CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022345Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-345
Brand Name:	Potiga™ Tablets
Generic Name:	Ezogabine
Sponsor:	Valeant Pharmaceuticals & GlaxoSmithKline
Type of Dosage Form:	Immediate release film-coated tablet
Strengths:	50, 200, 300, and 400 mg
Indication:	Adjunctive treatment of partial onset seizures
OCP Reviewers:	Ta-Chen Wu, Ph.D.
OCP Team Leader (Acting):	Veneeta Tandon, Ph.D.
OCP Division:	DCP-1 HFD-860
OND Division:	Division of Neurology Drug Products HFD-120
Submission Date:	April 15, 2011
Type of Submission:	Complete Response (Class 1) Resubmission

BACKGROUND:

The Sponsor submitted a complete response to the Agency's Complete Response Letter, including labeling recommendation, dated November 30, 2010. The NDA 22-345 for POTIGA (ezogabine) tablets was originally submitted on October 30, 2009. The proposed indication is adjunctive treatment of partial onset seizures in patients 18 years of age and older.

Noted in this complete response resubmission the Sponsor proposed to increase the maximum maintenance dose to 1200 mg/day (400 mg tid). To support the changes in labeling languages in Clinical Pharmacology sections, the Sponsor provided three supporting documents with respect to potential for digoxin interaction with ezogabine, hepatic impairment dosing guidance, and potential for antiepileptic drugs (AED) drug interaction with ezogabine. The main changes of the labeling recommendations are summarized below.

1. Potential for Digoxin Interaction with Ezogabine:

Sections of digoxin interaction were added, as presented below.

7.2 Digoxin

Data from an in vitro study showed that the N-acetyl metabolite of ezogabine (NAMR) inhibited P-glycoprotein–mediated transport of digoxin in a concentration-dependent manner, indicating that NAMR may inhibit renal clearance of digoxin. Administration of POTIGA at therapeutic doses may increase digoxin serum concentrations. Serum levels of digoxin should be monitored [*see Clinical Pharmacology (12.3)*].

(b) (4)

[redacted]

Rationale:
The N-acetyl metabolite of ezogabine (NAMR) inhibited digoxin transport in a concentration-dependent manner in an in-vitro study. Efflux inhibitions on P-glycoprotein (P-gp) transport activity for digoxin (a probe substrate) were 33%, 56%, and 70% with NAMR concentrations of 1μM (264ng/mL), 10μM (2643 ng/mL), and 100μM (26430 ng/mL), respectively. The I/IC50 ratios for NAMR were estimated to be >0.1, and thus the inhibitory potential on P-gp mediated digoxin elimination via kidney exists, especially when the maximum maintenance dose is increased to 1200 mg/day.

The Table below details the mean steady-state NAMR concentrations observed in the pivotal clinical Study VRX-RET-E22-301 in epileptic patients and the correlation with the in vitro results.

Ezogabine Daily Dose	600mg	900mg	1050mg	1200mg
Number of subjects	(2)	(4)	(4)	(4)
Cmax (±SD) ng/mL	780	885±419	1402±544	1523±612
Free NAMR (55%) at Cmax	429	486.75	771.1	837.65
Ratio FreeNAMR/2643ng/mL	0.16	0.18	0.29	0.32

A formal IC50 for NAMR was not calculated however the value of 2643 ng/mL could be considered close to the IC50 value.

OCP Recommendation:
Based on an in vitro study, NAMR metabolite was found to be an inhibitor of the efflux transporter P-gp at concentrations of NAMR expected after administration of proposed doses therapeutic levels of ezogabine. Therefore, we request that the sponsor conduct a study in humans as a Post Marking Requirement (PMR) to investigate the impact of NAMR as an inhibitor for P-gp using digoxin as a probe substrate.

2. Hepatic Impairment Dosing Guidance:

The Sponsor proposes to reduce the starting dose to half (i.e., 50 mg tid) and the maximum maintenance dose to 600 mg/day for patients with moderate hepatic impairment, as oppose to the 750 mg/day recommended by the Agency based on the approximate 50% increase in systemic exposure of ezogabine. Per the Sponsor, the proposed dosing regimens are based on the pharmacokinetic simulations for different starting doses. In addition, the starting dose of 100 mg tid would results in greater variability in this patient population. "The predicted steady state ezogabine Cmax and AUC(0-24) values for the initial starting dose of 100 mg TID were generally similar to or

higher than those predicted for healthy subjects, whereas, a reduction in the initial starting dose to 50 mg TID showed that the individual predicted steady state Cmax and AUC(0-24) values were completely contained within the range of the values predicted for healthy subjects." With that, the sponsor proposed to reduce both starting and maintenance doses in patients with moderate hepatic impairment to ½.

Reviewer's comment:
Based on results of the dedicated hepatic impairment study, the maintenance dose of 750 mg/day as recommended for patients with moderate impairment is expected to have similar AUC to that observed in healthy subjects; whereas the 600 mg/day would result in lower exposure. However, we do not consider the Sponsor's arguments, including the in-house PK simulation, convincing against the maximum 750 mg/day in this patient population. In addition, details of the simulation to support the Sponsor's claim were not available for the Agency's review. Details of the dosing instruction are presented in "Section 4. Dosing Recommendations for Specific Populations"of this review.

3. Potential for AED Drug Interaction with Ezogabine:

The Sponsor does not agree with FDA suggestion to include the information regarding phenytoin and carbamezepine from Study 3065A1-202 in the Drug Interaction Section (Section 7). Specifically, citing limited numbers of subjects in Study 3065A1-202, the Sponsor proposes to rely on results of population PK analysis of pooled data to show that concomitant AEDs had no significant impact on ezogabine. The Sponsor acknowledges the inducing effect of phenytoin and carbamezepine on ezogabine clearance but proposes no dose adjustment.

Reviewer's comment:
The Agency believes that the numbers of the subjects, though relatively limited, who were on concomitant phenytoin and carbamezepine from this specific study were sufficient enough to warrant dosage adjustment based on the observed inducing effects. Therefore, the recommended labeling languages for the pertinent drug-interaction sections have been revised and presented in a tabular format, as shown below.

7. DRUG INTERACTIONS
7.1 Antiepileptic Drugs

The potentially significant interactions between POTIGA™ and concomitant AEDs are summarized in the following Table:

AED	Dose of AED (mg/day)	POTIGA™ Dose (mg/day)	Influence of POTIGA™ on AED	Influence of AED on POTIGA™	Dosage Adjustment
Carbamazepine [a] *	600-2400	300-1200	None	31% decrease in AUC; 23% decrease in Cmax;	Consider an increase in POTIGA™ dosage [b]
Phenytoin [a] *	120-600	300-1200	None	34% decrease in AUC; 18% decrease in Cmax;	Consider an increase in POTIGA™ dosage [b]

[a] Based on trough concentrations in a Phase 2 study

(b) (4)

* Inducers for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs)

[See Clinical Pharmacology (12.3)]

12.3 Pharmacolokinetcs

Interactions with Antiepileptic Drugs*:* The interactions between POTIGA and concomitant AEDs are summarized in the following Table:

AED [a]	Dose of AED (mg/day)	POTIGA Dose (mg/day)	Influence of POTIGA on AED	Influence of AED on POTIGA	Dosage Adjustment
Carbamazepine [b] *	600-2400	300-1200	None	31% decrease in AUC; 23% decrease in Cmax; 28% increase in clearance; 5.3-hours shortening in half-life	An increase in POTIGA™ dosage needs to be considered [c]
Phenytoin [b] *	120-600	300-1200	None	34% decrease in AUC; 18% decrease in Cmax; 33% increase in clearance	An increase in POTIGA™ dosage needs to be considered [c]
Topiramate [b]	250-1200	300-1200	None	None	None
Valproate [b]	750-2250	300-1200	None	None	None
Phenobarbital	90	600	None	None	None
Lamotrigine	200	600	18% decrease in AUC; 22% increase in clearance; 5-hours shortening in half-life	None	None
Others [d]			None	None	None

(b) (4)

(b) (4)

* Inducers for uridine 5'-diphosphate (UDP)-glucuronyltransferases (UGTs)

4. Dosing Recommendations for Specific Populations:

Dosing Recommendations for Specific Populations in Section 2 of the label have been revised to a tabular format, as presented below.

2. DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

Table 1. Dosing Recommendations

Specific Population	Initial Dose	Titration	Maximum Dose
General Dosing			
General population (including patients with mild renal or hepatic impairment)	100 mg 3 times daily (300 mg per day)	Increase by no more than 50 mg 3 times daily, at weekly intervals	400 mg 3 times daily (1,200 mg per day)
Dosing in Specific Populations			
Geriatrics (patients >65 years)	50 mg 3 times daily (150 mg per day)	Increase by no more than 50 mg 3 times daily, at weekly intervals	250 mg 3 times daily (750 mg per day)
Renal impairment (patients with CrCL <50 mL per min or end-stage renal disease on dialysis)	50 mg 3 times daily (150 mg per day)		200 mg 3 times daily (600 mg per day)
Hepatic impairment (patients with Child-Pugh 7-9)	50 mg 3 times daily per week (150 mg per day)		250 mg 3 times daily (750 mg per day)
Hepatic impairment (patients with Child-Pugh >10)	50 mg 3 times daily per week (150 mg per day)		200 mg 3 times daily (600 mg per day)

Deleted: /

CONCLUSIONS AND RECOMMENDATIONS:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the Sponsor's complete response for the NDA 22-345, including the labeling, and finds it acceptable from an OCP perspective provided that the Sponsor agrees with the Phase IV commitment (PMR). In addition, agreement on the labeling language should be reached between the Sponsor and the Agency.

PHASE IV RECOMMENDATIONS:

The office of Clinical Pharmacology requests the following PMR:

A study in humans for the evaluation of the acetyl metabolite of ezogabine (NAMR) as an inhibitor for P-glycoprotein (P-gp) using digoxin as a probe substrate

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Reviewer, Neurology Drug Products, DCP-1, OCP

Veneeta Tandon, Ph.D.
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Mehul Mehta, Ph.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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06/06/2011

VENEETA TANDON
06/06/2011

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

Individual Study Reviews

(Question-Based Review for Potiga is in DARRTS dated 11/20/2010)

NDA:	22-345
Brand Name:	Potiga™
Generic Name:	Retigabine (Ezogabine)
Sponsor:	Valeant Pharmaceuticals & GlaxoSmithKline
Type of Dosage Form:	Immediate release film-coated tablet
Strengths:	50, (b) (4) 200, 300, and 400 mg
Indications:	Adjunctive treatment of partial onset seizures
OCP Reviewers:	Ta-Chen Wu, Ph.D., Kristina Dimova, Ph.D.
OCP Team Leader:	Angela Yuxin Men, M.D., Ph.D.
Pharmacometrics Reviewers/ Secondary Review	Joo-Yeon Lee, Ph.D., Yaning Wang, Ph.D.
Pharmacogenomics Reviewers/Secondary Review	Li Zhang, Ph.D., Issam Zineh, Pharm.D. M.P.H.
OCP Division:	DCP-1 HFD-860
OND Division:	Division of Neurology Drug Products HFD-120
Submission Date:	October 30, 2009, November 29, 2009, February 26, 2010, March 11, 2010, April 9, 2010, May 11, 2010, June 4, 2010
Type of Submission:	New, Standard NDA

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4. Appendices

4.4 Individual Study Reviews

4.4.1 General Clinical Pharmacology

Study 3065A1-100

Title: Clinical Trial to Assess Tolerability, Safety, and Pharmacokinetics of Orally Administered D-23129 in Healthy Male Volunteers

Objective: To evaluate the Safety, tolerability and pharmacokinetics of single doses of D-23129

Dose and Drug Products:

Strength	Batch No.
placebo, capsules	9508301
25 mg D-23129, capsules	9508302
100 mg D-23129, capsules	9508303

Planned dose steps (b) (4) 50, (b) (4) 200, 400, (b) (4)

Study Population: N=16 planned and enrolled

Study Design:
This was a randomized, double-blind, placebo controlled, alternating panel design. The healthy male subjects were randomized to two groups going through 3 dose steps (N=8 for each step to receive placebo (N=2), a "nominal dose" (N=5), or a "leading dose" (i.e. the nominal dose of the next step in the other group, N=1)).

Pharmacokinetic Sampling:
Plasma: pre-dose, 20 and 40 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24h post-dose
Urine: 0-2, 2-4, 4-8, 8-12, 24-36, and 36-48h post-dose

Pharmacokinetic Assessments:
The following PK parameters were estimated from plasma and urine data using non-compartmental methods: Cmax, Tmax, AUC0-t, AUC0-∞, λz, t1/2, CL/F, Vz/F, fe. Descriptive statistics were applied to PK parameters, safe parameters, and AEs.

Bioanalytical Method:
Plasma and urine samples were analyzed using a validated HPLC method. The performance of the assay during sample analysis is summarized in the table below.

