplete urine collection (N = 5);

b Excluded all data for Subject 001171 due to early term (see Section 4.2.6);

c Excluded urine for Subject 001171 due to early term (see Section 4.2.6) and excluded urine data for Subject 001160 due to incomplete urine collection during fasted cohort (N=4).

Mean gabapentin blood concentration-time plot after 600 mg, 1200 mg and 1800 mg XP13512 administration under fasted condition in Japanese is shown in the following figure:

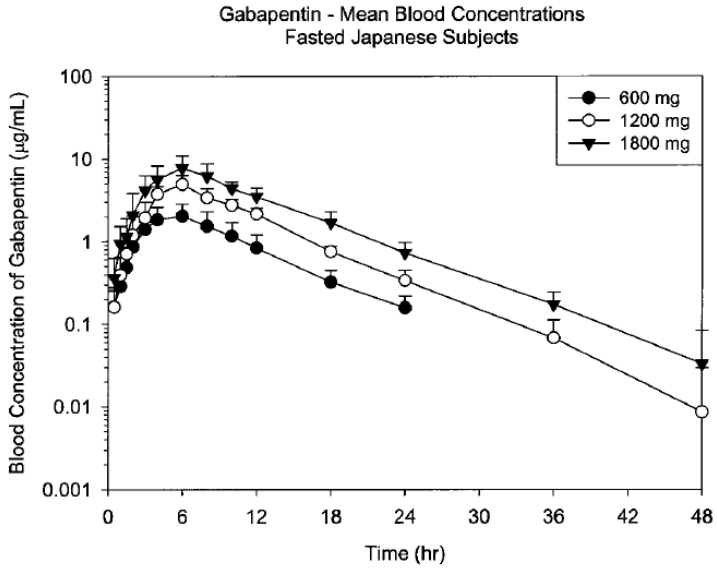


Figure K-1. Mean (SD) concentrations of gabapentin in blood of fasted Japanese subjects after oral administration of XP13512 Sustained Release tablets in Study XP072/8825-CL-0001 (N = 6 per treatment)

Mean gabapentin blood concentration-time plot after 600 mg, 1200 mg and 1800 mg XP13512 administration under fasted condition in Caucasians is shown in the following figure:

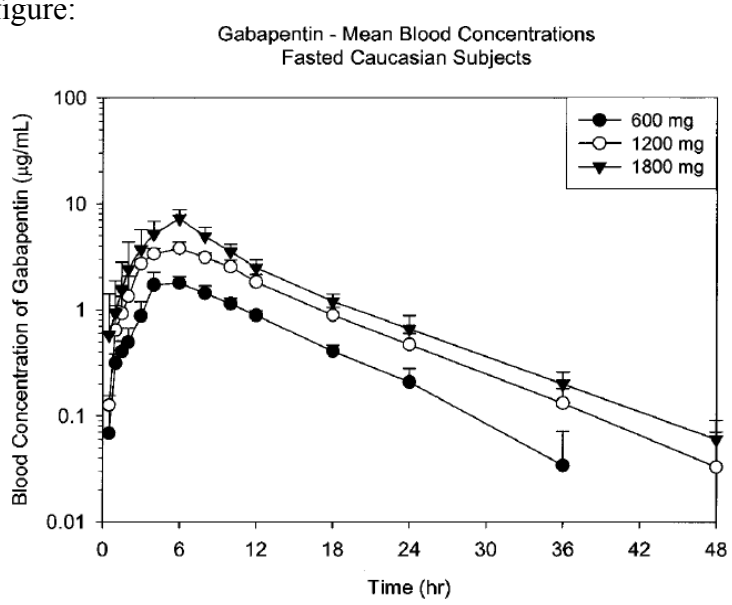


Figure K-7. Mean (SD) concentrations of gabapentin in blood of fasted Caucasian subjects after oral administration of XP13512 Sustained Release tablets in Study XP072/8825-CL-0001 (N = 6 per treatment)

- Cmax of released gabapentin in blood were 2.47, 5.08, and 8.59 µg.hr/mL at 600, 1200, and 1800 mg XP13512 doses, respectively, in Japanese under fasted conditions while the corresponding Cmax in Caucasians were 1.94, 4.09 and 7.51 µg/mL.
- The corresponding AUCinf values were 21.3, 47.1, and 83.3 µg.hr/mL, respectively, in Japanese under fasted conditions while the AUCinf in Caucasian were 21.0, 46.6, and 70.9 µg.hr/mL.
- Bioavailability as gabapentin were 49.5%, 74.0%, and 60.2%, respectively, in Japanese under fasted conditions while the bioavailability in Caucasians were 49.3%, 54.7%, and 68.9%.
- The corresponding t1/2 values were 4.89, 5.31, and 5.68 hours, respectively, in Japanese under fasted conditions while the t1/2 in Caucasians were 6.10, 6.91, and 6.79 hours.
- Tmax were similar among all dose groups (4.35 hr, 5.67 hr, and 4.52 hr in Japanese and 5.33 hr, 4.67 hr, and 5.67 hr in Caucasians).

Dose proportionality:

Slopes of linear correlation between dose and gabapentin PK parameters at 600, 1200 and 1800 mg in Japanese and Caucasian and 95% confidence intervals are shown below:

Table 14.2.1 Results of Analysis of Gabapentin Pharmacokinetic Parameters versus XP13512 Dose using Linear Regression of the Data from the 600 mg, 1200 mg, and 1800 mg Doses in Fasted Subjects

		Slope of Linear Regression Model	
Population	PK Parameter	Point Estimate	95% Confidence Interval
Japanese	C_{max}	1.130	(0.813, 1.447)
	AUC_{inf}	1.254	(1.017, 1.492)
	$Ae_{(0-48)}$	1.213	(0.778, 1.647)
Caucasian	C_{max}	1.225	(1.038, 1.413)
	AUC_{inf}	1.109	(0.970, 1.248)
	$Ae_{(0-48)}$	1.287	(0.994, 1.581)

Source: Table 5.8 and Table 5.11 (Appendix 16.1.13)

- In Japanese, Cmax and Ae(0-48) were proportional to the doses while AUCinf showed slightly greater than dose proportional.
- Similarly, in Caucasian, AUCinf and Ae(0-48) appeared to be proportional to the doses while Cmax showed slightly greater than dose proportional.
- In general, gabapentin showed dose proportionality between 600 to 1800 mg doses of XP13512 based on the statistical data above.

Food effect:

Mean gabapentin blood concentration-time plot after 1800 mg XP13512 administration under fasted and fed conditions in Japanese is shown in the following figure:

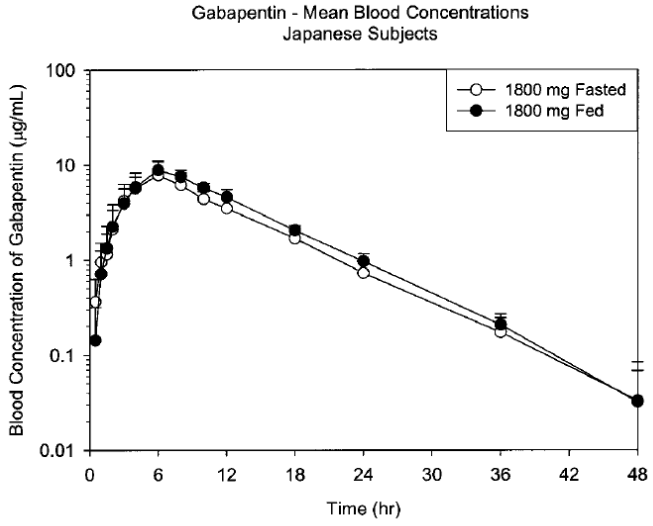


Figure K-6. Mean (SD) concentrations of gabapentin in blood after oral administration of 1800 mg (3 × 600 mg) XP13512 Sustained Release tablets in fasted and fed Japanese subjects in Study XP072/8825-CL-0001 (N = 6 per treatment)

Mean gabapentin blood concentration-time plot after 1800 mg XP13512 administration under fasted and fed conditions in Caucasians is shown in the following figure:

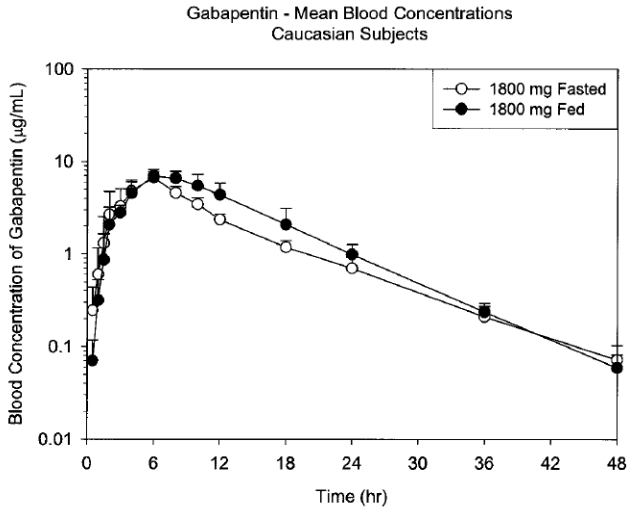


Figure K-12. Mean (SD) concentrations of gabapentin in blood after oral administration of 1800 mg (3 × 600 mg) XP13512 Sustained Release tablets in fasted and fed Caucasian subjects in Study XP072/8825-CL-0001 (N = 5 per treatment)

Geometric mean ratios (Fed/Fasting) and 90% confidence interval for gabapentin PK parameters are shown below:

Table 14.2.3 Geometric Mean Ratios (Feb/Fasting) and 90% Confidence Intervals for Gabapentin Pharmacokinetic Parameters using the Data from the 1800 mg Cohorts

		Geometric Mean Ratio (Fed/Fasting)	
Population	PK Parameter	Point Estimate	90% Confidence Interval
Japanese	C_{max}	1.108	(0.856, 1.435)
	AUC_{last}	1.213	(1.078, 1.366)
	AUC_{inf}	1.206	(1.069, 1.360)
Caucasian	C_{max}	1.015	(0.847, 1.217)
	AUC_{last}	1.277	(1.000, 1.631)
	AUC_{inf}	1.301	(1.065, 1.589)

Source: Table 5.10 and Table 5.13 (Appendix 16.1.13)

- In Japanese, the bioavailability of XP13512 as gabapentin was enhanced by food. Food delayed the peak concentration of gabapentin by approximately 2 hours and increased the exposure (expressed as AUCinf) and oral bioavailability of gabapentin by 22% and 24%, respectively.
- In Caucasian, food delayed the peak concentration of gabapentin by approximately 1 hour and increased the exposure of gabapentin by 32%.
- Exposure increased significantly under fed condition in both Japanese and Caucasian by ~20 to 30% AUC.

Race:

Mean gabapentin blood concentration-time plot after 600, 1200 and 1800 mg XP13512 administration in Japanese and Caucasian under fasted condition are shown in the following figure:

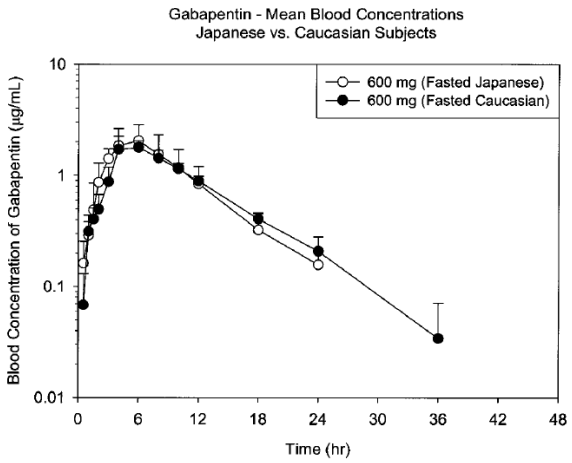


Figure K-13. Mean (SD) concentrations of gabapentin in blood after oral administration of 600 mg XP13512 Sustained Release tablets in fasted Japanese and Caucasian subjects in Study XP072/8825-CL-0001 (N = 6 per group)

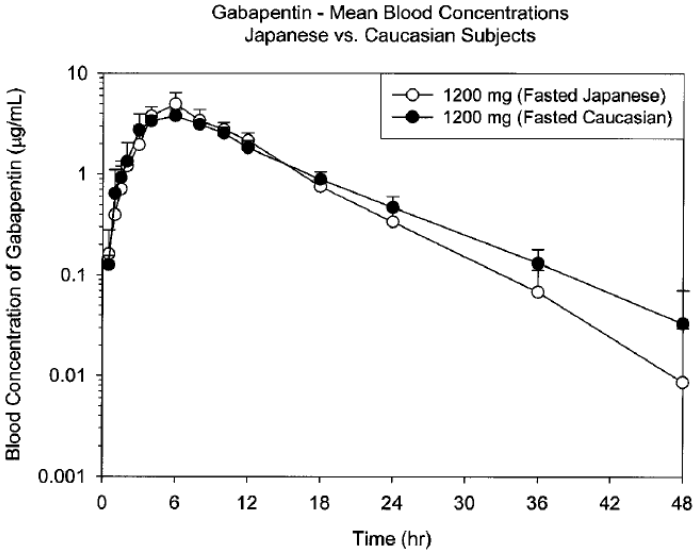


Figure K-14. Mean (SD) concentrations of gabapentin in blood after oral administration of 1200 mg (2 × 600 mg) XP13512 Sustained Release tablets in fasted Japanese and Caucasian subjects in Study XP072/8825-CL-0001 (N = 6 per group)

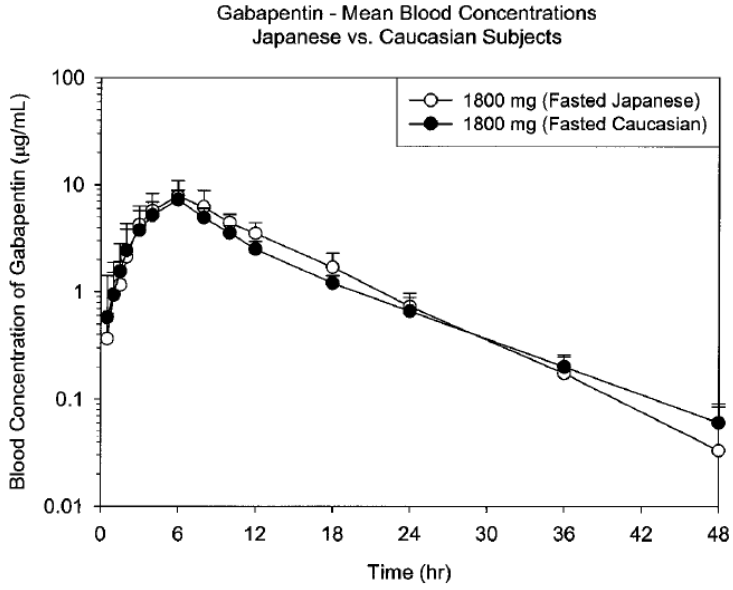


Figure K-15. Mean (SD) concentrations of gabapentin in blood after oral administration of 1800 mg (3 × 600 mg) XP13512 Sustained Release tablets in fasted Japanese and Caucasian subjects in Study XP072/8825-CL-0001 (N = 6 per group)

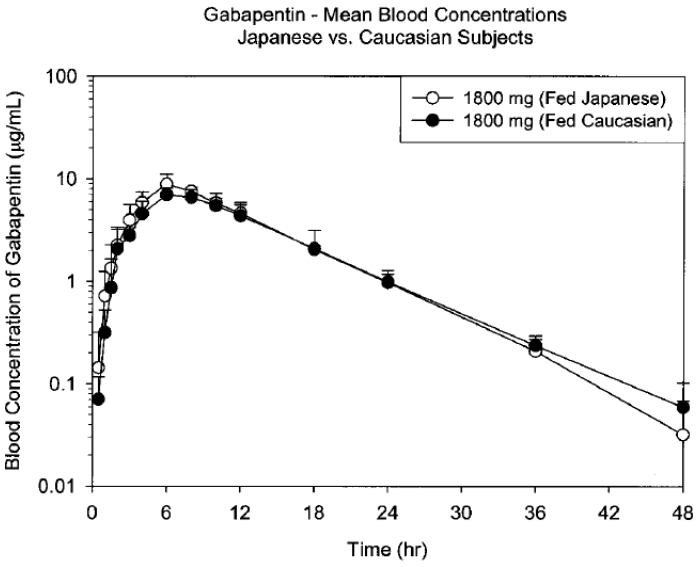


Figure K-16. Mean (SD) concentrations of gabapentin in blood after oral administration of 1800 mg (3 × 600 mg) XP13512 Sustained Release tablets in fed Japanese and Caucasian subjects in Study XP072/8825-CL-0001 (N = 5 for Caucasians and 6 for Japanese)

Geometric mean ratios (Japanese/Caucasian) and 95%confidence interval for gabapentin PK parameters are shown below:

Table 14.2.4 Geometric Mean Ratios (Japanese/Caucasian) and Confidence Intervals for Gabapentin Pharmacokinetic Parameters using the Data from the 600 mg, 1200 mg, 1800 mg Fasted Cohorts and the 1800 mg Fed Cohorts

PK parameter	Dose (mg)	Geometric Mean Ratio(Japanese/Caucasian)		
		Point Estimate	90% Confidence Interval	95% Confidence Interval
C_{max}	600 (Fasted)	1.247	(0.933, 1.667)	(0.873, 1.782)
	1200 (Fasted)	1.214	(0.984, 1.498)	(0.937, 1.572)
	1800 (Fasted)	1.115	(0.869, 1.430)	(0.821, 1.514)
	1800 (Fed)	1.288	(1.057, 1.570)	(1.009, 1.644)
AUC_{inf}	600 (Fasted)	0.981	(0.771, 1.247)	(0.730, 1.317)
	1200 (Fasted)	1.010	(0.886, 1.152)	(0.859, 1.188)
	1800 (Fasted)	1.166	(0.973, 1.398)	(0.934, 1.457)
	1800 (Fed)	1.130	(0.928, 1.376)	(0.886, 1.441)

Source: Table 5.14 and Table 5.16 (Appendix 16.1.13)

- The exposure of gabapentin by Cmax and AUCinf in Japanese and Caucasians were comparable at all dose levels and under both fasted and fed conditions.

XP13512 pharmacokinetics in blood:

Descriptive statistics for XP13512 PK parameters after XP13512 administration in Japanese and Caucasian are shown in the following table:

Table 2.2. Mean Pharmacokinetic Parameters for XP13512 in Blood After Oral Dosing of XP13512 Sustained Release Tablet Formulation in Japanese and Caucasian Subjects (Study XP072/8825-CL-0001)

Population	Group	XP13512 Dose (mg)	Food	N	C_{max} (µg/mL)	T_{max} (hr)	AUC_{last} (µg.hr/mL)
Japanese	A	600	Fasted	6	0.009	4.67	0.013
	B	1200	Fasted	6	0.056	6.68	0.185
	C	1800	Fasted	6	0.080	6.00	0.312
			Fed	6	0.031	3.83	0.078
Caucasian	A	600	Fasted	6	0.060	6.33	0.101
	B	1200	Fasted	6	0.046	5.50	0.150
	C	1800	Fasted	6	0.147	4.42	0.234
				5 [a]	0.096	5.20	0.156
			Fed	5 [a]	0.031	5.00	0.108

Abbreviations: C_{max} = maximum concentration; T_{max} = time to C_{max}; AUC = area under the concentration-time curve; a Excluded data for Subject 001171 due to early term (see Section 4.2.6).

Mean XP13512 blood concentration-time plot after 600 mg, 1200 mg and 1800 mg XP13512 administration under fasted condition in Japanese is shown in the following figure:

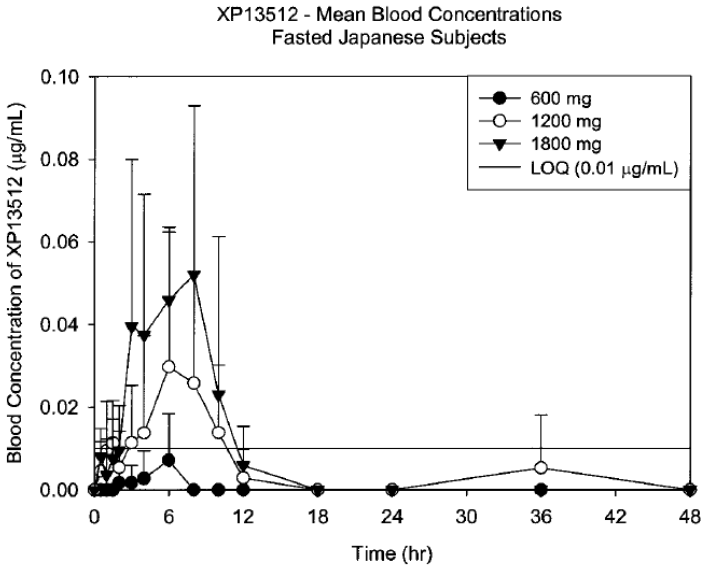


Figure 6.6. Mean (SD) concentrations of XP13512 in blood of fasted Japanese subjects after oral administration of XP13512 Sustained Release tablets in Study XP072/8825-CL-0001 (N = 6 per treatment)

Mean XP13512 blood concentration-time plot after 600 mg, 1200 mg and 1800 mg XP13512 administration under fasted condition in Caucasians is shown in the following figure:

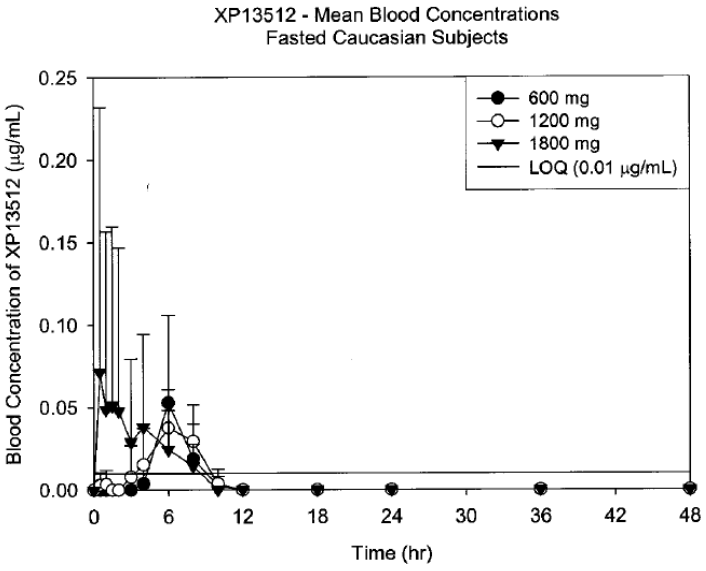


Figure 6.20. Mean (SD) concentrations of XP13512 in blood of fasted Caucasian subjects after oral administration of XP13512 Sustained Release tablets in Study XP072/8825-CL-0001 (N = 6 per treatment)

- The exposure to prodrug, XP13512, was low and variable at all dose levels in both Japanese and Caucasian subjects
- The Cmax of XP13512 in blood was ≤ 2.1% of the corresponding Cmax of gabapentin in Japanese subjects, and ≤ 4% in Caucasian subjects (except for one Caucasian subject at the 600 mg dose, where the Cmax of XP13512 was 7% of gabapentin).
- The AUClast of XP13512 in blood was ≤ 0.73% of the corresponding AUCinf of gabapentin in all Japanese and Caucasian subjects at all dose levels.

Gabapentin lactam exposure:

Urinary recovery data of gabapentin lactam was shown below:

Table 5.5. Mean Pharmacokinetic Data for Gabapentin Lactam in Urine After Oral Administration of XP13512 Sustained Release Tablets to Healthy Japanese Subjects in Study XP072/8825-CL-0001 (N = 6 per group)

Population	Dose (mg)		Gabapentin Lactam PK Parameter	
			$Ae_{(0-48)}$ (mg)	%R
Japanese	600	Mean	0.016	0.006
	Fasted	SD	0.007	0.003
		Min	0.008	0.003
		Max	0.028	0.010
		CV%	47.5	47.7
	1200	Mean	0.056	0.010
	Fasted	SD	0.045	0.008
		Min	0.004	0.001
		Max	0.136	0.024
		CV%	79.9	80.1
	1800	Mean	0.088	0.011
	Fasted	SD	0.039	0.005
		Min	0.053	0.006
		Max	0.157	0.019
		CV%	44.8	44.9
	1800	Mean	0.076	0.009
	Fed	SD	0.016	0.002
		Min	0.059	0.007
		Max	0.101	0.012
		CV%	20.9	21.0

Abbreviations: $Ae_{(0-48)}$ = amount excreted in urine in 48 hr; %R = percent dose excreted in urine.

Table 5.6. Mean Pharmacokinetic Data for Gabapentin Lactam in Urine After Oral Administration of XP13512 Sustained Release Tablets to Healthy Caucasian Subjects in Study XP072/8825-CL-0001 (N = 6 per group)

Population	XP13512 Dose (mg)		Gabapentin Lactam PK Parameter	
			$Ae_{(0-48)}$ (mg)	%R
Caucasian	600	Mean	0.151	0.054
	Fasted	SD	0.121	0.043
		Min	0.019	0.007
		Max	0.322	0.115
		CV%	80.4	80.2
	1200	Mean	0.287	0.051
	Fasted	SD	0.174	0.031
		Min	0.113	0.020
		Max	0.516	0.093
		CV%	60.7	60.8

Abbreviations: $Ae_{(0-48)}$ = amount excreted in urine in 48 hr; %R = percent dose excreted in urine.

Table 5.6 (continued). Mean Pharmacokinetic Data for Gabapentin Lactam in Urine After Oral Administration of XP13512 Sustained Release Tablets to Healthy Caucasian Subjects in Study XP072/8825-CL-0001 (N = 6 per group)

Population	XP13512 Dose (mg)		Gabapentin Lactam PK Parameter	
			$Ae_{(0-48)}$ (mg)	%R
Caucasian	1800 [a]	Mean	0.793	0.095
	Fasted	SD	0.919	0.110
		Min	0.068	0.008
		Max	2.38	0.285
		CV%	116	116
	1800 [b]	Mean	0.912	0.109
	Fasted	SD	1.02	0.122
		Min	0.068	0.008
		Max	2.38	0.285
		CV%	111	112
	1800 [c]	Mean	0.255	0.031
	Fed	SD	0.065	0.008
		Min	0.172	0.021
		Max	0.323	0.039
		CV%	25.6	25.1
	1800 [b]	Mean	0.238	0.029
	Fed	SD	0.061	0.007
		Min	0.172	0.021
		Max	0.318	0.038
		CV%	25.8	25.2

Abbreviations: $Ae_{(0-48)}$ = amount excreted in urine in 48 hr; %R = percent dose excreted in urine.

a N = 5. Excluded data for Subject 001160 due to incomplete urine collection for the fasted cohort.

b N = 4. Excluded data for Subject 001160 due to incomplete urine collection for the fasted cohort and excluded data for Subject 001171 due to early term (see Section 4.2.6).

c N = 5. Excluded data for Subject 001171 due to early term (see Section 4.2.6).

- The levels of gabapentin lactam in blood were below the limit of quantitation (10 ng/mL) in both Japanese and Caucasian subjects at all dose levels, except for 2 Japanese subjects under fasted condition in the 1800 mg group. In these 2 subjects, very low levels of gabapentin lactam (≤ 17.4 ng/mL) were observed at 6 hours postdose.
- The mean percent dose excreted as gabapentin lactam in urine at all dose levels was ≤ 0.01% for Japanese subjects and ≤ 0.1 for Caucasian subjects.

Conclusions:

- The pharmacokinetic profile of XP13512 SR tablets was similar in Japanese and Caucasian subjects.
- Pharmacokinetics of gabapentin after oral administration of XP13512 were linear over the dose range of 600 mg to 1800 mg in fasted Japanese and Caucasian subjects.
- Oral bioavailability was consistently high (≥ 49%) across all dose levels in both Japanese and Caucasian subjects.
- Administration of XP13512 SR tablets after a high fat meal increased the exposure (AUC) to gabapentin in Japanese and Caucasian subjects by 20 to 30 %, consistent with previous observations in previous XP13512 studies in Caucasian subjects.
- Exposure to prodrug and gabapentin lactam in Japanese and Caucasian subjects was very low (≤ 4% and < 0.1%, respectively, of corresponding gabapentin exposure).

Reviewer's Comment:

- *One Caucasian who received placebo showed gabapentin (323 ng/mL) and XP13512 (10.1 ng/mL) concentrations at 1.5 hours post-dose. Although the levels were low, this data suggested certain errors in study conduct which put the reliability of this study in question.*
- *Similarly, subjects 1132 and 1165 who received placebo, were found to have gabapentin levels of 14600ng/mL at 12-24 hours and 1730 ng/mL at 24-36 hours, respectively.*

Study XP-073: ***A Double-Blind, Placebo-Controlled, Ascending Multiple Dose Study of XP13512 ER in Healthy Japanese Subjects***

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Multiple-dose, sequential, double-blind, placebo-controlled</td></tr>
<tr><td>Study Population</td><td>N=31 enrolled, 29 completed
Age: Male 20-53 years (mean 31 years)
Female 21-37 years (mean 28 years)
Gender: 14 males, 15 females
Weight: Male 49.4-85.2 kg (mean 64.8 kg)
Female 40.4-67.1 kg (mean 52.0 kg)
Race: 31 Japanese (100%)</td></tr>
<tr><td>Dosage and Administration</td><td>~16 Japanese subjects per group with 8 males and 8 females. 6 of them received XP13512 and 2 of them received placebo.

Group A: XP13512 1200 mg SR tablet or placebo BID (fed)
Group B: XP13512 1800 mg SR tablet or placebo BID (fed)

<table>
<tr><th>Group</th><th>Number of Subjects</th><th>Treatment</th><th>Condition</th></tr>
<tr><td>Group A</td><td>~ 16 Japanese
(8 males and 8 females)</td><td>1200 mg or placebo
(twice daily)</td><td>Fed</td></tr>
<tr><td>Group B</td><td>~ 16 Japanese
(8 males and 8 females)</td><td>1800 mg or placebo
(twice daily)</td><td>Fed</td></tr>
</table>
<table>
<tr><th>Study Drug</th><th>Drug Batch Numbers</th></tr>
<tr><td>XP13512 600 mg tablet</td><td>3051595R</td></tr>
<tr><td>Identical Placebo tablet</td><td>3049685R</td></tr>
</table>

Diet:
Before each morning dose, subjects fasted for approximately 10 hours until breakfast and 4 hours after dose. Drinking water and other caffeine-free clear liquids was allowed and encouraged throughout the study, except within 2 hours postdose.

At the last dose (day 6), all subjects drank 240 mL of water 2 h and 1 h prior to dosing and 240 mL at 2, 4, 6, 12 and 24 h post-dose.

Alcohol was prohibited for 72 hours prior to dosing until study completion.</td></tr>
<tr><td>Sampling: Blood</td><td>Day 1-5: 0 hour (AM and PM)
Day 6: at predose (0 hour), and 1, 3, 5, 6, 7, 8, 10, 12, 24, 36 and 48 hours. The samples were analyzed for blood and plasma concentrations of gabapentin, XP13512 and gabapentin lactam.</td></tr>
<tr><td>Sampling: Urine</td><td>Day 6: 0-4, 4-8, 8-12 and 12-24 hours.</td></tr>
</table>

Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 10.1% Inter-day accuracy: 91.7-102 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.77% Inter-day accuracy: 95.8-101 % Long term Stability: 83 days at -80 ^{o}C Gabapentin lactam: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.94% Inter-day accuracy: 94.7-98.3 % Long term Stability: 83 days at -80 ^{o}C
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 5.76% Inter-day accuracy: 97.7-104 % Long term Stability: 782 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Gabapentin lactam 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine

	Inter-day Precision (%CV for Quality Controls) : 4.57% Inter-day accuracy: 101-104 % Long term Stability: 236 days at -80 °C and 42 days at -20 °C Gabapentin lactam: Linear range : 10-2500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.60% Inter-day accuracy: 102-104 % Long term Stability: 231 days at -80 °C and 42 days at -20 °C
PK Assessment	Gabapentin, XP13512 and gabapentin lactam in blood: Css,max Tmax, Css,min, T ½, AUC, and AUCinf Gabapentin or gabapentin-lactam in urine: Ae, %F, and CLr
Safety Assessment	Treatment-emergent adverse events (TEAEs), clinical laboratory test values (hematology, chemistry, and urinalysis), vital signs (blood pressure, pulse rate, and oral body temperature), electrocardiograms (ECGs), physical examinations, and concomitant medication.

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood:

Descriptive statistics for gabapentin PK parameters after XP13512 administration in Japanese are shown in the following table:

Table 5.1. Mean Pharmacokinetic Data for Gabapentin in Blood at Steady State (Day 6) After Twice Daily Oral Administration of XP13512 Sustained Release Tablets to Healthy Japanese Subjects in Study XP073/8825-CL-0002

XP13512 Dose	Gender	N		Gabapentin PK Parameter in Blood					
				$C_{SS,max}$ (µg/mL)	$C_{SS,min}$ (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{SS} (µg.hr/mL)	CLss/F L/hr
1200 mg B.I.D (2 × 600 mg SR Tablets B.I.D)	Male	5	Mean	7.79	3.87	6.10	4.78	68.2	9.21
			SD	1.14	0.535	1.23	0.39	5.68	0.728
			Min	6.25	3.32	5.17	4.11	63.3	8.11
			Max	9.05	4.66	8.17	5.09	77.0	9.88
			CV%	14.6	13.8	20.1	8.15	8.33	7.91
	Female	6	Mean	8.90	2.96	5.97	5.52	64.9	10.1
			SD	2.37	0.994	1.30	2.52	15.4	2.24
			Min	6.71	1.67	5.17	3.64	49.2	7.36
			Max	12.9	4.61	8.17	10.5	85.0	12.7
			CV%	26.7	33.6	21.8	45.6	23.7	22.2
	Overall	11	Mean	8.39	3.38	6.03	5.19	66.4	9.67
			SD	1.92	0.914	1.21	1.84	11.6	1.71
			Min	6.25	1.67	5.17	3.64	49.2	7.36
			Max	12.9	4.66	8.17	10.5	85.0	12.7
			CV%	22.8	27.1	20.0	35.4	17.5	17.6
1800 mg B.I.D (3 × 600 mg SR Tablets B.I.D)	Male	5	Mean	11.8	4.01	5.33	5.13	89.1	10.7
			SD	1.87	0.680	0.37	0.71	12.7	1.54
			Min	9.71	2.95	5.17	4.36	74.1	9.18
			Max	14.1	4.75	6.00	6.25	102	12.7
			CV%	15.9	16.9	6.99	13.8	14.2	14.4
	Female	6	Mean	16.6	4.85	5.58	4.69	120	7.95
			SD	2.66	0.950	0.46	1.04	18.8	1.13
			Min	12.6	3.34	5.17	3.92	101	6.15
			Max	19.8	5.85	6.00	6.57	153	9.29
			CV%	16.0	19.6	8.17	22.2	15.6	14.3
	Overall	11	Mean	14.4	4.47	5.47	4.89	106	9.21
			SD	3.37	0.908	0.42	0.89	22.4	1.91
			Min	9.71	2.95	5.17	3.92	74.1	6.15
			Max	19.8	5.85	6.00	6.57	153	12.7
			CV%	23.4	20.3	7.69	18.2	21.2	20.8

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $T_{1/2}$ = half-life; AUC_{SS} = area under the concentration-time curve at steady state; CL_{SS}/F = clearance at steady state.

Mean gabapentin blood concentration-time plots after 1200 mg and 1800 mg XP13512 BID administration in Japanese are shown in the following figure:

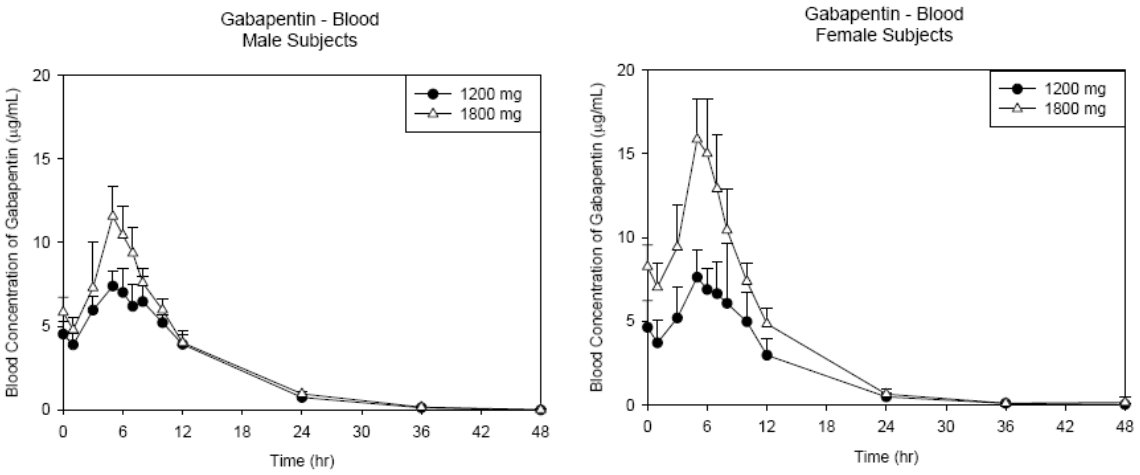


Figure 6.2. Effect of gender on mean (SD) concentrations of gabapentin in blood at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

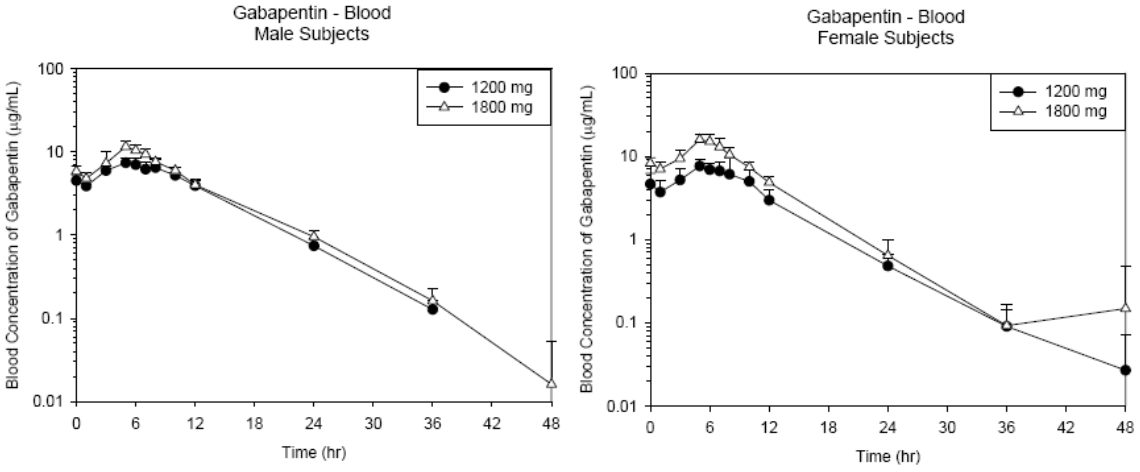


Figure U-2. Effect of gender on mean (SD) concentrations of gabapentin in blood at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

- Maximum concentrations of gabapentin in blood and plasma at steady state were achieved within 5 to 8 hr after dosing.
- The overall mean half-life of the apparent terminal elimination phase for gabapentin levels in blood and plasma (T1/2) was in the range of 4.79 to 5.19 hr.
- The overall mean maximum concentration of gabapentin in blood at steady state (Css, max) ranged from 8.39 µg/mL at the 1200 mg b.i.d. to 14.4 µg/mL at the 1800 mg b.i.d.
- The overall mean minimum concentration for gabapentin in blood at steady state (Css, min) ranged from 3.38 µg/mL at the 1200 mg b.i.d. to 4.47 µg/mL at the 1800 mg b.i.d..