		Retigabine (plasma)	Retigabine (urine)
Method:		HPLC	HPLC
Standard Curve:	Range:	3.1-800 ng/mL	12.5-2000 ng/mL
	Precision:	< ± 15%	< ± 15%

	Accuracy:	< ± 20%	< ± 20%
LOQ:		3.1 ng/mL	12.5 ng/mL
QC:		6.25, 50, 400 ng/mL	50, 200, 800 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%

RESULTS

Demographics:
All subjects were European origin (Caucasian). Age ranged 24-43 years (mean ~32 years). Weight ranged 55-110 kg (mean ~80 kg).
Prematurely discontinued: N=3 due to tolerability, disease, and other reasons
Completed assessments: N=12

Pharmacokinetics:
Figure 1. Mean (±SD) Plasma Concentration-Time Profiles of Retigabine after Single Oral Administration of 50 to 600 mg Retigabine

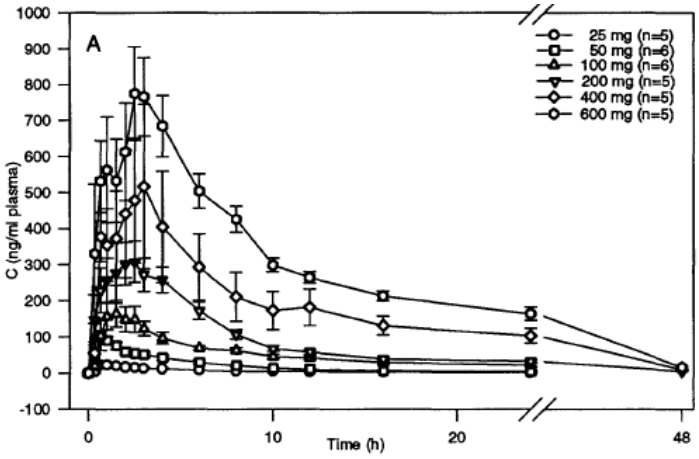


Table 1. Pharmacokinetic Parameters of Retigabine in Plasma after Administration of Single Oral Doses of Retigabine

	$C_{max\,1}$ (ng/ml)					$C_{max\,2}$ (ng/ml)		
Dose (mg)	Geo-Mean	CV_{in} (%)	Median	Min	Max	Median	Min	Max
25	47	25.4	41 (n=5)	37	66	27 (n=2)	24	31
50	104	27.5	110 (n=6)	65	134	65 (n=5)	45	116
100	192	45.5	210 (n=6)	105	305	151 (n=5)	80	289
200	396	20.7	378 (n=5)	310	542	280 (n=3)	139	343
400	470	58.5	456 (n=5)	296	1146	497 (n=4)	199	1329
600	825	21.0	742 (n=5)	663	1063	1042 (n=2)	1026	1058

	$t_{max\,1}$ (h)			$t_{max\,2}$ (h)		
Dose (mg)	Median	Min	Max	Median	Min	Max
25	0.66 (n=5)	0.66	1.0	3.3 (n=2)	2.5	4.0
50	0.66 (n=6)	0.66	1.0	2.5 (n=5)	1.5	3.0
100	1.50 (n=6)	0.66	2.0	3.0 (n=5)	2.5	8.0
200	1.50 (n=5)	0.33	2.5	4.0 (n=3)	2.0	4.0
400	0.66 (n=5)	0.66	2.0	2.8 (n=4)	2.0	3.0
600	0.66 (n=5)	0.33	4.0	1.75 (n=2)	1.0	2.5

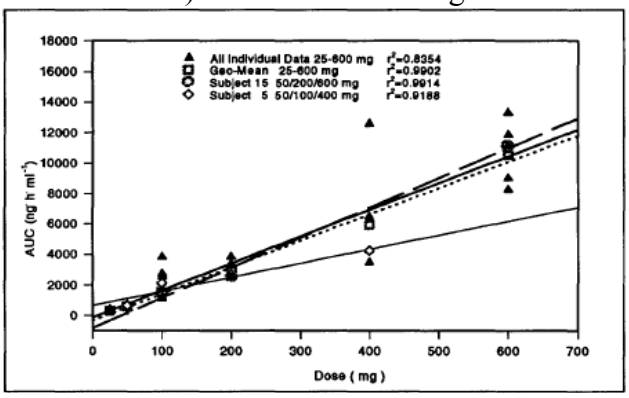
	$AUC_{0-\infty}$ (ng·h/ml)				
Dose (mg)	Geo-Mean	CV_{in} (%)	Median	Min	Max
25	313	27.7	327	203	404
50	584	20.0	586	425	717
100	1545	33.8	1611	1107	2132
200	2952	18.8	2734	2525	3817
400	5945	52.7	6253	3447	12576
600	10552	19.9	11133	8251	13305

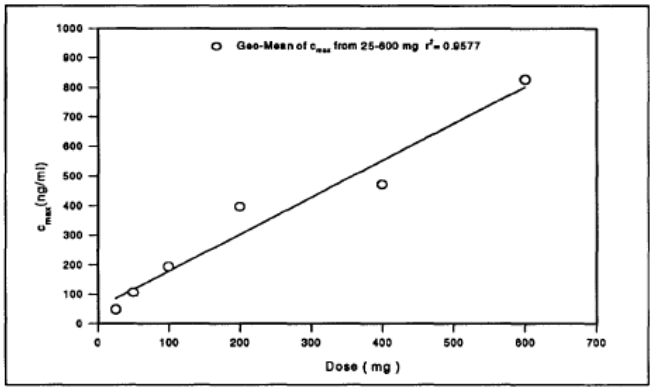
	$t_{1/2}$ (h)					
Dose (mg)	Geo-Mean	Mean	CV_{in} (%)	Median	Min	Max
25	10.0	11.3	63.8	13.5	5.3	17.3
50	8.4	10.2	82.9	10.2	3.2	20.5
100	9.9	10.3	25.4	10.8	6.4	14.8
200	9.8	10.2	30.9	10.1	7.3	15.5
400	9.7	10.1	30.6	10.3	7.1	13.7
600	9.1	9.2	17.3	9.3	7.3	10.7

Table 2. Cumulative Excretion of Retigabine (Free and N-glucuronide) in Urine after Administration of Single Oral Doses of Retigabine

	f_e (0-48 h) (h)				
Dose (mg)	Geo-Mean	Mean	Median	Min	Max
25	26.9	28.5	28.0	14.1	40.1
50	26.3	27.2	25.7	18.3	37.4
100	28.7	29.4	27.7	22.0	41.6
200	23.9	26.1	22.5	14.1	44.6
400	21.8	22.3	22.0	15.3	28.2
600	19.1	19.7	16.9	15.2	28.2

Dose linearity: Regression of geometric means of AUC (r^2= 0.9902) and Cmax (r^2= 0.9577) are shown in the Figures below.





Safety: No death or SAE, and no clear correlation between PK and AE were observed.

CONCLUSION:

- The PK parameters from single oral doses of retigabine were approximately dose-proportional over the dose range of 25-600 mg. Retigabine was rapidly absorbed and elimination values were typically around 10 hours.
- The terminal t1/2 was about 10.5h, suggesting that bid regimen may be more suitable should be considered.

- The second peak phenomenon observed in plasma concentration-time profiles suggests potential enterohepatic re-circulation of the drug or other unknown mechanisms.
- An oral single dose of 400~600 mg was considered to be the maximum tolerable dose in healthy subjects.

Study 3065A1-101

Title: Investigation Into the tolerability, safety and steady state kinetics after repeated oral administration for 29 days of D-23129 In healthy volunteers

Objectives: To investigate the safety, tolerability and steady-state pharmacokinetics in healthy male subjects

Dose and Drug Products:

1.	D100	D-23129, 25 mg	2x 2 capsules per day	batch 9601306
2.	D200	D-23129, 100 mg	2x 1 capsule per day	batch 9601307
3.	D400	D-23129, 100 mg	2x 2 capsules per day	batch 9601307
4.	PLA	Placebo	2x 1 (group B) or 2x 2 (group A, C) capsules per day	batch 9511305

Study Population: 48 healthy male subjects planned and enrolled; 2 subjects in Group C terminated due to CNS-related AEs

Study Design:
This was a randomized, double-blind, placebo controlled within each dose step; sequentially increasing dose steps in 3 parallel groups. 48 subjects were randomized to 3 treatment groups. In each dose step 16 subjects received either placebo (N=4) or 0-23129 (N=12) as presented below:

- Group A: 2 x 50 mg p.o. or matching placebo per day
- Group B: 2 x 100 mg p.o. or matching placebo per day
- Group C: 2 x 200 mg p.o. or matching placebo per day

Duration of treatment per subject: single doses in the morning on study days 1-29, BID on study days 2-28

Pharmacokinetic Sampling:
Plasma: predose, 20 and 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 (not on day 29), 24, 36, 48h post-dose; only predose on Days 2 - 6, 7, 14, 21, 26, 27, and 28
Urine: first day 0-2 h, 2-4 h, 4-8 h, 8-12 h, 12-24 h postdose; last day 0-2 h, 2-4 h, 4-8 h, 8-12 h, 12-24 h, 24-36 h, 36-48 h postdose.

Pharmacokinetic Assessments:
The following PK parameters of retigabine and acetyl-metabolite (AWD21-360) were estimated from plasma and urine data using non-compartmental methods: Cmax, Css, Tmax, AUC0-t, AUC0-∞, λz, t1/2, CL/F, Vz/F, Css, AUC0-τ, and R_A (accumulation ratio). Descriptive statistics were applied to PK parameters, safe parameters, and AEs.

Bioanalytical Method:
Plasma and urine samples were analyzed using a validated HPLC method. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-101

		Retigabine (plasma)	AWD21-360 (plasma)
Method:		HPLC	HPLC
Standard Curve:	Range:	6.3-2000 ng/mL	12.5-2000 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%
LOQ:		6.3 ng/mL	12.5 ng/mL
QC:		12.5, 200, 800 ng/mL	50, 200, 800 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

RESULTS

Demographics:
All subjects were European origin (Caucasian).

Dose	N	Age (years)		Weight (kg)	
		mean	range	mean	range
D100	12	32.8	23 - 44	81.1	58 - 105
D200	12	31.3	23 - 40	76.4	53 - 89
D400	12	31.8	28 - 36	77.6	66 - 95
PLA	12	31.2	22 - 41	76.0	65 - 90

Age ranged 24-43 years (mean ~32 years). Weight ranged 55-110 kg (mean ~80 kg).
Prematurely discontinued: 2 subjects in Group C due to CNS-related AEs
Completed assessments: N=12

Pharmacokinetics:
Figure 1. Mean Plasma Retigabine Concentration-Time Profiles Following Single (SD) and Multiple (MD) Twice-Daily Dose Administration of 50, 100 and 200 mg of Retigabine

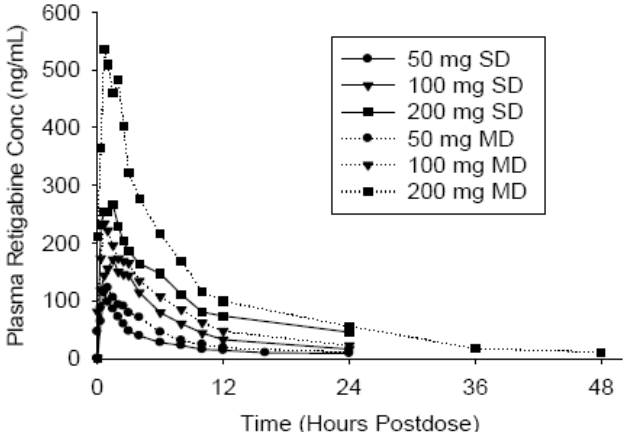
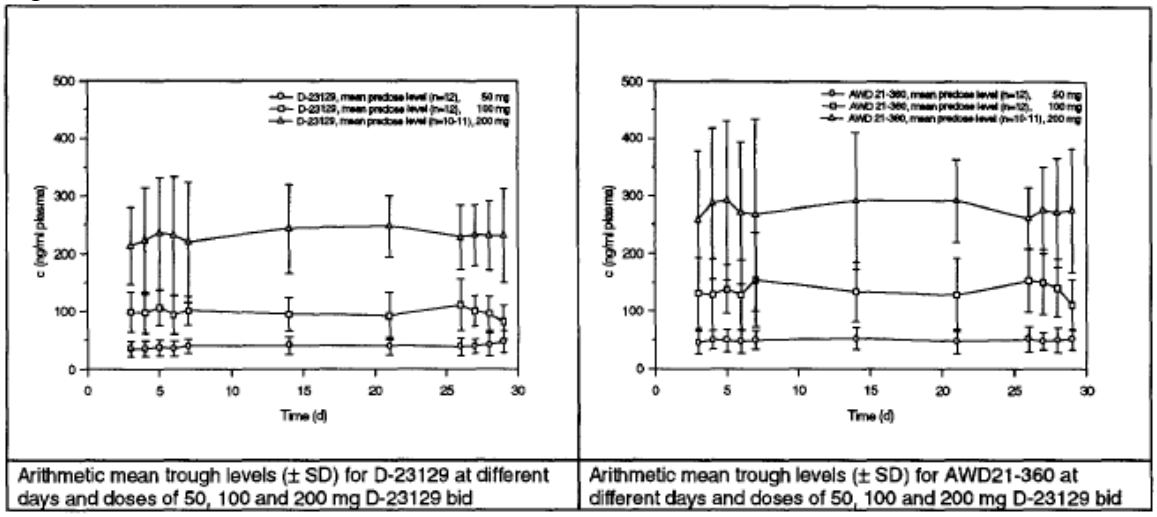


Figure 2. Mean trough levels of Retigabine and its metabolite AWD21-360 during exposure.



Arithmetic mean trough levels (± SD) for D-23129 at different days and doses of 50, 100 and 200 mg D-23129 bid

Arithmetic mean trough levels (± SD) for AWD21-360 at different days and doses of 50, 100 and 200 mg D-23129 bid

Table 1. Pharmacokinetic Parameters of Retigabine and Metabolite in Plasma after Administration of Single Oral Doses of Retigabine

No. of Sub (n=12)*	C_{max} (ng/ml) D-23129						
Single dose	$Mean_{Geo}$	CV_{ln} (%)	Median	Min	Max	95% CI_{ln} lower	95% CI_{ln} upper
50 mg	124.3	68.8	123.3	43.6	329.9	83.7	184.6
100 mg	237.7	44.7	239.4	107.2	536.5	181.2	311.7
200 mg	295.6	68.7	256.8	120.5	960.8	199.1	438.9
Multiple dose	$C_{ss,max}$ (ng/ml) D-23129						
50 mg	156.1	62.5	153.9	59.9	423.0	108.4	224.8
100 mg	269.3	49.3	297.1	140.8	691.7	200.2	362.2
200 mg	581.2	37.8	503.6	344.2	1112.8	454.7	743.0
Single dose	C_{max} (ng/ml) AWD21-360						
50 mg	92.1	42.2	89.4	50.9	180.8	71.2	119.1
100 mg	161.5	33.5	175.2	75.9	224.8	131.3	198.7
200 mg	204.0	36.0	195.4	133.4	369.4	163.5	254.7
Multiple dose	$C_{ss,max}$ (ng/ml) AWD21-360						
50 mg	136.6	30.0	126.5	94.8	212.2	113.4	164.6
100 mg	248.4	29.1	252.0	152.9	379.0	207.2	297.7
200 mg	453.0	24.4	411.6	373.2	777.9	385.4	532.5

* n=11 for 200 mg multiple dose

No. of Sub (n=12)*	AUC ($ng \cdot h \cdot ml^{-1}$) D-23129				AUC ($ng \cdot h \cdot ml^{-1}$) AWD21-360			
Single dose	$Mean_{geo}$	CV_{ln} (%)	95% CI_{ln} lower	95% CI_{ln} upper	$Mean_{geo}$	CV_{ln} (%)	95% CI_{ln} lower	95% CI_{ln} upper
50 mg	622.2	33.9	504.6	767.3	728.0	51.0	536.3	988.2
100 mg	1552.4	28.9	1269.0	1817.8	1642.2	43.9	1246.1	2123.5
200 mg	3272.2	35.7	2587.6	4016.5	3492.8	44.0	2659.2	4540.8
Multiple dose	$AUC_{0-\tau}$ ($ng \cdot h \cdot ml^{-1}$) D-23129				$AUC_{0-\tau}$ ($ng \cdot h \cdot ml^{-1}$) AWD21-360			
50 mg	625.0	34.3	505.8	772.3	807.5	32.3	661.1	986.3
100 mg	1331.3	32.2	1090.5	1625.1	1720.4	34.5	1390.6	2128.5
200 mg	2840.6	31.5	2310.0	3493.0	3206.3	27.3	2678.4	3838.2