Gabapentin pharmacokinetic in plasma:

Descriptive statistics for gabapentin PK parameters after XP13512 administration in Japanese are shown in the following table:

Table 5.2. Mean Pharmacokinetic Data for Gabapentin in Plasma and Urine at Steady State (Day 6) After Twice Daily Oral Administration of XP13512 Sustained Release Tablets to Healthy Japanese Subjects in Study XP073/8825-CL-0002

XP13512 Dose	Gender	N		Gabapentin PK Parameter in Plasma and Urine									
				$C_{SS,max}$ (µg/mL)	$C_{SS,min}$ (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{SS} (µg.hr/mL)	CLss/F L/hr	$Ae_{(0-12)}$ (mg)	$Ae_{(0-24)}$ (mg)	CLr (L/hr)	F (%)
1200 mg B.I.D (2 × 600 mg SR Tablets B.I.D)	Male	5	Mean	8.75	4.11	5.37	4.88	76.7	8.17	524 [a]	653 [a]	7.00 [a]	83.8 [a]
			SD	1.49	0.522	0.45	0.42	4.50	0.473	NA	NA	NA	NA
			Min	7.41	3.49	5.17	4.22	72.1	7.53	489	572	6.29	78.2
			Max	11.1	4.66	6.17	5.27	83.0	8.67	559	733	7.70	89.4
			CV%	17.1	12.7	8.33	8.54	5.86	5.79	NA	NA	NA	NA
	Female	6	Mean	8.10	3.47	6.11	4.72	66.7	9.78	383	502	5.90	61.4
			SD	1.41	1.43	1.24	1.09	15.0	2.19	54.7	103	1.04	8.73
			Min	6.12	1.87	5.17	3.49	48.4	7.32	305	326	4.84	48.9
			Max	9.52	6.03	8.17	6.69	85.4	12.9	463	615	7.51	74.1
			CV%	17.4	41.3	20.3	23.0	22.5	22.3	14.3	20.5	17.6	14.2
	Overall	11	Mean	8.40	3.76	5.77	4.79	71.2	9.05	419 [b]	540 [b]	6.17 [b]	67.0 [b]
			SD	1.42	1.12	1.00	0.82	12.2	1.78	82.0	119	1.08	13.1
			Min	6.12	1.87	5.17	3.49	48.4	7.32	305	326	4.84	48.9
			Max	11.1	6.03	8.17	6.69	85.4	12.9	559	733	7.70	89.4
			CV%	16.9	29.7	17.3	17.0	17.1	19.7	19.6	22.1	17.5	19.5
1800 mg B.I.D (3 × 600 mg SR Tablets B.I.D)	Male	5	Mean	13.5	4.31	5.50	5.09	101	9.41	696	900	6.97	74.2
			SD	2.08	0.483	0.46	0.49	12.9	1.27	92.4	77.7	1.20	9.84
			Min	10.6	3.66	5.17	4.59	82.9	8.20	611	785	5.83	65.1
			Max	15.5	5.00	6.00	5.85	114	11.3	817	958	8.73	87.1
			CV%	15.4	11.2	8.30	9.69	12.7	13.5	13.3	8.63	17.2	13.3
	Female	6	Mean	18.2	5.28	5.61	4.56	136	6.99	719	907	5.32	76.6
			SD	2.88	1.18	0.76	1.28	20.2	0.922	98.3	148	0.778	10.5
			Min	14.5	3.78	5.17	3.43	118	5.45	549	654	4.39	58.5
			Max	22.5	6.60	7.02	7.05	172	7.94	839	1093	6.31	89.5
			CV%	15.8	22.4	13.6	28.0	14.8	13.2	13.7	16.3	14.6	13.7
	Overall	11	Mean	16.1	4.84	5.56	4.80	120	8.09	708	904	6.07	75.5
			SD	3.44	1.02	0.62	1.00	24.7	1.63	91.6	116	1.27	9.78
			Min	10.6	3.66	5.17	3.43	82.9	5.45	549	654	4.39	58.5
			Max	22.5	6.60	7.02	7.05	172	11.3	839	1093	8.73	89.5
			CV%	21.4	21.2	11.1	20.7	20.5	20.2	12.9	12.8	21.0	12.9

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $T_{1/2}$ = half-life; CL_{SS}/F = clearance at steady state; AUC_{SS} = area under the concentration-time curve at steady state; $Ae_{(0-12)}$ = amount excreted in urine in 12 hr; $Ae_{(0-24)}$ = amount excreted in urine in 24 hr; CLr = renal clearance; F = Bioavailability based on urinary recovery; NA = Not applicable; a N = 2 for males; b N = 8 for overall mean calculation. Urine data for Subjects 211, 212, and 214 were excluded from statistical calculation due to uncertainty in the accuracy of the estimated amount excreted of gabapentin in urine.

Mean gabapentin plasma concentration-time plots after 1200 mg and 1800 mg XP13512 BID administration in Japanese are shown in the following figure:

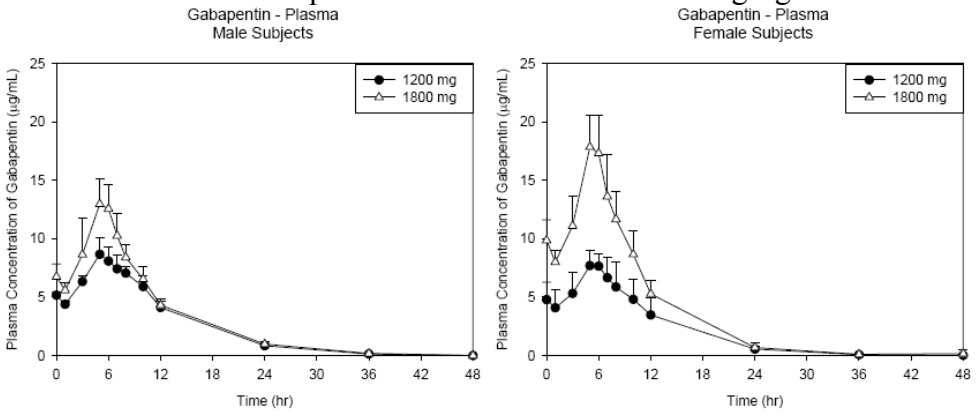


Figure 6.7. Effect of gender on mean (SD) concentrations of gabapentin in plasma at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

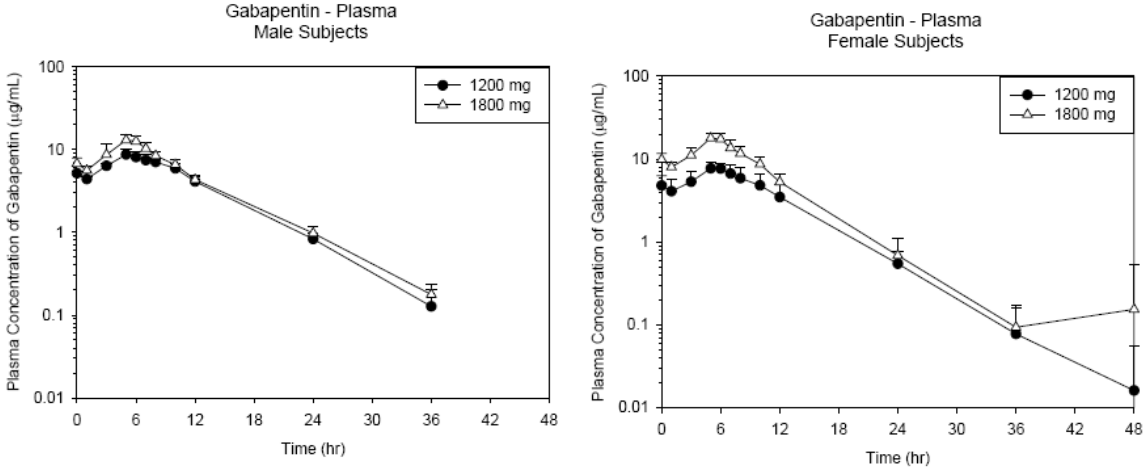


Figure U-5. Effect of gender on mean (SD) concentrations of gabapentin in plasma at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

- The Cmax gabapentin in plasma ranged from 8.40 µg/mL at the 1200 mg b.i.d. to 16.1 µg/mL at the 1800 mg b.i.d.
- The Cmin gabapentin in plasma ranged from 3.76 µg/mL at the 1200 mg b.i.d. to 4.84 µg/mL at the 1800 mg b.i.d.
- Mean oral bioavailability of gabapentin from XP13512 was consistently high (≥ 67%) at both dose levels.

Relationship between plasma and blood gabapentin concentrations following administration of XP13512:

Correlation of blood and plasma gabapentin concentrations is shown below:

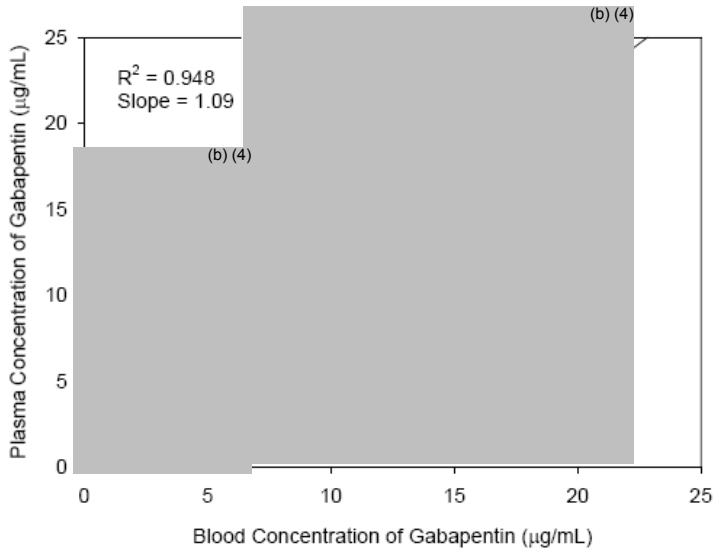


Figure 6.21. Relationship between blood and plasma concentrations of gabapentin after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002

- There was a linear relationship between the concentrations of gabapentin determined in blood and those in plasma.
- Plasma concentrations of gabapentin were ~ 9% higher than the corresponding blood concentrations.
- These data indicate that postsampling conversion of XP13512 to gabapentin was not significant.
- These results support the continued use of plasma sampling as the primary source of PK data in future XP13512 clinical studies.
- The blood to plasma ratio of gabapentin in Japanese subjects was consistent with that observed in Caucasians.

Steady state:

Gabapentin blood trough concentration-time plots are shown below:

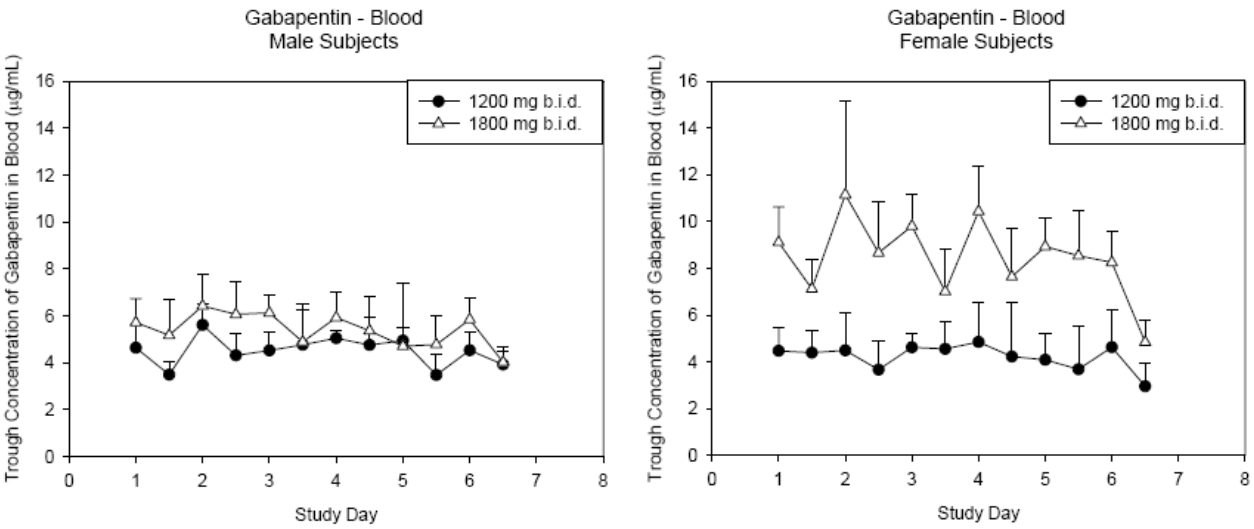


Figure 6.12. Effect of gender on mean (SD) trough concentrations of gabapentin in blood on Days 1 through 6 after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

- Steady state was reached within 1 day of initiating the target dose level.

Dose proportionality:

Geometric mean ratios (1800 mg/1200 mg) for gabapentin PK parameters at 1200 and 1800 mg BID in Japanese and 90% and 95% confidence intervals are shown below:

Table 5.7 Comparisons of Dose Normalized PK Parameters for Gabapentin using the Data from the 1200 mg and 1800 mg B.I.D. XP13512 Doses in Japanese Subjects

				Geometric Mean Ratio (1800 mg/1200 mg)		
Matrix	Gender	N [a]	Parameter	Point Estimate	90% Confidence Interval	95% Confidence Interval
Blood	Overall	11	$C_{SS,max}$/dose	1.141	(0.968, 1.346)	(0.935, 1.394)
			$C_{SS,min}$/dose	0.899	(0.742, 1.089)	(0.713, 1.133)
			AUC_{SS}/dose	1.058	(0.918, 1.220)	(0.891, 1.257)
	Male	5	$C_{SS,max}$/dose	1.007	(0.838, 1.210)	(0.802, 1.264)
			$C_{SS,min}$/dose	0.687	(0.569, 0.830)	(0.544, 0.868)
			AUC_{SS}/dose	0.866	(0.755, 0.993)	(0.730, 1.026)
	Female	6	$C_{SS,max}$/dose	1.267	(1.013, 1.584)	(0.963, 1.667)
			$C_{SS,min}$/dose	1.124	(0.835, 1.512)	(0.780, 1.618)
			AUC_{SS}/dose	1.251	(1.020, 1.535)	(0.973, 1.608)
Plasma	Overall	11	$C_{SS,max}$/dose	1.265	(1.097, 1.459)	(1.065, 1.504)
			$C_{SS,min}$/dose	0.879	(0.723, 1.069)	(0.694, 1.114)
			AUC_{SS}/dose	1.121	(0.972, 1.293)	(0.944, 1.332)
	Male	5	$C_{SS,max}$/dose	1.031	(0.852, 1.248)	(0.814, 1.306)
			$C_{SS,min}$/dose	0.701	(0.608, 0.808)	(0.588, 0.837)
			AUC_{SS}/dose	0.873	(0.775, 0.983)	(0.753, 1.012)
	Female	6	$C_{SS,max}$/dose	1.501	(1.257, 1.792)	(1.207, 1.866)
			$C_{SS,min}$/dose	1.062	(0.756, 1.493)	(0.699, 1.614)
			AUC_{SS}/dose	1.381	(1.135, 1.681)	(1.085, 1.759)
Urine	Overall [b]	8-11	$Ae_{(0-12)}$/dose	1.138	(0.999, 1.297)	(0.972, 1.333)
	Male [c]	2-5	$Ae_{(0-12)}$/dose	0.881	(0.715, 1.087)	(0.674, 1.152)
	Female	6	$Ae_{(0-12)}$/dose	1.250	(1.074, 1.455)	(1.038, 1.506)

a Number of subjects per dose
b N = 8 for 1200 mg b.i.d and 11 for 1800 mg b.i.d.
c N = 2 for 1200 mg b.i.d and 5 for 1800 mg b.i.d.

- Exposure to gabapentin in blood and plasma at steady state (measured by AUCss,Css,max, or Css,min values) was proportional to the oral XP13512 dose over the dose range 1200 to 1800 mg twice daily.

Evaluation of covariates:

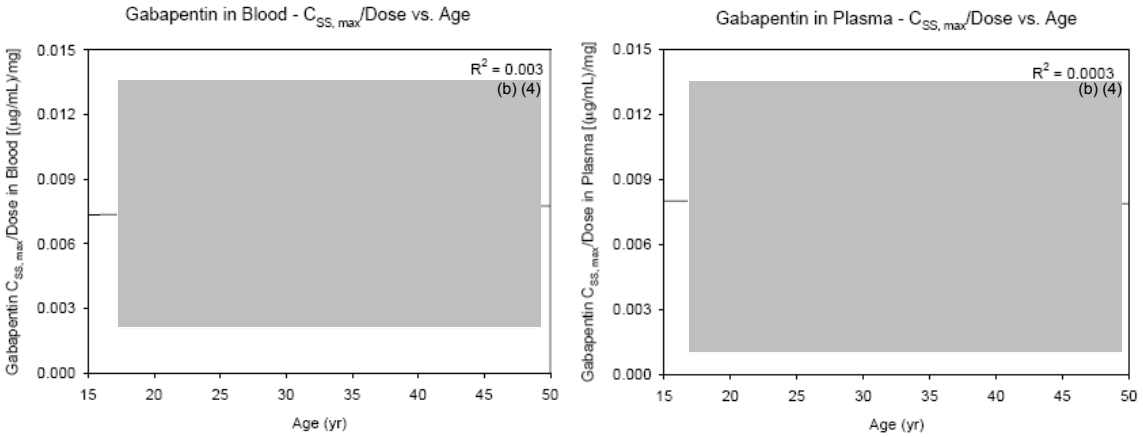


Figure 6.46. Relationship between age and XP13512 dose-normalized $C_{SS, max}$ of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

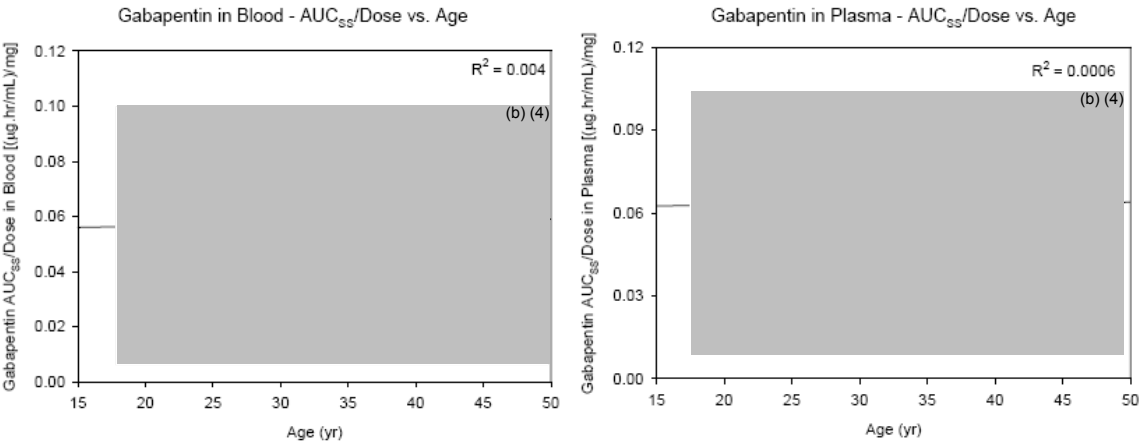


Figure 6.47. Relationship between age and XP13512 dose-normalized AUC_{SS} of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

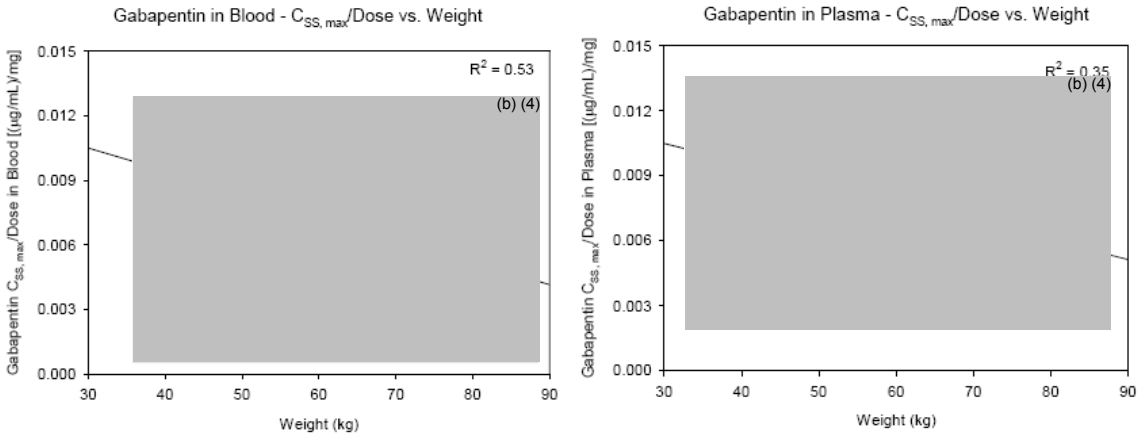


Figure 6.48. Relationship between body weight and XP13512 dose-normalized $C_{SS, max}$ of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

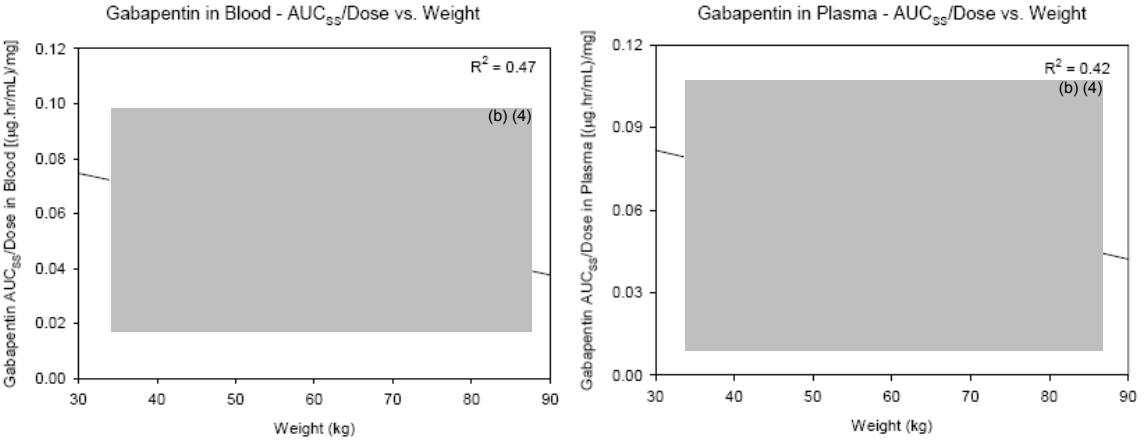


Figure 6.49. Relationship between body weight and XP13512 dose-normalized AUC_{SS} of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

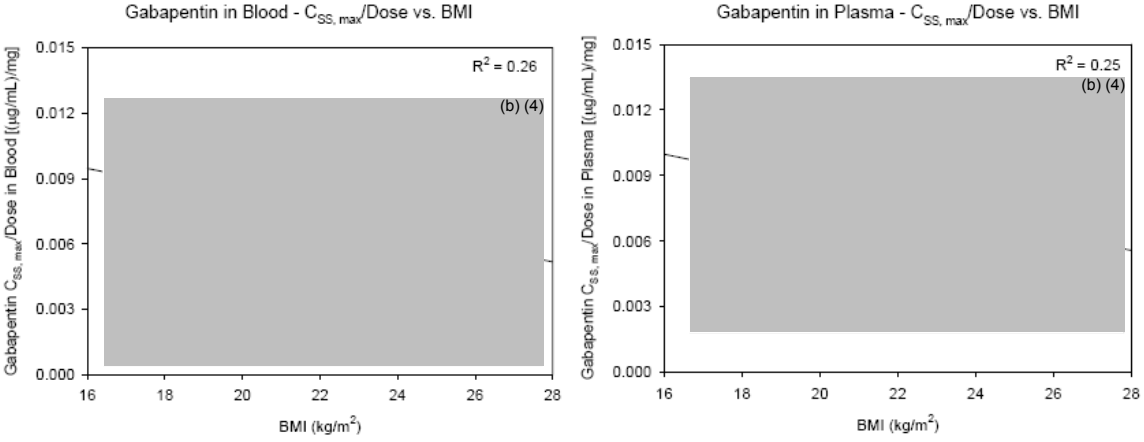


Figure 6.50. Relationship between BMI and XP13512 dose-normalized $C_{max, SS}$ of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

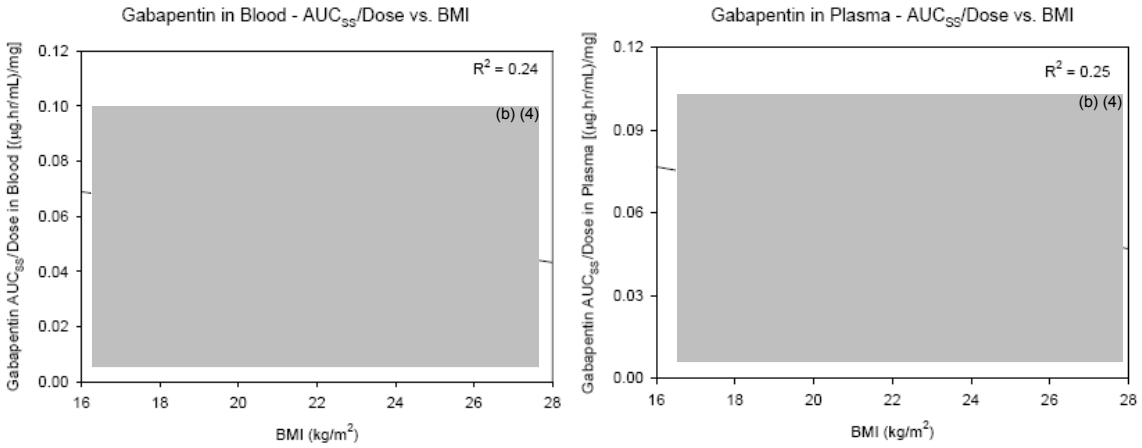


Figure 6.51. Relationship between BMI and XP13512 dose-normalized AUC_{SS} of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

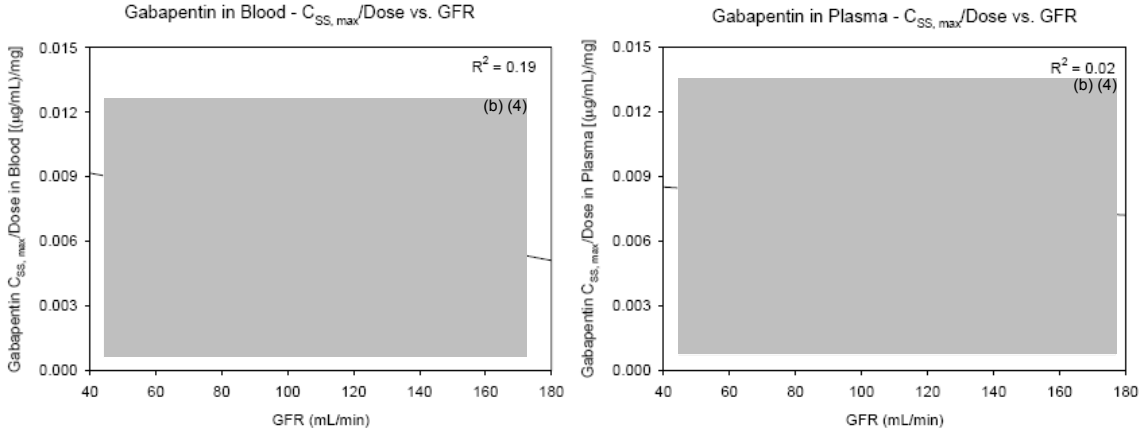


Figure 6.52. Relationship between GFR and XP13512 dose-normalized $C_{max, SS}$ of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

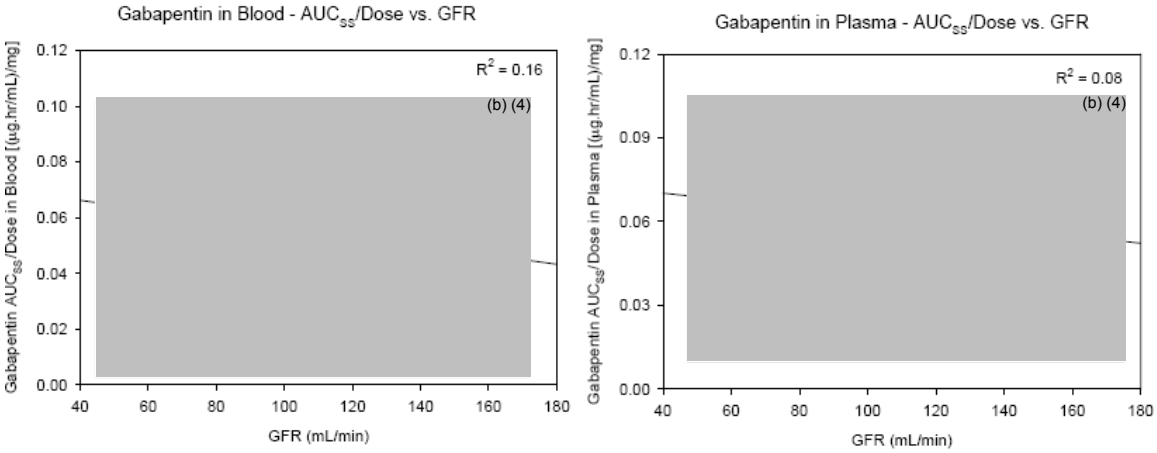


Figure 6.53. Relationship between GFR and XP13512 dose-normalized AUC_{SS} of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

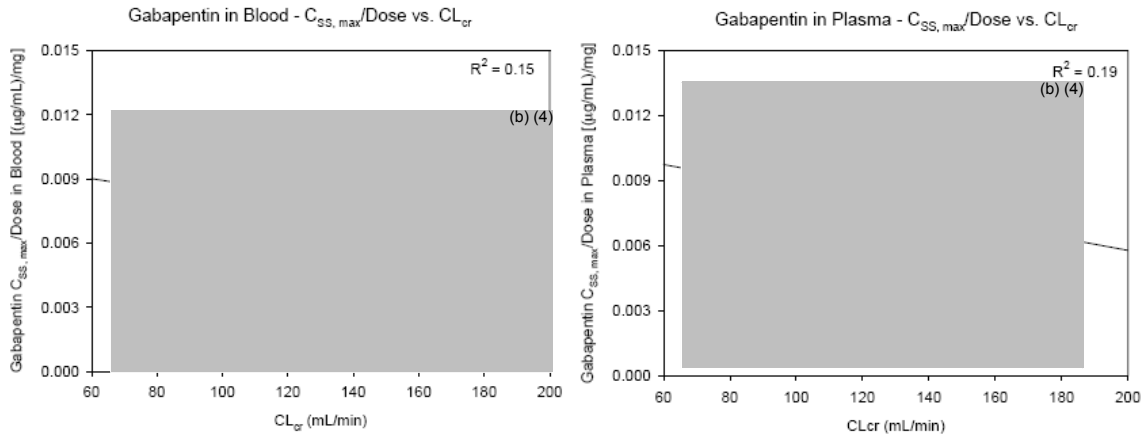


Figure 6.54. Relationship between creatinine clearance (CL_{cr}) and XP13512 dose-normalized $C_{max, SS}$ of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

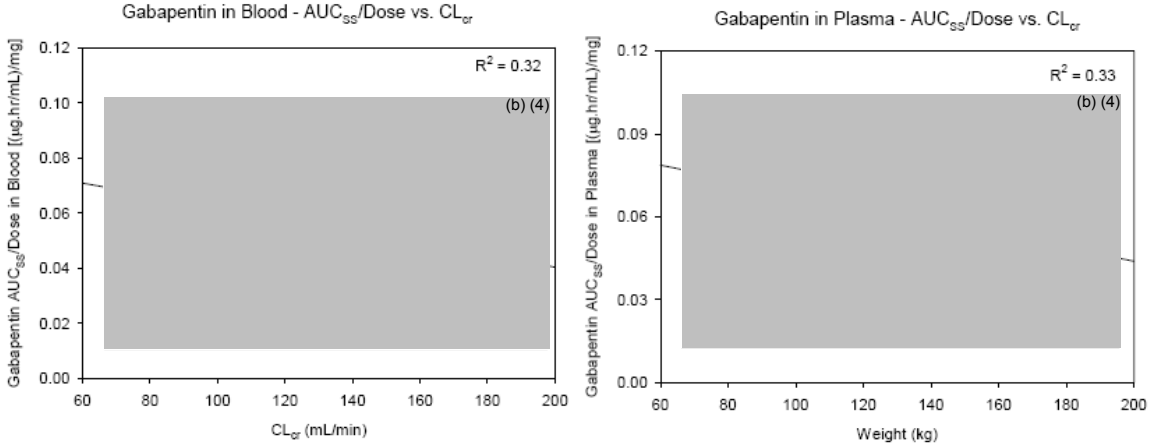


Figure 6.55. Relationship between creatinine clearance (CL_{cr}) and XP13512 dose-normalized AUC_{SS} of gabapentin in blood or plasma after oral administration of XP13512 Sustained Release tablets to Japanese subjects in Study XP073/8825-CL-0002

- There was no apparent correlation between dose-normalized Css, max and AUCss in blood or plasma of gabapentin and age.
- The correlation coefficient (R^2) between dose-normalized Css, max in blood or plasma of gabapentin and body weight is 0.53 and 0.35, respectively. The correlation coefficient (R^2) between dose-normalized AUCSS in blood or plasma of gabapentin and body weight is 0.47 and 0.42, respectively.
- The correlation coefficient (R^2) between dose-normalized CSS, max in blood or plasma of gabapentin and BMI is 0.26 and 0.25, respectively. The correlation coefficient (R^2) between dose-normalized AUCss in blood or plasma of gabapentin and BMI is 0.24 and 0.25, respectively.
- The correlation coefficient (R^2) between dose-normalized Css, max in blood or plasma of gabapentin and GFR is 0.19 and 0.02, respectively. The correlation coefficient (R^2) between dose-normalized AUCss in blood or plasma of gabapentin and GFR is 0.16 and 0.08, respectively.
- The correlation coefficient (R^2) between dose-normalized Css, max in blood or plasma of gabapentin and CLcr is 0.15 and 0.19, respectively. The correlation

coefficient (R^2) between dose-normalized AUCss in blood or plasma of gabapentin and CLcr is 0.32 and 0.33, respectively.

Gender:

Geometric mean ratios (Female/Male) and 90% and 95%confidence interval for gabapentin PK parameters are shown below:

Table 5.8 Geometric Mean Ratios (Female/Male) and Confidence Intervals for Gabapentin PK Parameters

Matrix	XP13512 Dose B.I.D.	N [a] Male/Female	PK Parameter	Geometric Mean Ratio (Female/Male) Point Estimate	90% Confidence Interval	95% Confidence Interval
Blood	1200 mg	5/6	$C_{SS,max}$	1.121	(0.886, 1.419)	(0.838, 1.500)
			$C_{SS,min}$	0.734	(0.544, 0.991)	(0.508, 1.063)
			AUC_{SS}	0.933	(0.763, 1.140)	(0.728, 1.195)
	1800 mg	5/6	$C_{SS,max}$	1.410	(1.175, 1.693)	(1.126, 1.767)
			$C_{SS,min}$	1.201	(0.964, 1.497)	(0.915, 1.576)
			AUC_{SS}	1.348	(1.145, 1.588)	(1.102, 1.650)
Plasma	1200 mg	5/6	$C_{SS,max}$	0.924	(0.762, 1.120)	(0.729, 1.171)
			$C_{SS,min}$	0.795	(0.564, 1.119)	(0.521, 1.213)
			AUC_{SS}	0.852	(0.704, 1.032)	(0.673, 1.080)
	1800 mg	5/6	$C_{SS,max}$	1.345	(1.127, 1.604)	(1.082, 1.671)
			$C_{SS,min}$	1.204	(0.977, 1.483)	(0.930, 1.558)
			AUC_{SS}	1.349	(1.160, 1.569)	(1.120, 1.625)
Urine	1200 mg	2/6	$Ae_{(0-12)}$	0.727	(0.584, 0.904)	(0.552, 0.957)
			CLr	0.837	(0.644, 1.089)	(0.601, 1.166)
	1800 mg	5/6	$Ae_{(0-12)}$	1.031	(0.884, 1.203)	(0.852, 1.247)
			CLr	0.766	(0.644, 0.910)	(0.618, 0.948)

a Number of subjects per gender

- There were no obvious differences in PK parameters for gabapentin derived from XP13512 between male and female Japanese subjects.
- The exposure to gabapentin in plasma was slightly higher in female than male subjects at the 1800 mg b.i.d. dose, possibly due to a lower body weight range.

XP13512 pharmacokinetics in blood:

Descriptive statistics for XP13512 PK parameters after XP13512 administration in Japanese are shown in the following table:

Table 5.3. Mean Pharmacokinetic Data for XP13512 in Blood at Steady State (Day 6) After Twice Daily Oral Administration of XP13512 Sustained Release Tablets to Healthy Japanese Subjects in Study XP073/8825-CL-0002

XP13512 Dose	Gender	N		XP13512 PK Parameter in Blood			
				$C_{SS,max}$ (µg/mL)	$C_{SS,min}$ (µg/mL)	T_{max} (hr)	AUC_{SS} (µg.hr/mL)
1200 mg B.I.D (2 × 600 mg SR Tablets B.I.D)	Male	5	Mean	0.019	0.00	3.72	0.086
			SD	0.022	0.00	1.25	0.037
			Min	0.00	0.00	3.00	0.056
			Max	0.052	0.00	5.17	0.127
			CV%	111	NA	33.6	43.0
	Female	6	Mean	0.024	0.00	4.63	0.067
			SD	0.017	0.00	1.53	0.043
			Min	0.00	0.00	3.00	0.010
			Max	0.044	0.00	6.00	0.121
			CV%	69.1	NA	33.0	64.0
	Overall	11	Mean	0.022	0.00	4.29	0.074
			SD	0.018	0.00	1.42	0.039
			Min	0.00	0.00	3.00	0.010
			Max	0.052	0.00	6.00	0.127
			CV%	82.6	NA	33.0	52.9
1800 mg B.I.D (3 × 600 mg SR Tablets B.I.D)	Male	5	Mean	0.032	0.00	3.50	0.099
			SD	0.024	0.00	2.52	0.051
			Min	0.00	0.00	1.00	0.031
			Max	0.057	0.00	7.00	0.154
			CV%	76.6	NA	71.9	52.1
	Female	6	Mean	0.051	0.00	3.50	0.143
			SD	0.043	0.00	1.22	0.105
			Min	0.012	0.00	3.00	0.025
			Max	0.131	0.00	6.00	0.318
			CV%	85.5	NA	35.0	73.6
	Overall	11	Mean	0.042	0.00	3.50	0.125
			SD	0.036	0.00	1.72	0.087
			Min	0.00	0.00	1.00	0.025
			Max	0.131	0.00	7.00	0.318
			CV%	84.8	NA	49.0	69.5

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; AUC_{SS} = area under the concentration-time curve at steady state; NA = Not applicable.

Mean XP13512 blood concentration-time plots after 1200 mg and 1800 mg XP13512 BID administration in Japanese are shown in the following figure:

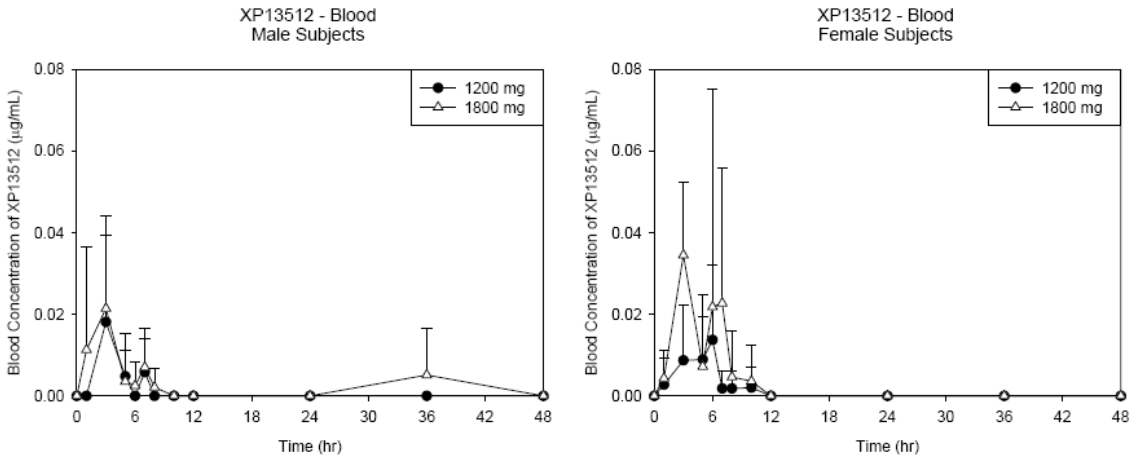


Figure 6.23. Effect of gender on mean (SD) concentrations of XP13512 in blood at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

- Exposure to prodrug in blood after oral dosing of XP13512 SR tablets was low and variable at both dose levels.
- The CSS,max and AUCSS of XP13512 in blood was generally ≤ 1% of the corresponding parameters for gabapentin.

Gabapentin lactam exposure:

Blood concentrations and urinary recovery data of gabapentin lactam were shown below:

Table 5.4. Mean Pharmacokinetic Data for Gabapentin Lactam in Blood and Urine at Steady State (Day 6) After Twice Daily Oral Administration of XP13512 Sustained Release Tablets to Healthy Japanese Subjects in Study XP073/8825-CL-0002

XP13512 Dose	Gender	N		Gabapentin Lactam PK Parameter						
				$C_{SS,max}$ (µg/mL)	$C_{SS,min}$ (µg/mL)	T_{max} (hr)	AUC_{SS} (µg.hr/mL)	$Ae_{(0-12)}$ (mg)	$Ae_{(0-24)}$ (mg)	%R [a]
1200 mg B.I.D (2 × 600 mg SR Tablets B.I.D)	Male	5	Mean	0.002	0.00	8.17	0.016	0.039 [b]	0.055 [b]	0.007 [b]
			SD	0.005	0.00	NA	NA	NA	NA	NA
			Min	0.00	0.00	8.17	0.016	0.038	0.047	0.007
			Max	0.011	0.00	8.17	0.016	0.040	0.062	0.007
			CV%	224	NA	NA	NA	NA	NA	NA
	Female	6	Mean	0.007	0.002	5.18	0.173	0.043	0.058	0.008
			SD	0.011	0.006	NA	NA	0.009	0.020	0.002
			Min	0.00	0.00	5.17	0.123	0.033	0.037	0.006
			Max	0.026	0.014	5.20	0.223	0.056	0.090	0.010
			CV%	159	245	NA	NA	21.3	33.8	21.3
	Overall	11	Mean	0.005	0.001	6.18	0.121	0.042 [c]	0.057 [c]	0.007 [c]
			SD	0.009	0.004	1.72	0.104	0.008	0.017	0.001
			Min	0.00	0.00	5.17	0.016	0.033	0.037	0.006
			Max	0.026	0.014	8.17	0.223	0.056	0.090	0.010
			CV%	185	332	27.9	85.9	18.8	30.0	18.8
1800 mg B.I.D (3 × 600 mg SR Tablets B.I.D)	Male	5	Mean	0.002	0.00	6.00	0.010	0.052	0.074	0.006
			SD	0.005	0.00	NA	NA	0.013	0.016	0.002
			Min	0.00	0.00	6.00	0.010	0.033	0.051	0.004
			Max	0.011	0.00	6.00	0.010	0.067	0.092	0.008
			CV%	224	NA	NA	NA	25.2	21.9	25.2
	Female	6	Mean	0.047	0.039	6.08	1.51	0.114	0.149	0.014
			SD	0.111	0.094	NA	NA	0.133	0.160	0.016
			Min	0.00	0.00	5.17	0.011	0.032	0.053	0.004
			Max	0.273	0.231	7.00	3.01	0.384	0.473	0.046
			CV%	234	245	NA	NA	117	107	117
	Overall	11	Mean	0.027	0.021	6.06	1.01	0.086	0.115	0.010
			SD	0.082	0.070	0.92	1.73	0.100	0.120	0.012
			Min	0.00	0.00	5.17	0.010	0.032	0.051	0.004
			Max	0.273	0.231	7.00	3.01	0.384	0.473	0.046
			CV%	306	332	15.2	171	116	104	116

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; AUC_{SS} = area under the concentration-time curve at steady state; $Ae_{(0-12)}$ = amount excreted in urine in 12 hr; $Ae_{(0-24)}$ = amount excreted in urine in 24 hr;
NA = Not applicable; a %R = Percentage of dose excreted in urine;
b N = 2 for males; c N = 8 for overall mean calculation. Urine data for Subjects 211, 212, and 214 were excluded from statistical calculation.

Mean gabapentin lactam blood concentration-time plots after 1200 mg and 1800 mg XP13512 BID administration in Japanese are shown in the following figure:

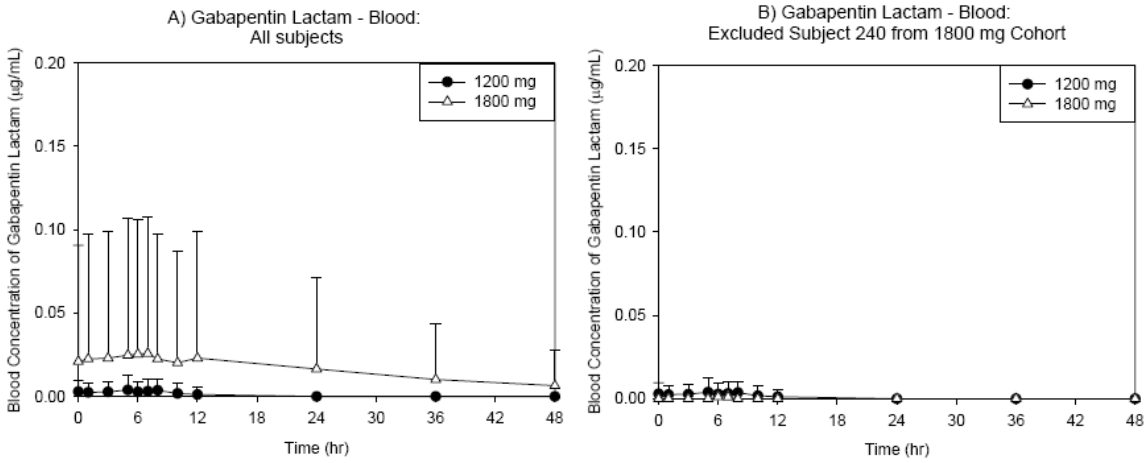


Figure 6.32. Overall mean (SD) concentrations of gabapentin lactam in blood at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (A) included all subjects, N = 11 per dose level; B) excluded Subject 240 from the mean and SD calculation for the 1800 mg b.i.d. cohort)

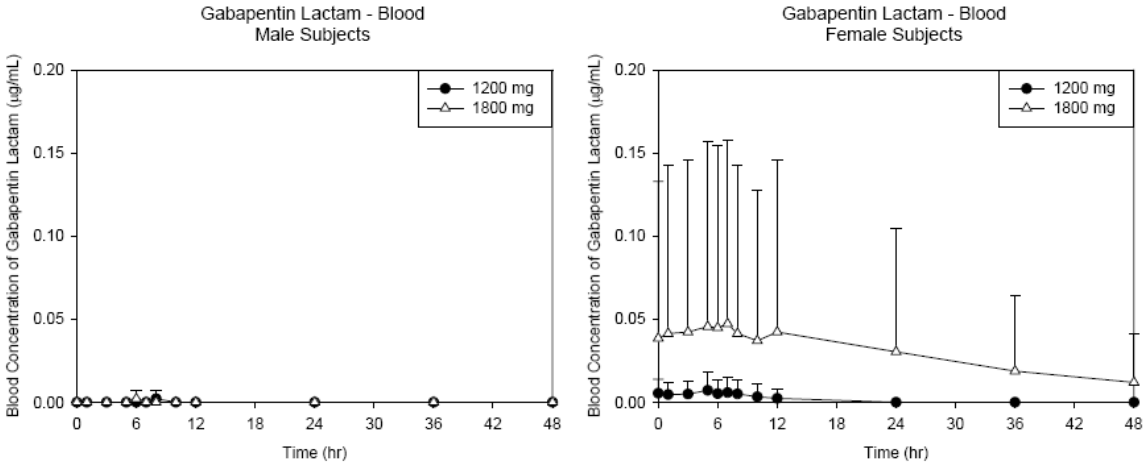


Figure 6.33. Effect of gender on mean (SD) concentrations of gabapentin lactam in blood at steady state (Day 6) after twice daily oral administration of 1200 or 1800 mg doses of XP13512 Sustained Release tablets to healthy Japanese subjects in Study XP073/8825-CL-0002 (N = 5 to 6 per gender/dose level)

- Exposure to gabapentin lactam in blood after oral dosing of XP13512 SR tablets was low and variable at both dose levels.
- The CSS,max and AUCSS of gabapentin lactam in blood were generally ≤ 1% of the corresponding parameters for gabapentin.
- The mean percent dose excreted as gabapentin lactam in urine at all dose levels was very low (≤ 0.01%).

Conclusions:

- Steady state was reached within 1 day of initiating the target dose level.
- Gabapentin exposures were proportional to the oral XP13512 doses over the dose range of 1200 mg twice daily to 1800 mg twice daily.

- Mean oral bioavailability of gabapentin from XP13512 was consistently high (≥ 67%) at both dose levels.
- There were no obvious differences in pharmacokinetic parameters for gabapentin derived from XP13512 between male and female Japanese subjects.
- Exposure to prodrug (XP13512) and gabapentin lactam in blood after oral dosing of XP13512 SR tablets was low and variable at both dose levels (≤ 1% of the corresponding parameters of gabapentin). In addition, the mean percent dose excreted as gabapentin lactam in urine at all dose levels was very low (≤ 0.01%).

Reviewer's Comment:

- *Two subjects who received placebo showed gabapentin (133 ng/mL and 7.81 µg/mL) plasma concentrations on day 5 pre-AM dose. One subject who received 1800 mg XP13512 had blood and plasma concentrations below quantitation at the same time point. In addition, one subject in 1800 mg group had an unusual terminal phase. The sponsor stated this might be the result of sample handling error. These findings suggested certain errors in study conduct which put the reliability of this study in question.*

4.1.4 EXTRINSIC FACTORS

Study XP-067: ***A Phase 1, Open-Label, Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of XP13512 Sustained Release (SR) Tablets Co-administered with Naproxen in Healthy Adult Subjects***

The pathway of absorption of XP13512 is believed to include active transport via a nutrient transporter, monocarboxylate transporter 1 (MCT1) which is expressed at high levels in the intestinal tract. Several approved drugs are known to be substrates for MCT1, including naproxen. The objectives of this study were to evaluate the potential for pharmacokinetic drug-drug interaction of XP13512 SR tablets and naproxen when administered concomitantly at steady-state and to evaluate the safety and tolerability.

A brief overview of some essential components of the study design are given below:

<table>
<tr><td>Study Design</td><td>Multiple-dose, 3 periods, open-label crossover, fed condition</td></tr>
<tr><td>Study Population</td><td>N=12
Age: 18-53 years (mean 31 years)
Gender: 8 males, 4 females
Weight: 57.9-99.5 kg (mean 71.6 kg)
Race: 10 Caucasian (83.3%) and 2 African-American (16.7%)</td></tr>
<tr><td>Dosage and Administration</td><td>All 12 Subjects received 3 treatment periods.

Period 1:1200 mg QD of XP13512 tablets for 5 days (Days 1 to 5) in the fed state in the morning.
Period 2: 500 mg BID, dosed every 12 hours, regimen of naproxen (Naprosyn®) for 5 days (Days 6 to 10) in the fed state in the morning and evening.
Period 3:1200 mg QD of XP13512 (in the morning) and 500 mg (BID, dosed every 12 hours) dose of naproxen for 5 days (Days 11 to 15) in the fed state in the morning and evening.

<table>
<tr><th rowspan="2">Subject Number</th><th colspan="3">Treatment</th></tr>
<tr><th>Period 1
Days 1 to 5</th><th>Period 2
Days 6 to 10</th><th>Period 3
Days 11 to 15</th></tr>
<tr><td>007 [a]</td><td rowspan="13">1200 mg XP13512, SR tablets QD</td><td rowspan="13">500 mg Naproxen BID</td><td rowspan="13">1200 mg XP13512, SR tablets QD and 500 mg Naproxen BID</td></tr>
<tr><td>009</td></tr>
<tr><td>013</td></tr>
<tr><td>014</td></tr>
<tr><td>015</td></tr>
<tr><td>019</td></tr>
<tr><td>021</td></tr>
<tr><td>022</td></tr>
<tr><td>023</td></tr>
<tr><td>024</td></tr>
<tr><td>026 [b]</td></tr>
<tr><td>027</td></tr>
</table>
a Subject 007 was early terminated due to a pruritic allergic rash developed on Day 11 (the first day of co-administration of XP13512 and naproxen).
b Subject 026 was early terminated due to investigator judgment.

Standard meal: moderate fat content (30% calories from fat)</td></tr>
</table>

	<table><tr><th>Drug</th><th>Dose/Form/Route</th><th>Frequency/Duration</th><th>Batch Number</th></tr><tr><td>Naproxen</td><td>250 mg/tablets/oral</td><td>2x250 mg BID (Days 6-10) 2x250 mg BID (Days 11-15)</td><td>E8102A</td></tr><tr><td>XP13512</td><td>600 mg/SR tablet/oral</td><td>2x600 mg QD (Days 1-5) 2x600 mg QD (Days 11-15)</td><td>3051595R</td></tr></table> Diet: Subjects were fasted overnight for at least 10 hours before each morning dosing. During the first 8 h of the fasting period, water and clear liquids were allowed *ad libitum* to all subjects. All subjects drank 240 mL of water or clear liquids 2 h and 1 h prior to dosing and 240 mL 2 h after dosing. No additional fluids were allowed from 2 h prior to dosing until 2 h post dose. At each of 2, 4, 6, 12, and 24 h post-morning dose, 240 mL of fluid was to be consumed. Alcohol was prohibited for 72 hours prior to dosing until study completion.
Sampling: Blood	At predose (0 hour), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18 and 24 hours after morning dosing on Days 5, 10 and 15. The samples were analyzed for blood concentrations of gabapentin and XP13512 and plasma concentrations of naproxen.
Sampling: Urine	0-4, 4-8, 8-12, 12-24, 24-36 hours after morning dosing on Days 5, 10 and 15.
Analysis (Blood)	Method LC/MS/MS Lower Limits of Quantitation Blood Gabapentin 50 ng/mL XP13512 10 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 10.1% Inter-day accuracy: 91.7-102 % Long term Stability: 83 days at -80 ^{o}C XP13512: Linear range : 10-2500 ng/mL in blood Inter-day Precision (%CV for Quality Controls) : < 6.77% Inter-day accuracy: 95.8-101 % Long term Stability: 83 days at -80 ^{o}C

Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Naproxen 0.500 µg/mL Naproxen: Linear range : 0.500-50.0 µg/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 3.6% Inter-day accuracy: 99.7-105.3 % Long term Stability: 204 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Naproxen 0.500 µg/mL Gabapentin: Linear range : 50-12500 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : 5.14% Inter-day accuracy: 98.1-105 % Long term Stability: 330 days at -80 ^{o}C and 791 days at -20 ^{o}C Naproxen: Linear range : 0.500-50.0 µg/mL in urine Inter-day Precision (%CV for Quality Controls) : < 5.2% Inter-day accuracy: 99.0-102 % Long term Stability: 92 days at -20 ^{o}C
PK Assessment	Gabapentin and XP13512 in blood and naproxen in plasma: $C_{ss,max}$, T_{max}, $C_{ss,min}$, $t_{1/2}$, AUC_{ss} and CL_{ss}/F Gabapentin and naproxen in urine: Am, Am (0-24) for gabapentin and Am (0-12) for naproxen and CLr
Safety Assessment	Adverse event (AE) assessments, electrocardiograms (ECGs), physical examinations, clinical laboratory tests, vital signs, and concomitant medications

Pharmacokinetic Results:

Gabapentin pharmacokinetics in blood:

Descriptive statistics for gabapentin PK parameters after XP13512 administration with or without concomitant dosing of naproxen are shown in the following table:

Table 5.1. Mean Pharmacokinetic Parameters for Gabapentin in Blood and Urine Determined at Steady State after Oral Administration of XP13512 SR Tablets in Fed Healthy Subjects when Co-administered Alone and with Naproxen in Study XP067

Treatment	Study Day	N		PK Parameter for Gabapentin										
				$C_{SS,max}$ (µg/mL)	T_{max} (hr)	$C_{SS,min}$ (µg/mL)	$T_{1/2}$ (hr)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	AUC_{SS} (µg*hr/mL)	CL_{SS}/F (L/hr)	Vd/F (L)	$Ae_{(0\text{-}24)}$ (mg)	CLr (L/hr)	F (%)
1200 mg XP13512 QD	5	11	Mean	6.17	5.18	0.666	5.76	63.3	63.3	10.1	86.1	449	7.13	71.8
			SD	1.25	1.08	0.127	1.10	11.2	11.2	1.74	28.3	78.4	0.900	12.5
			Min	4.68	4.00	0.497	4.53	47.0	47.1	7.41	51.6	294	5.75	47.1
			Median	5.54	5.00	0.649	5.35	59.8	59.9	10.4	80.6	437	7.17	70.0
			Max	8.19	8.00	0.902	7.33	84.3	84.3	13.3	125	539	8.71	86.2
		10*	Mean	6.10	5.20	0.667	5.64	63.8	63.9	10.1	83.9	450	7.09	72.0
			SD	1.29	1.14	0.133	1.08	11.7	11.7	1.82	28.8	82.5	0.938	13.2
			Min	4.68	4.00	0.497	4.53	47.0	47.1	7.41	51.6	294	5.75	47.1
			Median	5.52	5.00	0.639	5.24	62.9	63.0	9.95	73.2	457	7.02	73.1
			Max	8.19	8.00	0.902	7.33	84.3	84.3	13.3	125	539	8.71	86.2
1200 mg XP13512 QD + 500 mg Naproxen BID	15	10	Mean	6.52	5.80	0.707	5.73	71.6	71.7	8.87	74.5	476	6.71	76.1
			SD	0.918	1.03	0.274	1.02	10.1	10.1	1.27	22.1	55.5	0.921	8.88
			Min	5.11	4.00	0.00	4.46	57.1	57.2	7.31	51.3	366	5.72	58.6
			Median	6.21	6.00	0.755	5.47	71.1	71.1	8.79	68.9	492	6.67	78.8
			Max	8.34	8.00	1.01	7.28	85.4	85.5	10.9	115	536	8.30	85.7

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $T_{1/2}$ = half-life; $AUC_{(0\text{-}tlast)}$ = area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last}); AUC_{SS} = area under the concentration-time curve at steady state; CL_{SS}/F = apparent clearance after oral dosing at steady state; V_d/F = apparent volume of distribution; $Ae_{(0\text{-}24)}$ = amount excreted in 24 hr; CLr = renal clearance; F(%) = Percent of gabapentin dose recovered in urine in 24 hr post-dose.
Note: Subject 026 was early terminated due to investigator judgment.
* Subject 007 was early terminated due to a pruritic allergic rash developed on Day 11 (the first day of co-administration of XP13512 and naproxen). For comparison, the PK data for Subject 007 was excluded from statistical calculations.

Mean gabapentin blood concentration-time plot after XP13512 administration with or without concomitant dosing of naproxen is shown in the following figure:

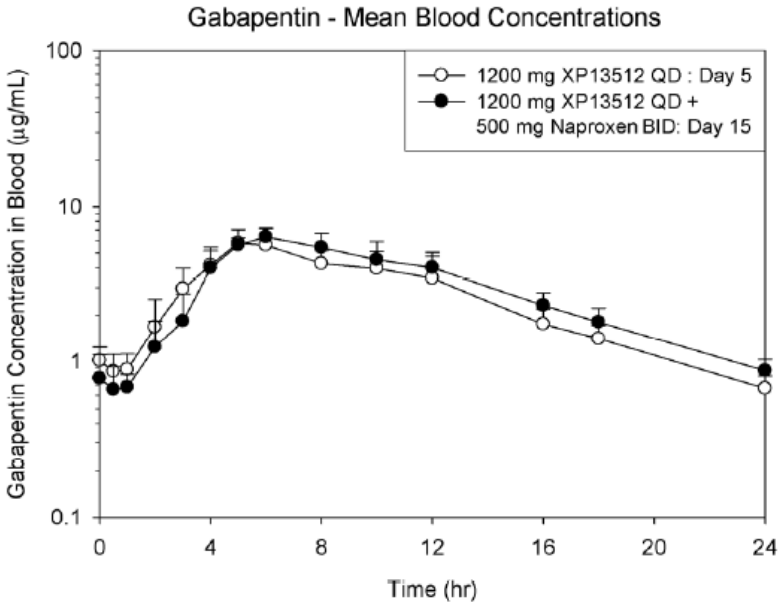


Figure K-1. Mean (SD) concentrations of gabapentin in blood determined at steady state of fed healthy subjects following once daily oral dosing of 1200 mg XP13512 alone or following co-administration of twice daily oral dosing of 500 mg naproxen in Study XP067 (N = 10 subjects per treatment, Subject 007 was excluded from mean and SD calculations due to early termination during Period 3)

Statistical comparison of blood concentrations for gabapentin PK Parameters by geometric mean ratios and 90% confidence intervals:

Gabapentin PK Parameter	Geometric Mean Ratio [(XP13512 + Naproxen)/XP13512]	
	Point Estimate	90% Confidence Interval
$C_{SS,\,max}$	1.08	(1.00, 1.16)
AUC_{SS}	1.13	(1.08, 1.19)

- Css,max of gabapentin in blood were observed as 6.10 µg/mL and 6.52 µg/mL after XP13512 dose alone and naproxen co-administration, respectively.
- AUCss of gabapentin in blood were 63.9 µg*hr/mL and 71.7 µg*hr/mL after XP13512 dose alone and naproxen co-administration, respectively.
- The bioavailability of gabapentin by urinary recovery were 72.0% and 76.1% after XP13512 dose alone and naproxen co-administration, respectively.
- Although the average of Css,max and AUCss of gabapentin were slightly increased by 8% and 13%, respectively, these estimates were within 90 % CI (0.8-1.25) indicating no significant difference of gabapentin exposure when dosed as XP13512 alone or combined with naproxen.

XP13512 pharmacokinetics in blood:

Descriptive Statistics for XP13512 PK Parameters after XP13512 administration with or without concomitant dosing of naproxen are shown in the following table:

Table 5.2. Mean Pharmacokinetic Parameters for XP13512 in Blood Determined at Steady State after Oral Administration of XP13512 SR Tablets in Fed Healthy Subjects when Co-administered Alone and with Naproxen in Study XP067

Treatment	Study Day	N		PK Parameter for XP13512				
				$C_{SS,max}$ (µg/mL)	T_{max} (hr)	$C_{SS,min}$ (µg/mL)	$AUC_{(0\text{-}tlast)}$ (µg*hr/mL)	AUC_{SS} (µg*hr/mL)
1200 mg XP13512 QD	5	11	Mean	0.045	4.18	0.00	0.106	0.129
			SD	0.024	1.60	0.00	0.047	0.045
			Min	0.022	1.00	0.00	0.067	0.077
			Median	0.043	4.00	0.00	0.081	0.141
			Max	0.103	6.00	0.00	0.202	0.184
		10*	Mean	0.045	4.30	0.00	0.107	0.127
			SD	0.025	1.64	0.00	0.050	0.049
			Min	0.022	1.00	0.00	0.067	0.077
			Median	0.041	4.50	0.00	0.080	0.118
			Max	0.103	6.00	0.00	0.202	0.184
1200 mg XP13512 QD + 500 mg Naproxen BID	15	10	Mean	0.039	4.31	0.00	0.089	0.140
			SD	0.027	1.06	0.00	0.059	0.048
			Min	0.018	3.00	0.00	0.027	0.093
			Median	0.033	4.50	0.00	0.084	0.121
			Max	0.111	6.00	0.00	0.200	0.212

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $AUC_{(0\text{-}tlast)}$ = area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last}); AUC_{SS} = area under the concentration-time curve at steady state.
Note: Subject 026 was early terminated due to investigator judgment.

* Subject 007 was early terminated due to a pruritic allergic rash developed on Day 11 (the first day of co-administration of XP13512 and naproxen). For comparison, the PK data for Subject 007 was excluded from statistical calculations.

Mean XP13512 blood concentration-time plot after XP13512 administration with or without concomitant dosing of naproxen is shown in the following figure:

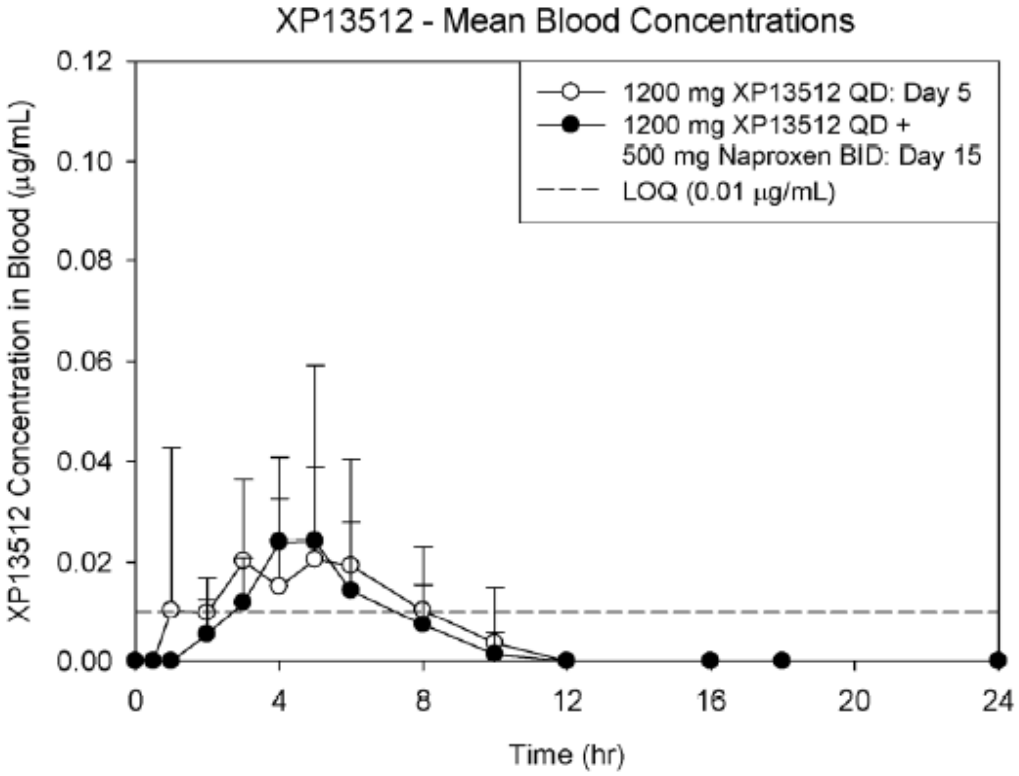


Figure 6.4. Mean (SD) concentrations of XP13512 in blood determined at steady state of fed healthy subjects following once daily oral dosing of 1200 mg XP13512 alone or following co-administration of twice daily oral dosing of 500 mg naproxen in Study XP067 (N = 10 subjects per treatment, Subject 007 was excluded from mean and SD calculations due to early termination during Period 3)

- Css,max of XP13512 in blood were observed as 0.045 µg/mL and 0.039 µg/mL after XP13512 dose alone and naproxen coadministration, respectively.
- AUCss of XP13512 in blood were 0.127 µg*hr/mL and 0.140 µg*hr/mL after XP13512 dose alone and naproxen co-administration, respectively.
- Css,max and AUCss of XP13512 in blood were ≤ 1.65% (0.27-1.65%) and ≤ 0.34% (0.04-0.34%) of the corresponding Css,max and AUCss of gabapentin.
- These results were consistent with previous findings and indicated the prodrug exposure is very low after administration of XP13512 regardless of concomitant dosing of naproxen.

Naproxen pharmacokinetics in plasma:

Descriptive Statistics for naproxen PK Parameters after naproxen administration with or without concomitant dosing of XP13512 are shown in the following table:

Table 5.3. Mean Pharmacokinetic Parameters for Naproxen in Plasma and Urine Determined at Steady State after Oral Dosing of Naproxen in Fed Healthy Subjects when Co-administered Alone and with XP13512 in Study XP067

Treatment	Study Day	N		PK Parameter for Naproxen									
				$C_{SS,max}$ (µg/mL)	T_{max} (hr)	$C_{SS,min}$ (µg/mL)	$T_{1/2}$ (hr)	AUC_{SS} (µg*hr/mL)	CL_{SS}/F (L/hr)	Vd/F (L)	$Ae_{(0-12)}$ (mg)	CLr (L/hr)	R (%)
500 Naproxen BID	10	11	Mean	99.3	4.01	56.4	11.4	871	0.581	9.39	221	0.257	44.1
			SD	9.06	0.90	8.47	4.88	102	0.065	3.65	33.4	0.049	6.69
			Min	84.3	2.00	46.1	7.01	725	0.458	5.62	157	0.172	31.4
			Median	101	4.00	53.9	9.51	857	0.584	8.14	223	0.260	44.5
			Max	112	5.00	76.2	21.3	1090	0.689	17.9	271	0.325	54.2
		10*	Mean	99.2	3.92	56.7	11.7	874	0.579	9.67	223	0.259	44.6
			SD	9.54	0.88	8.89	4.98	107	0.068	3.72	34.2	0.052	6.84
			Min	84.3	2.00	46.1	7.01	725	0.458	5.62	157	0.172	31.4
			Median	102	4.00	56.5	9.63	859	0.582	8.92	225	0.262	45.0
			Max	112	5.00	76.2	21.3	1090	0.689	17.9	271	0.325	54.2
1200 mg XP13512 QD + 500 mg Naproxen BID	15	10	Mean	97.8	4.81	53.2	10.0	860	0.589	8.51	218	0.256	43.7
			SD	9.54	1.40	9.81	3.89	112	0.071	3.55	21.2	0.029	4.24
			Min	82.7	3.02	42.1	5.15	723	0.463	4.10	183	0.193	36.7
			Median	98.3	4.50	52.6	9.78	835	0.599	8.20	217	0.251	43.4
			Max	111	8.00	71.2	18.9	1080	0.692	16.6	254	0.294	50.8

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $T_{1/2}$ = half-life; AUC_{SS} = area under the concentration-time curve at steady state; CL_{SS}/F = apparent clearance after oral dosing at steady state; V_d/F = apparent volume of distribution; $Ae_{(0-12)}$ = amount excreted in 12 hr; CLr = renal clearance; R(%) = Percent of naproxen dose recovered in urine in 12 hr post-dose.
Note: Subject 026 was early terminated due to investigator judgment.
* Subject 007 was early terminated due to a pruritic allergic rash developed on Day 11 (the first day of co-administration of XP13512 and naproxen). For comparison, the PK data for Subject 007 was excluded from statistical calculations.

Mean naproxen plasma concentration-time plot after naproxen administration with or without concomitant dosing of XP13512 is shown in the following figure:

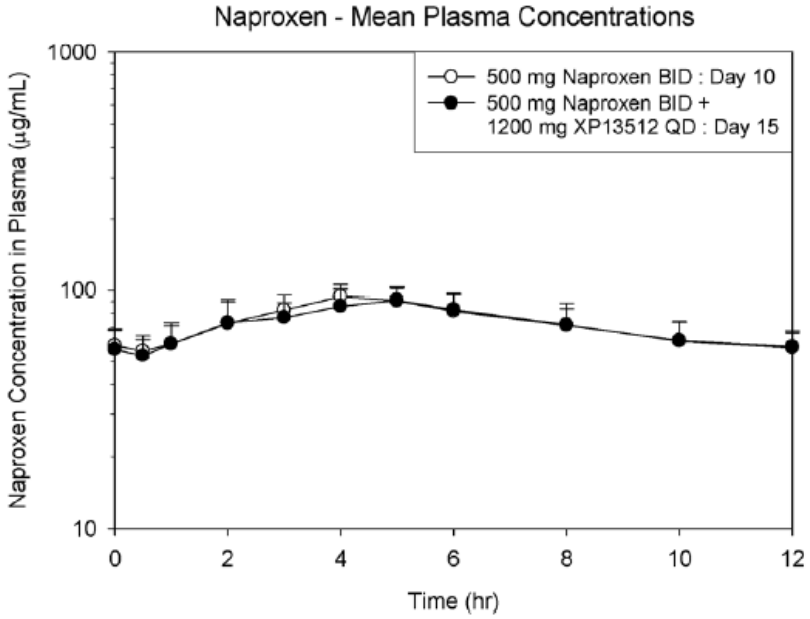


Figure L-1. Mean (SD) concentrations of naproxen in plasma determined at steady state of fed healthy subjects following twice daily oral dosing of 500 mg naproxen alone or following co-administration of once daily oral dosing of 1200 mg XP13512 in Study XP067 (N = 10 subjects per treatment, Subject 007 was excluded from mean and SD calculations due to early termination during Period 3)

Statistical comparison of plasma concentrations for naproxen PK Parameters by geometric mean ratios and 90% confidence intervals:

Naproxen PK Parameter	Geometric Mean Ratio [(XP13512 + Naprcxen)/Naproxen]	
	Point Estimate	90% Confidence Interval
$C_{SS,\ max}$	0.99	(0.95, 1.03)
AUC_{SS}	0.98	(0.94, 1.03)

- Css,max of naproxen in plasma were observed as 99.2 µg/mL and 97.8 µg/mL after naproxen dose alone and XP13512 co-administration, respectively.
- AUCss of naproxen in plasma were 874 µg*hr/mL and 860 µg*hr/mL after naproxen dose alone and XP13512 co-administration, respectively.
- The bioavailability of naproxen by urinary recovery were 44.6% and 43.7% after naproxen dose alone and XP13512 co-administration, respectively,
- The estimated geometric mean ratios were close to one for both parameters (Cmax and AUC). Both parameters were within 90 % CI (0.8-1.25) indicating no

significant difference of naproxen exposure when dosed as naproxen alone or combined with XP13512.

Conclusions:

- No clinically relevant change in gabapentin exposure was observed when XP13512 was dosed in combination with naproxen compared to when XP13512 was dosed alone.
- Similarly, no effect on either XP13512 or naproxen exposures was observed when XP13512 and naproxen were dosed concomitantly.
- Based on these results, there is no indication that XP13512 has the potential to interact with other monocarboxylate transporter-1 (MCT-1) substrates at the site of absorption.

Reviewer's Comment:

- *The subjects abstained from smoking only through the in-clinic portion of the study and caffeine was not controlled. The potential influences of smoking and caffeine intake on the results of the study are therefore not clear.*
- *Naproxen has a Tmax of ~4h and t1/2 of ~11h based on the data shown above, however, the blood was only collected for 12h. The t1/2 estimation might not be accurate.*

Study XP-068: ***A Phase 1, Open-Label, Fed, Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of XP13512 Sustained Release (SR) Tablets Co-Administered with Cimetidine (Tagamet®) in Healthy Adult Subjects.***

Gabapentin renal excretion is believed to involve a component of active secretion via an organic cation transporter (OCT2) present in the kidney. Cimetidine, an antacid of the histamine H_2-antagonist class, is a known substrate for this same elimination pathway. It has previously been shown that co-administration of oral cimetidine with oral gabapentin produces a 14% decrease in the mean apparent oral clearance of gabapentin, presumably by competition for the OCT2 transporter. This study was conducted to evaluate the potential for pharmacokinetics drug-drug interaction between XP13512 and cimetidine and to explore the safety and tolerability of concomitanly use of XP13512 and cimetidine.

A brief overview of some essential components of the study design is given below:

<table>
<tr><td>Study Design</td><td>Multiple-dose, 3 periods, open-label, fed condition</td></tr>
<tr><td>Study Population</td><td>N=12
Age: 20-43 years (mean 25 years)
Gender: 11 males, 1 female
Weight: 55.0-86.5 kg (mean 74.7 kg)
Race: 10 Caucasian (83.3%) and 2 African-American (16.7%)</td></tr>
<tr><td>Dosage and Administration</td><td>All 12 Subjects received 3 treatment periods.

Period 1: XP13512 1200 mg SR tablets QD in the morning with food for 4 days (Days 1 to 4).
Period 2: cimetidine (Tagamet®) 400 mg QID with food for 4 days (Days 5 to 8). The last daily dose was administered at bedtime (without a meal).
Period 3: XP13512 1200 mg SR tablets QD in the morning and cimetidine 400 mg QID for 4 days (Days 9 to 12) administered with food. The last daily dose of cimetidine was administered at bedtime (without a meal).

<table>
<tr><th>Period</th><th>Treatment Regimen</th><th>Days</th><th>Condition</th></tr>
<tr><td>1</td><td>XP13512 1200 mg, SR tablets (once daily)</td><td>1 to 4</td><td>Fed</td></tr>
<tr><td>2</td><td>Cimetidine 400 mg (four times daily)</td><td>5 to 8</td><td>Fed
(except for the last daily dose)</td></tr>
<tr><td>3</td><td>XP13512 1200 mg, SR tablets (once daily)
and cimetidine 400 mg (four times daily)</td><td>9 to 12</td><td>Fed
(except for the last daily dose)</td></tr>
</table>
SR = sustained release.

Standard meal: moderate fat content (30% calories from fat)

<table>
<tr><th>Drug</th><th>Dose/Form/Route</th><th>Frequency</th><th>Batch Number</th></tr>
<tr><td>XP13512</td><td>600 mg oral SR tablets</td><td>1200 mg once daily</td><td>3051595R</td></tr>
<tr><td>Cimetidine</td><td>200 mg oral tablets</td><td>400 mg four times daily</td><td>3051091</td></tr>
</table>
SR = sustained release.</td></tr>
</table>

	Diet: Subjects were fasted starting from 1:00 am prior to each morning dose. All subjects drank 240 mL of water 2 h and 1 h prior to dosing and 240 mL 2 h and 4 h after morning dosing. No additional fluids were allowed from 2 h prior to dosing until 4 h post morning dose. At each of 6, 12, 18 and 24 h post-morning dose, 240 mL of water or clear fluid was to be consumed. Alcohol was prohibited for 72 hours prior to dosing until study completion.
Sampling: Plasma	At predose (0 hour), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 16, 18 and 24 hours after morning dosing on Days 4, 8 and 12. The samples were analyzed for plasma concentrations of gabapentin and cimetidine.
Sampling: Urine	0-3, 3-6, 6-12, 12-24 hours after morning dosing on Days 4, 8 and 12.
Analysis (Plasma)	Method LC/MS/MS Lower Limits of Quantitation Plasma Gabapentin 80 ng/mL Cimetidine 5.00 ng/mL Gabapentin: Linear range : 80-10000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 5.76% Inter-day accuracy: 97.7-104 % Long term Stability: 782 days at -20 ^{o}C Cimetidine: Linear range : 5.00-1000 ng/mL in plasma Inter-day Precision (%CV for Quality Controls) : < 4.3% Inter-day accuracy: 96.1-98.7 % Long term Stability: 85 days at -20 ^{o}C
Analysis (Urine)	Method LC/MS/MS Lower Limits of Quantitation Urine Gabapentin 50 ng/mL Cimetidine 5.00 ng/mL Gabapentin: Linear range : 50-12500 ng/mL in urine

	Inter-day Precision (%CV for Quality Controls) : 5.14% Inter-day accuracy: 98.1-105 % Long term Stability: 330 days at -80 ^{o}C and 791 days at -20 ^{o}C <u>Cimetidine:</u> Linear range : 5.00-1000 ng/mL in urine Inter-day Precision (%CV for Quality Controls) : < 15% Inter-day accuracy: 93.9-98.7 % Long term Stability: 165 days at -20 ^{o}C
PK Assessment	Gabapentin and cimetidine in plasma: $C_{ss,\,max}$, T_{max}, $C_{ss,\,min}$, $t_{1/2}$, AUC_{ss} and CL_{ss}/F Gabapentin and cimetidine in urine: Am, Am (0-24) for gabapentin and Am (0-6) for cimetidine and CLr
Safety Assessment	Adverse event (AE) monitoring, 12-lead electrocardiograms (ECGs), physical examinations, clinical laboratory evaluations, and vital signs

Pharmacokinetic Results:

Gabapentin pharmacokinetics in plasma:

Descriptive statistics for gabapentin PK parameters after XP13512 administration with or without concomitant dosing of cimetidine are shown in the following table:

Table 5.1. Mean Pharmacokinetic Parameters for Gabapentin in Plasma and Urine Determined at Steady State after Oral Administration of XP13512 SR Tablets in Fed Healthy Subjects when Co-administered Alone and with Cimetidine in Study XP068

Treatment	Study Day	N		PK Parameter for Gabapentin									
				$C_{SS,max}$ (µg/mL)	T_{max} (hr)	$C_{SS,min}$ (µg/mL)	$T_{1/2}$ (hr)	AUC_{SS} (µg*hr/mL)	CL_{SS}/F (L/hr)	Vd/F (L)	$Ae_{(0-24)}$ (mg)	CLr (L/hr)	F (%)
1200 mg XP13512 QD	4	12	Mean	7.05	5.61	0.819	6.32	70.8	9.00	82.0	420	6.02	67.1
			SD	1.20	0.54	0.229	1.14	10.0	1.40	17.8	82.6	1.31	13.2
			Min	4.43	5.00	0.538	4.48	51.7	7.33	48.3	273	3.20	43.7
			Median	7.16	6.00	0.782	6.04	70.8	8.83	81.1	448	6.05	71.7
			Max	9.01	6.10	1.37	8.91	85.3	12.1	111	534	8.27	85.4
1200 mg XP13512 QD+ 400 mg Cimetidine QID	12	12	Mean	7.44	5.53	1.30	8.12	87.6	7.20	83.7	428	4.95	68.5
			SD	0.935	0.70	0.523	1.57	9.05	0.719	14.5	34.7	0.682	5.55
			Min	6.12	4.00	0.087	5.52	75.3	6.00	58.5	375	3.61	59.9
			Median	7.38	6.05	1.35	8.07	85.6	7.30	80.0	425	5.04	67.9
			Max	9.15	6.05	2.29	11.8	104	8.30	108	488	6.20	78.0

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $T_{1/2}$ = half-life; AUC_{SS} = area under the concentration-time curve at steady state; CL_{SS}/F = apparent clearance after oral dosing at steady state; V_d/F = apparent volume of distribution; $Ae_{(0-24)}$ = amount excreted in 24 hr; CLr = renal clearance; F(%) = Percent of gabapentin mg-eq dose recovered in urine in 24 hr post-dose.