* n=11 for 200 mg multiple dose

No. of Sub (n=12)*	AUC ratio (md/sd)	
Dose	D-23129 $Mean_{geo}$	AWD21-360 $Mean_{geo}$
50 mg	1.00	1.11
100 mg	0.86	1.05
200 mg	0.83	0.88

* n=11 for 200 mg multiple dose

No. of Sub (n=12)*	$t_{1/2}$ (h) D-23129			$t_{1/2}$ (h) AWD21-360		
Single dose	Median	Min	Max	Median	Min	Max
50 mg	9.69	3.04	33.75	5.18	2.77	13.92
100 mg	8.30	6.16	22.48	7.45	3.24	15.35
200 mg	11.40	8.47	26.57	10.87	5.27	32.12
Multiple dose	$t_{1/2}$ (h) D-23129			$t_{1/2}$ (h) AWD21-360		
50 mg	5.71	2.97	27.66	5.03	3.58	13.38
100 mg	8.75	2.93	14.98	7.30	2.99	17.27
200 mg	9.22	7.57	11.01	8.35	4.47	10.22

* n=11 for 200 mg multiple dose

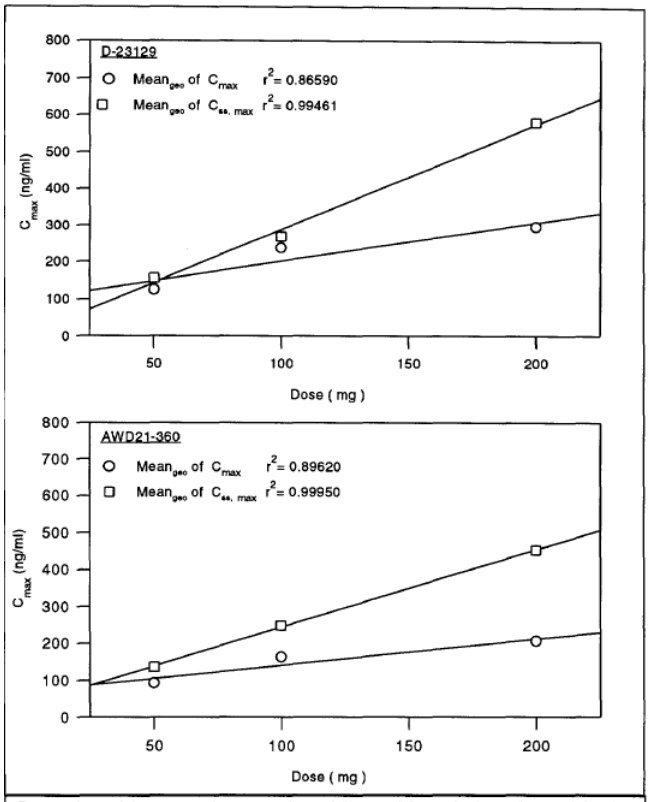
- The t1/2 is slightly shorter at steady-state (8.6 h vs. 11.3 h of SD).

Table 2. The Estimated AUC Metabolic Ratios (Parent Drug to the Metabolite AWD21-360) Following SD and BID Doses of Retigabine

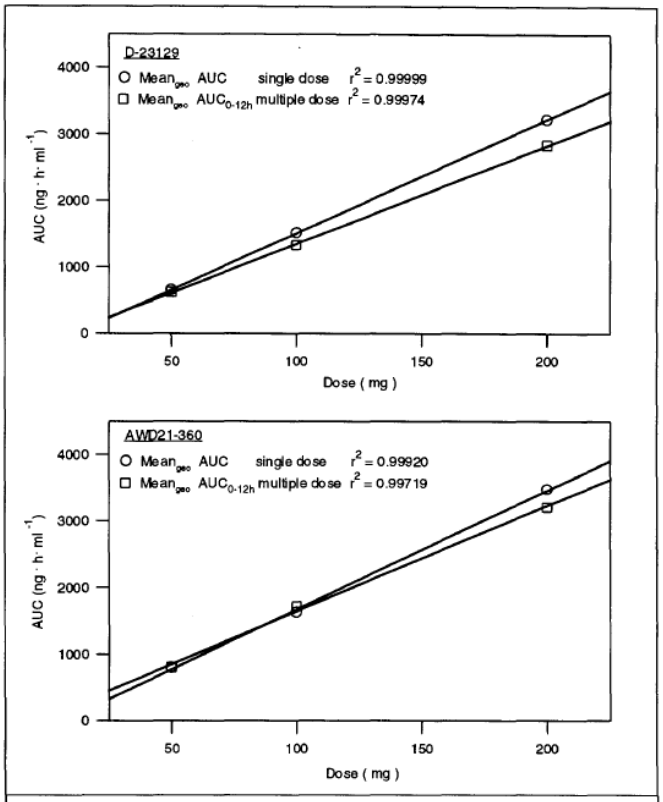
Dose	$R_{AUC\ (P/M)}$ (sd)				$R_{AUC\ (P/M)}$ (md)			
(n=12)*	$Mean_{geo}$	CV_{ln}	95% CI_{ln} lower	95% CI_{ln} upper	$Mean_{geo}$	CV_{ln}	95% CI_{ln} lower	95% CI_{ln} upper
50 mg	0.85	56.3	0.61	1.19	0.77	37.2	0.62	0.97
100 mg	0.95	34.3	0.76	1.15	0.77	25.0	0.66	0.91
200 mg	0.94	22.7	0.80	1.07	0.89	18.7	0.78	1.00

* n=11 for 200 mg multiple dose

Dose linearity: Regression of geometric means of Cmax and AUC are shown in the Figures below.



Regressions of the geometric mean values of C_{max} and $C_{ss,max}$ in dependence of the dose for D-23129 and AWD21-360



Regressions of the geometric mean values of $AUC_{0-\infty}$ and $AUC_{0-\tau}$ in dependence of the dose for D-23129 and AWD21-360

Safety: No death or SAE were reported. 2 subjects in Group C terminated prematurely due to CNS-related AEs (severe dizziness). Dizziness was the most important ADR with a steep increase in 400mg group. Frequently reported AEs included headache, fatigue, and dizziness. There seems to be a dose-dependent increase of disorders related to the extrapyramidal (e.g. ataxia, speech disorder, involuntary muscle contractions) and the autonomic (e.g. dry mouth, increased saliva, xerophthalmia, mydriasis) nervous system. Overall, repeated oral doses up to 400 mg/day were reported to be safe in healthy subjects.

CONCLUSION:

- The pharmacokinetics of retigabine and its metabolite (AWD21-360) after single or repeated doses were characterized by fast absorption, and linear kinetics at dose range of 50~200 mg BID (or 100~400 mg/day). The Cmax and AUC values increased linearly with the doses, with slightly better correlations at steady-state given BID dosing regimen.
- There was a tendency for AUCs of retigabine and metabolite AWD21-360 to slightly reduce at steady-state following higher doses of retigabine, suggesting the slight effects of dose and dose frequency.
- There was slight tendency for accumulation (1.3~1.9) of the plasma levels for parent drug following BID doses. Similar results were observed for metabolite AWD21-360.

Study 3065A1-102

Title: Ascending multiple dose tolerance study of retigabine (GKE-841) in healthy male subjects

Objectives: To assess the safety, tolerability, and preliminary pharmacokinetics of ascending, multiple oral doses (q12h) of retigabine in healthy male subjects for 15 days

Dose and Drug Products:
Fixed doses (200, 400, 500, or 600 mg per day) of retigabine were given in groups 1 through 4, supplied as 25 mg (batch no. = VV 97/02) and 100 mg (batch no. = VV 97/04) capsules. Matching placebo capsules: batch no. =VV 91/01.

Study Population: 45 planned, 45 enrolled, 34 completed, and 45 analyzed.

Study Design:
This was a double-blind, placebo-controlled, multiple-dose escalation study to assess the safety, tolerability, and PK of retigabine administered orally q12h (8AM and 8PM) for 15 days. Forty-five healthy male subjects were sequentially assigned to 5 treatment groups, with 9 subjects in each group (N=6 retigabine; N=3 placebo). The retigabine doses were 100 mg BID (Group 1), 200 mg BID (Group 2), 250 mg BID (Group 3), 300 mg BID (Group 4), and, after a protocol amendment, Group 5 received a starting dose of 200 mg BID which was titrated up to 350 mg BID with increments of 50 mg BID after a 3-day safety and tolerability evaluation (see table below).

Day	Dosing Schedule (mg)	Total Daily Dose (mg)
1	1 x 200[a]	200
2 to 3	200 q12h[b]	400
4 to 7	250 q12h	500
8 to 11	300 q12h	600
12 to 14	350 q12h	700
15	1 x 350[a]	350

Pharmacokinetic Sampling:
PK plasma samples: predose, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 h postdose on Days 1, with additional 36 h and 48 h time points for Day 15
Trough samples: predose on Days 3, 7, 13, and 14, and at 12h on Day 14.
Urine samples: predose, Days 14~16 (* information was unclear; no data was reported.)

Pharmacokinetic Assessments:
The following PK parameters of retigabine and acetyl-metabolite (AWD21-360) on Day 1 and Day 15 were estimated from plasma data using noncompartmental methods: Cmax, Css, Tmax, AUC0-t, AUC0-∞, λz, t1/2, CL/F (retigabine only), and Vz/F (retigabine only). Dose-linearity and time-dependence of the PK were assessed by using ANOVA and a power function to AUC and Cmax estimates.

Bioanalytical Method:

Plasma and urine samples were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-102

		Retigabine (plasma)	AWD21-360 (plasma)
Method:		HPLC/MS/MS	HPLC/MS/MS
Standard Curve:	Range:	1-1000 ng/mL	2.5-1000 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%
LOQ:		1 ng/mL	2.5 ng/mL
QC:		3, 15, 150, 750 ng/mL	3, 15, 150, 750 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

RESULTS

Demographics:

All subjects were European origin (Caucasian).

Dose	N	Age (years)		Weight (kg)	
		mean	range	mean	range
D100	12	32.8	23 - 44	81.1	58 - 105
D200	12	31.3	23 - 40	76.4	53 - 89
D400	12	31.8	28 - 36	77.6	66 - 95
PLA	12	31.2	22 - 41	76.0	65 - 90

A total of 45 males: aged 21-44 years (mean, 31 years); weighed 61-97 kg (mean, 79 kg); 10 Caucasians and 8 Black receiving active treatments.

Completed assessments: N=34

Eleven (24%) subjects were prematurely withdrawn because of AE (11 %) and other non-medical events (11%) reasons. There was no subject exclusion for safety and PK analyses.

Pharmacokinetics:

Retigabine:

Figure 1. Mean Retigabine Plasma Concentration-Time Profiles After Single and Multiple Twice-Daily Oral Retigabine Administration

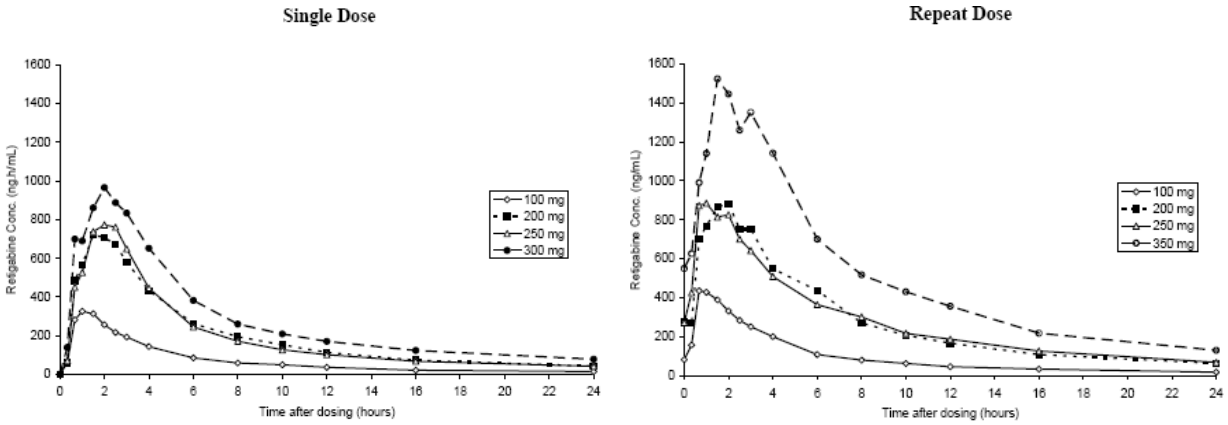


Table 1. Pharmacokinetic Parameters of Retigabine in Plasma after Administration of Single and Q12h Oral Doses of Retigabine

Treatment	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng.h/mL)	$t_{1/2}$ (hr)	CL/F (L/h/kg)
100 mg q12h					
Day 1	414 ± 282	1.5 ± 0.8	1831 ± 739	8.4 ± 1.9	0.72 ± 0.17
Day 15	498 ± 255	0.9 ± 0.3	1914 ± 789	7.2 ± 1.0	0.71 ± 0.24
200 mg q12h					
Day 1	819 ± 202	1.8 ± 0.5	5134 ± 1663	7.4 ± 2.9	0.58 ± 0.20
Day 15	978 ± 169	1.5 ± 0.9	5279 ± 984	7.0 ± 1.4	0.51 ± 0.10
250 mg q12h					
Day 1	842 ± 352	1.7 ± 0.7	5136 ± 994	7.9 ± 3.3	0.62 ± 0.15
Day 15	993 ± 370	0.9 ± 0.3	5184 ± 1665	6.8 ± 1.0	0.67 ± 0.28
300 mg q12h					
Day 1	1071 ± 287	1.4 ± 0.7	7823 ± 884	9.2 ± 3.0	0.53 ± 0.07
350 mg q12h (titration)					
Day 15	1593 ± 198	2.1 ± 0.6	9522 ± 874	7.0 ± 1.6	0.51 ± 0.05
Intrasubject variability (%)	--	--	28.5	21.1	18.0
p-values from the ANOVA associated with dose difference[b]					
Day 1	0.78	0.56	0.10	0.64	0.27
Day 15	0.71	0.01	0.11	0.95	0.27

a: Parameters are presented as mean ± SD. n = 6 except for 200 mg q12h Day 1 where n = 12 and 350 mg q12h where n = 4.
b: C_{max} and AUC were normalized for a 100-mg dose.

- Retigabine CL/F and Vz/F normalized by BW were significantly lower in black subjects, resulting in higher exposure.

Table 2. Mean trough levels of retigabine after q12h doses

Dose Group[a]	Day 14, 0 h (ng/mL)	Day 14, 12 h (ng/mL)	Day 15, 0 h (ng/mL)	Day 15, 12 h (ng/mL)
100 mg:				
Mean ± SD	88.7 ± 36.1	53.1 ± 17.9	82.3 ± 36.0	46.2 ± 16.1
P-value	0.0096		0.0076	
200 mg:				
Mean ± SD	296 ± 107	198 ± 88	279 ± 140	167 ± 44
P-value	0.003		0.046	
250 mg:				
Mean ± SD	234 ± 79	195 ± 100	272 ± 80	187 ± 75
P-value	0.098		0.017	
350 mg (titration):				
Mean ± SD	na	na	550 ± 84	356 ± 78
P-value			0.034	

a: n = 6, except for the titration group where n = 4; na = not available.

Dose linearity:

Single-dose: Power models showed that exponential slope was not different from 1 for Cmax ($3.11 \cdot Dose^{1.02}$) but was significantly different for AUC ($4.34 \cdot Dose^{1.31}$).

- Confounding factor might have come from the uneven distribution Blacks and Whites among dose groups.

Repeated-dose: Power models showed that exponential slope was not different from 1 for Cmax ($5.33 \cdot Dose^{0.96}$) and AUC ($5.23 \cdot Dose^{1.27}$).

AWD21-360:

Table 3. Pharmacokinetic Parameters of AWD21-360 in Plasma after Administration of Q12h Oral Doses of Retigabine

Treatment	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng.h/mL)	$t_{1/2}$ (hr)
100 mg q12h				
Day 1	187 ± 52	2.8 ± 1.1	1831 ± 404	6.2 ± 0.7
Day 15	310 ± 47	2.2 ± 0.5	2212 ± 344	6.7 ± 1.2
200 mg q12h				
Day 1	376 ± 67	3.0 ± 1.1	4748 ± 1644	7.1 ± 2.4
Day 15	746 ± 167	2.3 ± 0.6	6082 ± 1619	7.0 ± 1.6
250 mg q12h				
Day 1	437 ± 125	2.9 ± 0.9	4923 ± 508	7.3 ± 2.7
Day 15	712 ± 197	2.8 ± 0.6	5700 ± 1550	6.9 ± 1.2
300 mg q12h				
Day 1	528 ± 140	3.8 ± 0.6	7339 ± 1812	8.6 ± 1.6
350 mg q12h (titration)				
Day 15	874 ± 75	3.1 ± 0.6	7692 ± 1463	7.2 ± 1.5
Intrasubject variability (%)	--	--	23.3	14.3
p-values from the ANOVA associated with dose difference[b]				
Day 1	0.90	0.31	0.22	0.29
Day 15	0.047	0.07	0.08	0.95

a: Parameters are presented as mean ± SD. n = 6 except for 200 mg q12h Day 1 where n = 12 and 350 mg q12h where n = 4.
b: C_{max} and AUC were normalized for a 100 mg dose.

Dose linearity:

Single-dose: Power models showed that exponential slope was not different from 1 for Cmax ($2.32 \cdot Dose^{0.95}$) and for AUC ($6.92 \cdot Dose^{1.21}$).

Repeated-dose: Power models showed that exponential slope was not different from 1 for Cmax ($69.3 \cdot Dose^{0.86}$) and AUC ($22.7 \cdot Dose^{1.01}$).

Safety: No death or SAE were reported. Similar AE profiles were reported in the fixed dose groups and in the titration group. Common AEs included mild to moderate dizziness (most frequent), headache, asthenia, nausea, abnormal thinking, and somnolence. AEs led to withdrawal from the study for 4 (67%) subjects in the retigabine 300-mg ql2h group and for 1 (17%) subject in the retigabine titration 200- to 350-mg ql2h group. MTD was reported to be 500 mg/day (250 mg ql2h) given fixed doses, but >600 mg/day under dose titration (i.e., subjects reached 700 mg/day (350 mg ql2h) without dose-limiting AEs).

CONCLUSION:

- After single and q12h oral dosing of retigabine doses of 100~350 mg, retigabine was rapidly absorbed and cleared with a t1/2 of about 7 hours. Acetylated metabolite of retigabine, AWD21-360, was also rapidly formed and exhibited the similar PK properties to the parent drug.

- The exposure of retigabine and AWD21-360 were approximatley dose-proportional after single dose or at steady-state, with similar PK properties as reported in other Phase 1 studies.
- Accumulation ratio for AUC following q12h dosing was approximatley 1.5 for retigabine and 1.8 for AWD21-360.
- Lower CL/F (25%) and Vz/F (32%) were reported in Black subjects vs. Whites, which resulted in higher exposure (36%) and average steady-state concentrations (37%).
- With up-titration dosing regimen, the sponsor reported that subjects reached 700 mg/day (350 mg ql2h) without dose-limiting AEs.

Study 3065A1-107

Title: A 30-day safety and tolerability study of various titration regimens of retigabine (GKE-841) in healthy male subjects

Objectives: To assess the safety, tolerability, and pharmacokinetics of various titration regimens over a period of 30 days.

Drug Products:
Retigabine: 25-mg capsules, batch no. = VV 97/05; 100-mg capsules, batch no. = VV 97/04; matching placebo, batch no. = VV 97/01.

Study Population: 18 planned, 9 enrolled, 0 completed, 9 analyzed

Dose Selection: The highest planned titrated dose of 1000 mg q12h (~29 mg/kg) represented a maximum target dose expected to be safe in humans based on animal data. The present study evaluated doses of 2.9~29 mg/kg (based on 70 kg of BW) to determine a MTD in healthy volunteers. Preliminary data of study 30651-102 suggested that tolerability can be improved by titration.

Study Design:
This was a single-center, placebo-controlled, double-blind (unblinded third party), sequential treatment group study in 9 healthy male subjects given daily oral doses of 200, 400, 500, 600, 700, 800, 900, 1000, 1100 and 1200 mg (as 100~600 mg BID). Dose escalation was every 3 days over a total duration of 30 days in Cohort 1. In Cohort 2, total daily doses of up to 2000 mg (up to 1000 mg BID) were planned. Schedule for the 1 titration treatment groups are shown below.

TABLE 6.3.4A. SCHEDULE FOR THE TITRATION IN TREATMENT GROUP 1

Study Day	Unit Dose every 12 hours	Total Daily Dose
1	single 1 x 200 mg dose in AM	200 mg
2 - 4	200 mg	400 mg
5 - 7	250 mg	500 mg
8 - 10	300 mg	600 mg
11 - 13	350 mg	700 mg
14 - 16	400 mg	800 mg
17 - 19	450 mg	900 mg
20 - 22	500 mg	1000 mg
23 - 25	550 mg	1100 mg
26 - 29	600 mg	1200 mg
30	single 1 x 600 mg dose in AM	600 mg

TABLE 6.3.4B. SCHEDULE FOR THE TITRATION IN TREATMENT GROUP 2

Study Day	Unit Dose every 12 hours	Total Daily Dose
1	single 1 x 200 mg dose in AM	200 mg
2 - 4	200 mg	400 mg
5 - 7	300 mg	600 mg
8 - 10	400 mg	800 mg
11 - 13	500 mg	1000 mg
14 - 16	600 mg	1200 mg
17 - 19	700 mg	1400 mg
20 - 22	800 mg	1600 mg
23 - 25	900 mg	1800 mg
26 - 29	1000 mg	2000 mg
30	single 1 x 1000 mg dose in AM	1000 mg

Pharmacokinetic Sampling:

PK plasma samples: on Day 1 up to 24 hours postdose after a single oral dose of 200 mg from a total of 6 subjects

Pharmacokinetic Assessments:

The following PK parameters were estimated from plasma data using noncompartmental methods: Cmax, Css, Tmax, AUC0-t, AUC0-∞, λz, t1/2, CL/F, Vz/, CLm/(F·fm) (=Dose/AUC) of AWD21-360.

Bioanalytical Method:

Plasma and urine samples were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-107

		Retigabine (plasma)	AWD21-360 (plasma)
Method:		HPLC/MS/MS	HPLC/MS/MS
Standard Curve:	Range:	1-1000 ng/mL	2.5-1000 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%
LOQ:		1 ng/mL	2.5 ng/mL
QC:		3, 15, 150, 750 ng/mL	3, 15, 150, 750 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%

Comment: The bioanalytical methods were found acceptable.

RESULTS

Pharmacokinetics:

Table 1. Pharmacokinetic Parameters of Retigabine in Plasma after Administration of Single Oral Dose of 200-mg Retigabine

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)	MTR_{po} (h)
Mean ± SD	878 ± 176	2.0 ± 0.3	5.4 ± 0.5	4686 ± 1110	0.56 ± 0.14	4.3 ± 0.8	7.3 ± 0.5
Range	625 - 1074	1.5 - 2.5	4.6 - 6.1	3162 - 5854	0.41 - 0.80	3.4 - 5.3	6.7 - 8.0
Geometric Mean	862	2.0	5.4	4568	0.55	4.3	7.3

Table 2. Pharmacokinetic Parameters of AWD21-360 in Plasma after Administration of Single Oral Dose of 200-mg Retigabine

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	$CLm/(F•f_m)$ (L/h/kg)
Mean ± SD	437 ± 210	3.0 ± 0.6	6.4 ± 0.9	3938 ± 996	0.68 ± 0.19
Range	256 - 805	2.5 - 4.0	5.3 - 7.4	2585 - 5290	0.49 - 0.98
Geometric Mean	401	3.0	6.3	3831	0.66

Safety: The 9 subjects in Cohort 1 were enrolled but did not complete the study because of AEs, including ventricular tachycardia (2 episodes of 3 beats run; reported as a SAE), ventricular ectopic beats and viral enteritis. Study was terminated early. The highest achieved dose of retigabine was 500 mg q12h reached on day 20 by 1 subject in cohort 1. Cohort 2 was not conducted because of AEs.

CONCLUSION:

- The PK data generated from the PK samples up to 24 h after the 1st dose are not considered reliable in view of the insufficient PK sampling time based on the t1/2 values (~10 h) reported in other studies.

Study 3065A1-200/201

Title: Efficacy, tolerability, safety and pharmacokinetics of orally administered D-23129 in patients with partial onset seizures

Objectives: To assess efficacy, tolerability, safety of an add-on treatment, and pharmacokinetics in steady state in subjects with partial onset seizures, with 3 titration schemes up until the maximum tolerated dose

Dose and Drug Products:

25 mg capcules: VV 96/01, VV 97/03, VV 98/02
100 mg capsules: VV 96/02, VV 97/04, VV 97/06, VV 98/06

- Starting doses: 25 mg, 100 mg, or 200 mg (all administered BID)
- Titration: until the individually maximum tolerated dose with a weekly increase by 25 mg/d, or 100 mg/d, or 200 mg/d
- Maintenance treatment: 350 mg/d to 2400 mg/d

- Taper off: reducing the dose by 25% every 7 days for those who did not want to participate in a long-term follow up studies

Study Population: 20 evaluable patients planned (10 each for Study 3065A1-200 or D23129-8001, and Study 3065A1-201 or D23129-8005)

Study Design:
Study D-23129-8001 (or 3065A1-200) and -8005 (or 3065A1-201) were for the first retigabine trials conducted in epileptic patients to assess for the titration schedule, the maintenance dose, the tolerability and the efficacy in human. The study medication will be titrated until the maximum tolerated dose, depending on individual tolerability

- Study 3065A1-200: 38 patients enrolled, titrated to the maximum tolerated dose.
- Study 3065A1-201: 8 patients enrolled, titrated to a maximum tolerated dose ranging from 350 to 2400 mg/day in the maintenance phase
- PK analysis: 40 patients enrolled in these 2 studies who had received retigabine 50, 100 and 200 mg BID for at least 6 days

Plasma levels of D-23129 and its acetyl-metabolite AWD21-360 were determined from 12-h PK sampling after the morning dosing on day 7 (from day 4 to day 12) to generate the steady-state PK parameters in patients.

Pharmacokinetic Sampling:
Plasma samples: predose, and 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h postodse.

Pharmacokinetic Assessments:
The following PK parameters of retigabine and acetyl-metabolite (AWD21-360) were estimated from plasma data using noncompartmental methods: Cmax,ss, Tmax, AUC0-12, t1/2, Ctough,ss, peak-trough ratio, HVD (half value duration- duration of Cp >50% of Cmax), MRT, and CL/F.

Bioanalytical Method:
Plasma and urine samples were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method. The lower limit of quantification (LOQ) for D-23129 was 1.0 ng/ml with a limit of detection (LOD) of 0.5 ng/ml. The LOQ for AWD21-360 was 2.5 ng/ml with an LOD of 0.5 ng/ml. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-200

		Retigabine (plasma)	AWD21-360 (plasma)
Method:		HPLC/MS/MS	HPLC/MS/MS
Standard Curve:	Range:	1.0-1000 ng/mL	2.5-1000 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%
LOQ:		1.0 ng/mL	2.5 ng/mL
QC:		3*, 15, 150, 750 ng/mL	3*, 15, 150, 750 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%

* Precisions for low QC (3.0 ng/ml) were 21.2% and 21.7% for retigabine and AW021-360, respectively, slightly exceeding the 20%.

Assay performance for Study 3065A1-201

		Retigabine (plasma)	AW021-360 (plasma)
Method:		HPLC/MS/MS	HPLC/MS/MS
Standard Curve:	Range:	1.0-1000 ng/mL	2.5-1000 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%
LOQ:		1.0 ng/mL	2.5 ng/mL
QC:		3, 15, 150, 750 ng/mL	3, 15, 150, 750 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

RESULTS

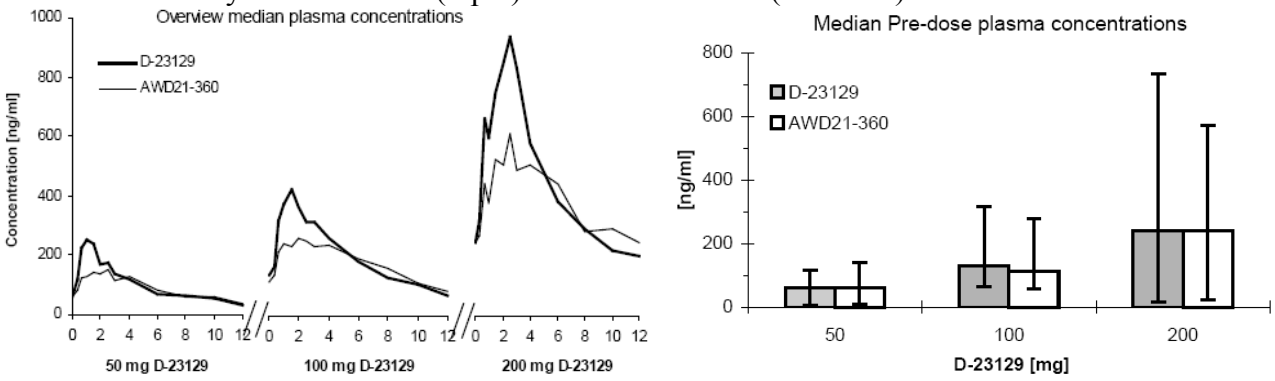
Demographics:

A total of 46 Caucasian patients, 27 women and 19 men, aged 18-49 years (mean 34 years), weighed 50-99 kg (mean 70 kg), with no. of seizures at baseline 3-217 (mean 17.2), were enrolled in the study.