Mean gabapentin plasma concentration-time plot after XP13512 administration with or without concomitant dosing of cimetidine is shown in the following figure:

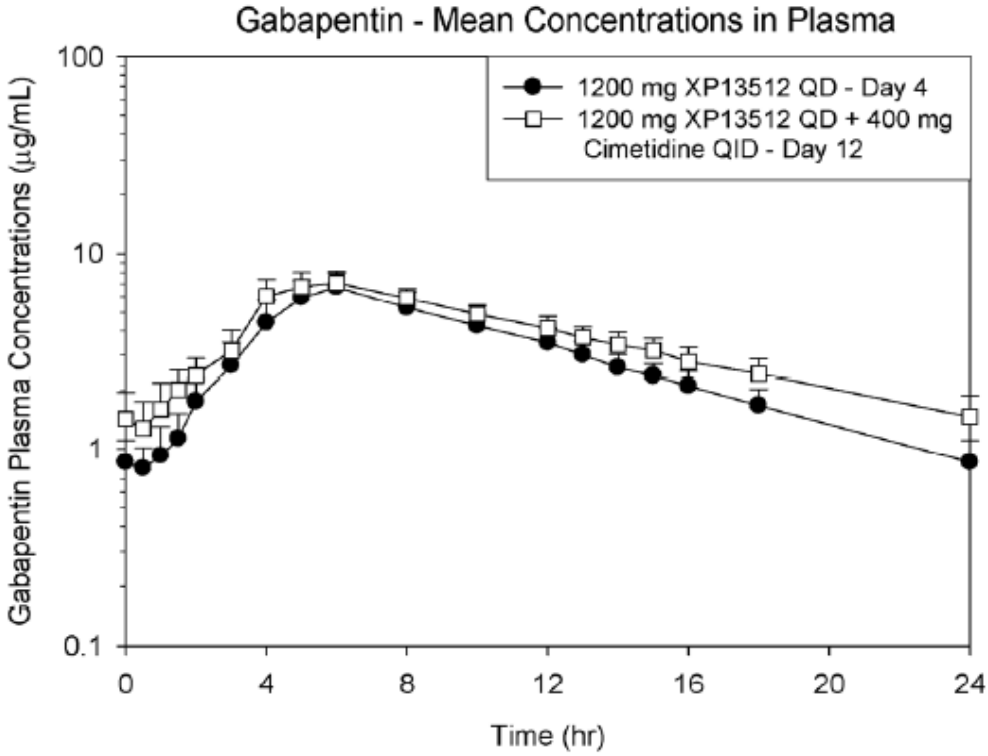


Figure I-1. Mean (SD) concentrations of gabapentin in plasma determined at steady state of fed healthy subjects following once daily oral dosing of 1200 mg XP13512 alone or following co-administration of QID oral dosing of 400 mg cimetidine in Study XP068 (N = 12 subjects per treatment)

Statistical comparison of plasma concentrations for gabapentin PK Parameters by geometric mean ratios and 90% confidence intervals:

Table 8 Statistical analysis of pharmacokinetic parameters for XP13512 with cimetidine pharmacokinetics versus XP13512 alone

Gabapentin pharmacokinetic	Geometric Mean Ratio [(XP13512 + Cimetidine)/XP13512]	
parameter	Point estimate	90% confidence interval
$C_{SS,\,max}$	1.06	0.98, 1.15
AUC_{SS}	1.24	1.17, 1.32

Source Data: Attachment 3, Table 5.5

$C_{ss,\,max}$ = maximum concentration at steady state; AUC_{ss} = area under the concentration versus time curve

- Css,max of gabapentin in plasma were observed as 7.05 μg/mL and 7.44 μg/mL after XP13512 dose alone and cimetidine co-administration, respectively.
- AUCss of gabapentin in plasma were 70.8 μg*hr/mL and 87.6 μg*hr/mL after XP13512 dose alone and cimetidine co-administration, respectively.
- CLss/F of gabapentin were 9.00 L/hr and 7.20 L/hr after XP13512 dose alone and cimetidine co-administration, respectively.
- The bioavailability of gabapentin by urinary recovery were 67.1% and 68.5% after XP13512 dose alone and cimetidine co-administration, respectively.
- Css,max of gabapentin after administration of XP13512 alone or when concomitantly dosed with cimetidine were similar with the geometric mean ratio close to 1 and within 90% CI of 80-125.
- AUCss of gabapentin was statistically significant increased by 24% when XP13512 was concomitantly dosed with cimetidine compared to XP13512 administration alone.
- Consistent with the increase of AUC, CLss/F was decreased by 20% when XP13512 was concomitantly dosed with cimetidine compared to XP13512 administration alone.
- The increased exposure of gabapentin was not considered clinically significant.

Cimetidine pharmacokinetics in plasma:

Descriptive Statistics for cimetidine PK Parameters after cimetidine administration with or without concomitant dosing of XP13512 are shown in the following table:

Table 5.2. Mean Pharmacokinetic Parameters for Cimetidine in Plasma and Urine Determined at Steady State after Oral Dosing of Cimetidine in Fed Healthy Subjects when Co-administered Alone and with XP13512 in Study XP068

Treatment	Study Day	N		PK Parameter for Cimetidine									
				$C_{SS,max}$ (µg/mL)	T_{max} (hr)	$C_{SS,min}$ (µg/mL)	$T_{1/2}$ (hr)	AUC_{SS} (µg*hr/mL)	CL_{SS}/F (L/hr)	Vd/F (L)	$Ae_{(0-6)}$ (mg)	CLr (L/hr)	R (%)
400 Cimetidine QID	8	12	Mean	2.34	2.42	0.650	2.38	8.45	47.9	165	167	19.9	41.7
			SD	0.395	0.67	0.122	0.34	0.948	5.56	32.2	37.5	4.65	9.39
			Min	1.87	2.00	0.440	1.88	6.76	39.5	117	102	11.6	25.5
			Median	2.25	2.00	0.683	2.35	8.49	47.1	177	173	20.7	43.3
			Max	3.28	4.00	0.864	2.92	10.1	59.2	197	214	28.3	53.6
1200 mg XP13512 QD + 400 mg Cimetidine QID	12	12	Mean	2.26	2.42	0.641	2.74	8.36	48.5	194	142	17.1	35.5
			SD	0.493	0.76	0.149	0.79	1.03	6.01	69.2	36.9	4.11	9.22
			Min	1.68	1.50	0.398	2.03	6.68	40.0	121	85.0	9.51	21.3
			Median	2.13	2.02	0.633	2.42	8.01	49.9	177	148	17.6	37.1
			Max	3.11	4.00	0.940	4.51	10.0	59.9	367	207	23.1	51.7

Abbreviations: $C_{SS,max}$ = maximum concentration at steady state; T_{max} = time to $C_{SS,max}$; $C_{SS,min}$ = minimum concentration at steady state; $T_{1/2}$ = half-life; AUC_{SS} = area under the concentration-time curve at steady state; CL_{SS}/F = apparent clearance after oral dosing at steady state; V_d/F = apparent volume of distribution; $Ae_{(0-6)}$ = amount excreted in 6 hr; CLr = renal clearance; R (%) = Percent of cimetidine dose recovered in urine in 6 hr post-dose.

Mean cimetidine plasma concentration-time plot after cimetidine administration with or without concomitant dosing of XP13512 is shown in the following figure:

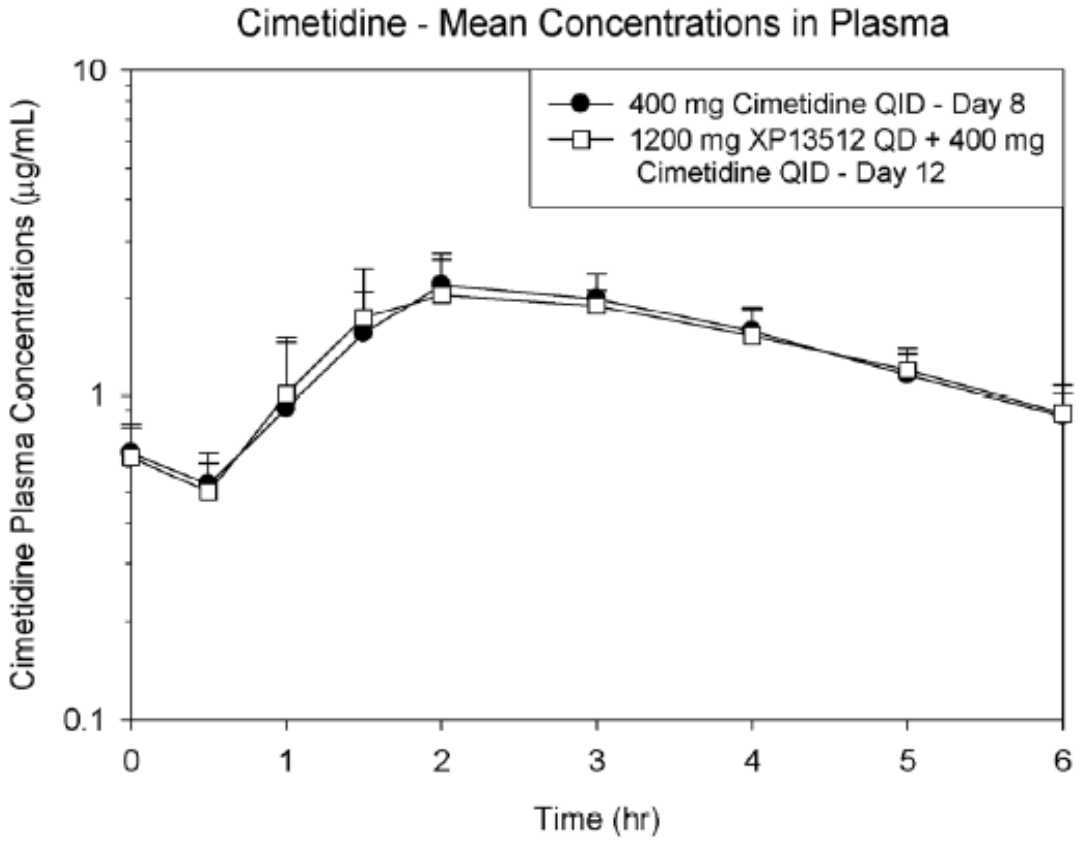


Figure J-1. Mean (SD) concentrations of cimetidine in plasma determined at steady state of fed healthy subjects following QID oral dosing of 400 mg cimetidine alone or following co-administration of once daily oral dosing of 1200 mg XP13512 in Study XP068 (N = 12 subjects per treatment)

Statistical comparison of plasma concentrations for cimetidine PK Parameters by geometric mean ratios and 90% confidence intervals:

Table 10 Statistical analysis of pharmacokinetic parameters for XP13512 with cimetidine versus cimetidine alone

Cimetidine pharmacokinetic	Geometric Mean Ratio [(XP13512 + cimetidine)/cimetidine]	
parameter	Point estimate	90% confidence interval
$C_{ss,max}$	0.96	0.90, 1.02
AUC_{SS}	0.99	0.95, 1.03

Source Data: Attachment 3, Table 5.5

$C_{ss,max}$ = maximum concentration at steady state; AUC_{ss} = area under the concentration versus time curve

- Css,max of cimetidine in plasma were observed as 2.34 µg/mL and 2.26 µg/mL after cimetidine dose alone and XP13512 co-administration, respectively.
- AUCss of cimetidine in plasma were 8.45 µg*hr/mL and 8.36 µg*hr/mL after naproxen dose alone and XP13512 co-administration, respectively.
- The bioavailability of cimetidine by urinary recovery were 41.7% and 35.5% after cimetidine dose alone and XP13512 co-administration, respectively,
- The estimated geometric mean ratios were close to one for both parameters. Both parameters were within 90 % CI (0.8-1.25) indicating no significant difference of cimetidine exposure when dosed as cimetidine alone or combined with XP13512.

Conclusions:

- Gabapentin AUCss increased slightly by 24% when XP13512 was dosed with cimetidine compared to XP13512 dosed alone.
- Gabapentin CLss/F decreased slightly by 20% when XP13512 was dosed with cimetidine compared to XP13512 dosed alone.
- These results are consistent with published information for gabapentin when concomitantly dosed with cimetidine.
- No effect on cimetidine exposure was observed when XP13512 and cimetidine were co-administered.
- It is considered that there is no clinically relevant drug-drug interaction between XP13512 and cimetidine based on these results.

Reviewer's Comment:

- *The elimination half-life of gabapentin is longer when co-administered as XP13512 with cimetidine compared with XP13512 dosed alone (8.12h vs 6.32 h). Although the plasma concentration-time profile looked slightly different due to the increased half-life, this result is consistent with decreased apparent oral clearance of gabapentin.*
- *Cimetidine has the Tmax of ~2.4h and t1/2 of ~2.4h based on the data shown above, however, the blood were only collected for 6h. The t1/2 estimation might not be accurate.*

4.1.5 IN VITRO STUDIES

Study BIO-2003-002:

In Vitro Biologic Transport Studies of XP13512 and XP13497

Several experiments were conducted and summarized in this report to evaluate the potential transporters for XP13512, XP13497 and gabapentin. Different systems were utilized, including Caco-2 MDCK monolayers, artificial lipid membranes, active transport by Intestinally-Expressed transporters (MCT-1, SMVT, other transporters and P-gp) and active transport by kidney transporter (OCT2).

Below is the information of tested compounds:

Table 2.1. Compound Batch Numbers and Purity Based on LC/MS/MS Analysis

Compound	Batch	Prodrug (% w/w)	Lactam (% w/w)	Gabapentin (% w/w)
XP13512 (b) (4)	GMP Lot 2892.A.03.1	(b) (4) (b) (4)	(b) (4)	ND
XP13497 Sodium Salt	I003GV		No Data	No Data
XP16654 Calcium Salt	I003GU		No Data	No Data
XP17814 S-Isomer	I004G1		No Data	No Data
XP17815 R-Isomer	I004G2		No Data	No Data

ND – Not detected.

I. Caco-2 and MDCK transepithelial transport

To determine the ability of XP13497 or XP13512 to cross epithelial cells, apical-to-basolateral and basolateral-to-apical transport across both Caco-2 and MDCK cells was studied.

Method:

Caco-2 and MDCK cells were seeded into 24-well transwell plates with 3μm filters (Corning/Costar, Acton, MA) at a density of 500,000 cells/well and allowed to differentiate in the transwell plates; 21 days for Caco-2 or five days for MDCKcells. Test compounds were dissolved into either pH 6.5 (apical MES buffer) or pH 7.4 (basolateral HBSS buffer) at concentrations of 100 to 200 μM and added to the appropriate chambers. Samples were removed from the receiving chambers at various time points and transport was measured by determining the concentration of XP13512 and gabapentin (produced by esterase cleavage within the epithelial cells) by LC-MS-MS. Apparent permeability coefficients (Papp) were calculated using the following equation:

$$P_{app}\ (cm/sec) = \frac{V \bullet dC}{A \bullet C_0 \bullet dt}$$

V = volume of receiving chamber (apical = 0.125cm3; basolateral = 0.875cm3)
dC/dt = steady state rate of appearance of test compound and gabapentin in receiving chamber after primary lag time (μM/sec)
C0 = concentration of compound in the donor chamber (μM)
A = area of the transwell (0.33cm^2)

Integrity of the monolayer is measured by determining the permeability of ^{3}H-inulin. If greater than 0.5% of the inulin was detected in the receiving chamber, the transwells were discarded.

Results:

Permeability data for XP13497 and XP13512 (sum of prodrug and released gabapentin) in Caco-2 and MDCK cells are shown below:

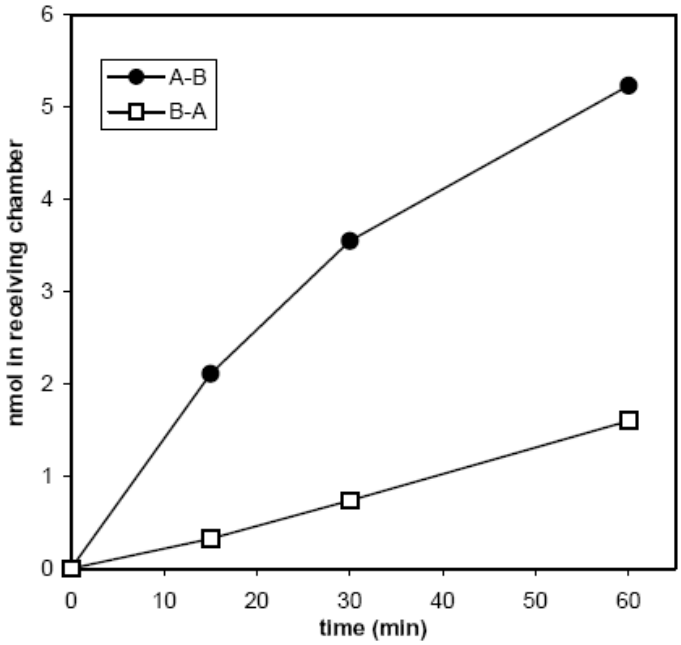
4.1 Permeability Coefficients (P_{app}) for Transepithelial Transport of XP13497 and XP13512 Across Caco-2 and MDCK Monolayers

Test Compound	Caco-2			MDCK		
	P_{app} (cm/sec) x 10^6		A-B/B-A ratio	P_{app} (cm/sec) x 10^6		A-B/B-A ratio
	A → B	B → A		A → B	B → A	
XP13497	60	12	5.0	48	12	4.0
XP13512	31	5.7	5.4	35	11	3.2
Gabapentin	3.2	3.4	0.94	0.73	0.25	2.9

- A 5- fold apical (A) to basolateral (B) preference for both XP13512 and XP13497 transcellular flux was observed in Caco-2 monolayers indicating an active uptake process.
- The A-B permeability was 3.1 to 6.0 x 10^{-5} cm/sec which implies the compound will be well absorbed in vivo, based on the sponsor.
- Similar results were observed in MDCK.
- The permeability of gabapentin is much lower than the prodrugs in both cells and no marked difference was observed between the transport in two directions for Caco-2 cells.

The time course of XP13497 transport across Caco-2 cells expressed in terms of total compound (sum of XP13497 and released gabapentin) is shown below:

5.1 Time Course of Transepithelial Transport of XP13497 Across Polarized Caco-2 Cell Monolayers



XP13497 was tested for its ability to cross Caco-2 monolayers as described in methods. 100 µM of compound was added to either the apical (●) or basolateral (□) chamber in duplicate and aliquots of the receiving chamber were sampled at various time points. Concentrations of both prodrug and gabapentin produced by esterase cleavage within the cells were determined. Data are mean values for each time point and are expressed as nmol of total drug (the sum of prodrug and gabapentin) measured in the receiving chamber vs. time.

- The transport in the basolateral to apical (B-A) direction is linear over 60 min.
- The apical-to-basolateral (A-B) transport appears to be a mixture of both linear and saturable transport.

Conclusion:

- These results suggest that the gabapentin prodrug has the potential to be better absorbed *in vivo* than gabapentin itself and that a portion of this absorption may be the result of active transport.

Reviewer's comments:

- What's the rationale of using a different salt form for testing? Isn't XP13512 more representative (although they show similar trend)?

II. Transport across Artificial Lipid Membranes

The parallel artificial membrane assay (PAMPA) was used to study the possible passive diffusion of XP13497 or XP13512, independent of active transport mechanisms.

Method:

Artificial membranes were formed by adding 4 µL of 2% (w/v) dioleoylphosphatidylcholine (DOPC) in dodecane onto the hydrophobic filters (0.45 µM polyvinylidene fluoride) on the base of the wells of a 96-well donor plate. 150 µL of each test compound (50 µM) in 0.1M Tris buffer (pH 6.5 or 7.4) were added to the donor wells in triplicate, and this plate was placed onto a 96-well acceptor plate in which each well contained 400 µL 0.1 M Tris, pH 7.4. Samples of the donor and receiver chambers were removed for analysis of peak area of the compound of interest by LC-MS-MS after two hours at room temperature. The permeability coefficient through the artificial membrane (Pam) was calculated (1) using the following equation:

$$P_{am}\ (cm/sec) = -2.303 \bullet \frac{V_{dn}V_{rec}}{V_{dn}+V_{rec}} \bullet \frac{1}{St} \bullet \log\left(1 - \frac{\text{peak area}_{receiver}}{\text{peak area}_{donor}}\right)$$

V_{dn} = volume of the donor compartment (0.15 cm^3)
V_{rec} = volume of the receiver compartment (0.40 cm^3)
S = membrane area (0.2 cm^2)
t = incubation time (7200 s)

Data are compared to control compounds with high, medium, and low passive permeability properties (diltiazem, metoprolol, and acyclovir, respectively).

Results:

The permeability of tested compounds is shown in the table below:

4.2 Permeability Coefficients (P_{am}) of Various Compounds in the Parallel Artificial Membrane Permeability Assay (PAMPA)

Test Compound	P_{am} (cm/sec) x 10^6	
	pH in donor chamber	
	6.5	7.4
XP13512	0.65	0.095
XP13497	0.66	0.038
Gabapentin	0.02	0.026
Diltiazem	7.0	31
Metoprolol	0.018	0.16
Acyclovir	0.02	0.02

- The permeability coefficient for the prodrug was greater at the lower pH, consistent with this compound having higher passive permeability properties in its uncharged state. The Pam value of 0.66 x 10^{-6} cm/sec at pH 6.5 is comparable to that of metoprolol (medium passive permeability properties) at pH7.4 (0.16x10^{-6}).

Conclusion:

- These results suggest that XP13497 and XP13512 have some ability to diffuse passively across cells depending on the local pH.

III. Active Transport by Intestinally-Expressed Transporters

Several transporters (MCT-1, SMVT, other transporters and P-gp) were tested since transepithelial transport data suggested these compounds interact with apically expressed intestinal transporters.

III.A MCT-1 Transport

Human embryonic kidney (HEK) cells were utilized since MCT-1 is expressed at high levels endogenously in these cells.

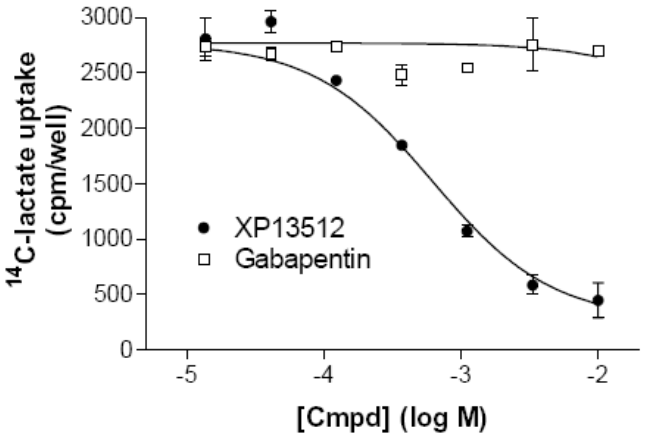
Method:

Radiolabel Competition Assays: Cells expressing a transporter of interest (100,000 cells/well) were plated into white 96- well clear bottom plates that had been precoated with poly-D-lysine. Cells were grown at 37ºC under standard cell culture conditions for one to two days before use. For tet-inducible cell lines, 1µg/ml of doxycycline was added to the wells one day before assaying. Radiolabeled substrate (50 to 100,000 cpm/well) was added to each well in the presence and absence of various concentrations of test compound in duplicate. Plates were incubated at room temperature for 2 to 60 min. Excess radiolabeled substrate was removed and cells were washed three times with a 96-well plate washer with cold assay buffer. Scintillation fluid was added to each well; the plates are sealed and counted in a 96-well plate-based scintillation counter. Data were graphed as radiolabeled substrate uptake (cpm) per well, and IC50 curves were analyzed using non-linear regression analysis with Prism.

Results:

The uptake of a MCT-1 substrate, ^{14}C-lactate, with the presence of XP13512 or gabapentin is shown below:

5.2 Effect of XP13512 and Gabapentin on ^{14}C-Lactate Uptake into MCT-1-Expressing HEK Cells

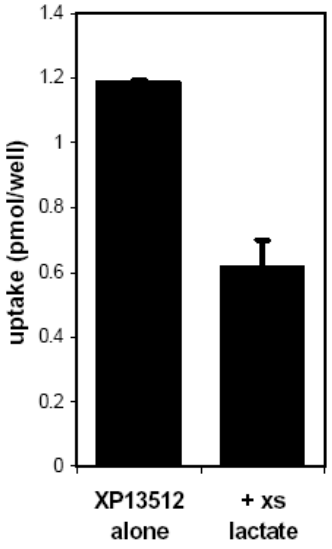


HEK cells endogenously expressing MCT-1 were incubated with radiolabeled ^{14}C-lactate in the presence of various concentrations of XP13512 or gabapentin in duplicate as described in methods. Resulting ^{14}C-lactate uptake at each concentration is expressed as cpm/well. Error bars represent S.E.M.

- XP13512 inhibited the uptake of lactate with IC50 of 620 µM.
- Gabapentin did not interact with MCT-1.

Based on this result, to test whether XP13512 was specifically transported by MCT-1, cells were treated with compound alone or with compound in the presence of an excess of lactate to block the MCT-mediated transport. Data is shown in the figure below:

5.3 Uptake of XP13512 into HEK Cells Expressing MCT-1

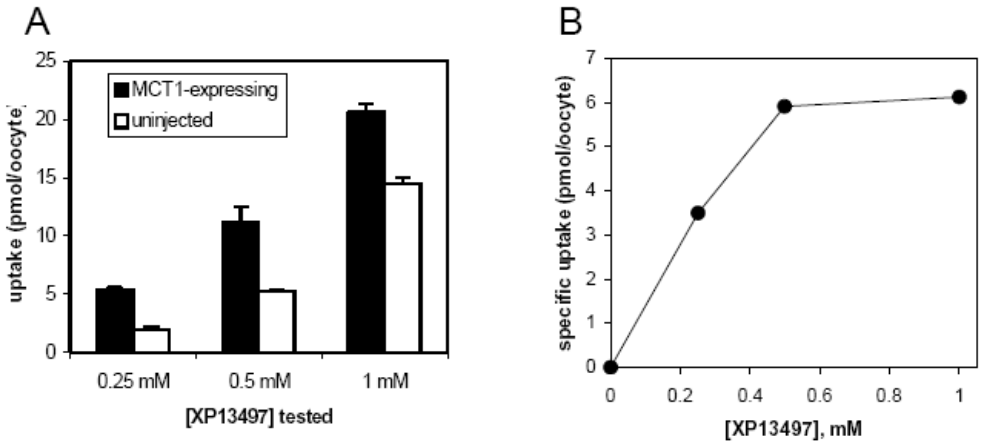


HEK cells endogenously expressing MCT-1 were incubated with 1 mM XP13512 in the presence and absence of 10 mM lactate as described in methods. Intracellular concentrations of the prodrug and of gabapentin derived from the prodrug were detemined by LC-MS-MS. Data (the mean of four determinations) are expressed as pmol of total drug [prodrug + gabapentin] per well. Error bars represent S.E.M.

- Approximately 50% of the uptake measured in these cells could be inhibited by lactate demonstrating that transport of this compound into cells is in part mediated by MCT-1.

To further verify the specificity of the prodrug to the transporter, a recombinant system was utilized. cRNA for MCT-1 were injected into *Xenopus laevis* oocytes. The uptake of XP13497 into MCT-1 expressing and uninjected oocytes was compared to dissect the passive and MCT-mediated components of transport for this compound. Uptake of XP13497 and gabapentin derived from this compound were measured in extracts from these cells.

5.4 Uptake of XP13497 into Oocytes Expressing MCT-1



Various concentrations of XP13497 were incubated with oocytes expressing MCT-1 or uninjected oocytes as described in methods. Intracellular concentrations of prodrug were determined by LC-MS-MS analysis.

A: Comparison of uptake of various concentrations of prodrug into expressing and non-expressing oocytes. Results are from four oocytes at each condition and are expressed as pmol of [prodrug + gabapentin] per oocyte +/- S.E.M.

B: Specific uptake of XP13497 into MCT-1-expressing oocytes. Intracellular prodrug concentrations obtained with uninjected oocytes were subtracted from the values obtained with MCT-1-expressing oocytes and graphed as specific uptake vs. test concentration.

- A significant uptake was observed and a portion of the uptake is MCT-1 associated.
- Uptake saturation was observed with a Km of approximately 220 μM and a Vmax of approximately 6 pmol/oocyte.

Conclusion:

- These results indicate that XP13497 or XP13512 can enter cells passively, and it is also a substrate for MCT-1 with an affinity in the mid-micromolar range.

Reviewer's comments:

- *Again, what's the rationale of testing XP13497(sodium salt of XP13512) instead of XP13512?*

III.B SMVT Transport

A cell line recombinantly expressing SMVT was used and XP13512 and gabapentin were tested for their ability to inhibit the uptake of ^{3}H-biotin, a natural substrate for SMVT, into these cells.

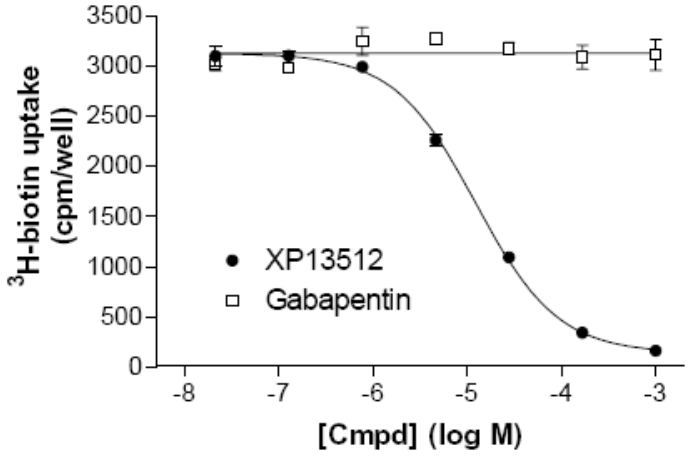
Method:

Radiolabel competition assays were utilized as previously described.

Results:

The uptake of a natural substrate for SMVT, ^{3}H-biotin, with the presence of XP13512 or gabapentin is shown below:

5.5 Effect of XP13512 and Gabapentin on ^{3}H-Biotin Uptake into SMVT-Expressing Cells



CHO cells recombinantly expressing SMVT were incubated with radiolabeled ^{3}H-biotin in the presence of various concentrations of XP13512 or gabapentin in duplicate as described in methods. Resulting ^{3}H-biotin uptake at each concentration is expressed as cpm/well +/- S.E.M.

- XP13512 inhibits biotin uptake with an IC50 of 12 μM.
- Gabapentin itself did not interact with SMVT.

The ability of XP13512 to induce currents in *Xenopus laevis* oocytes expressing SMVT was also studied since SMVT is known to be an electronic sodium dependent transporter.

Method:

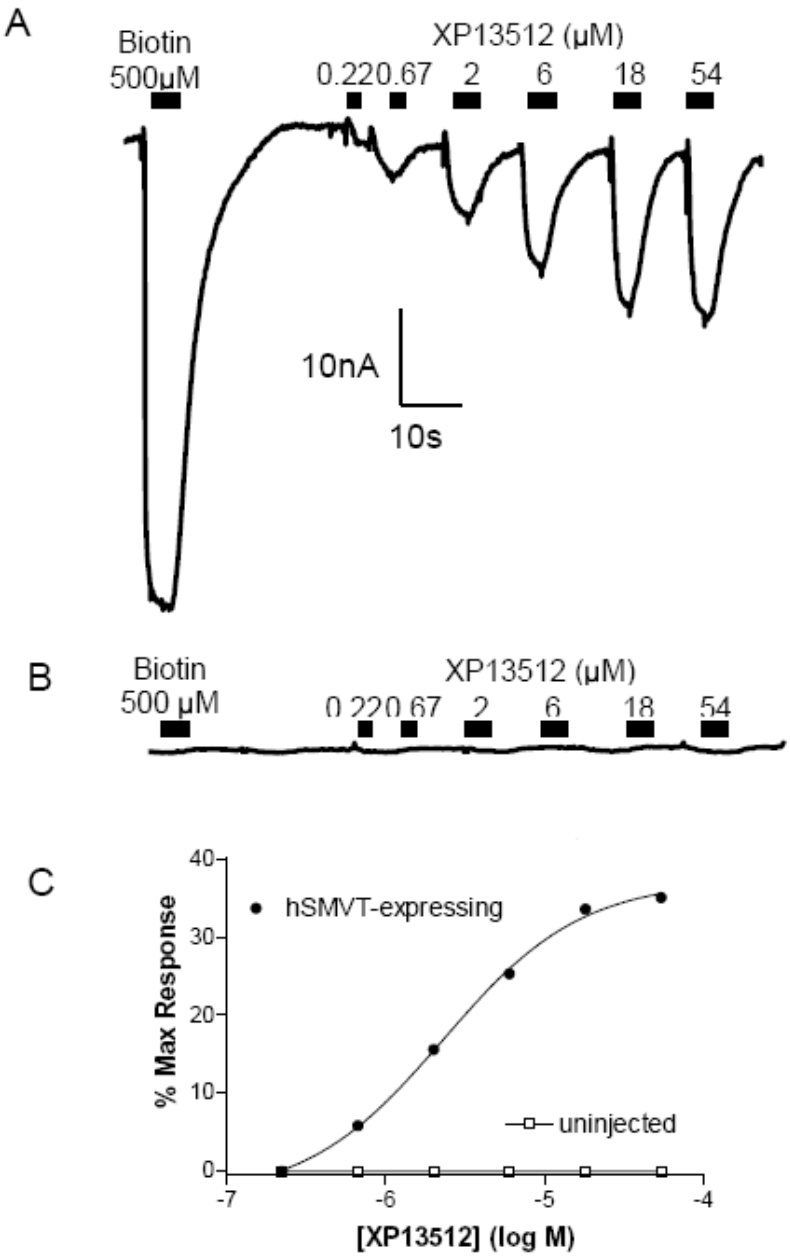
Oocyte Electrophysiology Assays: Oocytes were harvested from *Xenopus laevis* frogs using standard protocols. Once the follicles had been manually removed, the oocytes were injected

with cRNA for SMVT. Two to four days post-injection, the oocytes were used in standard two-electrode voltage clamp electrophysiology experiments. Radiolabel uptake studies with ^{3}H-biotin confirmed the expression of the transporter on the surface of the oocytes. Test compounds were applied to the oocyte in the bath solution for ~ 2-5 seconds and the induced currents were monitored. Controls included testing compounds in buffers without sodium and on oocytes not expressing the transporter of interest. Maximal current values observed after compound addition were expressed as a percent of the maximal response seen with 0.5 mM biotin to normalize for the variations of transporter expression that can be seen on different days or with different batches of oocytes. Dose response curves were analyzed by non-linear regression using Prism.

Results:

The currents induced in oocytes expressing SMVT by XP13512 are shown in the figure below:

5.6 XP13512-induced Currents in SMVT-Expressing Oocytes



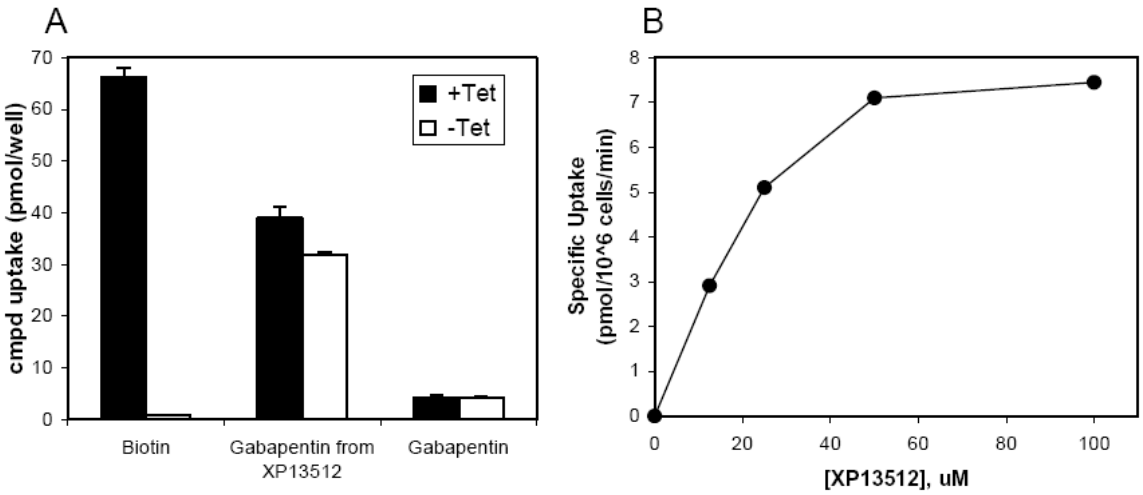
XP13512 was tested for its ability to induce currents in oocytes expressing SMVT as described in methods. Various concentrations of XP13512 were incubated for the indicated time with oocytes expressing (**A**) or not expressing (**B**) SMVT. 500 µM biotin was used as a positive control. Maximal induced currents at each concentration were normalized to the maximal biotin response and these values were graphed vs. the concentrations tested (**C**).

- The currents are dose-dependent and the maximum response for the prodrug is close to 40% of that seen with biotin.

- These responses are specific to SMVT-mediated transport since no currents were induced in uninjected oocytes.
- The results of relative maximum currents suggest that XP13512 is a substrate for SMVT with a Km of ~ 3 µM and a Vmax of ~ 40% of that produced by biotin.

To verify the specificity of prodrug to the transporter, a recombinant system was utilized. XP13512 uptake into HEK cells conditionally expressing SMVT upon treatment with tetracycline was evaluated. Cells with and without tetracycline induction were treated with 50 µM biotin, XP13512 or gabapentin. After uptake was complete, biotin, XP13512 and gabapentin, or gabapentin, respectively, were measured in extracts of these cells

5.7 Uptake of XP13512 into Tetracycline-induced SMVT-Expressing HEK Cells



HEK cells expressing SMVT were tested for their ability to transport XP13512 and gabapentin.

A: Uptake of control (biotin), XP13512 or gabapentin. 50 µM of biotin, XP13512, and gabapentin were incubated in quadruplicate with tet-inducible SMVT cells that been treated with tetracycline (+Tet) or were untreated (-Tet) in the presence of 10 mM phenylalanine. Cells were extracted as described in methods, and the intracellular concentration of biotin, prodrug and gabapentin were determined. Compound concentrations are expressed as pmol per well +/- S.E.M.

B: Specific uptake of XP13512 into SMVT-expressing cells. Various concentrations of XP13512 were incubated (in quadruplicate) with both induced and non-induced SMVT conditionally expressing cells. Intracellular concentrations of gabapentin derived from the prodrug were determined by subtracting the values obtained from the uninduced cells from those of the induced cells. Results are graphed as pmol/10^6 cells/min vs. concentration tested.

- SMVT expression was required for biotin uptake, and no specific uptake of gabapentin was seen. No XP13512 was measured in these cells; however, gabapentin derived from XP13512, presumably via intracellular esterases, was detected. The level of uptake was high, and a portion of that uptake appears to be mediated by SMVT.
- When various concentrations (0-100 µM) of XP13512 were incubated with either SMVT expressing or non-expressing cells, the specific uptake of XP13512 could be determined. The uptake was saturable with a Km of ~ 20 µM, comparable to what was

seen for the affinity of this compound for SMVT in competition and electrophysiological assays.

Conclusion:

- These results indicate that while XP13512 can enter cells passively, and it is also a substrate for SMVT with an affinity in the mid-micromolar range.

Reviewer's comments:

- *No in vivo study was conducted to evaluate possible interaction of SMVT inhibitors.(Note: while there are couple of known SMVT substrates and inhibitors, they are not well established at this time)*

III.C Other Transporters

Other transporter systems that were tested for their ability to interact with XP13497 or XP13512 were the proposed gabapentin transporters, LAT-1, OCT2, OCTN1, and OCTN2.

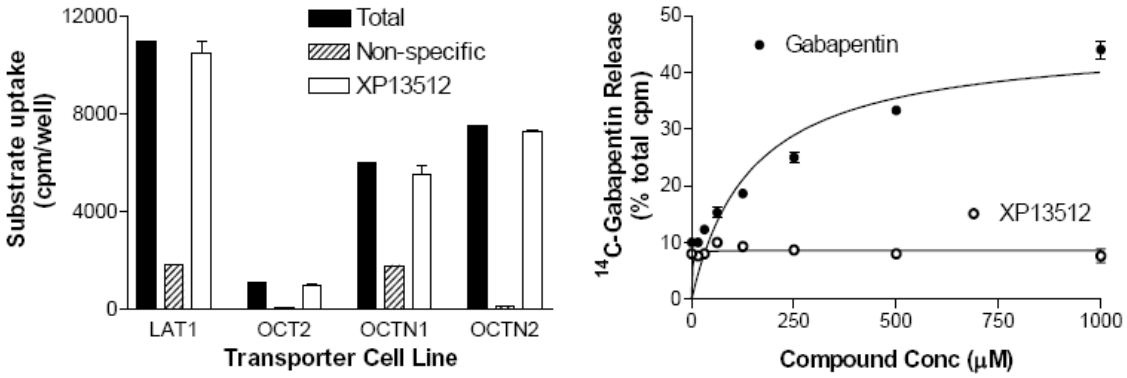
Method:

Uptake into Mammalian Cells or Oocytes: To directly measure the transport of test compounds by specific transporters, both mammalian and oocyte recombinant expression systems were used. 10 mM phenylalanine was included in all samples to inhibit the uptake of gabapentin through the endogenous large neutral amino acid transporter (LAT-1) expressed in HEK cells. Excess compound was removed by washing with cold assay buffer, and cells were lysed and prepared for LC-MS-MS analysis.

LAT-1 Exchange Assay: LAT-1 is an obligate exchanger; therefore, substrate activity can be measured by preloading LAT-1-expressing cells with radiolabeled substrate, and testing compounds for their ability to stimulate the efflux of the radiolabeled compound. For this assay, 100,000 KB cells per well were plated into 96-well plates. One or two days after seeding, the growth media was removed, the cells were washed twice with HBSS, and incubated with 100,000 cpm of 14C-gabapentin for 30 min. After washing the cells four times to remove the unincorporated radiolabeled substrate, various concentrations of either unlabeled gabapentin or XP13512 were added to the cells and incubated for 90 sec at room temperature. An aliquot of the incubation solution was removed from each well and place into a new 96-well plate. Scintillation fluid was added to both the cell plate and the supernatant plate and the radioactivity in each well was determined using a scintillation counter. Data are graphed as the fraction of radioactivity effluxed per well vs. test compound tested and both EC50 and Vmax are obtained using non-linear regression analysis with Prism Software.

Results:

5.8 Interaction of XP13512 with Gabapentin Transporters



A: Competition of XP13512 for Uptake with Radiolabeled Substrates on Various Transporters. Cells expressing various transporters were incubated with radiolabeled substrate alone (black bars; total), radiolabeled substrate with an excess of unlabeled substrate (striped bars; non-specific), or 0.5 mM XP13512 (white bars). Incorporated counts were determined by scintillation counting of the washed cells. Substrates: LAT1: ^{14}C-Gabapentin; OCT2 & OCTN1: ^{14}C -TEA; OCTN2: ^{3}H-Carnitine

B: Compound-stimulated Substrate Efflux from LAT-1 Expressing Cells. KB cells endogenously expressing hLAT-1 were preloaded with ^{14}C-gabapentin. Efflux of the radiolabel was measured after treating the cells with various concentrations of unlabeled gabapentin or XP13512. Data are expressed as a percent of the total radioactivity efflux vs. compound concentration tested.

- XP13512 did not interact with LAT-1 or the organic cation transporters (IC50 > 1 mM). 500μM of XP13512 did not significantly inhibit the uptake of radiolabeled substrates for these transporters, while an excess of unlabeled substrate decreased the uptake by 70 – 98%.
- XP13512 did not stimulate the release of radiolabeled gabapentin from pre-loaded LAT-1 expressing cells. The dose-response of compound-stimulated efflux of radiolabeled ^{14}C-gabapentin from KB cells endogenously expressing hLAT-1 was observed. Gabapentin stimulates this efflux with an EC50 of 33μM, while no effect was seen with concentrations of XP13512 up to 1 mM.

Conclusion:

- These results suggest that XP13512 does not interact with the gabapentin transporters.

III.D P-glycoprotein transporter

Several *in vitro* assays were used to test the effect of XP13497 and/or XP13512 on Pglycoprotein (P-gp), an important transporter for mediating compound efflux out of cells. P-gp is an ATP-dependent transporter, and hydrolysis of ATP is linked to substrate transport. Therefore, the ability of XP13497 to stimulate ATPase activity in insect cell membranes overexpressing aculovirally-produced human P-gp was tested.

Method:

P-glycoprotein assays: A series of P-gp *in vitro* assays were used. Compound stimulated ATPase activity was measured using commercially available insect cell membranes expressing human P-gp in an NADH-linked coupled assay system. Calcein inhibition assays were carried out using MES-SA-DX5 cells overexpressing human P-gp and Calcein-AM as described. Bidirectional transport assays were measured in an MDCK cell line expressing recombinant human P-gp under the control of a promoter inducible by either tetracycline or doxycycline. Cells were seeded into 24-well transwell plates with microporous membrane filters obtained from Millipore at a density of 50,000 cells/well (0.71×10^6 cells/cm^2) in the presence or absence of 1μg/ml doxycycline to induce the expression of recombinant human P-gp, and allowed to grow to confluence and differentiate for three days. The integrity of the monolayers were determined using ^{3}H-inulin as described above.

Prior to initiating the experiments, the media was removed from donor and receiver chambers and replaced with HBSS buffer at pH 7.4 at 37^{o}C. The studies were initiated by adding appropriate concentrations of test compound (XP13512 or known control substrates) to either the apical or basolateral chamber. The transwell plate was incubated at 37^{o}C. At various times (typically 30min, 1hr, 2hr), aliquots were removed from the receiving chamber, diluted 4-fold with ethanol, and quantitatively analyzed using LC/MS/MS. At least duplicate wells were used in each experiment, and each experiment was repeated at least twice on different days. Papp values were calculated as described previously, except that the volume of the receiving chamber was 0.400 cm^3 (apical) or 0.800 cm^3 (basolateral) for these experiments, and the surface area of the transwell monolayer was 0.70cm^3.

P-gp activity was assessed by comparing the Papp values in both directions. Compounds that are substrates of the apically expressed P-gp decrease permeability from the apical to basolateral direction (A-B), and increase permeability in the basolateral to apical direction (B-A). The net flux ratio (R) was calculated as the ratio of Papp in the B-A direction divided by Papp in the A-B direction:

$$R = Papp\ (B\text{-}A) / Papp\ (A\text{-}B)$$

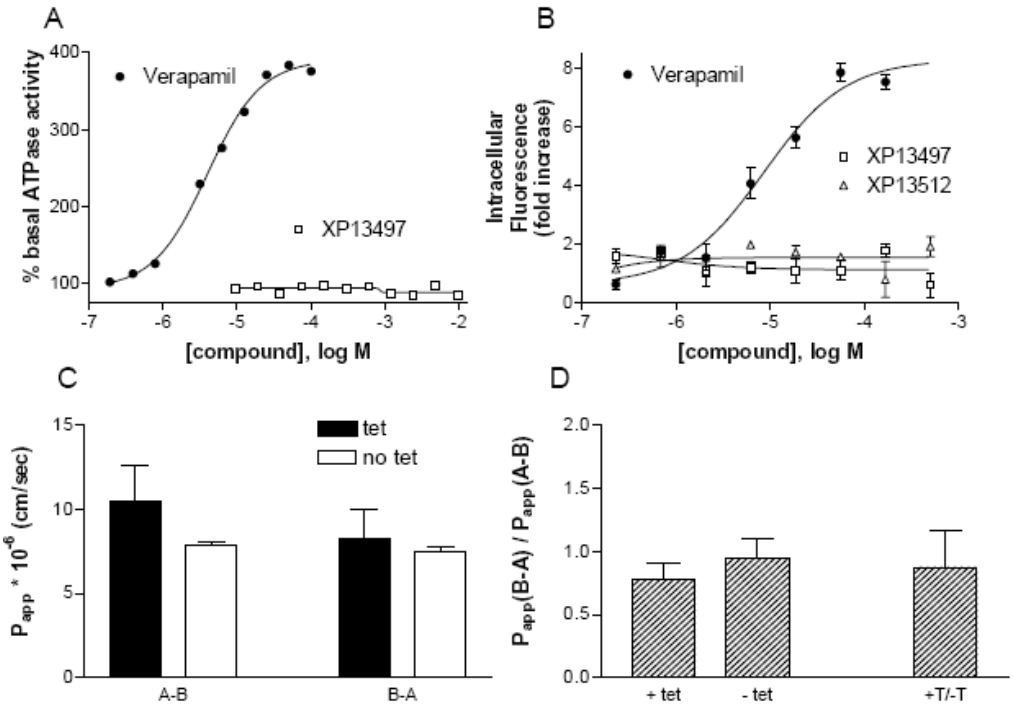
Control cells that were not induced by tetracycline or doxycycline may have expressed basal levels of P-gp as well as other efflux pumps or transporters that could potentially have interfered with the analysis of results. To correct for this activity, the net flux ratio of induced cells that overexpress P-gp was divided by the net flux ratio of uninduced cells to obtain RE, the efflux ratio resulting exclusively from induced P-gp activity:

RE = R+Tet / Rno tet

Compounds that demonstrate an RE > 2 are defined as P-gp substates.

Results:

5.9 Interaction of XP13512 and XP13497 with P-glycoprotein



A: Activation of P-gp ATPase activity. Various concentrations XP13497 or verapamil in duplicate were tested for their ability to stimulate ATPase activity in membranes derived from High-five insect cells that have been infected with baculovirus expressing P-glycoprotein as described in methods. Results are expressed as the mean of the percent of basal ATPase activity vs. concentration tested.

B: Competition for Calcein efflux. Various concentrations of XP13512, XP13497 or verapamil were tested in duplicate for their ability to inhibit calcein efflux in MES cells overexpressing human P-gp as described in methods. Results are graphed as the mean increase in intracellular fluorescence vs. concentration tested. Error bars represent S.E.M.

C: Apparent Permeability Values for XP13512 Transport across MDCK cells Inducibly Expressing P-gp. XP13512 (50μM) was added to either the apical or basolateral chamber of cells that had been induced (black bars, tet) or not induced (white bars, no tet) to express P-gp. XP13512 and gabapentin were measured in the receiving chambers and the P_{app} values were calculated.

D: Net Flux and Efflux Ratios for XP13512 across these Cells. The net flux ratios for P-gp expressing (+tet) and non-expressing (-tet) cells and the efflux ratio (+T/-T) were calculated as described in the text. Since the efflux ratio is less than two, XP13512 is not a substrate for P-gp

- No increase in ATPase activity with XP13497 was seen over the concentration range tested (10 μM – 10 mM) while verapamil, a good P-gp substrate, demonstrated a nearly 4-fold increase in basal ATPase activity at 100 μM and a Km of 4 μM.
- Verapamil is an effective competitor with calcein for P-gp transport with a Km of 8.6 μM while neither XP13512 nor XP13497 inhibited P-gp activity at the concentrations tested (up to 0.5 mM). These results suggest that XP13512 is not an inhibitor of P-gp based on the sponsor.
- The Papp values for both directions of transport and in cells both expressing (+ tet) or not expressing (no tet) P-gp are within the same range at ~7.5 to 10 x 10^{-6} cm/sec.
- The net flux ratio in both expressing (+ tet) and non-expressing (- tet) cells and the efflux ratio (+T/-T) range from 0.77 to 0.94.

Conclusion:

- These results suggest that XP13512 is not an inhibitor or substrate of P-glycoprotein .

Reviewer's comments:

- *The data shown in the calcien effluxx study only suggested that XP13512 didn't interact with P-gp.*
- *Bi-directional assay utilizing tet on/off system is not the recommended method in the draft guidance, although with adequate control, this approach could be considered a definite method. While the detailed data showing transporters were turned on after adding tetracycline or doxycycline was not provided, the provided information is sufficient to conclude regarding Pgp.*

IV. Active Transport by Kidney Transporters

OCT2 is a kidney-specific xenobiotic transporter that can influence renal drug excretion and is a known pharmacological site for drug-drug interactions. To determine whether gabapentin is a substrate for OCT2, in vitro transport studies were performed using cloned human OCT2.

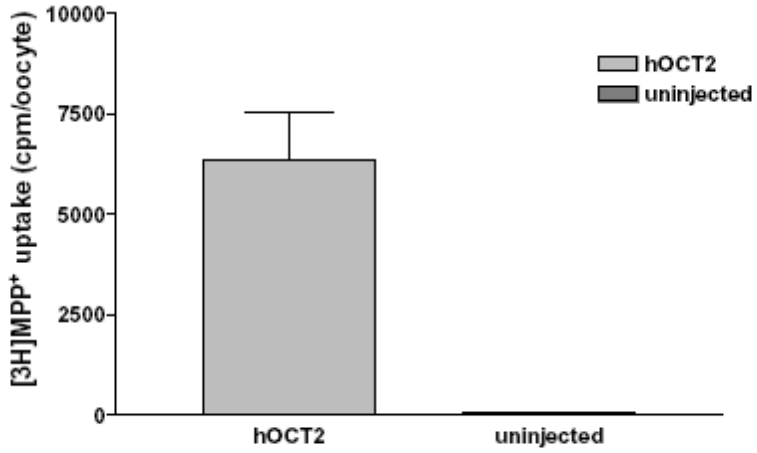
Method:

Oocyte uptake experiments described previously were conducted by injecting oocytes with cRNA encoding OCT2.

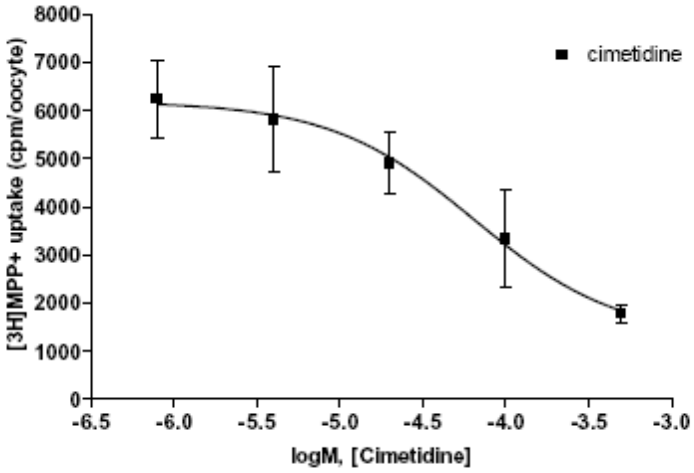
Results:

5.10 OCT2 Expression and Transport Activity in Oocytes

A



B



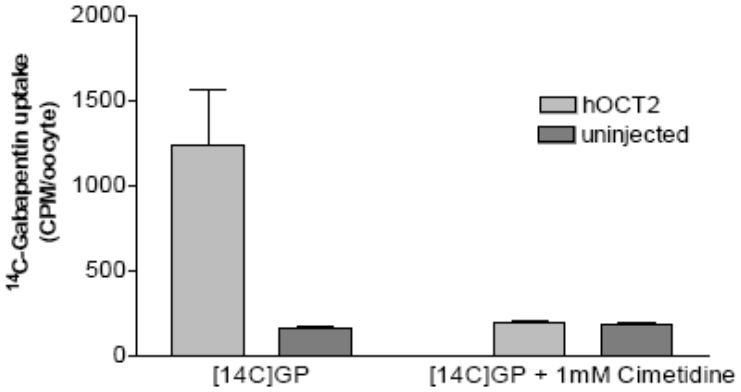
A: *Xenopus* oocytes expressing human OCT2 transport ^{3}H MPP^{+}. Oocytes injected with human OCT2 cRNA and control uninjected oocytes were evaluated for accumulation of a known OCT2 substrate (^{3}H MPP^{+}). Results are expressed as the average scintillation reading (CPM) per oocyte. Error bars represent S.E.M.

B: Cloned human OCT2 transport activity is inhibited by cimetidine. Uptake of ^{3}H MPP^{+} into oocytes expressing OCT2 was tested in the presence of increasing concentrations of cimetidine. Resulting MPP^{+} uptake at each concentration is expressed as cpm/well. Error bars represent S.E.M.

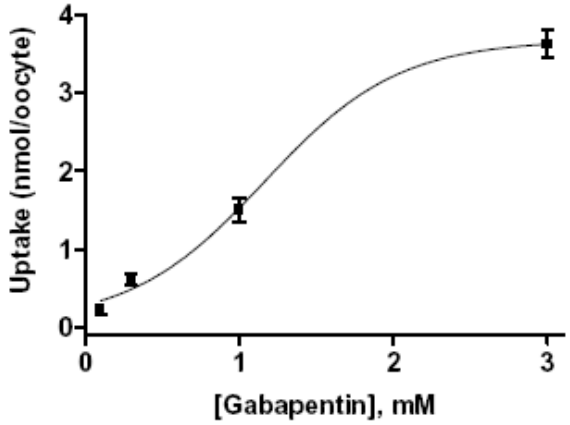
- Oocytes injected with human OCT2 cRNA exhibited strong accumulation of a known OCT2 substrate (^{3}H MPP+) compared with control uninjected oocytes.
- Cimetidine, an OCT2 inhibitor, exhibited a dose-dependent inhibition of ^{3}H MPP+ transport.

5.11 Gabapentin Transport by OCT2

A



B



A: *Xenopus* oocytes expressing human OCT2 transport ^{14}C gabapentin. Oocytes injected with human OCT2 cRNA and control uninjected oocytes were evaluated for accumulation of gabapentin in the presence and absence of 1 mM cimetidine, an OCT2 inhibitor. Results are expressed as the average scintillation reading (CPM) per oocyte. Error bars represent S.E.M.

B: Effect of gabapentin concentrations on uptake by OCT2. Uptake of unlabeled gapapentin into oocytes expressing OCT2. Resulting gabapentin uptake at each concentration is expressed as nmoles uptake per oocyte. Error bars represent S.E.M.

- Oocytes expressing OCT2 exhibited an 8-fold increase in ^{14}C gabapentin uptake compared with uninjected control oocytes, and this OCT2 specific uptake was fully inhibited by cimetidine.
- OCT2 transport of gabapentin was saturable, and the gabapentin transport affinity was determined to be 1.1 mM.

Conclusions:

- Gabapentin is a low-affinity transported substrate for the human OCT2 transporter and that cimetidine inhibits transport of gabapentin by OCT2.
- The low affinity observed for OCT transport of gabapentin (1.1 mM) suggests that it is unlikely that therapeutic plasma levels of gabapentin would alter renal excretion of other drugs also transported by OCT2. However, the possibility remains that renal gabapentin excretion could be altered by OCT2 inhibitors such as cimetidine.

Study PK-2003-002:

In Vitro Metabolism of the Gabapentin Prodrug XP13512 and its Sodium and Calcium Salts (XP13497 and XP16654).

Several experiments were conducted and summarized in this report to assess the chemical and metabolic stability of gabapentin prodrug, XP13512 and its sodium and calcium salt forms and XP13512 isomers, the inhibition potential and potential to be a substrate of major CYP450s and the protein binding of XP13512 in human serum albumin.

Below is the information of tested compounds:

Table 2.1. Compound Batch Numbers and Purity Based on LC/MS/MS Analysis

Compound	Batch	Prodrug (% w/w)	Lactam (% w/w)	Gabapentin (% w/w)
XP13512 (b) (4)	GMP Lot 2892.A.03.1	(b) (4)	(b) (4)	ND
XP13497 Sodium Salt	I003GV		No Data	No Data
XP16654 Calcium Salt	I003GU		No Data	No Data
XP17814 S-Isomer	I004G1		No Data	No Data
XP17815 R-Isomer	I004G2		No Data	No Data

ND – Not detected.

I. Chemical stability and metabolic stability of XP13512 and the sodium salt form, XP13497, and calcium salt form, XP16654

Method:

Chemical stability:

For the chemical stability studies, buffers were prepared at pH 2.0 (using 0.1M potassium phosphate and 0.5 M NaCl), pH 7.4, and pH 8.0 (using 0.1 M Tris-HCl and 0.5 M NaCl). Compounds (5 µM) were incubated with buffers at 37ºC for 1 hour in a temperature-controlled HPLC autosampler. Samples were injected at zero and 1 hour post-addition. Samples were analyzed by LC/MS/MS as described below.

Metabolic stability:

A. Plasma:

Compounds (5 μM) were incubated with 90% rat or human plasma at 37ºC for 1 hour. Samples were obtained at zero and 1 hour post-addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at -80ºC prior to analysis. Samples were analyzed by LC/MS/MS as described below.

B. Liver homogenate:

Compounds (5 μM) were incubated with rat and human liver S9 at 0.5 mg protein/mL in the presence of 1 mM NADPH at pH 7.4 and 37ºC for 1 hour. Samples were obtained at zero and 1 hour post-addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at -80ºC prior to analysis. Samples were analyzed by LC/MS/MS as described below.

C. Caco-2 cell homogenate

Caco-2 cells were grown in flasks over 21 days. Cells were then rinsed/scraped off into ice-cold 10 mM sodium phosphate/0.15 M potassium chloride, pH 7.4. Cells were lysed by sonication at 4ºC using a probe sonicator and centrifuged at 9,000 x g for 20 minutes at 4ºC and the resulting supernatent (Caco-2 cell homogenate S9 fraction) aliquots were transferred into 0.5 mL vials and stored at -80ºC prior to use. For stability studies, compounds (5 μM) were incubated with Caco-2 S9 (0.5 mg protein/mL) at pH 7.4 and 37ºC for 1 hour. Samples were obtained at zero and 1 hour post-addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at -80ºC prior to analysis. Samples were analyzed by LC/MS/MS as described below.

D. Pancreatin

Compounds (5 μM) were incubated with porcine pancreatin (10 mg/mL in pH 7.5 buffer) at 37ºC for 1 hour. Samples were obtained at zero and 1 hour post-addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at -80ºC prior to analysis. Samples were analyzed by LC/MS/MS as described below.

Results:

The chemical and metabolic stability data for XP13512 is shown in the table below:

Table 4.1. Stability of XP13512 in Tissues In Vitro

Tissue Preparation[1]	XP13512 Remaining (%)	Conversion to Gabapentin (%)	Conversion to Gabapentin Lactam (%)
Buffer, pH 2.0	98	ND[5]	ND
Buffer, pH 7.4	99	ND	ND
Buffer, pH 8.0	95	ND	ND
Pancreatin[2]	52	43	ND
Caco-2 S9[3]	18	75	ND
Rat Plasma, 90%	47	45	ND
Human Plasma, 90%	96	5	ND
Rat Liver S9[4]	25	71	ND
Human Liver S9[4]	4	81	ND

[1]All incubations were for 1 hour at 37°C. XP13512 concentration was 5 µM.
[2]Porcine pancreatin was 10 mg/mL in pH 7.5 buffer.
[3]Caco2 S9 (prepared by XenoPort) was 0.5 mg protein/mL at 7.4 pH.
[4]Liver S9 (b) (4) contained 0.5 mg/mL protein and 1 mM NADPH at pH 7.4.
[5]ND – Not detected (< 1%).

The chemical and metabolic stability data for XP13497 is shown in the table below:

Table 4.2. Stability of XP13497 in Tissues In Vitro

Tissue Preparation[1]	XP13512 Remaining (%)	Conversion to Gabapentin (%)	Conversion to Gabapentin Lactam (%)
Buffer, pH 2.0	101	ND[5]	ND
Buffer, pH 7.4	99	ND	ND
Buffer, pH 8.0	93	ND	ND
Pancreatin[2]	47	36	ND
Caco-2 S9[3]	9	87	ND
Rat Plasma, 90%	38	55	ND
Human Plasma, 90%	92	6	ND
Rat Liver S9[4]	19	76	ND
Human Liver S9[4]	3	88	ND

[1]All incubations were for 1 hour at 37°C. XP13512 concentration was 5 µM.
[2]Porcine pancreatin was 10 mg/mL in pH 7.5 buffer.
[3]Caco2 S9 (prepared by XenoPort) was 0.5 mg protein/mL at 7.4 pH.
[4]Liver S9 (b) (4) contained 0.5 mg/mL protein and 1 mM NADPH at pH 7.4.
[5]ND – Not detected (< 1%).

The chemical and metabolic stability data for XP16654 is shown in the table below:

Table 4.3. Stability of XP16654 in Tissues In Vitro

Tissue Preparation[1]	XP13512 Remaining (%)	Conversion to Gabapentin (%)	Conversion to Gabapentin Lactam (%)
Buffer, pH 2.0	100	ND[5]	ND
Buffer, pH 7.4	100	ND	ND
Buffer, pH 8.0	100	ND	ND
Pancreatin[2]	51	39	ND
Caco-2 S9[3]	12	85	ND
Rat Plasma, 90%	45	53	ND
Human Plasma, 90%	95	6	ND
Rat Liver S9[4]	22	74	ND
Human Liver S9[4]	2	86	ND

[1]All incubations were for 1 hour at 37°C. XP13512 concentration was 5 µM.
[2]Porcine pancreatin was 10 mg/mL in pH 7.5 buffer.
[3]Caco2 S9 (prepared by XenoPort) was 0.5 mg protein/mL at 7.4 pH.
[4]Liver S9 ((b) (4) contained 0.5 mg/mL protein and 1 mM NADPH at pH 7.4.
[5]ND – Not detected (< 1%).

The metabolic stability data for XP13512 isomers is shown in the table below:

Table 4.5. Stability of XP13512 Isomers in Tissues In Vitro

Tissue Preparation[1]	XP13512 Remaining (%)		Conversion to Gabapentin (%)		Conversion to Gabapentin Lactam (%)	
	XP17814 S-Isomer	XP17815 R-Isomer	XP17814 S-Isomer	XP17815 R-Isomer	XP17814 S-Isomer	XP17815 R-Isomer
Pancreatin[2]	70	28	27	70	ND[5]	ND
Caco-2 S9[3]	6	25	90	86	ND	ND
Rat Plasma, 90%	24	70	78	27	ND	ND
Human Plasma, 90%	93	89	9	3	ND	ND
Rat Liver S9[4]	3	48	97	59	ND	ND
Human Liver S9[4]	5	4	91	96	ND	ND

[1]All incubations were for 1 hour at 37°C. XP13512 concentration was 5 µM.
[2]Porcine pancreatin was 10 mg/mL in pH 7.5 buffer.
[3]Caco2 S9 (prepared by XenoPort) was 0.5 mg protein/mL at 7.4 pH.
[4]Liver S9 (b) (4) contained 0.5 mg/mL protein and 1 mM NADPH at pH 7.4.
[5]ND – Not detected (< 1%).

- The percentage converted to gabapentin and gabapentin lactam from XP13512, XP13497 and XP16654 at pH 2, 7.4 and 8 were under detectable.
- The remaining XP13512 are almost 100% indicating XP13512, XP13497 and XP16654 are chemically stable for 1 hour at 37°C over the pH 2 to 8.

- Similar levels of conversion to gabapentin (36-43%) were observed in all three salt forms after incubation in pancreatin and no formaton of lactam was observed.
- Rapid release of gabapentin (75-87%) was observed in all three salt forms after incubation with Caco-2 cell homogenate and no formaton of lactam was observed.
- Stability was greater in human plasma with 5-6 % release of gabapentin than in rat plasma with 45-55% release of gabapentin. No formaton of lactam was observed in either human or rat plasma.
- Similar amounts of gabapentin were released from all three salt forms after incubation with liver homogenate, regardless of species (71-76% in rat tissue and 81-88% in human tissue). No lactam was observed in liver incubations.
- For the XP13512 isomers, the hydrolysis was slow in human plasma, moderate in pancreatin and Caco-2 homogenate and rapid inhuman and rat liver and in ray plasma.

Conclusion:

- Based on the sponsor, all three salt forms are chemically stable to allow for absorption in vivo. However, the evaluation was checked for only 1 hour while the BCS guidance indicates 1 hour in gastric fluid and 3 hours in intestinal fluid. The conclusion that "the compound is stable to allow for absorption in vivo" therefore should not be made due to inadequate method for evaluation.
- The prodrug should rapidly undergo conversion to gabapentin without significant release of lactam following absorption.

Reviewer's comments:

- *Does pancreatin exist in intestinal lumen since it is a digestive enzyme? If so, the stability before absorption might be an issue (36-43% conversion).*

II Metabolism of XP13497 in various species

Method:

XP13497 (10 μM) was incubated with plasma, intestinal S9, lung S9, liver S9, and kidney S9 from rats, dogs, monkeys, and humans at 37ºC for 1 hour. All preparations contained 1 mg protein/mL. Samples were obtained at zero and intervals over 1 hour post-addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at -80ºC prior to analysis. Samples were analyzed by LC/MS/MS as described below. The rate of conversion of XP13512 to gabapentin in each matrix was calculated in pmol/min/mg protein.

Results:

The metabolic stability of XP13497 in tissues of different species was shown below:

Table 4.4. Metabolic Stability of XP13497 in Tissues from Different Species

Tissue Preparation[1]	Rate of Conversion to Gabapentin (pmol/min/mg protein)			
	Sprague-Dawley Rat	Beagle Dog	Cynomolgus Monkey	Human
Plasma	24.1	ND[3]	8.8	5.2
Intestine	189	99.2	184	196
Lung	88.6	86.9	107	68.5
Liver[2]	125	136	140	146
Kidney	180	141	173	168

[1]All incubations were for 1 hour at 37°C. XP13497 concentration was 10 µM. All preparations contained 1 mg protein/mL.
[2]Liver S9 was supplemented with 1 mM NADPH.
[3]ND – Not determined.

- In general, similar rate of hydrolysis of XP13497 to gabapentin was observed in tissues from rats, monkeys and humans while the hydrolysis rate in dogs was slower.

Conclusion:

- Rates of hydrolysis from XP13497 to gabapentin were similar in rats, monkeys and humans.

Reviewer's comments:

- *What's the rationale of testing XP13497 instead of XP13512? Data for XP13512 should be more representative.*

III Inhibition of specific CYP450 enzymes by XP13512

Method:

The ability of XP13512 to inhibit cytochrome P450-mediated metabolism was examined by standard methods using specific CYP450 isoforms expressed in bacculosomes (Supersomes™). The experimental conditions for each isoform studied are summarized in Table 2.4. Standard substrates were employed that generate fluorescent metabolites. Experiments were conducted in a 96 well format as described in the manufacturers literature (2). All incubations included an NADPH cofactor mix. The final concentration of CYP450 protein in each incubation was 2.5 to 5.0 pM. XP13512 and positive control compounds were serially diluted in the solution of NADPH generation system to give final concentrations of up to 400 µM. The resulting solutions were incubated with a specific CYP450 isoform and the related substrate at 37 °C for 15 to 45 minutes. A stop solution (80% acetonitrile / 20 % 0.5 M Tris base) was added to terminate the reaction. The samples were analyzed using a FlexStation fluorescence plate reader (Molecular Devices Corp., Sunnyvale, CA). The excitation and emission wavelengths for the analysis are shown in Table 2.4.

The percent inhibition of the formation of product was determined for each XP13512 concentration and for control inhibitors. Blank values were subtracted from the sample wells to obtain the net fluorescence signal. The concentrations of XP13512 that bracketed 50% inhibition (C_{High} and C_{Low}) were determined. The IC_{50} values for inhibition of each specific isoform were then determined from the bracketing concentrations and corresponding percent inhibition values via linear interpolation as follows:

$$IC_{50} = \frac{(50\% - \%I_{Low})}{(\%I_{High} - \%I_{Low})} \times (C_{High} - C_{Low}) + C_{Low}.$$

where C_{Low} and C_{High} are the concentrations bracketing 50% inhibition and $\%I_{High}$ and $\%I_{Low}$ are the corresponding percent inhibition values at the low and high concentrations, respectively. This is the calculation method recommended by the supplier of the Supersomes™ (2).

Table 2.4. Experimental Conditions for CYP450 Inhibition Studies

CYP Isoform	Substrate	Substrate Conc. (µM)	Control Inhibitor	Highest XP13512 Conc. (µM)	Incubation Time (min)	Excitation Wavelength (nm)	Emission Wavelength (nm)	CYP Conc. (pM)
CYP3A4	7-Benzyloxy-trifluoromethycoumarin	50	Ketoconazole	400	30	409	530	2.5
CYP1A2	3-Cyano-7-Ethoxycoumarin	5	Furafyline	400	15	409	460	2.5
CYP2C9	7-Methoxy-trifluoromethylcoumarin	75	Sulfaphenazole	400	45	409	530	2.5
CYP2C19	3-Cyano-7-Ethoxycoumarin	25	Tranylcypromine	400	30	409	460	2.5
CYP2D6	3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methyoxy-4-methylcoumarin)	1.5	Quinidine	400	30	390	460	5.0
CYP2E1	7-Methyoxy-4-trifluoromethyl coumarin	70	Diethyldithiocarbamic Acid	333	40	409	530	3.75

Results:

Table 4.6. Results of CYP450 Inhibition Studies

CYP450 Isoform	Control Substrate	Control Inhibitor	IC50 for Control Inhibitor (μM)		IC50 for XP13512 (μM)
			Measured	Reported	
CYP3A4	7-Benzyloxy-trifluoromethycoumarin	Ketoconazole	0.013	0.05	No inhibition
CYP1A2	3-Cyano-7-Ethoxycoumarin	Furafyline	2.9	1.3	No inhibition
CYP2C9	7-Methoxy-trifluoromethylcoumarin	Sulfaphenazole	0.25	0.27	No inhibition
CYP2C19	3-Cyano-7-Ethoxycoumarin	Tranylcypromine	2.0	0.75	No inhibition
CYP2D6	3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methyoxy-4-methylcoumarin)	Quinidine	0.006	0.014	No inhibition
CYP2E1	7-Methyoxy-4-trifluoromethyl coumarin	Diethyldithiocarbamic Acid	1.19	4.1	No inhibition

- No significant inhibition of CYP450s, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, by XP13512 were observed at concentrations up to 400 μM.

Conclusion:

- XP13512 is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Reviewer's comments:

- *Potential of XP13512 to inhibit CYP2C8 and CYP2B6 should be evaluated also.*

IV Metabolism of XP13512 by CYP450 enzymes

Method:

Studies were performed to determine the role of specific CYP450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1) in the metabolism of XP13512 using human liver S9 and standard inhibitors of each isoform. The experimental conditions for each isoform studied are shown in Table 2.5.1. Due to an assay interference from ketoconazole, the specific role of the CYP3A4 isoform was examined using Supersomes™ and comparing to a control incubation in the absence of CYP3A4 (Table 2.5.2). All experiments used 1 mM NADPH as the cofactor. Experiments were conducted in a 96 well format. The concentration of XP13512 in each incubation was 5 µM. Human liver S9 fraction or Supersomes were pre-incubated with each inhibitor and XP13512 was added to initiate the experiment. The disappearance of XP13512 was examined over the course of 10 minutes at 37°C. Samples were obtained at zero and 10 minutes post-addition and were immediately quenched with methanol to prevent further conversion. Quenched samples were frozen and maintained at –80°C prior to analysis. Samples were analyzed by LC/MS/MS as described below.

Table 2.5.1. Experimental Conditions for CYP450 Substrate Studies

CYP Isoform	System	Protein Conc. (mg/mL)	XP13512 Conc. (µM)	Control Inhibitor	Inhibitor Conc. (µM)	Incubation Time (min)
CYP1A2	Human Liver S9	0.5	5	Furafyline	25	10
CYP2C9	Human Liver S9	0.5	5	Sulfaphenazole	25	10
CYP2C19	Human Liver S9	0.5	5	Tranylcypromine	25	10
CYP2D6	Human Liver S9	0.5	5	Quinidine	25	10
CYP2E1	Human Liver S9	0.5	5	Diethyldithiocarbamic Acid	25	10

Table 2.5.2 Experimental Conditions for CYP3A4 Substrate Studies

CYP Isoform	System	CYP Conc. (pM)	XP13512 Conc. (µM)	Control Condition	Inhibitor Conc. (µM)	Incubation Time (min)
CYP3A4	CYP3A4 Supersomes	2.5	5	No CYP3A4	25	10

Results:

Table 4.7. Results of CYP450 Substrate Studies

CYP450 Isoform	System	Inhibitor	Percent XP13512 Remaining at 1 Hour		Evidence of CYP450 Metabolism
			No Inhibitor	With Inhibitor	
CYP1A2	Human Liver S9	Furafyline	60.5	60.0	NO
CYP2C9	Human Liver S9	Sulfaphenazole	65.8	63.4	NO
CYP2C19	Human Liver S9	Tranylcypromine	67.7	67.5	NO
CYP2D6	Human Liver S9	Quinidine	59.5	62.5	NO
CYP2E1	Human Liver S9	Diethyldithiocarbamic Acid	60.6	62.8	NO

Table 4.8. Results of CYP3A4 Substrate Studies

CYP450 Isoform	System	Percent XP13512 Remaining		Evidence of CYP3A4 Metabolism
		Zero Time	1 Hour	
CYP3A4	Supersome™	100	99.5	NO

Result and conclusion:

- XP13512 is not a substrate of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Reviewer's comments:

- *Potential of XP13512 to be a substrate of CYP2C8 and CYP2B6 should be evaluated as well.*

V Protein binding of XP13512 in human serum albumin (HSA)

Method:

Protein binding of XP13512 was determined by centrifugal ultrafiltration. XP13512 (5 - 100 uM) was incubated in human serum albumin (HSA) (10 mg/mL in 25 mM Tris buffer at pH 7.4) at 37 °C for 60 minutes. A control incubation of XP13512 was performed in the same buffer without HSA. The samples were transferred to Ultrafree-MC 30,000 MWt cutoff filters (Millipore, Billerica, MA) and centrifuged at 4300 rpm for 30 minutes. The unbound XP13512 concentration in the filtrates was determined by LC/MS/MS. The extent of protein binding was determined as follows:

$$\% \text{ Protein Binding} = 100 - ((\text{Peak Area}_{HSA} / \text{Peak Area}_{control}) \times 100)$$

where Peak Area_{HSA} is the peak area of XP13512 determined in the filtrate in the presence of HSA and $\text{Peak Area}_{control}$ is the peak area of XP13512 determined in the filtrate in the absence of HSA.

Results and conclusions:

- 78-87% XP13512 bound to human serum albumin was observed over the concentration range 5-100 μM.
- As reported before, protein binding of gabapentin in rat, monkey and human plasma is < 3%.

Reviewer's comments:

- *Although the results should be straight forward, data should be shown in more detail.*

Study XP-092:

Evaluation of CYP450 Induction Potential by the Gabapentin Prodrug XP13512 and Gabapentin

To evaluate the induction potential of gabapentin and its prodrug, XP13512, on cytochrome P450 (CYP450) enzymes, human hepatocytes from 3 different donors were utilized. Hepatocytes were tested with known inducers and test compounds. Enzyme activities of CYP1A2, CYP2B6 and CYP3A4 were measured using omeprazole as positive control for CYP1A2 and rifampicin as positive control for CYP2B6 and CYP3A4.

Based on the maximum clinical concentration in humans (C_{max}), 0.1x, 1x, and 10x C_{max} of the test compounds (2) were used along with known inducers in the assay:

Compound	**Concentration Tested (μM)**
Omeprazole (Control)	0.2, 2, 20
Rifampicin (Control)	0.2, 2, 20
XP13512	0.2, 2, 20
Gabapentin	10, 100, 1000

Results:

Selective substrates (positive controls):

- Significant induction of CYP1A2 up to 16-fold was observed with hepatocytes treated with 20 μM of omeprazole.
- Up to 6-fold and 12-fold induction of CYP2B6 and CYP3A4, respectively, were observed with hepatocytes treated with 20 μM of rifampicin.