Pharmacokinetics:

Retigabine:

Figure 1. Median Plasma Concentration-Time Profiles for Retigabine and AW021-360 from Study D23129-8001 (top 2) and D23129-8005 (bottom 2)



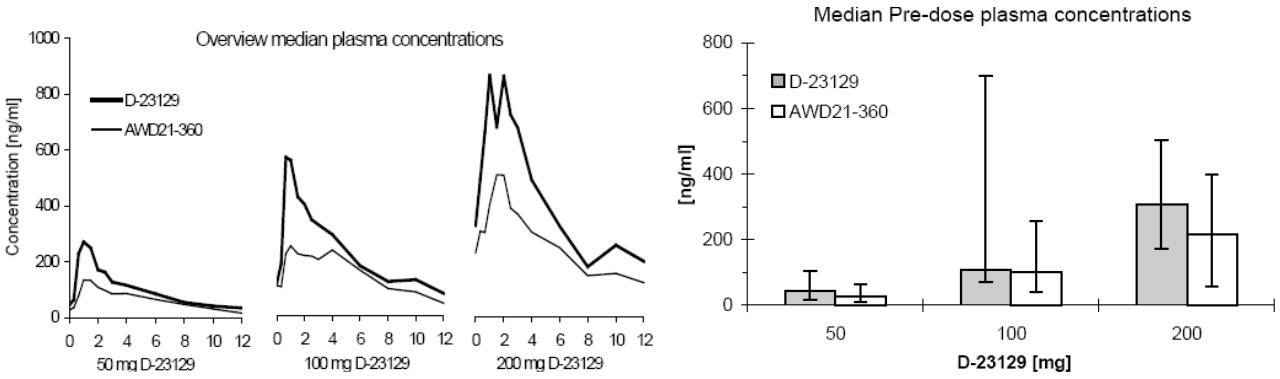


Table 1. Pharmacokinetic Parameters of Retigabine following Retigabine 50 mg, 100 mg, and 200 mg BID Dosing in Epileptic Patients with Partial-Onset Seizures (Study 3065A1-200 or D23129-8001)

Parameter	50 mg BID (N=7)	100 mg BID (N=8)	200 mg BID (N=7)
Cmax (ng/mL)	266 [283]	418 [458]	925 [1156]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(185 - 383)	(281 - 623)	(463. - 846)
AUC0-12h (ng*h/mL)	1181 [1256]	2247 [2405]	5299[a] [5862]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(816 - 1709)	(1581 - 3192)	(3113 - 9020)
Tmax (h)	0.70	1.08	1.00
Median (min, max)	(0.33, 10.0)	(0.97, 2.50)	(1.00, 4.00)
t1/2 (h)	4.27[a] [6.08]	4.18[a] [4.04]	4.81[a] [5.52]
Median (min, max)	(3.56, 16.5)	(3.23, 4.74)	(3.77, 8.58)
Ctrough (ng/mL)	51.4 [54.8]	107 [119]	159 [233]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(35.9 - 73.7)	(71.6 - 160)	(53.7 - 473)
Ratio Cpeak/Ctrough	5.17	3.90	5.32
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(4.31 -6.21)	(2.58 - 5.90)	(2.16 - 13.1)

a. N=6; values in [ ] represent arithmetic mean values

Table 2. Pharmacokinetic Parameters of Retigabine following Retigabine 50 mg, 100 mg, and 200 mg BID Dosing in Epileptic Patients with Partial-Onset Seizures (Study 3065A1-201 or D23129-8005)

Parameter	50 mg BID (N=6)	100 mg BID (N=7)	200 mg BID (N=5)
Cmax (ng/mL)	282 [287]	607 [625]	994 [1001]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(230 – 346)	(475 - 776)	(841 – 1174)
AUC0-12h (ng*h/mL)	1085[a] [1107]	2174[b] [2179]	5584[b] [5593]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(596 – 1975)	(1938 - 2440)	(5012 - 6221)
Tmax (h)	1.08[c]	1.05	1.08
Median (min, max)	(0.78, 1.49)	(0.67, 8.00)	(0.38, 2.53)
t1/2 (h)	6.00 [5.60][e]	5.53[d] [6.03]	4.78 [6.39]
Median (min, max)	(4.46, 112)	(3.99, 9.52)	(4.39, 9.20)
Ctrough (ng/mL)	43.3 [45.9]	143 [209]	289 [308]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(29.2 - 64.3)	(65.1 - 315)	(174 - 479)
Ratio Cpeak/Ctrough	6.54[c]	4.24	3.44
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(4.02 - 10.6)	(2.28 - 7.87)	(1.85-6.40)

[a] N=3, [b] N=4, [c] N=5, [d] N=6; [e] Patient #1 excluded as outlier (N=5); values in [ ] represent arithmetic mean

- Patient #1 at 50-mg dose had prolonged t1/2 (~112 h); however, the causes were unclear.

AW021-360:
Pharmacokinetic profiles were overall similar to what's reported in other Phase 1 studies in healthy volunteers.

Titration and Efficacy:
- The two faster 100 and 200 mg/week titration schemes allowed patients to achieve higher maintenance doses, which explains the greater efficacy observed (higher responder rates and seizure-free patients).
- The fast 200 mg/week titration scheme was less well tolerated, resulting in 6 (33%) patients discontinued from the study.
- The overall mean maintenance dose was reported to be 854 mg/d, with a dose range of 350~2400 mg/d as BID doses.
- A response rate of 12 of 34 (35%) patients of the PP (per protocol) population was observed, while 7 of them became seizure-free in the 3-month maintenance period. These patients received a retigabine dose between 600 and 1100 mg/day.
- The sponsor concluded that a rapid titration of at least 100 mg/week is reasonable.

Safety: No death but 4 SAE (epigastric post-prandial pain; abdominal pain; increased seizure frequency; and headache, numbness of the left side of the face, and weakness in the right arm) were reported. A total of 11 (24%) patients were discontinued from the study - noncompliance (6 patients) and AEs (5 patients).

CONCLUSION:
- PK of retigabine and its acetyl-metabolite was characterized by dose-proportionality and linearity in exposure (Cmax and AUC) in epileptic patients over a 50 ~ 200 mg BID dose range. The peak plasma concentrations of retigabine were reached at approximately 1 hour postdose. Both CL/F and estimated terminal t1/2 appear to be dose-independent.
- The terminal t1/2 values obtained in this study were shorter than that observed in Phase 1 studies. This observation could be due to the insufficient PK sampling duration (12 h) to allow a more accurate estimation for the terminal t1/2.
- Overall, retigabine PK parameters in epileptic patients as an add-on therapy were similar to respective values in healthy subjects observed in Phase 1 studies.
- Most enrolled patients were on concomitant carbamazepine or valproic acid therapy. However, conclusion for a lack of DDI cannot be drawn due to the small sample size.

Study VRX-RET-E22-303PK

Title: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-301): Pharmacokinetic Substudy

Objectives: To determine the steady-state pharmacokinetics of retigabine and the N-acetyl metabolite of retigabine (NAMR) over a single dosing interval in patients with partial seizure epilepsy on a stable dosing regimen of retigabine as monotherapy (at least 2 weeks) or as an adjunct to other anti-epileptic drugs (AEDs)

Dose and Drug Products: Retigabine 50-mg, 100-mg, 300-mg tablets for TID doses (i.e., total daily dose of 600–1200 mg/day), based on the individual's tolerance and response, using the patient's own supply dispensed as part of Study 303.

Study Population: All 16 completed the treatments and assessments. One subject was excluded from the PK analysis due to protocol violation.

Study Design:
This was a substudy for assessing the multiple-dose PK of retigabine and NAMR in epileptic patients with partial-onset seizures enrolled in an open-label extension to Study VRX-RET-E22-301. Fifteen patients who had maintained retigabine 200, 300, 350, or 400 mg TID (600–1200 mg/day) as monotherapy or as adjunct to established AEDs and for at least 2 weeks were included in the PK evaluation. Concomitant epileptic treatments included valproic acid, carbamazepine, phenytoin, lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, barbiturates, or benzodiazepines, or a vagal nerve stimulator (VNS). The VNS could be in addition to 1~3 AEDs.

Pharmacokinetic Sampling:
Plasma samples: predose, 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, and 8 hours after the AM dose (after an 8 h overnight fast) on Day1.

Pharmacokinetic Assessments:
The following PK parameters and descriptive statistics of retigabine and acetyl-metabolite were estimated from plasma data using noncompartmental methods and: Cmax, Cmin, Tmax, AUCτ, t1/2, FI (Fluctuation index = Cmax-Cmin)/Cavg×100%). Dose proportionality could not be formally assessed given the small number of patients in each group.

Bioanalytical Method:
Plasma and urine samples were analyzed using a validated liquid chromatography – mass spectrometry (LC- MS) analytical method. The calibration ranges in plasma were 5–2000 ng/mL for retigabine, and 15–2000 ng/mL for the N-acetyl metabolite of retigabine

RESULTS

Demographics:
All patients were Caucasian, 9 females and 7 males, with mean age of 39.9 years, mean weight of 86.7 kg, and mean height of 168.6 cm at baseline in Study 301. Patients are grouped according to dose but were not randomized.

Pharmacokinetics:

Retigabine:

Figure 1. Mean Plasma Retigabine (Left) and Its N-acetyl Metabolite (Right) Concentration as a Function of Time Following Administration of a Single Dose as Part of a Q8H Dosing Regimen

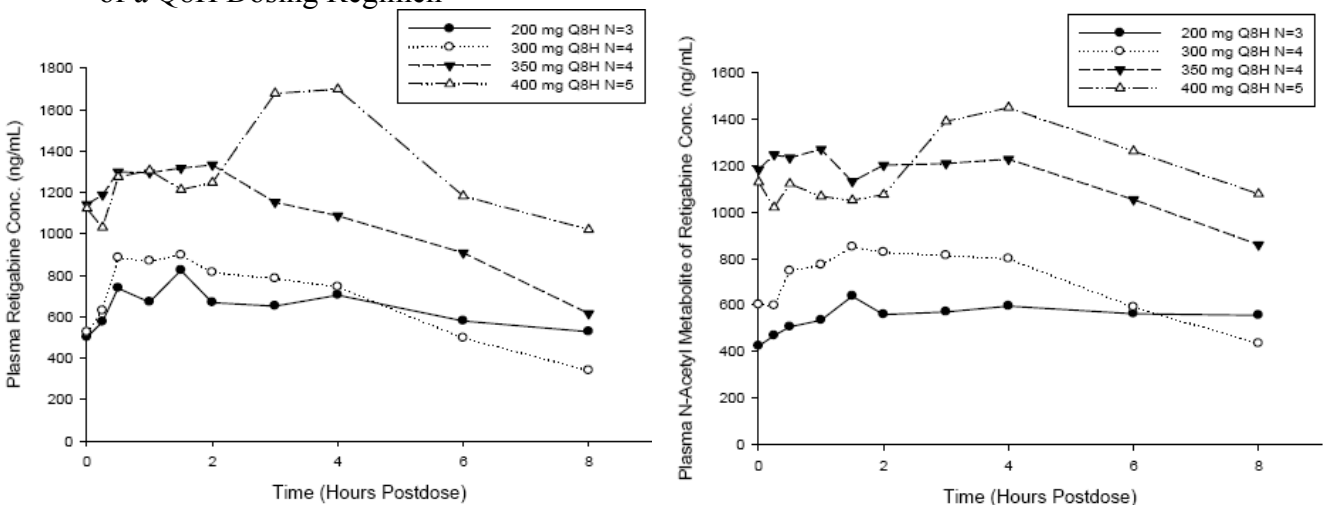


Table 1. Summary of Mean Plasma Retigabine Pharmacokinetic Parameters Following Administration of a Single Dose as Part of a Q8H Dosing Regimen

	200 mg TID (N=2)[a]	300 mg TID (N=4)	350 mg TID (N=4)	400 mg TID (N=5)
Pharmacokinetic Parameter	**Mean**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
C_{max} (ng/mL)	940	1014 ± 366	1432 ± 325	1850 ± 1001
t_{max} (hr)	1.0	1.0 ± 0.4	1.4 ± 0.8	2.3 ± 1.5
$AUC_{0-\tau}$ (ng·hr/mL)	5445	5267 ± 2069	8548 ± 1806	10698 ± 5121
C_{min} (ng/mL)	507	339 ± 156	743 ± 277	891 ± 156
C_{avg} (ng/mL)	681	658 ± 259	1068 ± 226	1337 ± 640
FI (%)	63.7	107.0 ± 25.5	65.0 ± 24.9	63.8 ± 23.6

[a] Patient 01403 was excluded from pharmacokinetic analysis.

- Mean projected total daily exposure at therapeutic doses ranged from 16635 ng·hr/mL at 200 mg TID to 32094 ng·hr/mL at 400 mg TID.

Table 2. Summary of Mean Plasma N-acetyl Metabolite of Retigabine Pharmacokinetic Parameters Following Administration of a Single Dose as Part of a Q8H Dosing Regimen

	200 mg TID (N=2)[a]	300 mg TID (N=4)	350 mg TID (N=4)	400 mg TID (N=5)
Pharmacokinetic Parameter	**Mean**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
C_{max} (ng/mL)	780	885 ± 419	1402 ± 544	1523 ± 612
t_{max} (hr)	2.92	1.66 ± 0.43	1.19 ± 0.63	2.20 ± 2.05
$AUC_{0-\tau}$ (ng·hr/mL)	4898	5551 ± 2788	9087 ± 2787	9847 ± 3141
C_{min} (ng/mL)	479	434 ± 242	854 ± 130	910 ± 139
C_{avg} (ng/mL)	612	694 ± 349	1136 ± 348	1231 ± 393
FI (%)	51.5	68.4 ± 26.3	44.0 ± 19.1	44.0 ± 24.6

[a] Patient 01403 was excluded from pharmacokinetic analysis.

CONCLUSION:

- Cmax and AUC0-τ values for retigabine and NAMR increased approximately dose-proportionally over the 200 mg TID to 400 mg TID dose range
- Mean projected Cmax and total daily exposure at therapeutic RTG doses are expected to be 1000-2000 ng/mL and 15000-30000 ng·hr/mL, respectively
- Fluctuation in retigabine concentrations (Cpeak/Ctrough) with the TID regimen was approximately 2~3-fold vs. 3.5~6.5-fold observed with BID dosing in Study 3065A1-200/201.
- Retigabine exposure data from this Phase 3 efficacy study (Study 301) was included for the exposure-response analysis for both efficacy and safety. Details are available in Pharmacometric review.