Test compounds:

Enzyme induction data for 3 isoforms in 3 different donors is shown below:

CYP1A2:

Table 1. Induction of CYP1A2 by control, XP13512 or gabapentin using Hepatocyte lot ZCA

Drug Conc (μM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Omeprazole)	XP13512	Gabapentin
0.2	1.6 (1.3 to 2.0)	1.0 (0.7 to 1.3)	-
2	4.7 (4.0 to 5.3)	1.3 (0.7 to 1.8)	-
10	-	-	1.0 (0.7 to 1.3)
20	13 (12 to 14)	1.0 (0.6 to 1.5)	
100	-	-	1.1 (0.7 to 1.4)
1000	-	-	1.0 (0.6 to 1.3)

Table 4. Fold Induction of CYP1A2 by control, XP13512 or gabapentin using Hepatocyte lot Hu4013

Drug Conc (uM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Omeprazole)	XP13512	Gabapentin
0.2	1.1 (0.9 to 1.3)	1.1 (0.9 to 1.3)	-
2	2.8 (2.2 to 3.3)	1.1 (0.8 to 1.3)	-
10	-	-	1.1 (0.7 to 1.5)
20	16 (7.5 to 24)	1.0 (0.7 to 1.4)	
100	-	-	1.1 (0.8 to 1.4)
1000	-	-	0.9 (0.6 to 1.2)

Table 7. Fold Induction of CYP1A2 by control, XP13512 or gabapentin using Hepatocyte lot Hu4019

Drug Conc (uM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Omeprazole)	XP13512	Gabapentin
0.2	1.4 (0.5 to 2.3)	1.1 (0.5 to 1.7)	-
2	2.9 (1.0 to 4.9)	1.1 (0.6 to 1.6)	-
10	-	-	1.1 (0.5 to 1.7)
20	13 (4.9 to 22)	1.2 (0.8 to 1.7)	
100	-	-	1.2 (0.5 to 1.8)
1000	-	-	1.2 (0.3 to 2.0)

CYP2B6:

Table 2. Induction of CYP2B6 by control, XP13512 or gabapentin using Hepatocyte lot ZCA

Drug Conc (μM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Rifampicin)	XP13512	Gabapentin
0.2	1.3 (1.1 to 1.5)	1.1 (0.8 to 1.3)	-
2	2.4 (1.6 to 3.3)	1.1 (0.8 to 1.3)	-
10	-	-	1.0 (1.0 to 1.1)
20	2.6 (2.2 to 3.1)	1.0 (0.7 to 1.3)	
100	-	-	1.0 (1.0 to 1.1)
1000	-	-	1.0 (0.7 to 1.3)

Table 5. Fold Induction of CYP2B6 by control, XP13512 or gabapentin using Hepatocyte lot Hu4013

Drug Conc (uM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Rifampicin)	XP13512	Gabapentin
0.2	1.5 (1.4 to 1.6)	1.1 (1.0 to 1.2)	-
2	2.7 (1.3 to 4.0)	1.2 (1.1 to 1.3)	-
10	-	-	1.0 (0.8 to 1.3)
20	5.6 (2.3 to 9.0)	1.2 (1.1 to 1.3)	
100	-	-	1.0 (0.8 to 1.2)
1000	-	-	1.1 (0.8 to 1.4)

Table 8. Fold Induction of CYP2B6 by control, XP13512 or gabapentin using Hepatocyte lot Hu4019

Drug Conc (uM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Rifampicin)	XP13512	Gabapentin
0.2	1.3 (0.8 to 1.7)	1.2 (1.0 to 1.4)	-
2	2.8 (1.9 to 3.6)	1.1 (0.9 to 1.3)	-
10	-	-	1.0 (0.7 to 1.4)
20	3.9 (2.8 to 5.0)	1.1 (0.9 to 1.2)	
100	-	-	1.1 (0.8 to 1.4)
1000	-	-	1.0 (0.7 to 1.3)

CYP3A4:

Table 3. Fold Induction of CYP3A4 by control, XP13512 or gabapentin using Hepatocyte lot ZCA

Drug Conc (μM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Rifampicin)	XP13512	Gabapentin
0.2	1.4 (1.0 to 1.8)	1.2 (0.9 to 1.5)	-
2	3.1 (2.2 to 3.9)	1.2 (0.9 to 1.5)	-
10	-	-	1.2 (1.0 to 1.4)
20	2.7 (2.0 to 3.5)	1.2 (0.9 to 1.5)	
100	-	-	1.2 (1.0 to 1.4)
1000	-	-	1.3 (0.9 to 1.6)

Table 6. Fold Induction of CYP3A4 by control, XP13512 or gabapentin using Hepatocyte lot Hu4013

Drug Conc (uM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Rifampicin)	XP13512	Gabapentin
0.2	3.7 (3.0 to 4.4)	1.0 (0.8 to 1.2)	-
2	5.5 (1.5 to 9.5)	1.0 (0.9 to 1.1)	-
10	-	-	1.0 (0.5 to 1.4)
20	12 (3.9 to 20)	1.0 (0.9 to 1.1)	
100	-	-	1.0 (0.7 to 1.4)
1000	-	-	0.9 (0.6 to 1.1)

Table 9. Fold Induction of CYP3A4 by control, XP13512 or gabapentin using Hepatocyte lot Hu4019

Drug Conc (uM)	Fold Induction, Mean (95% Confidence Interval)		
	Control (Rifampicin)	XP13512	Gabapentin
0.2	2.1 (1.6 to 2.6)	1.1 (1.0 to 1.2)	-
2	4.6 (3.6 to 5.6)	1.1 (1.0 to 1.1)	-
10	-	-	1.0 (0.8 to 1.2)
20	6.9 (5.4 to 8.3)	1.1 (0.9 to 1.2)	
100	-	-	1.0 (0.9 to 1.2)
1000	-	-	1.1 (0.8 to 1.3)

- In general, no significant induction of CYP1A2, CYP2B6 and CYP3A4 was observed for XP13512 and gabapentin as evidenced by average folds induction close to 1 and 95% CI including 1.
- One exception was 1.2 fold induction of CYP2B6 at 2 and 20 μM of XP13512 with lot Hu4013. The percent CYP2B6 induction relative to that of rifampicin by 2 and 20 μM of XP13512 was 11% and 4%, respectively, which was less than 40% of positive control, therefore is also considered not significant.

Conclusion

- XP13512 and gabapentin did not show potential for induction of CYP1A2, CYP2B6 and CYP3A4.

Study XP-095:

The Role of Human Carboxylesterases-1 and -2 (hCE-1 and hCE-2) in the Metabolism of XP13512

While XP13512 requires a hydrolysis process to convert to active drug, gabapentin, the specificity and the role of different carboxylesterases and their contributions were not known. This study was to utilize an in vitro system expressing human carboxylesterase-1 and -2 (hCE-1 and hCE-2) to evaluate the role of them to convert XP13512 to gabapentin.

Microsomes expressing specific activity of hCE-1 and hCE-2 in a tetracycline-inducible expression system and their controls (no activity) were extracted from stable clones which were selected after transfecting hCE-1 and hCE-2 to TREx HEK 293 cells. These microsomes were then used to incubate with XP13512 and measure for gabapentin formation.

The substrate specificity of expressed hCE-1 and hCE-2 was verified using selective substrates, clopidogrel and irinotecan, respectively. Comparable activity of hCE-1 and hCE-2 expressing microsomes was also demonstrated using a non-selective substrate, p-nitrophenylacetate.

TREx HEK 293 cells (human embryonic kidney cells) stably express the tet repressor were transfected with plasmids of hCE-1 or hCE-2. Cells expressing hCE-1 or hCE-2 were selected for single clone evaluation. Cells were incubated with or without 1 μg/mL tetracycline overnight. Tetracycline inactivates the tet repressor and allows expression of hCE-1 or hCE-2. Clones showing robust inducible expression were scaled up and reassayed. Microsomes were extracted and tested by both specific and non-specific substrates before utilizing for XP13512 evaluation.

Hydrolysis of control substrates

Specific substrates:

Clopidogrel and irinotecan at 60 μM and 3 μM, respectively, were incubated with microsomes expressing hCE-1 and hCE-2 enzymes from tetracycline-induced cells and their respective control microsomes isolated from non-induced cells at 37 °C. After the incubation for 20 minutes, the reaction was quenched with an equal volume of acetonitrile and the resulting mixture was centrifuged. The supernatant was analyzed by LC-MS/MS and the formation of clopidogrel carboxylate and 7-ethyl-10-hydroxy-camptothecin (SN-38) from clopidogrel and irinotecan, respectively, was determined.

The results of incubation of specific substrates with hCE-1 and hCE-2 expressing cells are shown below:

Table 5.1 Activities of Expressed Human Carboxylesterase- 1 and -2 (hCE-1 and hCE-2) for Selective Substrates

Substrate	Metabolite Formation#	Enzyme Preparation			
		hCE-1		hCE-2	
		Tetracycline-induced	Control Not induced	Tetracycline-induced	Control Not Induced
Clopidogrel	Clopidogrel carboxylate (nmol/mg)	21	0.38	BLQ*	BLQ
Irinotecan	SN-38 (pmol/mg)	0.57	0.87	31	1.9

Level of metabolite formation after 20 minute of incubation
* Below Level of Quantification

- Formation of clopidogrel carboxyate from clopidogrel was 55-fold higher with microsomes expressing hCE-1 than its non-induced control and no induced activity was observed with hCE-2 enzyme.
- Formation of 7-ethyl-10-hydroxycamptothecin (SN-38) from irinotecan was 16-fold higher with microsomes expressing hCE-2 than its non-induced control and no induced activity was observed with hCE-1 enzyme.
- Based on the sponsor, these results showed that the selectivity of the microsomal preparations is consistent with the literature.

Non-specific substrate:

A common substrate for these two enzymes, p-nitrophenylacetate (1 mM), was also incubated with the above-mentioned microsomes at room temperature for 10 minutes. p-Nitrophenol formation from p-nitrophenylacetate was monitored by absorbance at 405 nm in kinetic mode with a 96-well plate reader, SpectraMax 190 (Molecular Devices, Sunnyvale, CA). The concentration of p-nitrophenol was determined with a standard curve.

The results of incubation of the non-specific substrate with hCE-1 and hCE-2 expressing cells are shown below:

Table 5.2 Activities of Expressed Human Carboxylesterase- 1 and -2 (hCE-1 and hCE-2) for p-Nitrophenylacetate

p-Nitrophenol Formation (µmol/mg/min)	Enzyme Preparation			
	hCE-1		hCE-2	
	Tetracycline-induced	Control Not induced	Tetracycline-induced	Control Not Induced
Individual Activity	1.39 ± 0.01	0.02 ± 0.00	1.70 ± 0.05	0.05 ± 0.00
Mean Specific Activity*	1.37	-	1.65	-

* Corrected for background hydrolysis in control

- Both enzyme activities were induced by tetracycline and the activities were comparable with 1.4 vs 1.7 µmol/mg/mL, respectively.

Hydrolysis of XP13512

Preliminary experiments were conducted to optimize the incubation conditions so that the metabolism is linear with respect to time of incubation and protein concentration. XP13512 (50 µM) was incubated at 37 °C in triplicate with microsomes expressing hCE-1 and hCE-2 enzymes from tetracycline-induced cells and their respective control microsomes isolated from non-induced cells. After the incubation for 5 minutes, the reaction was quenched with an equal volume of acetonitrile and the resulting mixture was centrifuged. The supernatant was analyzed by LC-MS/MS and the levels of gabapentin were determined.

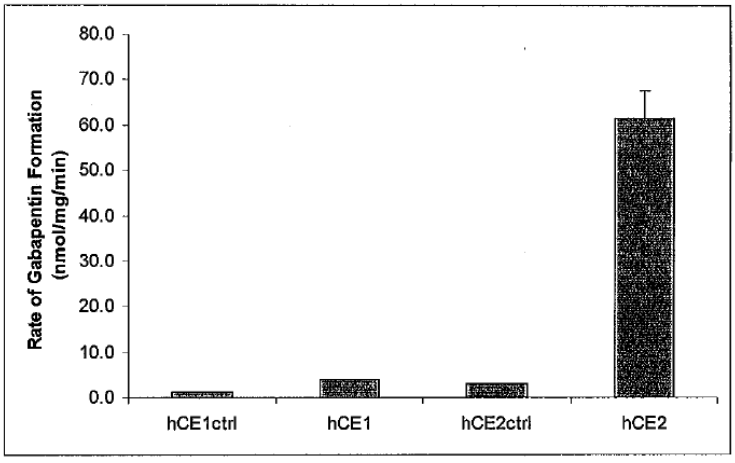
The results of incubation of XP13512 with hCE-1 and hCE-2 expressing cells are shown below:

Table 5.3 Substrate Studies of XP13512 incubated with Expressed Human Carboxylesterase- 1 and -2 (hCE-1 and hCE-2)

Gabapentin Formation (nmol/mg/min)	Enzyme Preparation			
	hCE-1		hCE-2	
	Tetracycline-induced	Control Not induced	Tetracycline-induced	Control Not Induced
Individual Activity	3.9 ± 0.021	1.1 ± 0.057	61 ± 6.1	3.0 ± 0.12
Mean Specific Activity*	2.8	-	58	-

* Corrected for background hydrolysis in control

Figure 6.1 Rate of Gabapentin Formation from XP13512 incubated with Expressed Human Carboxylesterase 1 and 2 (hCE-1 and hCE-2) and Their Respective Controls



- Formation of gabapentin from XP13512 was induced by 4 fold and 20 fold with expressed hCE-1 and hCE-2 enzymes, respectively, compared to their representative controls.
- The specific activity of hCE-2 towards XP13512 as the substrate after subtracting from its respective control was about 21-fold greater than that of hCE-1.
- These data suggest that hCE-2 is the major pathway of XP13512 metabolism whereas hCE-1 is the minor pathway.

Conclusion

- XP13512 hydrolysis is primarily catalyzed by hCE-2, a major human carboxylesterae present at high levels in intestinal tissues while a much smaller fraction of XP13512 is hydrolyzed by hCE-1.

Reviewer's comments:

- Does hCE-2 or hCE-1 (carboxylesterases) exist in the intestinal lumen? Literature search has been done and it does not seem to exist in the intestinal lumen.

4.1.6 BIOANALYTICAL METHODS

Report AA06480-01:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF XP13512, GABAPENTIN, AND GABAPENTIN LACTAM IN HUMAN WHOLE BLOOD (K_2EDTA) SUPERNATANT

Table 47 Summary of Validation Parameters for the Method Used to Support Studies XP006, XP018, XP019, and XP022

Matrix	Human Whole Blood (K_2EDTA) Supernatant		
Method	LC-MS/MS		
Regression	Quadratic ($1/x^2$)		
Analyte	XP13512	Gabapentin	Gabapentin Lactam
LLOQ	10 (ng/mL)	50 (ng/mL)	10 (ng/mL)
Linear range	10 to 2500 (ng/mL)	50 to 12,500 (ng/mL)	10 to 2500 (ng/mL)
QC samples	10, 30, 200, 1875, 2000, and 20,000 (DF=50) (ng/mL)	50,150, 1000, 9375, and 100,000 (DF=50) (ng/mL)	10, 30, 200, 1875, and 20,000 (DF=50) (ng/mL)
Accuracy and Inter-day precision (from all QCs)	-1 ≤ %bias ≤ 10% %CV ≤ 7.0%	-8% ≤ %bias ≤ 7% %CV ≤ 6.7%	-5% ≤ %bias ≤ 5% %CV ≤ 9.0%
Intra-day precision (from batch # 15 QCs)	%CV ≤ 6.5%	%CV ≤ 7.3%	%CV ≤ 6.8%
Freeze-thaw stability	6 cycles at -80°C		
Short term stability	25 hours at room temperature & white light conditions		
Long term stability	83 days at -80° C		
Stock Solution Stability	102 days in 50% methanol at -20°C	98 days in 50% methanol at -20°C	98 days in 50% methanol at -20°C
Internal Standard Stock Stability	(b) (4)		
Recovery	Not determined. The method was sufficiently sensitive at the LLOQ with consistent accuracy and precision over the validated calibration range.		

Report AA06480-02:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF XP13512, GABAPENTIN, AND GABAPENTIN LACTAM IN HUMAN URINE

Table 48 Summary of Validation Parameters for the Method Used to Support Studies XP006, XP009, XP018, XP019, XP022

Matrix	Human Urine		
Method	LC-MS/MS		
Regression	Quadratic ($1/x^2$)		
Analyte	XP13512	Gabapentin	Gabapentin Lactam
LLOQ	10 (ng/mL)	50 (ng/mL)	10 (ng/mL)
Linear range	10 to 2500 (ng/mL)	50 to 12,500 (ng/mL)	10 to 2500 (ng/mL)
QC samples	10, 30, 200, 1875, 2000, and 20,000 (DF=50) (ng/mL)	50,150, 1000, 9375, and 100,000 (DF=50) (ng/mL)	10, 30, 200, 1875, and 20,000 (DF=50) (ng/mL)
Accuracy and Inter-day precision (from all QCs)	-5 ≤ %bias ≤ -1% %CV ≤ 11.3%	-2% ≤ %bias ≤ 1% %CV ≤ 8.0%	-3% ≤ %bias ≤ 2% %CV ≤ 9.4%
Intra-day precision (from Batch #14 QCs)	%CV ≤ 10.2%	%CV ≤ 12.0%	%CV ≤ 12.5%
Freeze-thaw stability	6 cycles at -80°C		
Short term stability	12 hours at room temperature & white light conditions		
Long term stability	231 days at -80°C, 42 days at -20°C	236 days at -80°C, 42 days at -20°C	231 days at -80°C, 42 days at -20°C
Stock Solution Stability	140 days in 50% methanol at -20°C		
Internal Standard Stock Stability	(b) (4)		
Recovery	Not determined. The method was sufficiently sensitive at the LLOQ with consistent accuracy and precision over the validated calibration range.		

Report ZZ00216-01:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF GABAPENTIN IN HUMAN PLASMA (K_2EDTA)

Table 49 Summary of Validation Parameters for the Method Used to Support Studies XP009, XP021, XP022

Matrix	Human Plasma (K_2EDTA)
Method	LC-MS/MS
Regression	Linear (1/x)
Analyte	Gabapentin
LLOQ	80 (ng/mL)
Linear range	80 to 10,000 (ng/mL)
QC samples	80, 240, 1600, 7500, and 30,000 (DF=20) (ng/mL)
Accuracy and Inter-day precision (from QCs)	-5.1% ≤ %bias ≤ 3.8% %CV ≤ 9.5%
Intra-day precision (from batch #9 QCs)	%CV ≤ 5.2%
Freeze-thaw stability	6 cycles at -20°C
Short term stability	24 hours at room temperature & white light conditions
Long term stability	163 days at -20° C
Stock Solution Stability	213 days in 50% methanol at -20°C
Internal Standard Stock Stability	(b) (4)
Recovery	Not determined. The method was sufficiently sensitive at the LLOQ with consistent accuracy and precision over the validated calibration range.

Report VAL-A-HM-003:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF XP13512, GABAPENTIN, AND GABAPENTIN LACTAM IN HUMAN WHOLE BLOOD (K_2EDTA) SUPERNATANT

Table 50 Summary of Validation Parameters for the Method Used to Support Studies XP067, XP069, XP072, XP073

Matrix	Human Whole Blood (K_2EDTA) Supernatant		
Method	LC-MS/MS		
Regression	Quadratic ($1/x^2$)		
Analyte	XP13512	Gabapentin	Gabapentin Lactam
LLOQ	10 (ng/mL)	50 (ng/mL)	10 (ng/mL)
Linear range	10 to 2500 (ng/mL)	50 to 12,500 (ng/mL)	10 to 2500 (ng/mL)
QC samples	10*, 30, 200, 1900, 20,000 (DF=20)* (ng/mL) * Intra-run batch only	50*,150, 1000, 9500, 100,000 (DF=20)* (ng/mL) * Intra-run batch only	10*, 30, 200, 1900, 20,000 (DF=20)* (ng/mL) * Intra-run batch only
Accuracy and Inter-day precision (from all QCs, excluding LLOQ and QC-DF=20)	-4.2% ≤ %bias ≤ 1.0% %CV ≤ 6.77%	-8.3% ≤ %bias ≤ 2.0% %CV ≤ 10.1%	-5.3% ≤ %bias≤ -1.7% %CV ≤ 6.94%
Intra-day precision (from run #1 QCs, including LLOQ and QC-DF=20)	%CV ≤ 7.09%	%CV ≤ 13.4%	%CV ≤ 9.01%
Freeze-thaw stability*	6 cycles at -80°C		
Short term stability*	25 hours at room temperature & white light conditions		
Long term stability *	83 days at -80° C		
Stock Solution Stability	353 days in 50% methanol at -20°C *	320 days in 50% methanol at -20°C	353 days in 50% methanol at -20°C
Internal Standards Stock Stability	(b) (4)		
Recovery	The extraction efficiency was shown to be ≥ 96% for all analytes and ≥ 76% for both internal standards, at low, mid, and high QC concentrations.		

* Stability data based on validation testing performed at (b) (4)

Report VAL-A-HM-002:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF GABAPENTIN IN HUMAN URINE

Table 51 Summary of Validation Parameters for the Method Used to Support Studies XP044, XP057, XP066, XP067, XP068, XP086, XP087

Matrix	Human Urine
Method	LC-MS/MS
Regression	Linear (1/x2)
Analyte	Gabapentin
LLOQ	50 (ng/mL)
Linear range	50 to 12,500 (ng/mL)
QC samples	50*, 150, 1000, 9400, and 100,000* (DF=20 and DF=100) (ng/mL) * Intra-run batch only
Accuracy and Inter-day precision (from all QCs, excluding LLOQ and QC-DF)	-1.9% < %bias < 5% %CV < 5.14%
Intra-day precision (from 1st batch QCs, including LLOQ and QC-DF)	%CV < 4.93%
Freeze-thaw stability *	6 cycles at -80°C
Short term stability *	12 hours at room temperature & white light conditions
Long term stability *	330 days at -80°C, 791 days at -20°C
Stock solution stability*	320 days in 50% methanol at -20°C
Internal standard stock stability *	(b) (4)
Recovery	The extraction efficiencies of gabapentin and internal standard were shown to be > 95.7% and > 84.5% respectively at low, mid, and high QC concentrations.

* Stability data based on validation testing performed at (b) (4)

Report VAL-A-HM-004:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF GABAPENTIN AND GABAPENTIN LACTAM IN HUMAN URINE

Table 52 Summary of Validation Parameters for the Method Used to Support Studies XP072, XP073

Matrix	Human Urine	
Method	LC-MS/MS	
Regression	Quadratic ($1/x^2$)	
Analyte	Gabapentin	Gabapentin Lactam
LLOQ	50 (ng/mL)	10 (ng/mL)
Linear range	50 to 12,500 (ng/mL)	10 to 2500 (ng/mL)
QC samples	50*,150, 1000, 9500, 100000 (DF=20)* (ng/mL) * Intra-run batch only	10*, 30, 200, 1900, 20000 (DF=20)* (ng/mL) * Intra-run batch only
Accuracy and Inter-day precision (from all QCs, excluding LLOQ and QC-DF=20)	1.0% ≤ %bias ≤ 4.0% %CV ≤ 4.57%	2.0% ≤ %bias≤ 4.0% %CV ≤ 5.60%
Intra-day precision (from run #1 QCs, including LLOQ and QC-DF=20)	%CV ≤ 5.7%	%CV ≤ 6.37%
Freeze-thaw stability*	6 cycles at -80ºC	
Short term stability*	12 hours at room temperature & white light conditions	
Long term stability	236 days at -80° C[a]; 42 days at -20°C[b]	231 days at -80° C[a]; 42 days at -20°C[b]
Stock Solution Stability	320 days in 50% methanol at -20ºC	353 days in 50% methanol at -20ºC *
Internal Standards Stock Stability	(b) (4)	
Recovery	The extraction efficiency was shown to be ≥ 96.5% for all analytes and ≥ 79.1% for both internal standards, at low, mid, and high QC concentrations.	

a =Stability data based on validation testing performed at (b) (4)

b = Additional testing of freezer storage stability at -20°C is in progress and the validation report will be updated accordingly.

Report VAL-A-HM-001:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF GABAPENTIN IN HUMAN PLASMA (K_2EDTA)

Table 53 Summary of Validation Parameters for the Method Used to Support Studies XP044, XP045, XP052, XP053, XP057, XP060, XP066, XP068, XP073, XP078, XP081, XP083, XP086, XP087

Matrix	Human Plasma (K2EDTA)
Method	LC-MS/MS
Regression	Linear (1/x2)
Analyte	Gabapentin
LLOQ	80 (ng/mL)
Linear range	80 to 10,000 (ng/mL)
QC samples	80*, 240, 1600, 7500, and 30,000* (DF=20) (ng/mL) * Intra-run batch only
Accuracy and Inter-day precision (from all QCs, excluding LLOQ and QC-DF)	-2.3% < %bias < 4% %CV < 5.76%
Intra-day precision (from 1st accepted batch QCs, including LLOQ and QC-DF)	%CV < 2.83%
Freeze-thaw stability *	6 cycles at -20°C
Short term stability *	24 hours at room temperature & white light conditions
Long term stability *	782 days at -20°C
Stock solution stability*	320 days in 50% methanol at -20°C
Internal standard stock stability *	(b) (4)
Recovery	The extraction efficiencies of gabapentin and internal standard were shown to be > 88.8% and > 76.9% respectively at low, mid, and high QC concentrations.

* Stability data based on validation testing performed at (b) (4)

Report BAV-A-HM-005.VAL-1:

VALIDATION OF AN LC-MS/MS METHOD FOR THE DETERMINATION OF GABAPENTIN IN HUMAN DIALYSATE

Table 54 Summary of Validation Parameters for the Method Used to Support Study XP066

Matrix	Human Dialysate
Method	LC-MS/MS
Regression	Linear ($1/x^2$)
Analyte	Gabapentin
LLOQ	50 (ng/mL)
Linear range	50 to 12,500 (ng/mL)
QC samples	50*, 150, 1000, 9400, and 100,000* (DF=20) (ng/mL) * Intra-run batch only
Accuracy and Inter-day precision (from all QCs, excluding LLOQ and QC-DF)	-2.0% ≤ %bias ≤ 3% %CV ≤ 3.66%
Intra-day precision (from run #1 QCs, including LLOQ and QC-DF)	%CV ≤ 6.22%
Freeze-thaw stability	3 cycles at -20°C
Short term stability	22 hours at room temperature & white light conditions
Long term stability	Not Yet Determined. Inconsistent recovery was observed at the low QC level during initial stability testing.
Stock solution stability	320 days in 50% methanol at -20°C
Internal standard stock stability	(b) (4)
Recovery	The extraction efficiencies of gabapentin and internal standard were shown to be ≥ 102% and ≥ 96.3% respectively at low, mid, and high QC concentrations.

Note: Freezer storage stability data for this method has not yet been determined. Additional testing is in progress and the validation report will be updated accordingly.

4.2 Office of clinical Pharmacology: Pharmacometrics review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Will 600 mg dose be equally efficacious with less safety concern (sedation)?

Yes, 600 mg dose seems to provide a better benefit/risk profile than 1200 mg.

Benefit: Figure 1 shows the relationship between dose and primary endpoints for efficacy (IRLS- International Restless Leg Syndrome, CGI-I-Clinical Global Impression-Improvement) in seven studies. It shows that 600 mg would provide similar benefit in comparison to 1200 mg. The reason for lack of effect after 600 mg dose in study XP045 was not explored.

Risk:

Sedation: The sedative effects of 1200 and 1800 mg dose were evaluated using lane position variability as the outcome measure. Figure 2, Figure 3 shows the relationship between mean and individual gabapentin concentrations collected on Day 14, 15 and 16 in Study XP083. The effects of 600 mg dose on lane position variability cannot be determined due to high variability in the data. However, both 1200 mg and 1800 mg dose groups were similar to active-control (Diphenhydramine) in terms of changes in LPV. The sponsor did not evaluate the changes in lane position variability (safety indicator for sedative effects) after 600 mg dose.

Dizziness, Somnolence: Figure 4 shows that 1200 mg dose has more adverse events (numerical) in comparison to 600 mg.

Figure 1. **(TOP)** Mean (95% CI) Change from Baseline in IRLS Rating Scale Total Score to End of Treatment (All Completed RLS Clinical Studies with Efficacy Outcomes). **(BOTTOM)** Proportion of Responders on the Investigator-Rated CGI-I Scale at End of Treatment (All Completed RLS Clinical Studies with Efficacy Outcomes)

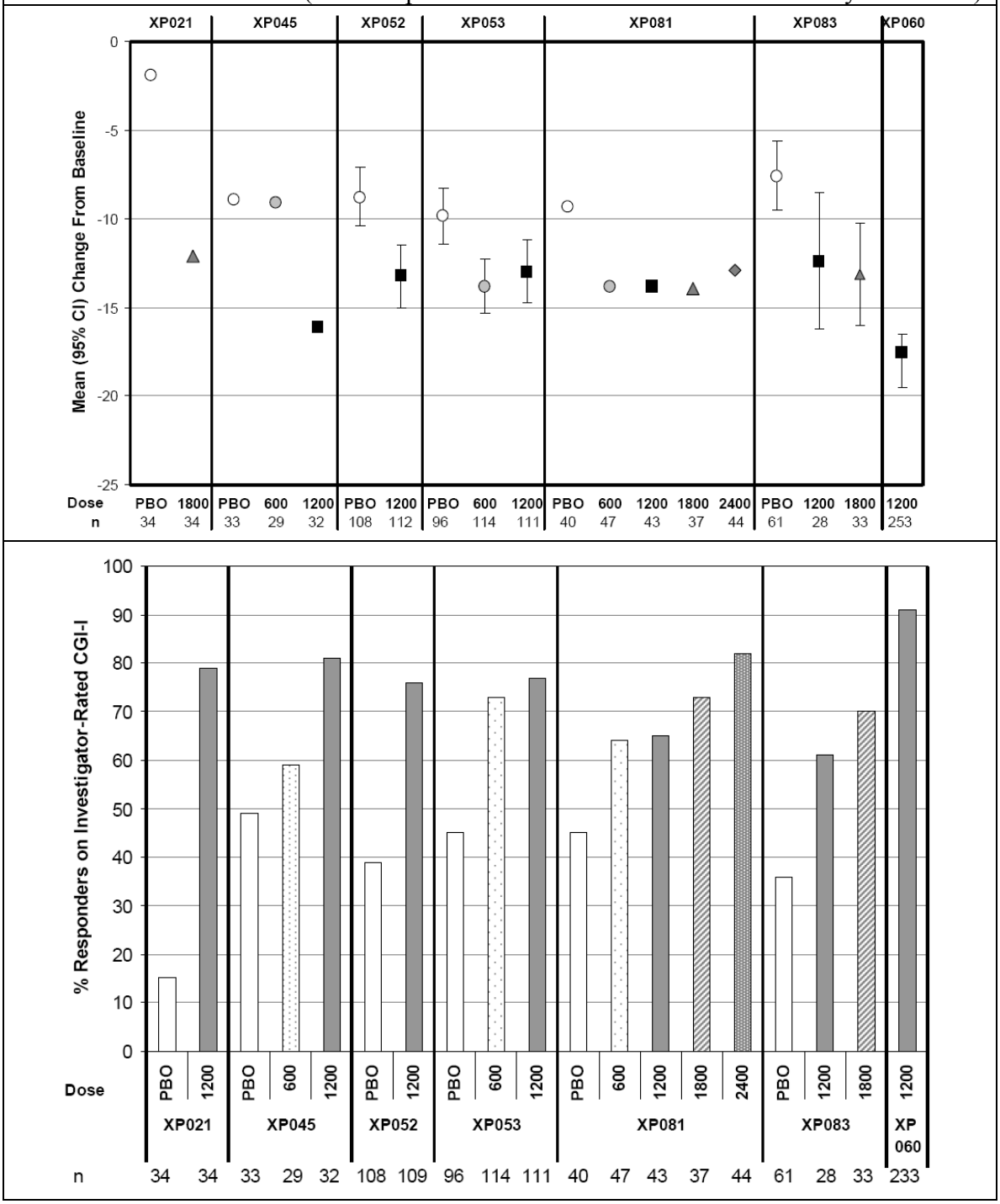


Figure 2. Relationship between mean concentrations of gabapentin (Day 14; 2h post-dose, Day 15; 14h post-dose on day 14, Day 16; 7h, Tmax) and baseline, placebo subtracted LPV (ft) in Study XP083. Shown in vertical lines are the observed mean steady state Cmax after 600, 1200 and 1800 mg in Study XP081 for reference purpose. Shown for reference (dotted line) is the change from baseline, placebo subtracted LPV for active control (Diphenhydramine; DPH)

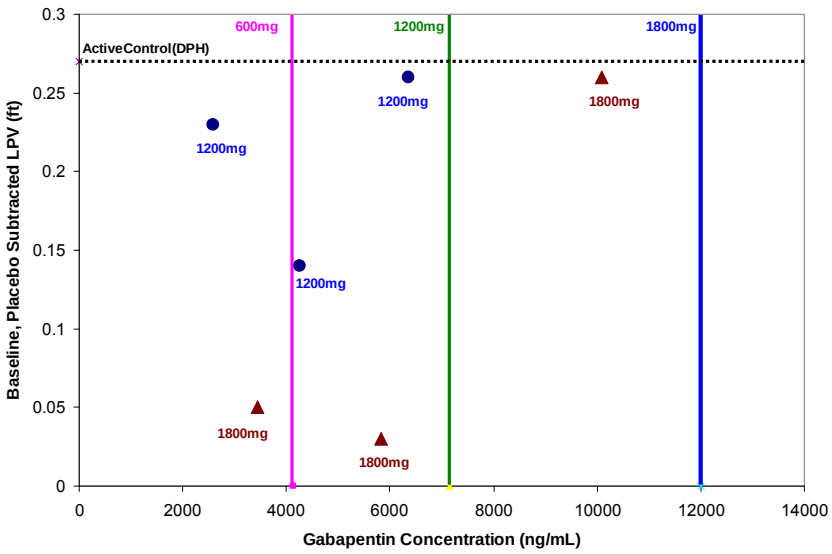


Figure 3. Relationship between change from baseline LPV and gabapentin concentrations after 1200 (LEFT) and 1800 (RIGHT) mg dose in study XP083. Shown for reference are the mean change from baseline LPV in placebo and diphenhydramine (DPH) groups.

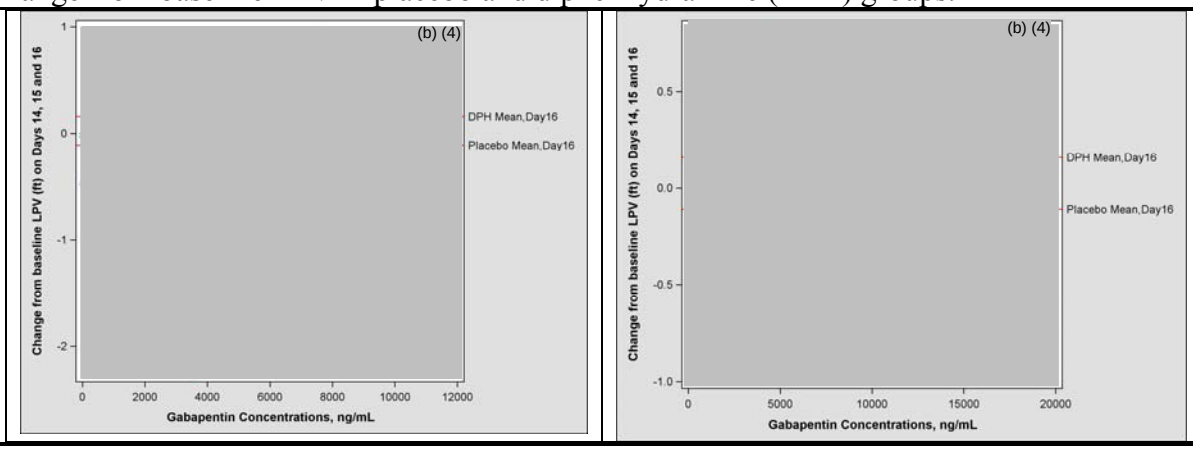
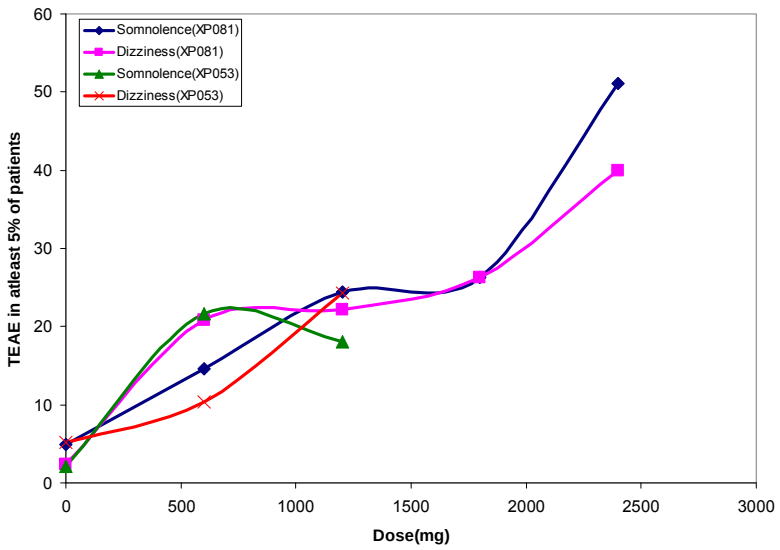


Figure 4. Relationship between dose and treatment emergent adverse events in atleast 5% of the patients. Shown are the data from two studies where various doses were studied.



Is the proposed dosing regimen of SOLZIRA® in patients with renal impairment acceptable?

No, if the benefit-risk is not acceptable at target doses of 1200 mg. The sponsor proposed dosing regimen in patients with renal impairment is shown in Table 1.

Table 1. Dosage of SOLZIRA® Tablets Based on Creatinine Clearance

Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
		(b) (4)

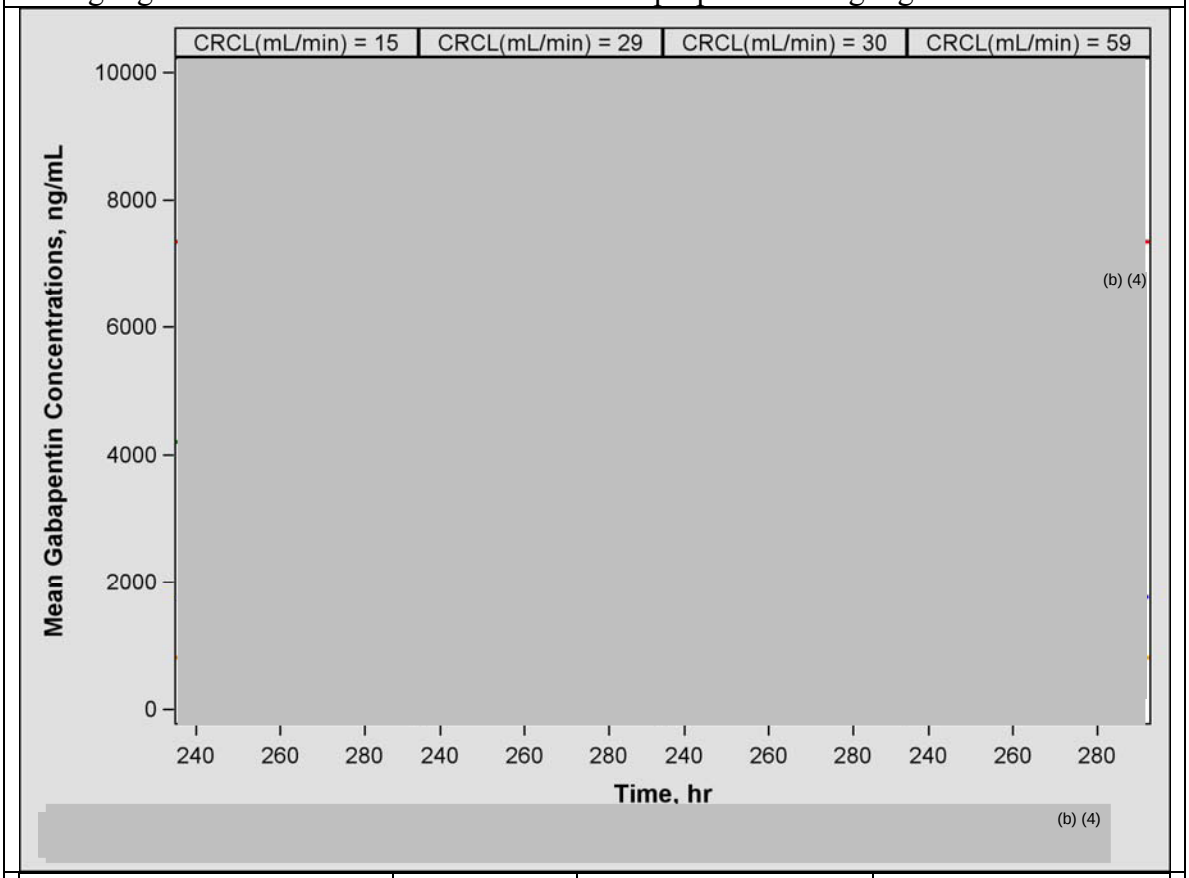
Table 2 shows the calculated Cmax, AUC at steady state ($C_{ss,max}$, AUC_{ss}) based on the dosing regimen proposed in Table 1. The sponsor concluded that simulated $C_{ss,max}$ and AUC_{ss} during steady state in subjects who require dosing adjustment are in the same range as those observed in subjects with normal renal function with the proposed dosage adjustment.

Table 2. Mean Pharmacokinetic Parameters for Gabapentin in Plasma at Steady State after Oral Dosing of 600 mg XP13512 Tablet in Subjects with Varying Renal Functions.

CrCL (mL/min)	Steady State PK Parameters in plasma after administration of XP13512	
	AUCss (ug*h/mL)	Cmax,ss (ug/mL)

Reviewer's Comments: The sponsor's proposed dosing regimen in patients with renal impairment is based on the relationship between gabapentin clearance and creatinine clearance (CrCL) derived from population pharmacokinetic analysis. The reviewer simulated the gabapentin concentration-time profile after administration of XP13512 tablets in patients with various degrees of renal function. The simulations were conducted using the dose/dosing regimen as proposed by the sponsor along with FDA's proposal as shown in Figure 5. The dosing regimen proposed by the sponsor and FDA are coded as D1 and D2 respectively. The reference lines show the observed Cmax, Ctrough at steady state after 600, 1200 mg dose in study XP081.

Figure 5. Mean steady-state simulated gabapentin concentrations based on zero order absorption model in a typical patient (Age=51, Weight=79 kg, Gender=Male) with creatinine clearance of 15, 29, 30 and 59 mL/min after administration of XP13512 using dosing regimens as shown in table below. Scenario=D1 reflects the sponsor's proposed dosing regimen. Scenario=D2 reflects the FDA's proposed dosing regimen.



Renal Function Creatinine Clearance (mL/min)	Scenario	Titration Dose Regimen	Target Dose Regimen
(b) (4)	D1	(b) (4)	
30-59	D2	300 mg per day for 3 days	600 mg per day starting day 4
(b) (4)	D1	(b) (4)	
15-29	D2	no titration	300 mg per day

Based on the simulations the following are the conclusions:

1. Patients with creatinine clearance 30-59 mL/min:
    - The sponsor's proposed dosing regimen [redacted] should be changed to 300 mg on Day 1, 2, 3 followed by 600 mg from Day 4 onwards. The FDA's proposal will avoid accidental dosing by patients on [redacted] as currently proposed by the sponsor.
    - Creatinine Clearance = 30 mL/min (Based on FDA's proposal)
        - The concentrations at steady-state in patients with creatinine clearance of 30 mL/min will be in the range of concentrations after 600 and 1200 mg dose in patients with normal renal function.
    - Creatinine Clearance=59 mL/min (Based on FDA's proposal)
        - The concentrations at steady-state will be in the range of concentrations after 600 mg dose in patients with normal renal function.
2. Patients with creatinine clearance 15-29 mL/min:
    - The sponsor's proposed dosing regimen [redacted] should be changed to 300 mg per day. The FDA's proposal will avoid accidental dosing of [redacted] by patients as currently proposed by the sponsor.
    - Creatinine Clearance=15 mL/min (Based on FDA's proposal)
        - The concentrations at steady-state in patients with creatinine clearance of 15 mL/min will be in the range of concentrations after 600 mg dose in patients with normal renal function.
    - Creatinine Clearance=29 mL/min (Based on FDA's proposal)
        - The peak concentrations at steady-state will be slightly lower (after accounting for the observation that the model underpredicts the Cmax) than the Cmax after 600 mg dose in patients with normal renal function. The concentrations at steady-state in general will be in the range of concentrations after 600 mg dose in patients with normal renal function.

Based on observed data

In patients with creatinine clearance ≥ 60mL/min, the target titration dose of [redacted] should be changed to 600 mg since both doses were equally efficacious in Study XP053 and XP081. Also the incidence of adverse events were higher (numerical) in [redacted] dose in comparison to 600 mg.

The dosing regimen as proposed by FDA is shown below.

Table 4. FDA proposed dosing regimen for XP13512 in patients with various degrees of renal function

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day

Other labeling statements based on population pharmacokinetic analysis

12.3 Pharmacokinetics

Distribution: Plasma protein binding of gabapentin has been reported to be <3%. (b) (4)

Reviewer's Comments: The proposed statement is based on population pharmacokinetic analysis. However, the reviewer recommends the following language in the label. The reviewer recommendations are based on estimated Vd/F from study XP068 (Table 5.1, Page 76 of 330 in xp068-report-body.pdf).

Distribution: Plasma protein binding of gabapentin has been reported to be <3%. The apparent volume of distribution of gabapentin in subjects receiving SOLZIRA is 82 L.

Recommendations

Based on benefit-risk profile of 1200 mg vs 600 mg dose, the sponsor should consider the following revised dosing guidelines in patients with various degrees of renal function.

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day

Label Statements

The current proposed labeling language in section 12.3 should be changed to

12.3 Pharmacokinetics

Distribution: Plasma protein binding of gabapentin has been reported to be <3%. (b) (4) The apparent volume of distribution of gabapentin in subjects receiving SOLZIRA is 82 L.

The current proposed dosing recommendations in patients with renal impairment should be changed as indicated.

Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	(b) (4) 600 mg per day starting day 4
30-59	(b) (4) 300 mg per day for 3 days	600 mg per day starting day (b) (4) 4
15-29	no titration	(b) (4) 300 mg per (b) (4) day
<15	Not recommended for use in patients with a CrCl <15 mL/min as it has not been adequately studied in this patient population and the dose cannot be reduced below 600 mg.	

Pertinent regulatory background

GlaxoSmithKline developed SOLZIRA for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS). Key diagnostic criteria for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant leg sensations, symptoms begin or worsen during periods of rest or inactivity such as lying or sitting, symptoms are partially or totally relieved by movement such as walking or stretching at least as long as the activity continues, and symptoms are worse or occur only in the evening or night. Difficulty falling asleep may frequently be associated with RLS. SOLZIRA is a pro-drug of gabapentin and is completely converted to gabapentin in vivo.

Results of Sponsor's Analysis

Sponsor conducted population pharmacokinetic analysis using data from Phase-I, Phase-II and Phase-III studies. The sponsor also explored the relationship between dose, AUC and efficacy, safety endpoints. However, in this review, population pharmacokinetic analysis is being presented since it was used to propose dose adjustments in patients with renal impairment and effects of gender on volume of distribution.

Population Pharmacokinetic Analysis

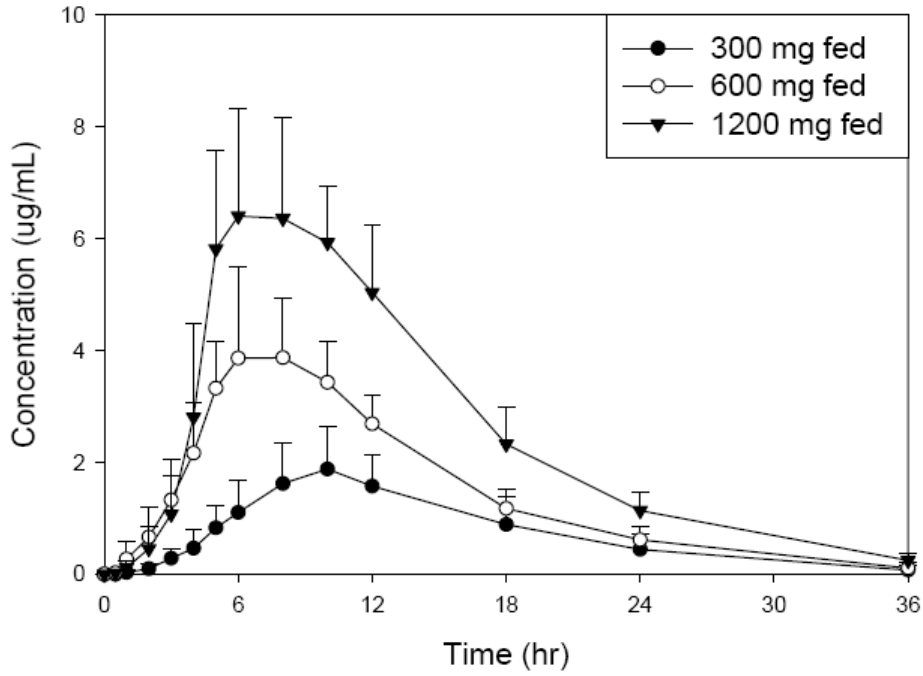
The demographic data of subjects used in the population pharmacokinetic analysis is shown in Table 5 below.

Table 5. **Demographic Data of Subjects from Phase I, II, and III Studies**

Statistic	Age (years) (n=994)	Weight (kg) (n=994)	Height (m) (n=994)	BMI (kg/m^2) (n=994)	Creatinine Clearance (mL/min) (n=842)
Mean	49.5	79.5	1.71	27.2	107
Median	50.6	78.9	1.70	27.2	104
SD	13.3	14.9	0.099	3.90	29.4
CV%	26.9	18.7	5.79	14.4	27.4
Minimum	18.3	43.6	1.37	17.0	15.6
Maximum	82.0	128	2.03	35.2	238

Sponsor described the pharmacokinetics of gabapentin using a one compartment model with zero-order absorption and lag time. The mean concentrations of gabapentin in plasma of fed subjects in Study XP044 (A Phase 1, Randomized, Cross-Over, Fed/Fasted Single-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Two Oral Sustained-Release Formulations of XP13512 in Healthy Adult Subjects) is shown in Figure 6.

Figure 6. Mean (SD) Concentrations of Gabapentin in Plasma of Fed Subjects After XP13512 SR 300 mg (N=12), 600 mg (N=12), and 1200 mg (N=12)



The estimates of the final pharmacokinetic parameters are shown in Table 6 below.

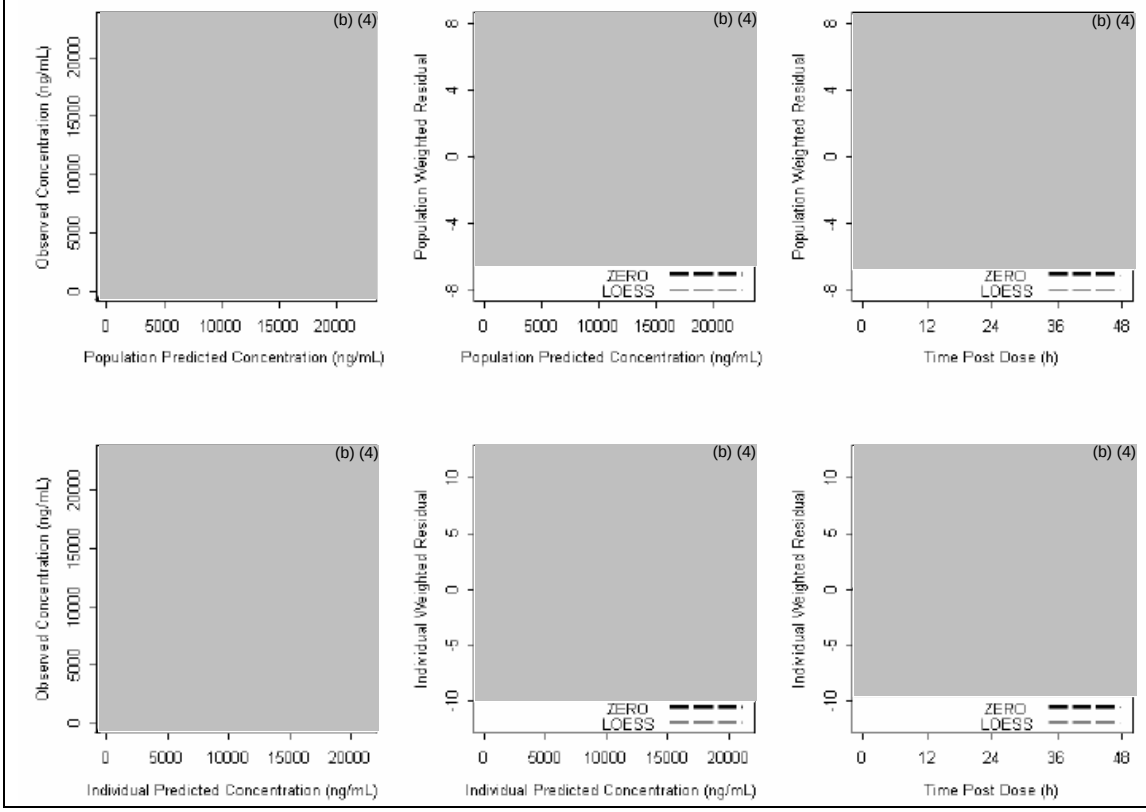
Table 6. Population PK parameters of gabapentin following administration of XP13512 – PK Model Including Covariates

Population PK Parameters	Estimates	IIV%
Absorption Parameters		
D (h)	6.86	22.0%
ALAG (h)	0.390	200%
Systemic Parameters		
CL/F (L/h)	6.74 for Men 5.74 For Women	20.5%
V/F (L)	86.3 for Men 65.6 for Women	33.9%
Covariate		
Effect of Weight on CL/F	0.228	NA
Effect of $CLCR_{TRUNC}$ on CL/F	0.675	NA
Effect of Weight on V/F	0.544	NA
Effect of Age on V/F	-0.239	NA
Error Model		
Additive Error (ng/mL)	667	NA
Proportional Error (%)	23.1%	NA

D: Duration of absorption, ALAG: lag time of absorption, CL/F, apparent clearance, V/F, apparent volume of distribution, $CRCL_{TRUNC}$, estimated creatinine clearance truncated to 150 mL/min, IIV: inter-individual variability, NA: not applicable.

Figure 7 shows the diagnostic plots for the final population pharmacokinetic model.

Figure 7. Goodness-of-Fit – Final PK Model of gabapentin following administration of XP13512



Reviewer's Comments: The reviewer analyzed the data and was able to derive similar estimates of the parameters.

Reviewer's Analysis

Introduction
NA

Objectives
NA

Methods

Data Sets
NA

Software
NA

Models
NA

Results
NA

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Meancmaxcmin.sas	SAS file for calculating steady state Cmax and Cmin in Study XP081	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\POPPK\OnServer\SponsorFinalModel\GoodnessofFit
XPtotalfinalJune20update.csv	NONMEM dataset for PK analysis by sponsor	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\POPPK\OnServer\Data
FINALRUN43.ctl	NONMEM control stream for PK analysis using zero order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\POPPK\OnServer\SponsorFinalModel
Dose600mgdual.csv	NONMEM control stream for PK analysis using dual first order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\POPPK\OnServer\Data
Covariatemodel.ctl	NONMEM control stream for PK analysis using dual first order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\POPPK\OnServer\DualFirstOrder\AbsFixed\CovariateModel
Renal.ctl	NONMEM control stream for simulating gabapentin concentrations in renal impairment subjects using zero order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\RenalImpairment
Renalsim.csv	Data file for simulating gabapentin concentrations in renal impairment subjects using zero order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\RenalImpairment
CovariateModel.ctl	NONMEM control stream for simulating gabapentin concentrations in renal impairment subjects using dual first order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\RenalImpairment
Renalsim_new1.csv	Data file for simulating gabapentin concentrations in renal impairment subjects using dual first order absorption model	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\RenalImpairment
Renal_updated.sas	SAS file for creating graphs as shown in Figure 5	\\cdsnas\PHARMACOMETRICS\Gabapentin_Enacarbil\RenalImpairment\renal.df

4.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA OR SUPPLEMENT

Office of Clinical Pharmacology ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Number	N 22-399	**Brand Name**	SOLZIRA™ Extended Release Tablets
OCP Division (I, II, III)	DCP-I	**Generic Name**	Gabapentin Enacarbil (XP13512)
Medical Division	HFD-120	**Drug Class**	gabapentinoids or alpha2delta ligands
OCP Reviewer	Ju-Ping Lai	**Indication(s)**	Restless Legs Syndrome (RLS)
OCPB Team Leader	Veneeta Tandon	**Dosage Form**	Extended Release Tablets (600 mg)
		Dosing Regimen	(b) (4) with food at 5PM
Date of Submission	1/9/2009	**Route of Administration**	Oral
Estimated Due Date of OCP Review	7/9/2009	**Sponsor**	GlaxoSmithKline (GSK)
Division Due Date	8/9/2009	**Priority Classification**	Standard
PDUFA Due Date	11/9/2009		

Clin. Pharm. and Biopharm. Information

This application for SOLZIRA™ (Gabapentin Enacarbil) Extended Release (ER) Tablets is being submitted as a 505(b)(1) submission for the treatment for moderate-to-severe primary Restless Legs Syndrome (RLS).

Oral gabapentin (Neurontin®) has been approved in the US for the treatment of post-herpetic neuralgia and as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in 2007 with the recommended dose of 1800 mg per day (600 mg TID). SOLZIRA™ (Gabapentin Enacarbil) is submitted as a new molecular entity, which is a transported prodrug of gabapentin designed and engineered to be stable in gastrointestinal contents and to be actively absorbed after oral dosing. Gabapentin Enacarbil converts to gabapentin rapidly by non-specific carboxylesterase primarily in enterocytes and to a lesser extent in the liver upon absorption. The concentration of intact prodrug in blood is transient and ≤ 2% of the corresponding gabapentin level. SOLZIRA™ is proposed to be marketed as 600 mg ER Tablets and dosed up to 1200 mg per day (QD).

The clinical development program for gabapentin enacarbil consists of 16 Phase I studies under IND 71,352 (b) (4). Efficacy of SOLZIRA™ was evaluated in 4 Phase II (XP021, XP045, XP081, and XP083) and 4 Phase III (XP052, XP053, XP060, and XP055) studies. Among these studies, 3 adequate and well-controlled studies (XP052, XP053, XP060) provided the primary efficacy data for RLS whereas 4 Phase II studies provided supportive data. Two population pharmacokinetic/ pharmacodynamic (PK/PD) analysis of efficacy and safety endpoints for RLS were also conducted (XP081, XP084) where XP084 using integrated data from Phase I, II and III studies for pharmacokinetic analysis and Phase II and Phase III studies for safety and efficacy analysis. Assessment of safety included data from all clinical studies. In addition, cardiac repolarization was investigated in a thorough QT study (XP078).

The formulation has been constant throughout the clinical development of this product. The commercial formulation is identical to the clinical formulations that used in Phase 1, 2, and 3 clinical studies.

Across the SOLZIRA™ clinical development program, a total of 1566 unique subjects (365 subjects from the clinical pharmacology studies and 1201 subjects in Phase II and III studies) were exposed to at least one dose of SOLZIRA™ as of the 31 March 2008 submission cut-off date.

<u>This NDA consists of</u>

- 16 Phase I studies:

- **Biopharmaceutics studies (5 studies):**

1. BA: XP087, XP022
   XP087: SD PK and food effect (↑exposure with food, regardless of fat content?)
   XP022: SD PK 1200 mg, fasted vs fed, IR vs SR (BA of SR > IR, Tmax ↑ with food)
2. BA/BE: XP019, XP057 and XP044
   XP019: SD 3 SR formulation vs 1 IR
   XP057: SD 2 SR formulations 1200 mg
   XP044: SD 300, 600 and 1200 mg, fasted vs high fat/calory (Dose proportional, Tmax ↑ by ~2-5 hours and exposure ↑ ~20% with food)

- [redacted] (b) (4))

- **Pharmacokinetic studies (10 studies):**
  1. Healthy subject PK: XP065, XP069, XP006 and XP018
     XP065: Mass Balance (total radioactivity in urine was 94.1% (where ^{14}C-gabapentin, accounted for a mean of 89.6%), with 5.2% of the radioactive dose recovered in faeces)
     XP069: SD 2400, 3600, 4800 and 6000 mg, standard fat/calory(Dose proportional up to 6000 mg. XP13512 < than 0.5% of the gabapentin exposure.)
     XP006: SD 350 mg, 700 mg, 1400 mg, 2100 mg, and 2800 mg(Dose proportional)
     XP018: MD 350 mg, 700 mg, 1400 mg, 2100 mg BID x 7 days(Dose proportional)
  2. Intrinsic factors: XP066, XP072 and XP073
     XP066: SD 600 mg, renal impairment and ESRD subjects on hemodialysis (CL↓)
     XP072: SD 600, 1200 and 1800 mg in Caucasian and Japanese (no race difference, dose proportional)
     XP073: MD 1200 and 1800 mg BID x 9-11 days in Japanese F/M (no gender effect)
  3. Extrinsic factors: XP067 and XP068
     XP067: 1200 mg QD+500 mg Naproxen BID (no significant changes in both drugs)
     XP068: 1200 mg QD+400 mg Cimetidine QID (no significant changes in both drugs, Gabapentin CLss/F ↓ 20% and AUCss ↑ 24% when coadministered)

- **Population PK/PD:** XP081, XP084

- **In vitro study:** BIO-2003-002, PK-2003-002, XP092 and XP095
  BIO-2003-002: In vitro transport study (XP13512 can be absorbed by both passive and active mechanisms. The transporters that may be responsible for the active uptake of these compounds *in vivo* include MCT-1 and SMVT.)
  PK-2003-002: plasma protein binding (~78-87%) and prodrug and gabapentin were not substrates, inducers and inhibitors of CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.
  XP092: CYP450 induction potential by gabapentin prodrug and gabapentin (No significant induction of CYP1A2, CYP2B6, or CYP3A4 was observed for XP13512 or gabapentin.)
  XP095: The role of human carboxylesterases-1 and -2 in the metabolism of gabapentin Enacarbil (hCE-2 play a predominant role in XP13512 metabolism)

- 4 Phase III studies (XP052, XP053, XP055, and XP060):
  XP052, XP053: pivotal efficacy,
  XP060 maintenance and
  XP055 long term safety.
- 4 Phase II studies (XP021, XP045, XP081 and XP083):
  XP021, XP045: efficacy,
  XP081: PopPK, dose/exposure response
  XP083: simulated driving performance, cognition and efficacy

- 1 QT evaluation study: XP078
- 2 Additional studies (XP009 and XP088)
  XP009: Efficacy, safety and PK in postherpetic neuralgia
  XP088: Simulated driving performance

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4	4	
I. Clinical Pharmacology				
Mass balance:	X	1	1	XP065
Isozyme characterization:	X	4	4	PK-2003-002, XP092
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	PK-2003-002
Transporters:			1	BIO2003-002
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	XP006
multiple dose:	X	2	2	XP018, XP073
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	3	3	XP044, XP069, XP072
fasting / non-fasting multiple dose:	X	1	1	XP081 (Phase II)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	2	2	XP067(Naproxen) and XP068(Cimetidine) DDI
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:	X	1	1	XP066
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:			2	E-Rfor efficacy and safety
Phase 3 clinical trial:				
Population Analyses -	X	1(1)	1	XP084, (XP081)
Data rich:	X	7		
Data sparse:	X	5		2 Phase II, 3 Phase III
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2	2	XP019, XP057
Bioequivalence studies -				
traditional design; single / multi dose:				

replicate design; single / multi dose:				
Food-drug interaction studies:	X	2	2	XP022, XP087
Dissolution:				
(b) (4)				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	159			
Total Number of Studies			**22**	
	16 PK + 2 Pop PK/PD+ 4 in vitro+ 4 Assay+ Literature			

Filability and QBR comments

I.	**"X" if yes**	Comments
II. Application filable?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
III. Comments sent to firm?	**X**	
IV.		
QBR questions (key issues to be considered)	• Is dose proportionality established in the therapeutic range? • Is there any food effect? • Is dose adjustment necessary for concomitant use of other drugs? • Is dose adjustment necessary for renal dysfunction patients?	
Other comments or information not included above	• Potential of prodrug and gabapentin to be a substrate, inhibitor or inducer of CYP 2C8 and a substrate or inhibitor of 2B6 were not evaluated.	
Primary reviewer Signature and Date	Ju-Ping Lai	
Secondary reviewer Signature and Date	Veneeta Tandon	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed formulation used.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?				
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of	x			

	appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Table 1 **Tabular Listing of All Clinical Studies** (presented by study type and ascending order of XenoPort study identifier)

XenoPort Study Identifier / GSK Study Identifier	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report) / Location of Report
Biopharmaceutic Studies						
XP019 / RXP111456	Safety, tolerability & PK of 3 ER formulations	R, OL, 2-period XO	Healthy subjects	3 different 600 mg XP13512 ER tablet formulations and 1 700 mg IR tablet formulation; Oral; Single dose	24	Completed (CSR) / m5.3.1.2
XP022 / RXP111458	Safety, tolerability & PK under fed & fasted conditions	R, OL, 3-period XO	Healthy subjects	XP13512 1200 mg in fed and fasted states; Neurontin® 600 mg, fasted state; Oral; Single dose	12	Completed (CSR) / m5.3.1.1
XP044 / RXP111459	Safety, tolerability & PK under fed & fasted conditions	R, OL, 2-period XO	Healthy subjects	XP13512 300 mg, 600 mg, and 1200 mg; two treatment periods (fed and fasted) at each dose; Oral; Single dose	36	Completed (CSR) / m5.3.1.2
XP057 / RXP111491	Single dose PK; comparison of 2 ER formulations	R, OL, 2-period XO	Healthy subjects	2 different XP13512 1200 mg ER tablet formulations; Oral; Single dose	12	Completed (CSR) / m5.3.1.2
XP086 / RXP111422	Safety, tolerability & PK; *in vitro/in vivo* correlation of XP13512 formulations & Neurontin®	R, OL, 5-period XO	Healthy subjects	Neurontin® 600 mg (2 x 300 mg) and 4 different XP13512 1200 mg ER tablet formulations (2 x 600 mg of each) under fasted conditions; Oral; Single dose	10	Completed (CSR) / m5.3.1.3
XP087 / RXP111423	Single dose PK, food effect	R, OL, 4-period XO	Healthy subjects	XP13512 1200 mg under fasted, low-fat, and moderate fat, and high fat conditions; Oral; Single dose	12	Completed (CSR) / m5.3.1.1
Pharmacokinetic Studies						
XP006 / RXP111489	Safety, tolerability, & PK	R, PC, ascending single dose	Healthy subjects	XP13512 IR (350, 700, 1400, 2100, & 2800 mg) or placebo, followed 1 week later by near-equimolar doses of Neurontin® (200, 400, 800, 1200, or 1400 mg); fasted state; Oral; Single Dose	50	Completed (CSR) / m5.3.3.1

XenoPort Study Identifier / GSK Study Identifier	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report) / Location of Report
XP018 / RXP111455	Safety, tolerability & PK	R, PC, DB ascending multiple dose	Healthy subjects	XP13512 IR (350, 700, 1400, and 2100 mg) or placebo BID; fasted state; Oral; 7 to 10 days	38	Completed (CSR) / m5.3.3.1
XP065 / RXP111492	Single dose PK and radiolabel recovery	NR, OL	Healthy subjects	Two gelatin capsules containing 300 mg ^{14}C-XP13512 (approximately 50 µCi) for a total dose of 600 mg XP13512 with approximately 100 µCi of ^{14}C-XP13512; fed state; Oral; Single dose	6	Completed (CSR) / m5.3.3.1
XP066 / RXP111524	Single dose PK renal impairment	NR, OL	Subjects with moderate or severe renal impairment or ESRD	XP13512 600 mg; fed state; Oral; Single dose	15	Completed (CSR) / m5.3.3.3
XP067 / RXP111411	Multiple dose PK, drug-drug interaction with Naproxen	NR, OL	Healthy subjects	XP13512 1200 mg OD for 5 days; Naproxen 500 mg BID for 5 days; XP13512 1200 mg OD plus Naproxen 500 mg BID for 5 days; fed state; Oral; 15 days (5 days on each of 3 treatments)	12	Completed (CSR) / m5.3.3.4
XP068 / RXP111419	Multiple dose PK, drug interaction with cimetidine	NR, OL	Healthy subjects	XP13512 1200 mg OD for 4 days; Cimetidine 400 mg QID for 4 days; XP13512 1200 mg OD plus cimetidine 400 mg QID for 4 days; fed state; Oral; 12 days (4 days on each of 3 treatments)	12	Completed (CSR) / m5.3.3.4
XP069 / RXP111420	Safety, tolerability, & PK; dose escalation to supra-therapeutic doses	R, DB, PC, XO, dose escalation	Healthy subjects	XP13512 2400 mg, 3600 mg, 4800 mg, and 6000 mg and placebo; fed state; Oral; Single dose	32	Completed (CSR) / m5.3.3.1
XP072 / RXP111493	Safety, tolerability and PK under fasting and fed conditions	R, DB, PC, ascending single dose	Healthy subjects (Japanese and Caucasian males)	XP13512 600 mg (fasted), 1200 mg (fasted), and 1800 mg (fasted and fed) and placebo; Oral; Single dose	48	Completed (CSR) / m5.3.3.3

XenoPort Study Identifier / GSK Study Identifier	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report) / Location of Report
XP073 / RXP111494	Safety, tolerability, and PK	R, DB, PC, ascending multiple dose	Healthy subjects (Japanese)	XP13512 1200 mg BID (fed) and 1800 mg BID (fed) or placebo; Oral; 9 to 11 days	31	Completed (CSR) / m5.3.3.3
XP084 / RXP111495	Population PK-PD Analysis	NA	NA	XP13512 600 mg to 2400 mg doses from Phase I (PK only), II and III studies	NA	Completed (PK/PD Report) / m5.3.3.5
Human Pharmacodynamic Studies						
XP078 / RXP111421	Thorough QT evaluation	R, DB, PC and AC, 4-period XO	Healthy subjects	XP13512 1200 mg and 6000 mg, placebo, and 400 mg moxifloxacin; fed state; Oral; Single dose	54	Completed (CSR) / m5.3.4.1
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
XP021 / RXP111457	Efficacy and safety	R, DB, PC, 2-period XO	Subjects with RLS	XP13512 600 mg 1 hour prior to bedtime (HS), to 600 mg at 5 PM plus 600 mg HS, to 600 mg at 5 PM plus 1200 mg HS (titrated over 5 days) and placebo; Oral; 14 days (active or placebo) then 7-day washout then 14 days (active or placebo)	38	Completed (CSR) / m5.3.5.1
XP045 / RXP111409	Efficacy and safety	R, DB, PC, PG	Subjects with RLS	XP13512 600 or 1200 mg, or placebo OD at 5 PM. The 1200 mg dose was titrated over 3 days from 600 mg at 5 PM for 2 days, to 1200 mg at 5 PM on the 3rd day; Oral; 14 days	95	Completed (CSR) / m5.3.5.1
XP052 / RXP110963	Pivotal efficacy and safety	R, DB, PC, PG	Subjects with RLS	XP13512 1200 mg or placebo OD; Oral; 12 weeks	222	Completed (CSR) / m5.3.5.1
XP053 / RXP111460	Pivotal efficacy and safety	R, DB, PC, PG	Subjects with RLS	XP13512 600 mg or 1200 mg or placebo OD; Oral; 12 weeks	325	Completed (CSR) / m5.3.5.1
XP060 / RXP111461	Maintenance of efficacy, safety	24-week SB; responders enter a 12-week, R, DB, PC, PG phase	Subjects with RLS	XP13512 1200 mg in single-blind phase; XP13512 1200 mg or placebo in double-blind phase; Oral; 36 weeks	327	Completed (CSR) / m5.3.5.1

XenoPort Study Identifier / GSK Study Identifier	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report) / Location of Report
XP081 / RXP111462	Population PK, dose/ exposure response, safety, tolerability	R, DB, PC, PG	Subjects with RLS	XP13512 600, 1200, 1800 or 2400 mg or placebo OD; Oral; 12 weeks	217	Completed (CSR) / m5.3.5.1
XP083 / RXP111463	Simulated driving performance, cognition, and efficacy	R, DB, PC & AC, PG	Subjects with RLS	XP13512 1200 or 1800 mg, placebo, or placebo plus diphenhydramine 50 mg (once on Day 16), OD; Oral; 16 days	130	Completed (CSR) / m5.3.5.4
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
XP055 / RXP111490	Long-term safety	OL extension of XP052, XP053, XP081, and XP083	Subjects with RLS	XP13512 1200 mg OD (reductions to 600 mg and increases to 1800 mg permitted based on efficacy and tolerability); Oral; 52 weeks	Target ≤600 (As of the 06 Dec 2007 data cut-off date, 581 subjects enrolled; 87 completed)	Ongoing / m5.3.5.2
Efficacy and Safety Studies: Other Studies						
XP009 / PXN111044	Efficacy, safety, and PK in post-herpetic neuralgia	R, DB, PC, PG	Subjects with post-herpetic neuralgia	Neurontin® 600 mg TID followed by a double-blind period with either XP13512 1200 mg BID or placebo; Oral; 11 days plus 14 days	115	Completed (CSR) / m5.3.5.4
XP088 / RXP111496	Simulated driving performance	Pilot, non-treatment	Healthy subjects and subjects with untreated RLS	None	30	Completed (CSR) / m5.3.5.4
NA / PXN110448	Efficacy, safety, and dose-response	R, P & AC, PG	Subjects with NP associated with DPN	XP13512 600 mg, 1200 mg, 1800 mg, placebo, BID or pregabalin 100 mg TID; Oral; 14 weeks	392 planned (As of 31 Mar 2008 data cut-off, 7 subjects screened; 1 subject randomized)	Ongoing / Refer to m5.3.5.3 ISS, Section 1.1.4.3 for description.

XenoPort Study Identifier / GSK Study Identifier	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Type of Report) / Location of Report
Non-GSK Sponsored Studies: Astellas-Sponsored Studies in Japan (contributing to safety exposure)						
8825-CL-0003	Efficacy and safety	R, DB, PC	Subjects with RLS	XP13512 (3 doses) or placebo; Oral; NA	400 planned	Ongoing / Refer to m5.3.5.3 ISS, Section 1.1.4.3 for description.
8825-CL-0005	NA	OL	Subjects with RLS	XP13512 (dose NA); Oral	NA	Ongoing / Refer to m5.3.5.3 ISS, Section 1.1.4.3 for description.
8825-CL-0007	Efficacy and safety	R, DB, PC	Subjects with painful DPN	XP13512 (3 doses) or placebo; Oral; NA	360 planned	Ongoing / Refer to m5.3.5.3 ISS, Section 1.1.4.3 for description.