Study 3065A1-117

Title: Tolerability of intravenous dose titration of retigabine administered as short-term infusion in healthy male subjects

Objective:

- To identify a tolerable intravenous dose of retigabine that will provide a pharmacokinetic profile in a subsequent absolute bioavailability study
- To investigate the pharmacokinetics and dose linearity of retigabine and its N-acetyl metabolite (AWD 21-360)

Dose and Drug Products:

- Retigabine: 50 mg in 50 ml 0.9% saline (batch t ld dose step: group B: 2.5 mg no.0282A71)
- Placebo solution: matched to the excipients of 50 ml short-term infusion within 15 retigabine (batch no. 0011-001/03)

Study Design:

This is a single-center, randomized, single-blind, single-dose escalation trial in an alternating panel design. A total of 16 healthy male subjects were to be recruited and 15 received a 50 ml retigabine or placebo infusion on 3 separate periods. Each subject was assigned to group A (N=7) or to group B (N=8). Each group was again assigned to 3 dose steps as shown below. Within each dose step 6 subjects were randomly assigned to retigabine, 1 or 2 subjects received placebo. The doses were separated in each group by a washout interval of at least 5 days. Blood samples for PK analysis were collected up to 48 hours after the end of the infusion.

- 1st dose step: group A (period I): 1 mg
- 2nd dose step: group B (period I): 2.5 mg
- 3rd dose step: group A (period II):: 5 mg
- 4th dose step: group B (period II):: 10 mg
- 5th dose step: group A (period III):: 5 mg
- 6th dose step: group B (period III):: 50 mg

Pharmacokinetic Sampling: Plasma: pre-dose, 5 and 10 min after start of infusion, at end of infusion (= t_0), and then 1, 3, 5, 10, 15, 20, 30, 45 min, 1, 2, 4, 6, 8, 12, 16, 24, 36, and 48 h after end of infusion.

The following PK parameters were estimated from plasma data using non-compartmental methods: Cmax, Tmax, AUC0-t, AUC0-∞, Clast, tlast, AUMC0-t, AUMC0-∞, λz, t1/2, CL, Vz, Vss, MRTiv, metabolic ratio (MR), and half value duration (HVD). Dose-dependent proportionality of exposure (AUC and Cmax) was assessed by regression.

Bioanalytical Method:
Plasma retigabine and AWD21-360 samples were analyzed using a validated HPLC-MS/MS analytical method at (b) (4) Calibration ranges were 1-1000 ng/mL and 2.5-1000 ng/mL for retigabine and AWD21-360, respectively. Quality control samples were in 4 concentrations (at 3, 15, 150, and 750 ng/ml) for both analytes. Assay performance during the study with respect to precision and accuracy were <20%.

RESULTS

Demographics: 16 planned, 17 enrolled, 15 analyzed. All subjects were male and of Caucasian origin. Ages were 23-44 years (mean 34.6 years); BMI ranged 22.1-30.8 kg/m^2 (mean 25.2 kg/m^2).

Pharmacokinetics:
Figure 1. Plasma Concentration-Time Profiles of Retigabine (Left) and AWD21-360 (Right) after i.v. Administration of 1-50 mg Retigabine in Healthy Subjects

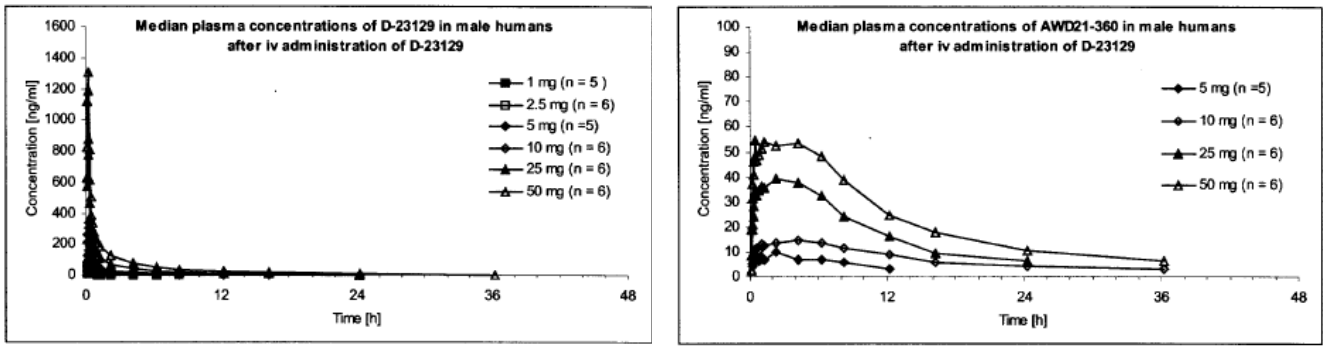


Table 1. Retigabine Pharmacokinetic Parameters After Administration of Single i.v. Doses of 1-50 mg Retigabine in Healthy Subjects

RTG Dose (mg)	$Mean_{geo}$ (95% $CI_{ln;}$ LL-UL)		Median (min-max)		$Mean_{geo}$ (95% $CI_{ln;}$ LL-UL)		
	C_{max} (ng/mL)	AUC (ng*h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vss (L/kg)	MRT_{iv} (h)
1.0	24.9 16.5-37.4	21.0 13.9-31.6	0.25 0.17-0.33	1.99 1.01-4.73	9.34 6.40-13.6	1.22 0.71-2.11	2.18 0.93-5.12
2.5	57.6 30.3-110	57.4 44.0-75.1	0.26 0.25-0.30	3.91 2.93-5.52	8.17 5.72-11.7	1.81 1.20-2.72	3.68 2.85-4.76
5.0	156 130-188	140 97.5-200	0.25 0.25-0.27	4.44 3.92-8.28	7.27 5.36-9.86	1.80 1.46-2.22	4.13 2.73-6.26
10.0	326 279-380	302 242-377	0.25 0.25-0.25	5.99 3.61-9.88	6.48 4.77-8.82	1.84 1.45-2.35	4.74 3.58-6.27
25.0	802 596-1079	849 598-1206	0.25 0.25-0.27	6.66 4.65-9.40	6.07 4.33-8.51	1.81 1.37-2.38	4.96 3.89-6.33
50.0	1198 887-1618	1495 1294-1727	0.25 0.25-0.25	6.95 5.29-8.02	6.31 5.52-7.21	2.20 1.79-2.71	5.80 4.73-7.12

Table 2. AWD21-360 Pharmacokinetic Parameters After Administration of Single i.v. Doses of 1-50 mg Retigabine in Healthy Subjects

Dose [mg]	$Mean_{geo}$ (95% CI_{ln} LL - UL)					Median (min - max)	
	C_{max} [ng/ml]	AUC [ng·h/ml]	$AUC_{tlast-inf}$ [%]	HVD [h]	MR	t_{max} [h]	$t_{1/2}$ [h]
5.0	8.83 (6.68-11.7)	109 (62.4-191)	31.7 (23.2-43.2)	9.05 (6.98-11.8)	1.28 (0.72-2.26)	1.25 (0.42-2.25)	6.68 (4.98-16.9)
10.0	19.6 (9.33-41.1)	309 (167-571)	22.8 (10.8-48.0)	10.5 (6.12-18.1)	1.06 (0.56-2.03)	2.75 (0.42-6.25)	10.1 (5.35-45.6)
25.0	42.3 (35.9-49.8)	580 (425-793)	6.84 (3.44-13.6)	10.0 (8.57-11.7)	1.46 (0.83-2.57)	1.13 (0.50-2.25)	7.23 (4.82-25.2)
50.0	57.8 (48.4-69.0)	946 (782-1143)	7.52 (4.07-13.9)	11.1 (9.64-12.7)	1.64 (1.35-1.99)	2.75 (0.50-4.25)	9.30 (8.03-14.0)

Table 3 Assessments for Dose-Proportionality for Retigabine and AWD21-360 After Administration of Single i.v. Doses of 1-50 mg Retigabine in Healthy Subjects

Pharmacokinetic Parameter	Equation	Coefficient of Determination r^2	Pharmacokinetic Parameter	Equation	Coefficient of Determination r^2
$AUC_{norm\ 70kg}$ versus dose	y=38.515x	0.9407	$AUC_{norm\ 70kg}$ versus dose	y=24.742x	0.6641
$C_{max,norm\ 70kg}$ versus dose	y=33.003x	0.8813	$C_{max,norm\ 70kg}$ versus dose	y=1.6233x	0.6091

Retigabine: Regression results from all individual values (n=34), dose range:1-50 mg
AWD21-360: Regression results from all individual values (n=23), dose range:5-50 mg

Table 4 Metabolic Ratio After Administration of Single i.v. Doses of 1-50 mg Retigabine in Healthy Subjects

Dose of Retigabine [mg]	$mean_{geo}$ AUC [ng·h/ml]		Metabolic ratio
	Retigabine (D-23129)	AWD21-360	
5	140	109	1.28
10	302	309	1.06
25	849	580	1.46
50	1495	946	1.64

Safety: No discontinuation occurred due to AEs. AEs related to study medication include somnolence, fatigue, euphoria, blurred vision, illusion, numbness, localized paresthesia, nystagmus, each mild to moderate in intensity, starting either during infusion or shortly afterwards, disappearing within minutes to 1-2 hrs mostly at 25 mg and 50 mg

doses. Blurred vision reported once was severe (50 mg dose). There were no safety-related issues in vital signs, 12-lead ECG, and clinical laboratory variables.

CONCLUSION:

- The systemic AUC and Cmax from single short-term i.v. infusion of retigabine were approximately dose-proportional over the dose range of 1-50 mg.
- The PK parameters across the dose range studied were similar, except for the CL and V values at 1 mg and 2.5 mg doses, likely due to the less well defined PK properties at such low doses.
- The terminal t1/2 values were approximately 6~7 hours.
- The single i.v. infusion of retigabine 50 mg was judged by the Sponsor to be a tolerable dose, but close to the maximum tolerated dose (MTD) in healthy males.

Study 3065A1-108-US and D-23129/FB20799

Title: A study of the metabolic pathways and mass balance of orally administered [^{14}C]-labeled GKE-841 in healthy male subjects

Objectives: To characterize the mass balance and metabolic pathways after administration of a single [^{14}C]-labeled oral dose of retigabine to healthy male subjects

Dose and Drug Products: Retigabine oral capsule, 200-mg with a specific activity of 0.965 µCi/mg, administered in fasted state, batch number = L-18382-42; (b) (4), control number 455-901.

Dosage Form (capsule)	Batch Number	Radiochemical Purity (%)	Chemical Purity (%)	Specific Activity (µCi/mg)
200 mg	L-18382-42	98.6	99.7	0.965 ± 0.004

Study Design:
This was an open-label, non-randomized single-dose study to characterize the mass balance, route of elimination and metabolic pathways of retigabine after single dosing in 6 healthy males under fasted state. Blood, urine and fecal samples, as well as hemacocrit and emesis, were collected up to 240 hours post-dose in to assess the metabolic profile and the amount of drug related material that was excreted.

Pharmacokinetic Sampling:
Plasma samples: predose, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 96, 120, 144, 168, 192, 216, and 240 h postdose.
Plasma samples for metabolite analysis: preodse, 0.67, 8, and 24 h postdose
Urine samples: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-96, 96-120, 120-144, 144-168, 168-192, 192-216, and 216-240 h postodse.
Fecal samples: throughout the study

Pharmacokinetic Assessments:

The following PK parameters of retigabine, its acetyl-metabolite (AWD21-360), and total plasma radioactivity were estimated using noncompartmental methods: Cmax, Tmax, AUC0-t, AUC0-∞, and t1/2. Plasma, urine and feces samples were analyzed to identify the different radiolabeled species. Descriptive statistics were employed.

Bioanalytical Method:
Blood, plasma, urine and fecal samples were assayed for total radioactivity by validated liquid scintillation counting. Retigabine and metabolite profiles in plasma, urine, and feces were further determined by validated LC/MS/MS analytical methods. Plasma concentrations of retigabine and its mono-acetylated metabolite, AWD21-360A, were determined by a HPLC/UV method. The assay performance of the HPLC/UV method during sample analysis for retigabine and AW021-360 is summarized in the table below.

Table. Assay performance for Study 3065A1-108 and D-23129/FB20799

		Retigabine (plasma)	AWD21-360 (plasma)
Method:		HPLC/UV	HPLC/UV
Standard Curve:	Range:	25-1000 ng/mL	25-1000 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%
LOQ:		12.5 ng/mL	12.5 ng/mL
QC:		50, 250, 750 ng/mL	50, 250, 750 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being ≤15%.

RESULTS

Demographics: 6 healthy men planned; 6 enrolled; 6 completed; 6 analyzed for safety and PK. They were White, aged 18-29 years (mean 23.2 years), and weighed 60-89 kg (mean 72.4 kg).

Pharmacokinetics:
Mass-Balance:
Figure 1. Retigabine, NAMR (AWD21-360) and [14C]-Retigabine (14C-GKE)-Derived Radioactivity Concentration-Time Profiles after Administration of a Single 200 mg Dose of [14C]-Retigabine in Healthy Male Volunteers (Mean ± SD, N=6)

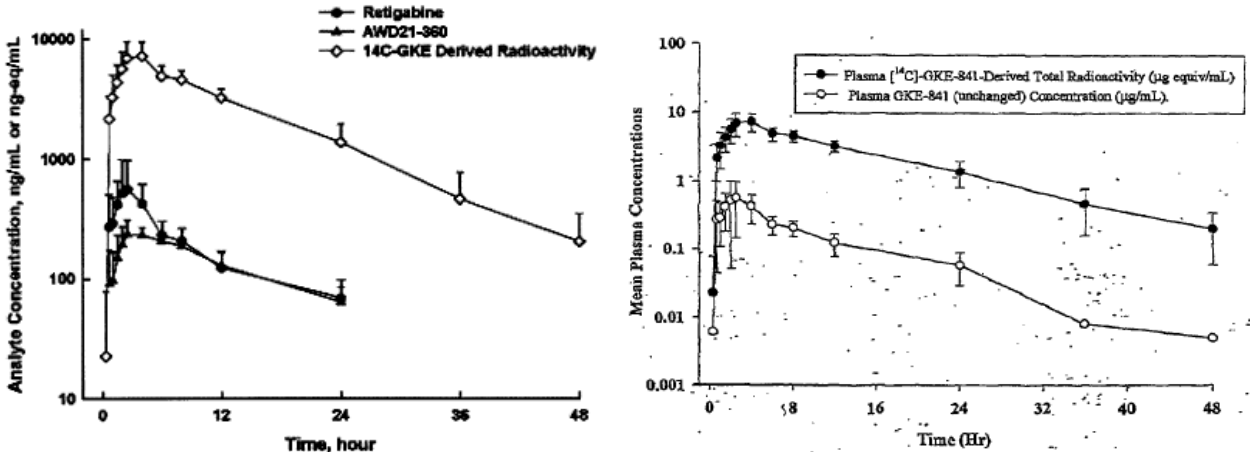


Figure 2. Mean Cumulative Recovery of 14C-Retigabine derived Radioactivity in Urine and Feces Following Administration of a Single Oral Dose of 200 mg (200 µCi) of 14C-Retigabine to Healthy Male Subjects

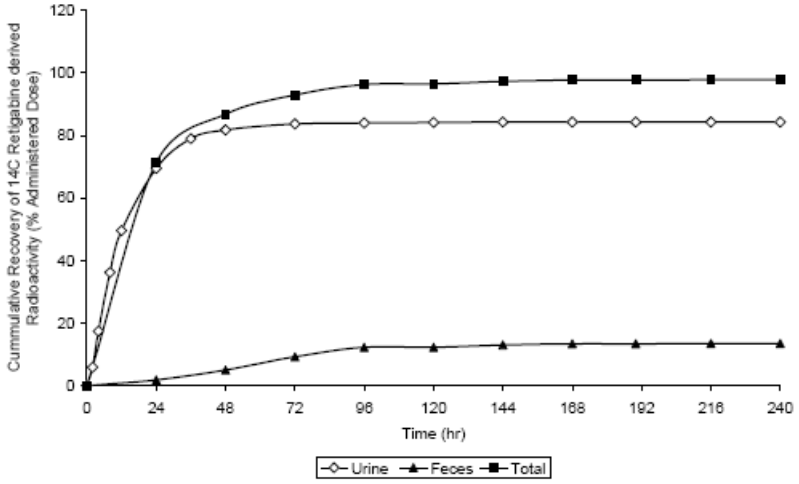


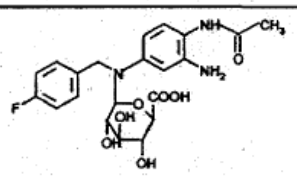
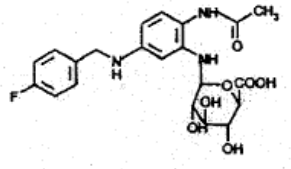
Table 1. Summaries of the PK parameters of retigabine, NAMR, and total radioactivity

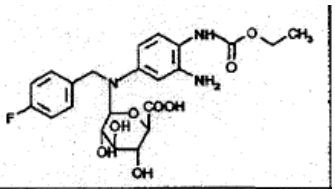
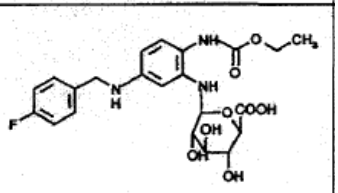
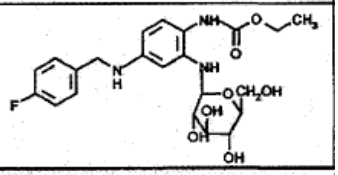
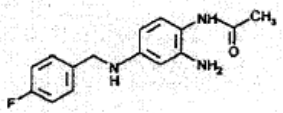
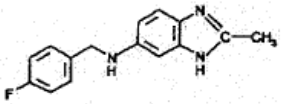
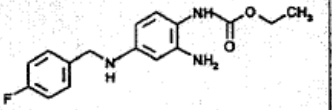
	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Retigabine				
Mean ± SD	674.1 ± 373.6	2.2 ± 1.3	9.1 ± 3.3	5287 ± 1737
Geometric Mean	591.1	1.8	8.4	5018
AWD21-360				
Mean ± SD	258.3 ± 35.5	3.3 ± 1.3	11.0 ± 2.4	4298 ± 823
Geometric Mean	256.0	3.1	10.7	4220
[^{14}C]-retigabine derived material				
Mean ± SD	8053 ± 2183	2.8 ± 0.9	8.5 ± 1.8	102111 ± 21256

- Comparison of plasma radioactivity-time profiles of total [14C]-retigabine derivatives vs. retigabine and NAMR suggests that the majority of plasma radioactivity was attributable to retigabine metabolite(s) other than NAMR.
- The t1/2 values for retigabine, NAMR and total radioactivity were similar.
- The whole blood-to-plasma ratio for the radioactivity ranged 0.55~0.68, indicating that retigabine does not significantly partition into cellular components of blood.
- Approximately 97.9% of the radiolabeled dose was recovered within 240 hours postdose, indicating that PK samplings were adequate to allow near complete recovery of drug-derived material. Of the total recovery, 84% was recovered in the urine and 13.5% recovered in the feces.
- Majority (93%) of administered radiolabel was recovered within 72 hours postdose.
- The contribution of retigabine and AWD21-360 to the Cmax of total radioactivity ranged 4.9~13.4% (8.38% based on mean values) and 2.0~5.0% (3.21% based on mean values), respectively.
- The contribution of retigabine and AWD21-360 to the AUC of total radioactivity ranged 3.3~8.4% (5.18% based on mean values) and 3.5~6.5% (4.21% based on mean values), respectively.
- Results indicate that retigabine metabolites accounted for more than 90% of total radioactivity in the plasma, and suggest that retigabine N-glucuronide is the dominant metabolite, as reported.
- Based on the mean plasma concentrations of retigabine and total radioactivity, unchanged drug (retigabine) accounted for 3.9~11.0% of the total radioactivity at all time points, suggesting that retigabine is extensively metabolized.

Metabolic Profile:

Table 2. Summary of the identified metabolites of retigabine in plasma, urine, and feces in man

Metabolite/ Synonym	Compartment	Proposal for structure
RT95 M 6	Plasma Urine	
RT107 M 5	Plasma Urine	

RT110 M 3	Plasma Urine	
RT116 M 1	Plasma Urine	
RT124 M 4	Plasma Urine	
RT126 M 2	Plasma Urine	
RT129	Faeces (*In vitro* faeces)	MW[1]: 607 It contains the retigabine substructure represented by the abundant fragment ion at m/z 316 as identified by LC/MS/MS analysis.
RT131 M 7	Urine	
RT137	Faeces (*In vitro* faeces)	MW[1]: 607 It contains the retigabine substructure represented by the abundant fragment ion at m/z 316 as identified by LC/MS/MS analysis.
RT146 Retigabine	Plasma Urine Faeces	
RT168	Faeces (*In vitro* faeces)	MW[1]: 618 It contains the retigabine substructure represented by the abundant fragment ion at m/z 316 as identified by LC/MS/MS analysis.

Plasma:
Seven metabolites were identified in human plasma (along with the parent drug): M6/RT95 (NAMR-N4-glucuronide), M5/RT107 (NAMR-N2-glucuronide), M3/RT110

(retigabine-N4-glucuronide), M1/RT116 (retigabine-N2-glucuronide), M4/RT124 (retigabine-N2-glucoside), M2/RT126 (NAMR) and M7/RT131 (cyclisation product of NAMR). The M1/RT116 (retigabine-N2-glucuronide) was the predominant species in plasma based on radioactive peak, followed by retigabine/RT146 and NAMR/RT126. Metabolites M5 and M6 were formed from M2 (NAMR) via glucuronidation.

* Noted that the sponsor reported that an unknown fraction of M1 metabolite (estimated ~10-20%) was converted back to [14C]-retigabine due to thermal stress after the solid phase extraction of plasma samples.

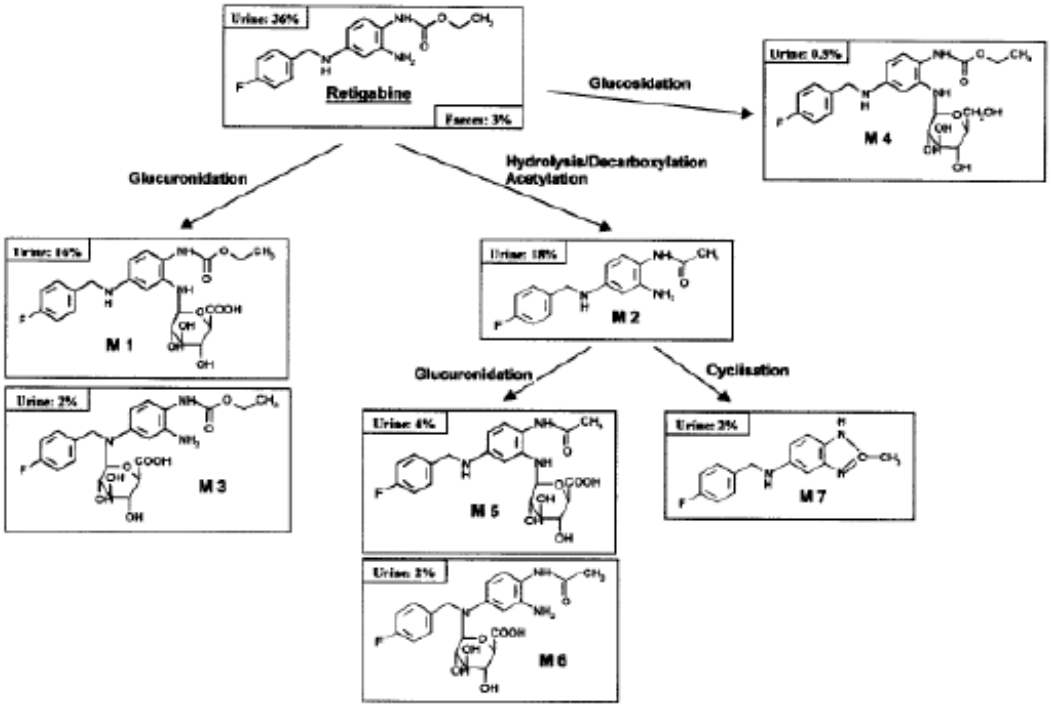
Urine:
Retigabine is mainly renal excreted as 7 metabolites, of which 6 were present in the plasma. The urine abundance in the following order: Retigabine > M2/NAMR > M1 > M5 > M3, M7, M6 > M4. The unchanged parent drug (RT146), the N-glucuronide M1 (RT116) and the acetyl metabolite M2 (RT126) accounted for approximately 70% of the dose excreted within 72 h, with the unchanged parent drug amounted to 36% of the radiolabeled dose in urine.

Table 3. Summary of excreted amounts of [14C]-retigabine and its major metabolites in urine accumulated over 0-72 h and expressed as percentage of dose

	Metabolite fraction excreted in urine (% of the dose)								
	RT95 (M6)	RT107 (M5)	RT110 (M3)	RT116 (M1)	RT124 (M4)	RT126 (M2, NAMR)	RT131 (M7)	RT146 (RTG)	Sum of other
Mean	1.6	3.8	1.9	16.4	0.5	17.9	1.8	**36.2**	3.7
CV (%)	25.0	26.3	31.6	17.1	1.1	8.9	1.1	3.9	20.6

Feces:
Approximately 3% of the dose was excreted in the feces as unchanged parent drug. Three new minor metabolites were found in feces (may be formed in the gut) but not found in the plasma or urine. No evidence of oxidative metabolism of retigabine was reported.

Proposed Metabolic Pathway:
Figure 3. Metabolic Pathways of [14C]-Retigabine in Healthy Males after Oral Dosing of 200 mg Retigabine as a Capsule (Excreted Amounts in Urine (0-72 h) and Feces (0-96 h) as % of Dose Administered)



CONCLUSION:

- Retigabine was extensively absorbed after oral administration, as evidenced by the great majority of the radioactivity being recovered in urine.
- Retigabine was mainly excreted renally as metabolites and unchanged parent drug. Retigabine metabolic pathways were primarily formation of the N-acetyl metabolite of retigabine (NAMR) and N-glucuronidation of both retigabine and NAMR via acetylation and glucuronidation, not by CYP enzymes.
- We notice that the sponsor had not monitored this predominant M1 metabolite in all of their clinical studies. However, the sponsor claimed that there was no evidence for a retigabine metabolite that would be expected to accumulate to a greater degree than parent itself.
- In view of the abundance of the M1 metabolite (N-glucuronide of retigabine) observed in both plasma and urine and its elimination pathway, the sponsor should have monitored the M1 metabolite levels in certain clinical studies. Even though this M1 metabolites was reported to be inactive, this reviewer believe that it would've been valuable to understand the PK profile and accumulation of this predominant inactive metabolite after repeated chronic doses or in specific populations, e.g., patients with renal impairment or hepatic impairment, as well as its potential correlation to any adverse events observed in patients. The knowledge of these aspects will be helpful in guiding for any potential dosage adjustment for specific patient populations.

4.4.2 Intrinsic Factors

Study VRX-RET-E22-102

Title: An Open-Label, Single-Dose, Parallel-Group, Pharmacokinetic Study of RWJ-333369 in Subjects with Normal Hepatic Function, Mild Hepatic Impairment, or Moderate Hepatic Impairment

Objectives: To determine the pharmacokinetics (PK) and safety of retigabine in healthy adult volunteers and in patients with varying degrees of hepatic impairment

Dose and Drug Products:
Retigabine 100-mg tablets: Lot VV06/09), orally administered under fasted conditions

Study Population: 24 subjects planned and enrolled; 6 healthy adult volunteers and 18 patients (N=6 per group)

Study Design:
This was an open-label, single-dose, parallel-group study to evaluate the effects of hepatic impairment on the PK of retigabine (RTG) and acetyl-metabolite (NAMR) after a single oral 100-mg dose of retigabine. Eligible 24 subjects were enrolled and assigned into the following treatment groups, with study duration of 4.5 days:

- Group 1: N=6 healthy subjects with normal liver function
- Group 2: N=6 patients with mild hepatic impairment (Child-Pugh scores of 5-6)
- Group 3: N=6 patients with moderate hepatic impairment (Child-Pugh scores of 7- 9)
- Group 4: N=6 patients with severe hepatic impairment (Child-Pugh scores > -9)

Blood and urine samples for PK analysis were collected for RTG and NAMR determination up to 96 hours after dosing. Safety, but not efficacy, assessment was performed during the study.

Pharmacokinetic Sampling:
Plasma samples: predose, at 20, 40, and 60 minutes, and 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 h postdose
Urine samples: Predose, 0–12, 12-24, 24–48, 48–72, and 72–96 h postdose

Bioanalytical Method:
Blood and urine samples were analyzed for retigabine and the N-acetyl metabolite of retigabine using chromatographic procedures developed at (b) (4) The calibration curves for plasma samples were 5–2000 ng/mL for retigabine, and 15–2000 ng/mL for the N-acetyl metabolite of retigabine.

Pharmacokinetic Analysis:
Plasma retigabine and the N-acetyl metabolite of retigabine PK parameters were estimated from plasma data using noncompartmental methods, including Cmax, Tmax, AUC0-t, AUC0-inf, kel, t1/2, and CL/F (retigabine only). Urinary PK parameters included CL_R and % excreted. The 90% confidence intervals (CIs) were constructed for

the difference in means on the ln-transformed exposure (Cmax, AUC0-t, and AUC0-inf) for each hepatic impairment group (Groups 2, 3, and 4) and the healthy subjects group (Group 1).

RESULTS

Demographics:

All subjects completed the study without withdrawal, and were included in PK analysis.