AC = Active control
BID = Twice daily
DB = Double-blind
CPSR = Clinical Pharmacology Study Report
CSR = Clinical Study Report
DPN = Diabetic peripheral neuropathy
ER = Extended release
ESRD = End stage renal disease
IR = Immediate release
ISS = Integrated Summary of Safety
NA = Not available or not applicable
NP = Neuropathic pain
NR = Non-randomized
OD = Once daily
OL = Open label
P = Placebo
PC = Placebo-controlled
PG = Parallel Group
PK = pharmacokinetics
R = Randomized
RLS = restless legs syndrome
SB = Single-blind
TID = three times daily
XO = Crossover

Appendix 1 Description of Clinical Studies

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP006 / RXP111489	1 center in US	07NOV03/ Completed/ 20DEC03 Total 50/ Target 50	Safety, tolerability, & PK of 5 single ascending doses of XP13512 IR	Randomized, placebo-controlled, ascending single dose	Healthy subjects	XP13512 IR (350, 700, 1400, 2100, & 2800 mg) or placebo, followed 1 week later by near-equimolar doses of Neurontin (200, 400, 800, 1200, or 1400 mg)/ Oral / Single Dose	50 randomized/ 49 completed	48% M/ 52% F 30 (18 to 55) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of XP13512, gabapentin & gabapentin-lactam	m5.3.3.1
XP009 / PXN111044	17 centers in US	21JUN04/ Completed/ 15MAR05 Total 115/ Target 160	Efficacy, safety, and PK in post-herpetic neuralgia	Double-blind, randomized, placebo-controlled, parallel design	Subjects with post-herpetic neuralgia	Neurontin 600 mg TID followed by a double-blind period with either XP13512 1200 mg BID or placebo/ Oral/ 11 days plus 14 days	Neurotonin: 115 entered/ 101 completed Placebo: 54 randomized / 47 completed XP13512: 48 randomized/ 45 completed	49% M/ 51% F 64.5 (23.0 to 87.2) years	Change in mean weekly pain scores from baseline assessment to the final study week	m5.3.5.4

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP018 / RXP111455	1 center in US	30NOV03/ Completed/ 06FEB04 Total 38/ Target 38	Safety, tolerability & PK of 4 ascending multiple doses of XP13512 IR	Randomized, placebo-controlled, ascending multiple dose	Healthy subjects	XP13512 IR (350, 700, 1400, and 2100 mg) or placebo BID/ Oral/ 7 to 10 days	38 randomized/ 37 completed	63% M/ 37% F 31 (19 to 49) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of XP13512 & gabapentin	m5.3.3.1
XP019 / RXP111456	1 center in UK	09JAN04/ Completed/ 05MAY04 Total 24/ Target 24	Safety, tolerability & PK of 3 ER formulations	Randomized, open-label, crossover	Healthy subjects	3 different 600 mg XP13512 ER formulations and 1 700 mg IR formulation/ Oral/ Single dose	Part 1: 12 randomized/ 12 completed Part 2: 12 enrolled/ 12 completed	100% M 27.9 (18 to 52) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of XP13512 & gabapentin	m5.3.1.2

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP021 / RXP111457	9 centers in US	09JUN04/ Completed/ 01DEC04/ Total 38/ Target ~40	Efficacy and safety	Double-blind, randomized, placebo-controlled, two-period crossover	Subjects with RLS	XP13512 600 mg 1 hour prior to bedtime (HS), to 600 mg at 5 PM plus 600 mg HS, to 600 mg at 5 PM plus 1200 mg HS (titrated over 5 days) and placebo/ Oral/ 14 days (active or placebo) then 7-day washout then 14 days (active or placebo)	XP13512 to placebo: 21 randomized / 19 completed Placebo to XP13512: 17 randomized / 15 completed	42% M/ 58% F 50.1 (19.7 to 72.7) years	Mean change from baseline to end of treatment (Week 2) in IRLS Rating Scale total score	m5.3.5.1
XP022 / RXP111458	1 center in US	01JUN04/ Complete/ 02JUL04 Total 12/ Target 12	Safety, tolerability & PK of a single 1200 mg XP13512 dose under fed & fasted conditions	Randomized, open-label, 3 treatment period, crossover	Healthy subjects	XP13512 1200 mg in fed and fasted states; Neurontin 600 mg, fasted state/ Oral/ Single dose	12 randomized/ 10 completed	58% M/ 42% F 52.9 (20 to 72) years	AEs, vital signs, ECGs, clinical laboratory tests. PK for XP13512 & gabapentin	m5.3.1.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP044 / RXP111459	1 center in US	07MAR05/ Completed/ 06MAY05 Total 36/ Target 36	Safety, tolerability & PK of 3 single doses of XP13512 under fed & fasted conditions	Open-label, randomized, crossover	Healthy subjects	XP13512 300, 600, and 1200 mg; two treatment periods (fed and fasted) at each dose/ Oral/ Single dose	36 randomized/ 34 completed	56% M/ 44% F 300 mg: 53.2, 600 mg: 48.3, 1200 mg: 45.5 (60 to 73) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of gabapentin	m5.3.1.2
XP045 / RXP111409	14 centers in US	31JAN05/ Completed/ 08JUN05/ Total 95/ Target 66	Efficacy and safety	Double-blind, randomized, placebo-controlled, parallel group	Subjects with RLS	XP13512 600 or 1200 mg, or placebo OD at 5 PM. The 1200 mg dose was titrated over 3 days from 600 mg at 5 PM for 2 days, to 1200 mg at 5 PM on the 3rd day. Oral/ 14 days	XP13512 600 mg: 29 randomized / 29 completed XP13512 1200 mg: 33 randomized / 31 completed Placebo: 33 randomized / 33 completed	38% M/ 62% F 50.5 (22.6 to 70.0) years	Mean change from baseline to end of treatment (Week 2) in IRLS Rating Scale total score	m5.3.5.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP052 / RXP110963	22 centers in US	13MAR06/ Complete/ 22FEB07/ Total 222/ Target 210	Pivotal efficacy and safety	Double-blind, randomized, placebo-controlled, parallel group	Subjects with RLS	XP13512 1200 mg or placebo OD/ Oral/ 12 weeks	XP13512 1200 mg: 114 randomized/ 100 completed Placebo: 108 randomized/ 92 completed	40% M/ 60% F 51.1 (18 to 81) years	Mean change from baseline to end of treatment (Week 12) in IRLS Rating Scale total score Proportion of responders at Week 12 on investigator-rated CGI-I	m5.3.5.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP053 / RXP111460	28 centers in US	21AUG06/ Complete/ 20DEC07/ Total 325/ Target 315	Pivotal efficacy and safety	Double-blind, randomized, placebo-controlled, parallel group	Subjects with RLS	XP13512 600 mg or 1200 mg or placebo OD/ Oral/ 12 weeks	XP13512 600 mg: 115 randomized/ 104 completed XP13512 1200 mg: 113 randomized/ 98 completed Placebo: 97 randomized / 77 completed	41% M/ 59% F 48.9 (21 to 71) years	Mean change from baseline to end of treatment (Week 12) in IRLS Rating Scale total score Proportion of responders at Week 12 on investigator-rated CGI-I	m5.3.5.1
XP055 / RXP111490	Not applicable (ongoing)	05JUN06/ Ongoing/ Target ≤600	Long-term safety	Open-label extension of XP052, XP053, XP081, and XP083	Subjects with RLS	XP13512 1200 mg OD (reductions to 600 mg and increases to 1800 mg are permitted based on efficacy and tolerability)/ Oral/ 52 weeks	Ongoing As of the 06 Dec 2007 data cut-off date, 581 subjects enrolled / 87 completed	Not applic-able (on-going)	Safety: AEs, vital signs, ECGs, clinical laboratory tests, Sudden Onset of Sleep (SOS) Questionn-aire, Epworth Sleepiness Scale (ESS)	m5.3.5.2

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP057 / RXP111491	1 center in US	31JAN06/ Complete/ 15FEB06 Total 12/ Target 12	Single dose PK; comparison of two extended release formulations	Open-label, randomized, 2-period crossover, single-dose	Healthy subjects	XP13512 1200 mg/ Oral/ Single dose	Sequence 1: 6 randomized/ 6 completed Sequence 2: 6 randomized/ 6 completed	67% M/ 33% F 41.0 (19 to 70) years	PK of gabapentin	m5.3.1.2
XP060 / RXP111461	27 centers in US	18APR06/ Complete/ 14NOV07/ Total 327/ Target 300	Maintenance of efficacy, safety	24-week single-blind with responders entering 12-week, double-blind, randomized, placebo-controlled, phase	Subjects with RLS	XP13512 1200 mg in single-blind phase; XP135121200 mg or placebo in double-blind phase/ Oral/ 36 weeks	XP13512 1200 mg DB-ITT: 96 randomized/ 84 completed Placebo DB-ITT: 98 randomized/ 84 completed Not randomized: 133 entered/ 27 completed	42% M/ 58% F 49.8 (19 to 82) years	Proportion of subjects who relapsed or withdrew due to lack of efficacy during the 12-week double-blind treatment period	m5.3.5.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP065 / RXP111492	1 center in US	30AUG07/ Complete/ 05OCT07 Total 6/ Target 6	Single dose PK and radiolabel recovery	Open-label, non-randomized	Healthy subjects	Two gelatin capsules containing 300 mg ^{14}C-XP13512 (approximately 50 µCi) for a total dose of 600 mg XP13512 with approximately 100 µCi of ^{14}C-XP13512/ Oral/ Single dose	6 enrolled/ 6 completed	100% M/ 0% F 37 (24 to 46) years	PK parameters based on plasma and whole blood conc-entrations of ^{14}C XP13512 total radioactivity	m5.3.3.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP066 / RXP111524	2 centers in US	02JAN07/ Complete/ 09NOV07 Total 15/ Target up to 18	Single dose PK renal impairment	Open-label	6 with severe renal impairment, up to 6 with moderate impairment, 6 with ESRD	XP13512 600 mg/ Oral/ Single dose	Severe renal impairment: 7 enrolled/ 7 completed Moderate renal impairment: 1 enrolled/ 1 completed ESRD: 7 enrolled/ 7 completed	Severe: 57% M/ 43% F 61.9 (28 to 76) years Mod: 86% M/ 14% F 45.5 (34 to 56) years ESRD: 0% M/ 100% F 74.5 years	AEs, vital signs, ECGs, clinical laboratory tests. PK of gabapentin	m5.3.3.3

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP067 / RXP111411	1 center in US	20APR07/ Complete/ 22MAY07 Total 12/ Target 12	Multiple dose PK, drug-drug interaction with Naproxen	Open-label, multiple dose, 3 treatment periods	Healthy subjects	XP13512 1200 mg OD for 5 days; Naproxen 500 mg BID for 5 days; XP13512 1200 mg OD plus Naproxen 500 mg BID for 5 days/ Oral/ 15 days (5 days on each of 3 treatments)	12 enrolled/ 10 completed	67% M/ 33% F 31 (18 to 53 years	AEs, vital signs, ECGs, clinical laboratory tests. PK of gabapentin and naproxen	m5.3.3.4
XP068 / RXP111419	1 center in US	11JUN07/ Complete/ 03JUL07 Total 12/ Target 12	Multiple dose PK, drug interaction with cimetidine	Open-label, multiple dose, 3 treatment periods	Healthy subjects	XP13512 1200 mg OD for 4 days; cimetidine 400 mg QID for 4 days; XP13512 1200 mg OD plus cimetidine 400 mg QID for 4 days/ Oral/ 12 days (4 days on each of 3 treatments)	12 enrolled/ 12 completed	92% M/ 8% F 24.6 (20 to 43) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of gabapentin and cimetidine	m5.3.3.4

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP069 / RXP111420	1 center in US	06SEP06/ Completed/ 27DEC06/ Total 32/ Target 32	Safety, tolerability, & PK of 4 single doses of XP13512; dose escalation to supra-therapeutic doses	Double-blind, randomized, placebo-controlled, crossover, dose escalation	Healthy subjects	XP13512 2400, 3600, 4800, and 6000 mg and placebo/ Oral/ Single dose	32 randomized/ 31 completed	44% M/ 56% F 31.2 (18 to 50) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of XP13512 & gabapentin	m5.3.3.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP072 / RXP111493	1 center in US	27APR06/ Complete/ 19SEP06 Total 48/ Target 48	Safety, tolerability and PK of single dose of XP13512 under fasting and fed conditions in Japanese and Caucasian subjects	Double-blind, randomized, placebo-controlled, ascending single dose	Healthy subjects (Japanese and Caucasian males)	XP13512 600 mg (fasted), 1200 mg (fasted), and 1800 mg (fasted and fed) and placebo/ Oral/ Single dose	Japanese XP13512: 18 randomized/ 18 completed Japanese Placebo: 6 randomized/ 6 completed Caucasian XP13512: 18 randomized 16 completed Caucasian Placebo: 6 randomized/ 6 completed	Japan XP: 100% M 30.9 (22 to 45) years Japan Pbo: 100% M 26.2 (21 to 32) years Cauc XP: 100% M 30.8 (20 to 43) years Cauc Pbo: 100% M 31.8 (25 to 44) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of XP13512	m5.3.3.3

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP073 / RXP111494	1 center in US	26SEP06/ Complete/ 08JAN07 Total 31/ Target ~32	Safety and tolerability, PK	Double-blind, randomized, placebo-controlled, ascending multiple dose	Healthy subjects (Japanese)	XP13512 1200 mg BID (fed) and 1800 mg BID (fed) or placebo/ Oral/ 9 to 11 days	XP13512: 24 randomized/ 22 completed Placebo: 7 randomized 7 completed	XP: 50% M/ 50% F 28.7 (20 to 48) years Pbo: 57% M/ 43% F 34.8 (27 to 53) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of XP13512, gabapentin, and gabapentin lactam	m5.3.3.3
XP078 / RXP111421	1 center in US	20JUL07/ Complete/ 03NOV07 Total 54/ Target 52	Thorough QT evaluation	Double-blind, randomized, placebo- and active controlled, four-period crossover	Healthy subjects	XP13512 1200 mg and 6000 mg, placebo, and 400 mg moxifloxacin/ Oral/ Single dose	54 randomized/ 48 completed	57% M/ 43% F 29.2 (18 to 50) years	The difference in time-matched baseline-adjusted individual-ized correction of the QT interval (QTcIb)	m5.3.4.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP081 / RXP111462	21 centers in US	16JAN07/ Complete/ 10JAN08/ Total 217/ Target 200	Population PK, dose/ exposure response, safety, tolerability	Double-blind, randomized, placebo-controlled, parallel group	Subjects with RLS	XP13512 600, 1200, 1800 or 2400 mg or placebo OD/ Oral 12 weeks	XP13512 600 mg: 48 randomized / 34 completed XP13512 1200 mg: 45 randomized / 31 completed XP13512 1800 mg: 38 randomized / 30 completed XP13512 2400 mg: 45 randomized / 33 completed Placebo: 41 randomized / 31 completed	36% M/ 64% F 48.0 (18 to 77) years	Relationship between gabapentin exposure and relief of symptoms (e.g. IRLS Rating Scale total score & proportion of responders on investigator-rated CGI-I)	m5.3.5.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP083 / RXP111463	19 centers in US	09APR07/ Complete/ 09NOV07/ Total 130/ Target 120	Simulated driving performance, cognition, and efficacy	Double-blind, randomized, placebo- and active-controlled, parallel group	Subjects with RLS	XP13512 1200 or 1800 mg, placebo, or placebo plus diphenhydramine (DPH) 50 mg (once on Day 16), OD/ Oral/ 16 days	XP13512 1200mg: 32 randomized/ 28 completed XP13512 1800mg: 34 randomized/ 33 completed Placebo: 34 randomized/ 32 completed Placebo + DPH: 30 randomized/ 28 completed	40% M: 60% F 46.8 (21 to 70) years	Change from baseline in overall lane position variability measured by simulated driving performance at the estimated time to maximum drug concentration (T_{max}) on Day 16	m5.3.5.4
XP084 / RXP111495	Not applicable	Not applicable	Population PK-PD Analysis	Not applicable	Not applicable	XP13512 600 mg to 2400 mg doses from Phase I (PK only), II and III studies	Not applicable	Not applic-able		m5.3.3.5

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP086 / RXP111422	1 center in US	15FEB07/ Completed/ 06APR07/ Total 10/ Target 10	Safety, tolerability & PK of 4 single doses of XP13512; *in vitro/in vivo* correlation of XP13512 formulations & Neurontin	Open-label, randomized, single dose, 5-period crossover	Healthy subjects	600 mg (2 x 300 mg) of Neurontin and 1200 mg (2 x 600 mg) of each of 4 different XP13512 tablet formulations (SR1, SR2, SR3, and SR4) under fasted conditions/ Oral/ Single dose	10 randomized/ 8 completed	100% M 27 (21 to 38) years	AEs, vital signs, ECGs, clinical laboratory tests. PK of gabapentin, and development of an *in vitro-in-vivo* correlation model	m5.3.1.3
XP087 / RXP111423	1 center in US	24NOV06/ Complete/ 29DEC06 Total 12/ Target 12	Single dose PK, food effect	Open-label, randomized, 4-period, crossover	Healthy subjects	XP13512 1200 mg under fasted, low-fat, and moderate fat, and high fat conditions/ Oral/ Single dose	12 randomized/ 10 completed	67% M/ 33% F 30.1 years	AEs, vital signs, ECGs, clinical laboratory tests. PK of gabapentin	m5.3.1.1

Xenoport Study Number/ GSK Study Number.	No. Study Centres Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
XP088 / RXP111496	1 center in US	04DEC06/ Complete/ 14MAR07 Total 30/ Target 30	Simulated driving performance in untreated subjects	Pilot study	Healthy subjects and subjects with currently untreated RLS	None	Healthy subjects: 15 enrolled/ 15 completed RLS subjects: 15 enrolled/ 15 completed	43% M/ 57% F 44.0 (19.5 to 73.6) years	Simulated driving performance	m5.3.5.4
NA / PXN110448	70 -80 centers in US	11MAR08/ Ongoing/ Target 392	Efficacy, safety, and dose-response	Double-blind, randomized, placebo- and active-controlled, parallel group	Subjects with NP associated with DPN	XP13512 600 mg, 1200 mg, 1800 mg, placebo, BID or pregabalin 100 mg TID/ Oral/ 14 weeks	As of 31 Mar 2008 data cut-off, 7 subjects screened and 1 subject randomized	NA	Change from baseline in mean 24-hour average pain intensity score based on an 11-point Pain Intensity Numerical Rating Scale.	Refer to m5.3.5.3 Integrated Summary of Safety, Section 1.1.4.3 for description

AE = adverse event; BID = twice daily, Cauc = Caucasian, DPH = diphenhydramine, DPN = Diabetic peripheral neuropathy, CGI-I = Clinical Global Impression - Improvement, ECG = electrocardiogram, ER = extended release, ESRD = end stage renal disease, IR = immediate release, IRLS = International Restless Legs Syndrome, Jap = Japanese, OD = once daily, Pbo = Placebo, PK = pharmacokinetics, RLS = Restless Legs Syndrome, ER = extended release, TID = three times daily, XP = XP13512, UK = United Kingdom, US = United States

Note: Additional ongoing studies contributing to safety exposure: Astellas-sponsored studies (RLS Study 8825-CL-0003, RLS Study 8825-CL-0005 and DPN Study 8825-CL-0007). Refer to m5.3.5.3 Integrated Summary of Safety, Section 1.1.4.3 for descriptions.

Table 1 **Summary of Phase II and III Studies Supporting Safety and Efficacy of XP13512 ER Tablets in the Treatment of Primary RLS**

Study Number	Phase	Design and Control	Primary Objectives	Duration	Regimens	Number of Subjects[1]
XP021	II	Double-blind, randomized, placebo-controlled, 2-period crossover	Efficacy & safety	14 days for each period	XP13512 1800 mg / Placebo Placebo/XP13512 1800 mg	34
XP045	II	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	14 days	Placebo / XP13512 1800 mg	29
					XP13512 1200 mg	32
					Placebo	33
XP081	II	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety, dose/exposure response	12 weeks	XP13512 600 mg	47
					XP13512 1200 mg	43
					XP13512 1800 mg	37
					XP13512 2400 mg	44
					Placebo	40
XP083	II	Double-blind, randomized, placebo-controlled, parallel group	Simulated driving performance, cognition, efficacy & safety	14 days (for efficacy)	XP13512 1200 mg	28
					XP13512 1800 mg	33
					Placebo	33
					Placebo plus diphenhydramine 50 mg (once on Day 16)	28
XP052	III	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	12 weeks	XP13512 1200 mg	112
					Placebo	108
XP053	III	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	12 weeks	XP13512 1200 mg (primary comparison)	111
					XP13512 600 mg	114
					Placebo	96
XP060	III	24-week single-blind phase with responders entering 12-week, double-blind, randomized, placebo-controlled, parallel group phase	Maintenance of efficacy & safety	36 weeks	Single-Blind: XP13512 1200 mg	311
					Double-Blind: XP13512 1200 mg	97
					Double-Blind: Placebo	96
XP055[2]	III	Long-Term Safety	Safety	52 weeks	XP13512 1200 mg	583[3]

1. Number of subjects in the following populations : Modified Intent-to-Treat Population for Studies XP052, XP053, XP081 and XP083; Intent-to Treat Populations for Single-Blind and Double-Blind Phases for Study XP060, and for Studies XP021 and XP045; Safety Population for Study XP055.
2. An interim analysis of safety data with a cut-off date of 06 December 2007 is included in the submission; in addition, data regarding serious adverse events, pregnancies, and deaths are included between 06 December 2007 and the submission cut-off date of 31 March 2008.
3. Some subjects were treatment-naïve (i.e., may have been randomized to placebo in parent study).

Table 1 Composition of XP13512 ER Tablets, 600 mg

Component	Quantity (mg/tablet)	Function	Reference to Standard
(b) (4)			

Note:

1. Assuming 100% conversion of XP13512 to gabapentin *in vivo*, 600 mg of XP13512 (MW 329.39) is equivalent to 312 mg of gabapentin (MW 171.24) on a molecular weight basis.
2. GlaxoSmithKline Internal Specification.
3. (b) (4)
4. Magnesium Stearate is of (b) (4)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22399	ORIG 1		SOLZIRA

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/s/

Ju Ping LAI
08/11/2009

YANING WANG
08/11/2009

RAMANA S UPPOOR
08/11/2009
Atul Bhattaram is the primary pharmacometrics reviewer.

MEHUL U MEHTA
08/11/2009

CLINICAL PHARMACOLOGY REVIEW

NDA:	**22399**
Brand Name:	Horizant
Generic Name:	Gabapentin Enacarbil
Dosage Form & Strength:	Extended Release Tablets, 600 mg
Indication:	Restless Legs Syndrome (RLS)
Applicant:	GlaxoSmithKline (GSK)
Submission:	505(b)(2), resubmission
Submission Dates:	10/6/2010
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Seongeun Julia Cho, Ph.D.
Team Leader:	Angela Yuxin Men, M.D., Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

The current submission for Horizant (Gabapentin Enacarbil) Extended Release (ER) Tablets is a resubmission of NDA 22-399 under section 505(b)(2), which was originally submitted by the sponsor as a 505(b)(1) submission for the treatment for moderate-to-severe primary Restless Legs Syndrome (RLS). The Agency issued a Complete Response (CR) letter on 2/17/2010 due to the concerns on the signal for pancreatic acinar cell tumors (adenoma, carcinoma) found in rats. Although there was no clinical signal for pancreatic cancer, the Agency determined that the treatment poses a risk for a life threatening cancer for patients with RLS.

In this submission, the sponsor provides complete response to the deficiencies identified in the CR letter. The resubmission contains new data and information on the safety margin and the lack of relevance to humans of pancreatic acinar cell tumors in rat and new epidemiologic data. The submission also includes a Final Safety Update (FSU), which provides updated safety information for gabapentin enacarbil. The sponsor states that since the 120-Day Safety Update (submitted to the Agency on 05/0102009) cut-off date 01/16/2009, 7 GSK-sponsored studies and 3 Astellas-sponsored studies have been completed. FSU provides safety information of these clinical studies. Among the studies is a Phase I single dose relative bioavailability clinical pharmacology study (PXN110882) in healthy volunteers, which is the subject of the current clinical pharmacology review. Since the main purpose of the current submission is to address the Agency's concern on pancreatic tumor potential in human by providing additional non-clinical and clinical safety data, clinical pharmacology evaluation of the study PXN110882 is supportive in nature.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical pharmacology section of the NDA 22-399 resubmission and found it acceptable from a clinical pharmacology perspective. The acceptability of the safety profile of the clinical pharmacology study PXN110882 will be reviewed by the clinical reviewer in DNP.

1.2 Post-Marketing Requirements

Not applicable

1.3 Summary of Clinical Pharmacology Findings

Gabapentin Enacarbil (Gen) converts to gabapentin rapidly by non-specific carboxylesterase primarily in enterocytes and to a lesser extent in the liver upon absorption. Ester hydrolysis is the only significant metabolic pathway. The concentration of intact pro-drug in blood after absorption is transient and $\leq 2\%$ of the corresponding gabapentin level.

One clinical pharmacology study (PXN110882) was completed and submitted in this application. Study PXN110882 was an open-label, randomized, single-dose, five-period, crossover study to evaluate the relative bioavailability of different formulations of Gen in 17 healthy volunteers. The study assessed two new 600 mg and two new 900 mg extended release tablet formulations in comparison with the 600 mg tablet of the current extended release formulation. All formulations were given at a dose of 1800 mg.

The analysis of pharmacokinetic profiles shows that AUC(0-∞) and Cmax of all formulations are comparable with an exception of one formulation (Formula Code AK, 900 mg test tablets), of which 90 % confidence interval for Cmax was marginally outside (90% CI: 0.765 - 0.936). Overall, values for AUC(0-∞) and Cmax in this study are consistent with those in previous studies (see below for details).

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the proposed mechanisms of action and therapeutic indication(s)?

The precise mechanism by which gabapentin is efficacious in RLS is unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but it does not modify GABAA or GABAB radioligand binding. It is not converted metabolically into GABA or a GABA agonist. It has been shown to bind to an auxillary subunit of voltage-activated calcium channels in rat brain in vitro; however its relationship to RLS is unknown.

The proposed indication is the treatment of moderate to severe primary RLS.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

HORIZANT (Gabapentin Enacarbil) is a prodrug of gabapentin and is formulated as an ER tablet. It is a white to off-white tablet containing 600 mg of gabapentin (XP13512).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dosage for HORIZANT is 600 mg once daily taken with food at about 5 PM (per labeling recommendation during the original review cycle).

2.2 Clinical Pharmacology

2.2.1 What are the PK characteristics of the drug and its major metabolite?

2.2.1.1 Single dose PK parameter

Single dose PK parameters of one reference formulation (AA) and 4 test formulations (AL, AM and AN and AK) were evaluated in an open-label, randomized, single dose, five-period crossover study in healthy volunteers.

Blood samples were collected for pharmacokinetic analyses of gabapentin over a 36-hour period following each single oral dose of five formulations.

Summary of key Plasma Gabapentin Pharmacokinetic Parameters

Treatment	N	AUC(0-t) (μg·h/mL)	AUC(0-∞) (μg·h/mL)	Cmax (μg/mL)	t½ (h)	Tmax (h)[2]
AA	16	112 (19.7)	115 (19.9)	9.88 (22.3)	5.50 (19.0)	6.00 (4.00 – 8.00)
AL	16	102 (19.7)	105 (19.2)	9.47 (24.1)	5.59 (19.3)	6.04 (6.00 – 18.0)
AM	16	98.4 (22.9)	101 (23.8)[3]	9.44 (29.3)	5.77 (21.2)[3]	6.00 (3.00 – 24.0)
AK	16	99.3 (30.9)	102 (30.8)	8.35 (26.9)	5.58 (23.0)	6.00 (6.00 – 14.0)
AN	16	106 (19.6)	110 (20.4)	9.03 (24.1)	5.62 (18.4)	7.00 (4.00 – 12.0)

(note 3: n=16 for all groups, except for AM, n=15)

Gabapentin pharmacokinetics were similar between the reference treatment and test formulations, with median Tmax values ranging from 6.00 to 7.00 h and mean t½ values ranging from 5.50 to 5.77 h. Low to moderate intersubject variability (18.4% to 30.9% CVb) was observed with these pharmacokinetic parameters.

AUC(0-∞) and Cmax values of test formulations AL, AM and AN were 5 – 10 % lower than the reference formulation AA. The 90% confidence intervals for AUC(0-∞) and Cmax for the test formulations AL, AM and AN, in comparison to reference formulation AA, were contained within the bioequivalence limits (0.8 to 1.25).

AUC(0-∞) and Cmax values of test formulations AK were 11% and 15% lower, respectively, than the reference formulation AA. The 90% CIs for Cmax for AK in comparison to AA were marginally outside (90% CI: 0.765 - 0.936), while those of AUC were within the bioequivalence limits.

2.2.1.2 Are the exposure of Gabapentin Enacarbil and Gabapentin in this study comparable to those in previous clinical studies?

The gabapentin Cmax values in plasma in this study following a single oral administration of various formulation of Gabapentin Enacarbil at 1800 mg were in the

range of 8.35 – 9.88 ug/ml. The gabapentin AUC(0-∞) values were in the range of 101 – 115 ug.h/ml.

The following is a table of the mean Cmax and AUC(0-∞) values for gabapentin reported in previous clinical studies summarized by this reviewer.

Study	Dose (mg)	Cmax (ug/ml)	AUC(0-∞) (ug.h/ml)	Comments
XP019	600	2.79	27.2	Blood, fasted
XP-022	1200 (2x600)	4.12	54.5	Blood, fasted
	1200 (2x600)	6.24	83.0	Blood, fed
XP-022	1200 (2x600)	5.37	72.4	Plasma, fasted
	1200 (2x600)	7.92	110	Plasma, fed
XP-044	300	2.26	27. 4	Plasma, fed
	600	4.41	54. 1	Plasma, fed
	1200	7.59	92. 4	Plasma, fed
XP-057	1200 (2x600)	6.93	98.7	Plasma, fed
XP-087	1200 (2x600)	5.04	58.8	Plasma, fasted
	1200 (2x600)	7.2	82.1	Plasma, fed
XP-006	700	6.55	53.0	Blood, fasted
	1400	11.3	85.0	Blood, fasted
	2100	15.7	120	Blood, fasted
XP-069	2400	11.4	118	Blood, fasted
	3600	16.2	175	Blood, fasted

For example, in Study XP019, the mean Cmax and AUC(0-∞) for gabapentin in blood following a single oral dose of (b) (4) tablet #030040 (1x 600 mg) in Group 2 were 2.79 ug/ml and 27.2 ug.h/ml.

Similarly, in Study XP-022, the mean Cmax and AUC(0-∞) for gabapentin in blood following a single oral dose of (b) (4); SR tablets 1200 mg (2x600mg) were 4.12 ug/ml and 54.5 ug.h/ml under the fasted condition and 6.24 ug/ml and 83 ug.h/ml under fed conditions. In this study, the mean Cmax and AUC(0-∞) for gabapentin in plasma were 5.37 ug/ml and 72.4 ug.h/ml under the fasted condition and 7.92 ug/ml and 110 ug.h/ml under the fed condition.

In Study XP-044, the mean Cmax and AUC(0-∞) for gabapentin in plasma following 300 mg, 600 mg, and 1200 mg were 2.26, 4,41, 7.59 ug/ml, respectively and 27.4, 54.1, 92.4 ug.h/ml, respectively under fed conditions.

The review of data in the original submission determined that Gabapentin Enacarbil exhibits dose proportionality over a single dose range of 300 mg to 6000 mg. Therefore, for a purpose of comparisons across the studies in this review, the exposure and Cmax values from previous studies were normalized for 300 mg. In addition, only the studies

reporting Cmax and AUC(0-∞) in plasma under fed conditions were considered in this comparison to match the study design of current study PXN110882.

Study	Dose (mg)	Cmax (ug/ml)	Cmax*	AUC(0-∞) (ug.h/ml)	AUC(0-∞)*	Comments
XP-022	1200	7.92	2.0	110	27.5	Plasma, fed
XP-044	300	2.26	2.26	27.4	27.4	Plasma, fed
	600	4.41	2.2	54.1	27.1	Plasma, fed
	1200	7.59	1.9	92.4	23.1	Plasma, fed
XP-057	1200	6.93	1.7	98.7	24.7	Plasma, fed
XP-087	1200	7.2	1.8	82.1	20.5	Plasma, fed
PXN110882(AA)	1800	9.88	1.6	115	19.2	Plasma, fed

* normalized values to 300 mg

The mean Cmax and AUC(0-∞) of Gabapentin Enacarbil (AA) in the current submission were comparable to those observed in Study XP-087.

2.3 Analytical section

2.3.1 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

Human plasma samples were analyzed for gabapentin concentrations using a validated HPLC-MS/MS method based on protein precipitation. The assay was validated over the gabapentin concentration range 50.0 to 50000 ng/mL in human plasma.

Quality controls were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. For the analysis to be acceptable, no more than one third of the quality control results were to deviate from the nominal concentration by more than 15%, with at least one quality control result acceptable at each concentration. Quality control results from this study met these acceptance criteria.

Matrix	Plasma
Method	HPLC-MS/MS
Linear Range	50 – 50,000 ng/ml
LLOQ	50 ng/m
QC concentrations	200, 4000, 40,000 ng/ml
Inter-day precision	< 5 %
Inter-day accuracy	< 5 %
Validation acceptable	

3. DETAILED LABELING RECOMMENDATIONS

Not Applicable

4. APPENDIX

4.1 Individual study report

Study Number: PXN110882

Title: An open-label, randomized, single dose, five-period crossover study to evaluate the relative bioavailability of different formulations of GSK1838262 in healthy volunteers.

Study period:
Initiation Date: 16 JAN 2009
Completion Date: 12 MAR 2009

Phase of development: I

Primary Objectives: To estimate the relative bioavailability of gabapentin (the active moiety) following oral administration of test formulations of GSK1838262 tablets, compared to the reference GSK1838262 tablet.

Methodology:
In order to provide a more convenient dosage regimen for subjects and to reduce tablet burden, new smaller 600 mg tablets have been developed together with 900 mg tablets (b) (4)

The four new formulations were tested against the 600 mg strength tablet of the current formulation to identify the most promising new formulations for further development. Doses of 1800 mg were given to make direct comparisons to the reference tablet.

Treatment administration:
All subjects received a single oral dose of the following treatments, following a standard meal, in random sequence:
A: GSK1838262 1800 mg dose in three 600 mg reference tablets, [Formula Code AA, batch number 081167678].
B: GSK1838262 1800 mg dose in three 600 mg test tablets, increased drug load with no (b) (4) [Formula Code AL, batch number, 081179717].
C: GSK1838262 1800 mg dose in three 600 mg test tablets, increased drug load (b) (4) Formula Code AM, batch number 081179775].
D: GSK1838262 1800 mg dose in two 900 mg test tablets, increased drug load with no (b) (4) [Formula Code AK, batch number 081179740].
E: GSK1838262 1800 mg dose in two 900 mg test tablets, increased drug load with no

[redacted](b) (4), [Formula Code AN, batch number 081179715].

Primary endpoints: AUC (0-∞), tmax and Cmax of gabapentin in plasma.

Pharmacokinetic Analyses
Blood samples were collected for pharmacokinetic analyses of gabapentin over a 36-hour period following each single oral dose of five formulations of GSK1838262 (at pre-dose, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 18, 24, 30 and 36 hr post-dose). Bioanalysis of gabapentin plasma concentrations was conducted using a validated analytical method based on protein precipitation followed by HPLC-MS/MS analysis. Pharmacokinetic analyses of gabapentin plasma concentration-time data were conducted using non compartmental methods.

Number of subjects:
A total of 17 subjects were randomized. Mean age was 39.3 years (range 19 to 64 years). Six subjects were female (35.3%) and 11 (64.7%) were male. One subject withdrew and, thus, PK data are provided on 16 subjects.

Results

Pharmacokinetics

Summary of key Plasma Gabapentin Pharmacokinetic Parameters

Treatment	N	AUC(0-t) (μg·h/mL)	AUC(0-∞) (μg·h/mL)	Cmax (μg/mL)	t½ (h)	Tmax (h)[2]
AA	16	112 (19.7)	115 (19.9)	9.88 (22.3)	5.50 (19.0)	6.00 (4.00 – 8.00)
AL	16	102 (19.7)	105 (19.2)	9.47 (24.1)	5.59 (19.3)	6.04 (6.00 – 18.0)
AM	16	98.4 (22.9)	101 (23.8)[3]	9.44 (29.3)	5.77 (21.2)[3]	6.00 (3.00 – 24.0)
AK	16	99.3 (30.9)	102 (30.8)	8.35 (26.9)	5.58 (23.0)	6.00 (6.00 – 14.0)
AN	16	106 (19.6)	110 (20.4)	9.03 (24.1)	5.62 (18.4)	7.00 (4.00 – 12.0)

2. Median (range)
3. n = 15

AUC(0-∞) and Cmax values of test formulations AL, AM and AN were 5 - 10% lower than the reference formulation AA. The 90% confidence intervals for AUC(0-∞) and Cmax for the test formulations AL, AM and AN, in comparison to reference formulation AA, were contained within the bioequivalence limits (0.8 to 1.25).

AUC(0-∞) and Cmax values of test formulations AK were 11% and 15% lower, respectively, than the reference formulation AA. The 90% CIs for Cmax for AK in comparison to AA were marginally outside (0.765 – 0.936), while those of AUC were within the bioequivalence limits.

Safety:

There were no deaths or serious adverse events (SAEs) reported in this study.

Table 8 Summary of all Drug-Related Adverse Events

Preferred Term	Number (%) of Subjects Reporting AE					
All drug-related AEs	AA (N=16)	AL (N=17)	AM (N=16)	AK (N=16)	AN (N=16)	Total (N=17)[1]
Any AE related to investigational product	8(50.0)	8(47.1)	8(50.0)	4(25.0)	10(62.5)	14(82.4)
Somnolence	3(18.8)	4(23.5)	0	1(6.3)	6(37.5)	9(52.9)
Dizziness	1(6.3)	2(11.8)	1(6.3)	1(6.3)	3(18.8)	5(29.4)
Euphoric mood	1(6.3)	1(5.9)	3(18.8)	0	1(6.3)	5(29.4)
Feeling drunk	1(6.3)	2(11.8)	3(18.8)	0	1(6.3)	4(23.5)
Disturbance in sexual arousal	2(12.5)	1(5.9)	1(6.3)	1(6.3)	1(6.3)	2(11.8)
Dizziness postural	1(6.3)	0	0	1(6.3)	0	1(5.9)
Headache	0	1(5.9)	0	0	0	1(5.9)
Feeling abnormal	0	0	0	0	1(6.3)	1(5.9)
Feeling of relaxation	1(6.3)	0	0	0	0	1(5.9)
Muscular weakness	0	0	0	1(6.3)	0	1(5.9)
Pain in extremity	1(6.3)	0	0	0	0	1(5.9)
Lip dry	0	0	0	0	1(6.3)	1(5.9)
Flushing	0	1(5.9)	0	0	0	1(5.9)

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/s/

SEONGEUN CHO
03/14/2011

YUXIN MEN
03/29/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-399	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	GlaxoSmithKline	**Team Leader:** Angelica Dorantes, Ph.D	
Trade Name:	Horizant™ Extended Release tablets	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Gabapentin enacarbil extended release tablets	**Date Assigned:**	NA
Indication:	Restless leg syndrome (RLS)	**Date of Review:**	Oct 23, 2009
Formulation/ Strength	(b) (4) tablet, 600 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp/Received Date**	**Date of informal/Formal Consult**	**DUE DATE**
Oct 8, Oct 15, Oct 23, 2009	Oct 8, Oct 15, Oct 23, 2009	NA	NA
Type of Submission:	Original NDA/Response to comments		
Type of Consult:	Sponsor's response to FDA comments on dissolution method and specifications/ (b) (4);		

REVIEW SUMMARY:

Gabapentin enacarbil (XP13512) (GE) is a prodrug developed to overcome the biopharmaceutical limitations of gabapentin. The proposed dose formulation is an extended release (ER) tablet intended to provide relief of the symptoms of primary restless leg syndrome. The proposed starting dose is 600 mg QD (b) (4) given at 5 PM with food.

Upon the review of the Biopharmaceutics section (dissolution method and specifications/ (b) (4)) of the original NDA submission, the following comments were submitted to the sponsor on October 2, 2009 regarding the dissolution method and specification:

a) The following dissolution specification are recommended for gabapentin enacarbil ER tablets:

USP Apparatus	Spindle Rotation Speed	Media Volume	Temperature	Medium	Specifications
II	50 rpm	900 mL	37°C	10 nM potassium phosphate monobasic buffer at pH 7.4 with 1% SLS	4 hours: (b) (4) 8 hours: 12 hours 24 hours

b) Your proposed dissolution method appears to be over-discriminating and not clinically relevant: the method discriminates between two batches that have equal in vivo performance. Consider the development of a more clinically relevant dissolution method that is not over-discriminating.
c) Provide stability data from the three primary batches to support the dissolution specification at the recommended time intervals.

On October 15, 2009, the sponsor submitted the following responses to the above comments:

Response to question a:
"GSK agrees to adopt the recommended specification sampling times, but with the revised acceptance criteria for the 8 and 12 hour sampling time points. The proposed revised specification is listed in Table 1."

Table 1

Proposed Specification	
Time (hrs)	% Released
4	(b) (4)
8	
12	
24	

The sponsor states that clinical study XP086 compared two batches of the same formulation, manufactured at the same scale, from the intended commercial site of manufacture. These batches (3049975R and 3053361R) which have the fastest and the slowest *in-vitro* release profile of all the current clinical trial supply batches using the, were shown to be bioequivalent.

The mean tablet dissolution for these batches at 8 hours and 12 hours ranged from (b) (4) , respectively, and the individual tablet dissolution test values ranged from (b) (4), respectively. The sponsor added that for pivotal clinical supplies, the mean dissolution at 8 hours and 12 hours ranged from (b) (4) , respectively, and the individual tablet dissolution test values ranged from (b) (4) respectively. GSK considers that the proposed revised dissolution specification is supported based on the similar pharmacokinetic concentration-time profiles between the (b) (4) batches with the highest and lowest dissolution rates and on

the dissolution data for phase 3 supplies.

Response to question b:
"GSK agrees that the dissolution method is over-discriminating for the in-vivo performance…….. Therefore, we conclude that this more discriminating dissolution method serves well as a process quality control tool. GSK accepts the Agency's concern that the method is over discriminating and will review the dissolution data once more experience is gained from the launch of the product and a greater number of commercial batches have been manufactured. At that time, if warranted, GSK will assess if any dissolution method changes are required. GSK therefore proposes to continue with the more discriminating dissolution method through product approval and launch".

The sponsor proposal is to keep the proposed dissolution method through product approval and launch.

Response to question c
"Dissolution data at specified timepoints are provided in the updated m3.2.P.8.3 provided with this response. These stability data fully support the proposed revised specification".

It is noted that the mean dissolution profiles (Stage 1) for some lots under stability do not meet the proposed FDA dissolution specifications, but meet the specification proposed by the sponsor.

A teleconference with the sponsor was held on October 21, 2009 to discuss the sponsor's responses to comments sent on Oct 2, 2009 (refer also to Biopharm review entered on DARRTS on September 30, 2009 and to the Sponsor's responses to comments received on Oct 8, 2008 (b) (4) The following agreements, which were also submitted in writing to the Agency on Oct 23, 2009, were reached during the teleconference:

- The Agency agreed on the following dissolution specifications for gabapentin enacarbil ER tablets:

USP Apparatus	Spindle Rotation Speed	Media Volume	Temperature	Medium	Specifications
II	50 rpm	900 mL	37°C	10 nM potassium phosphate monobasic buffer at pH 7.4 with 1% SLS	4 hours: (b) (4) 8 hours: 12 hours 24 hours

These specifications were set based on the mean ranges of % dissolved for two bioequivalent batches (3049975R and 3053361R) of gabapentin enacarbil

- (b) (4)

(b) (4)

RECOMMENDATION:
The ONDPQ/biopharmaceutics team has reviewed the dissolution specifications for gabapentin enacarbil ER tablets submitted under NDA 22-399 (S0032) on Oct 23, 2009. The proposed specifications had been previously discussed and agreed during a telecon with the sponsor on Oct 21, 2009. There are no additional comments to the sponsor at this time.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: DHenry, Adorantes, ChTele, MHeimann

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
.NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	(b) (4)

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SANDRA SUAREZ
10/26/2009

PATRICK J MARROUM
10/27/2009

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-399	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	GlaxoSmithKline	**Team Leader:** Angelica Dorantes, Ph.D	
Trade Name:	Horizant™ Extended Release tablets	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Gabapentin enacarbil extended release tablets	**Date Assigned:**	Aug 26, 2009
Indication:	Restless leg syndrome (RLS)	**Date of Review:**	Sep 28, 2009
Formulation/ Strength	Controlled release tablet, 600 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp/Received Date**	**Date of informal/Formal Consult**	**DUE DATE**
Jan 08, 2009	Jan 09, 2009	June 2009	Sep 30, 2009
Type of Submission:	Original NDA		
Type of Consult:	(b) (4)		

REVIEW SUMMARY:

Gabapentin enacarbil (XP13512) (GE) is a prodrug developed to overcome the biopharmaceutical limitations of gabapentin. The proposed dose formulation is an extended release (ER) tablet intended to provide relief of the symptoms of primary restless leg syndrome. The proposed starting dose is 600 mg QD (b) (4) given at 5 PM with food. Based on exposure-response analysis, the OCP is recommending a maintenance dose of 600 mg qd (b) (4)

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	(b) (4)

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/s/

SANDRA SUAREZ
09/30/2009

PATRICK J MARROUM
09/30/2009