Variable	Group 1 (N=6)	Group 2 (N=6)	Group 3 (N=6)	Group 4 (N=6)	Total (N=24)
Gender					
Female	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	6 (25.0)
Male	4 (66.7)	4 (66.7)	5 (83.3)	5 (83.3)	18 (75.0)
Age (years)					
Mean ± SD	43.3 ± 11.38	49.8 ± 5.67	51.8 ± 5.71	48.7 ± 6.12	48.4 ± 7.79
Race (n[%])					
White	5 (83.3)	6 (100.0)	5 (83.3)	5 (83.3)	21 (87.5)
Black	1 (16.7)	0	1 (16.7)	1 (16.7)	3 (12.5)
Ethnicity (n[%])					
Hispanic or Latino	1 (16.7)	0	0	2 (33.3)	3 (12.5)
Non-Hispanic or Non-Latino	5 (83.3)	6 (100.0)	6 (100.0)	4 (66.7)	21 (87.5)
Weight (kg)					
Mean ± SD	76.8 ± 17.09	91.9 ± 18.27	91.8 ± 31.53	79.1 ± 17.14	84.9 ± 21.62
BMI (kg/m^2)					
Mean ± SD	25.3 ± 5.14	30.5 ± 7.08	30.3 ± 7.64	26.4 ± 3.92	28.1 ± 6.19
Estimated Creatinine Clearance (mL/min)					
Mean ± SD	107.1 ± 24.0	127.3 ± 27.3	125.5 ± 44.3	112.7 ± 28.9	118.1 ± 31.2

Pharmacokinetics Summary:

Figure 1. Mean Plasma Retigabine Concentration-Time Profiles Following Administration of a Single 100 mg Retigabine Tablet in Healthy Subjects and in Patients with Hepatic Impairment

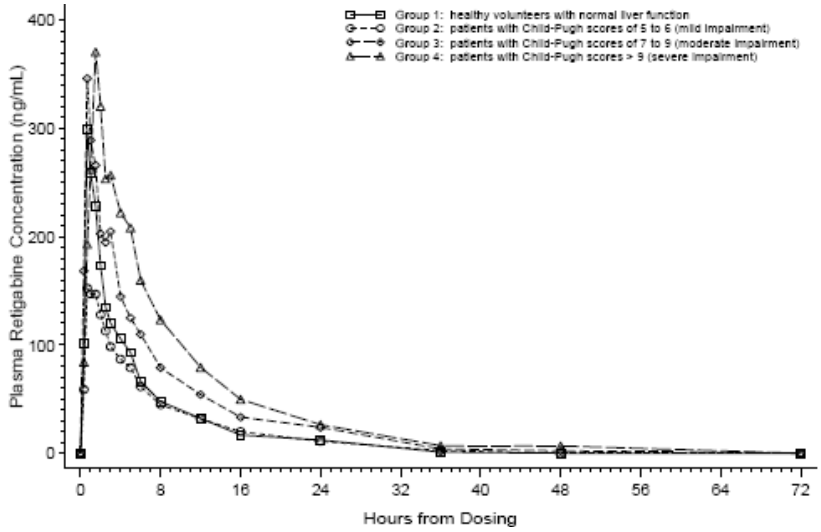


Table 1. Summary of Pharmacokinetic Parameters for Plasma Retigabine Following Administration of a Single 100 mg Retigabine Tablet in Healthy Subjects and in Patients with Hepatic Impairment

Analyte / Parameter	Mean ± SD			
	Group 1 (Healthy, N=6)	Group 2 (Mild, N=6)	Group 3 (Moderate, N=6)	Group 4 (Severe, N=6)
RTG				
AUC_{0-t} (ng*h/mL)	1329 ± 578	1126 ± 137	2116 ± 924	2861 ± 1164
AUC_{0-inf} (ng*h/mL)	1458 ± 658	1231 ± 169	2218 ± 930	3019 ± 1179
C_{max} (ng/mL)	308 ± 174	207 ± 58.0	364 ± 63.6	396 ± 199
t_{max} (h) [a]	0.667 (0.667, 1.00)	1.25 (0.667, 4.00)	0.667 (0.333, 1.50)	1.50 (1.00, 3.00)
$t_{1/2}$ (h)	7.31 ± 1.89	8.17 ± 2.17	6.46 ± 1.36	7.43 ± 1.11
CL/F (L/h)	80.0 ± 31.2	82.7 ± 12.6	53.5 ± 24.9	38.4 ± 16.5
CL_R (L/h)	13.1 ± 5.90	14.2 ± 3.12	9.77 ± 5.84	5.66 ± 1.99
NAMR				
AUC_{0-t} (ng*h/mL)	1497 ± 541	1069 ± 148	1789 ± 454	1827 ± 492
AUC_{0-inf} (ng*h/mL)	1694 ± 599	1262 ± 151	2159 ± 758	2253 ± 632
C_{max} (ng/mL)	173 ± 67.3	136 ± 14.8	187 ± 43.4	135 ± 41.9
t_{max} (h)[a]	1.50 (0.667, 3.00)	2.50 (0.667, 5.00)	2.75 (1.50, 4.00)	4.03 (2.00, 5.00)
$t_{1/2}$ (h)	6.214 ± 1.50	5.75 ± 1.05	7.66 ± 4.34	8.45 ± 1.71
CL_R (L/h)	4.88 ± 1.36	6.49 ± 2.07	5.50 ± 1.29	4.59 ± 1.80

a. Tmax is presented as median (minimum, maximum)

Table 2. Statistical Assessments of Retigabine and NAMR Systemic Exposure in Patients with Hepatic Impairment vs. Healthy Subjects

Pharmacokinetic Parameters	% MR (90% CI)		
	Group 2 vs Group 1	Group 3 vs Group 1	Group 4 vs Group 1
Retigabine			
AUC_{0-t} (ng*hr/mL)	90.75 (61.31, 134.33)	157.23 (106.22, 232.73)	214.32 (144.79, 317.24)
AUC_{0-inf} (ng*hr/mL)	90.79 (61.73, 133.53)	151.86 (103.25, 223.35)	209.04 (142.13, 307.46)
C_{max} (ng/mL)	72.50 (47.18, 111.39)	131.02 (85.27, 201.31)	127.27 (82.83, 195.54)
N-Acetyl Metabolite			
AUC_{0-t} (ng*hr/mL)	74.17 (57.57, 95.57)	122.12 (94.77, 157.35)	124.07 (96.29, 159.87)
AUC_{0-inf} (ng*hr/mL)	77.31 (58.88, 101.52)	126.74 (96.52, 166.42)	134.77 (102.63, 176.97)
C_{max} (ng/mL)	83.11 (63.07, 109.52)	112.97 (85.73, 148.87)	80.29 (60.93, 105.80)

Table 3. Impact of Various Degrees of Hepatic Impairment on Retigabine Exposure

Degree of Hepatic Impairment	Fold Increase (RTG)	
	AUC	Cmax
Mild	0.91	0.73
Moderate	1.5	1.3
Severe	2.1	1.3

Safety Summary:

A total of 23 AEs were reported by 11 (46%) subjects in this study, including 2 (33%) subjects in Group 1, 4 (67%) subjects in Group 2, 3 (50%) subjects in Group 3, and 2 (33%) subjects in Group 4. Most AEs were of mild in severity. There were no deaths or treatment-emergent SAEs reported in this study, and no subjects discontinued from the study due to an AE. The most common CNS-related AEs were mild dizziness, mild dysgeusia, and mild somnolence, reported by 2 (8%) subjects each in this study.

CONCLUSION:

- Degrees of hepatic function had effects on PK characteristics of both retigabine and NAMR.
- Compared to the healthy subjects, AUCs of retigabine were similar in subjects with mild hepatic impairment. However, AUCs were approximately 50% and 100% greater in patients with moderate and severe hepatic impairment, respectively, which can be attributed to the decreases in retigabine CL/F and retigabine CL_R values.
- There were approximately 30% (27-35%) increases in retigabine Cmax in patients with moderate and severe hepatic impairment.
- The trend in exposure incrases of NAMR metabolite was similar to those of retigabine, although the increases were smaller in comparison (20–35% higher in Groups 3 and 4 vs. Group 1).
- The terminal t1/2 remained similar for retigabine and NAMR metabolite in all 3 patient groups.
- Retigabine protein binding in various hepatic functions groups was not measured in this study. It is not entirely clear whether the increases in AUC observed in the hepatic impairment groups are mostly due to a decrease in intrinsic hepatic clearance secondary to the disease state rather than a change in plasma protein binding.
- The Sponsor proposed that a 50% dose reduction for retigabine based on AUC increases when use in patients with severe hepatic impairment. However, a dose reduction by 1/3 may be considered as an option for patients with moderate hepatic impairment in view of extents of exposure increases for both retigabine and NAMR metabolite.

Study VRX-RETE22-101

Title: Single-dose pharmacokinetics of retigabine in healthy subjects and patients with various degrees of renal insufficiency

Objectives: To determine and evaluate the pharmacokinetics (PK) and safety of a single oral dose of retigabine in normal volunteers and in patients with various degrees of renal insufficiency

Drug Products: Retigabine 100-mg oral tablets (Lot VV06/09); expiry date: October 2009

Study Population: 30 planned (6 healthy adult volunteers and 24 patients with varying degrees of renal impairment; 31 enrolled. Data from 28 subjects (6 healthy and 22 patients) were analyzed and reported.

Study Design:
This was an open-label, single-dose, parallel-group study with 100-mg retigabine doses. Study duration was 6-7 days. A total of 31 subjects were enrolled (6 healthy volunteers and 24 subjects with varying degrees of renal insufficiency) and 28 were grouped according to their creatinine clearance (CLcr) values:

- Group 1: CLcr >80 mL/min (healthy subjects with normal renal function)
- Group 2: CLcr ≥50 to ≤80 mL/min (mild renal impairment)
- Group 3: CLcr ≥30 to <50 mL/min (moderate renal impairment)
- Group 4: CLcr <30 mL/min (severe renal impairment)
- Group 5: Requiring dialysis (patients with ESRD, end-stage renal disease)

All subjects were dosed after at least an 8-hour overnight fast, and all groups remained in the unit until completion of all blood and urine sample collections up to 96 hours postdose for determination of plasma concentrations of retigabine and the N-acetyl metabolite (NAMR). Routine safety assessments were performed throughout the study.

Pharmacokinetic Assessments:

Plasma samples (Groups 1 - 4 and Group 5 (on a dialysis-free day)): at predose, 20, 40, and 60 minutes and 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 h postdose

Dialysate samples: Group 5, prior to the start of hemodialysis (0 hour), and at 0–1, 1–2, 2–3, 3–4, and 4–5 hours. Dialysis was not to begin sooner than 48 hours postdose.

Urine samples: Predose, and at 0–12, 12–24, 24–48, 48–72, and 72–96 hours postdose

Blood, urine, and dialysate samples were analyzed for retigabine and the N-acetyl metabolite of retigabine using chromatographic procedures developed at (b) (4). The calibration ranges were 5–2000 ng/mL for retigabine, and 15–2000 ng/mL for the N-acetyl metabolite of retigabine for plasma, urine, and dialysate. The retigabine limit of quantification in dialysate was ng/mL.

Pharmacokinetic Analysis:

The following plasma PK parameters of retigabine and NAMR were estimated from plasma data using noncompartmental methods: Cmax, Tmax, AUC_D (AUC during the time period of dialysis, Group 5 only, AUC0-inf, kel, t1/2, and CL/F (retigabine only). Urinary PK parameters included CLR and % excreted. PK parameters for dialysate retigabine and the N-AMR for Group 5 included A_D, CL_D ($CL_D=A_D/AUC_D$), and F_D (retigabine only, FD=CLD/(CL/F + CLD)). Descriptive statistics were employed for the individual and mean PK and exposure parameters. Linear regression of the relationship between individual's CLcr value vs. CL/F or CLR was plotted. ANOVA models, including group as a fixed effect, were used to study the effect of degree of renal impairment on selected exposure parameters. Point estimates and the 90% confidence intervals (CIs) were constructed for the difference in means on the ln-transformed least-squares mean (LSM) ratios for exposure (Cmax, AUC0-t, and AUC0-inf) for each renal impairment group (Groups 2, 3, 4 and 5) and the healthy subjects group (Group 1).

RESULTS

Demographics:

Variable	Group 1 (N=6)	Group 2 (N=5)	Group 3 (N=6)	Group 4 (N=5)	Group 5 (N = 6)	Total (N=28)
Gender						
Female	3 (50.0)	1 (20.0)	4 (66.7)	2 (40.0)	3 (50.0)	13 (46.4)
Male	3 (50.0)	4 (80.0)	2 (33.3)	3 (60.0)	3 (50.0)	15 (53.6)
Age (years)						
Mean ± SD	47.8 ± 19.7	66.6 ± 5.81	62.2 ± 14.4	66.8 ± 10.4	52.0 ± 13.6	58.5 ± 15.1
Race (n[%])						
Asian	0	0	1 (16.7)	0	0	1 (3.6)
Black or African American	1 (16.7)	0	1 (16.7)	0	6 (100.0)	8 (28.6)
White	5 (83.3)	5 (100.0)	4 (66.7)	5 (100.0)	0	19 (67.9)
Ethnicity (n[%])						
Hispanic or Latino	3 (50.0)	2 (40.0)	2 (33.3)	1 (20.0)	1 (16.7)	9 (32.1)
Non-Hispanic or Non-Latino	3 (50.0)	3 (60.0)	4 (66.7)	4 (80.0)	5 (83.3)	19 (67.9)
Weight (kg)						
Mean ± SD	82.0 ± 10.5	84.7 ± 19.2	77.4 ± 16.5	83.0 ± 14.4	85.9 ± 18.4	82.5 ± 15.1
Height (cm)						
Mean ± SD	170 ± 10.4	172 ± 6.84	163 ± 9.64	169 ± 7.99	171 ± 6.18	169 ± 8.47
BMI (kg/m^2)						
Mean ± SD	28.3 ± 2.96	28.5 ± 5.20	28.8 ± 2.92	29.1 ± 3.83	29.1 ± 4.98	28.8 ± 3.75
Estimated Creatinine Clearance (mL/min)						
Mean ± SD	121 ± 37.9	65.9 ± 6.57	37.6 ± 6.97	20.0 ± 6.06	N/A	62.8 ± 44.3

Note; Subjects 305 and 309 did not complete the study. Subjects 101, 304, and 703 had CLcr values belonging to Group 1, but these subjects had a medical history of mild to moderate renal disease, and data from these 5 subjects were excluded from analysis.

Pharmacokinetics Summary:

Plasma data:

Results of the similar degrees of plasma protein binding for carisbamate (59.2-65.2%) across the 3 groups of subjects with normal renal function, moderate and severe renal impairment, and end stage renal disease are shown in the Table 1.

Figure 1. Mean Plasma Retigabine Concentration-Time Profiles Following Administration of a Single 100 mg Retigabine Tablet in Healthy Subjects and in Patients with Renal Impairment

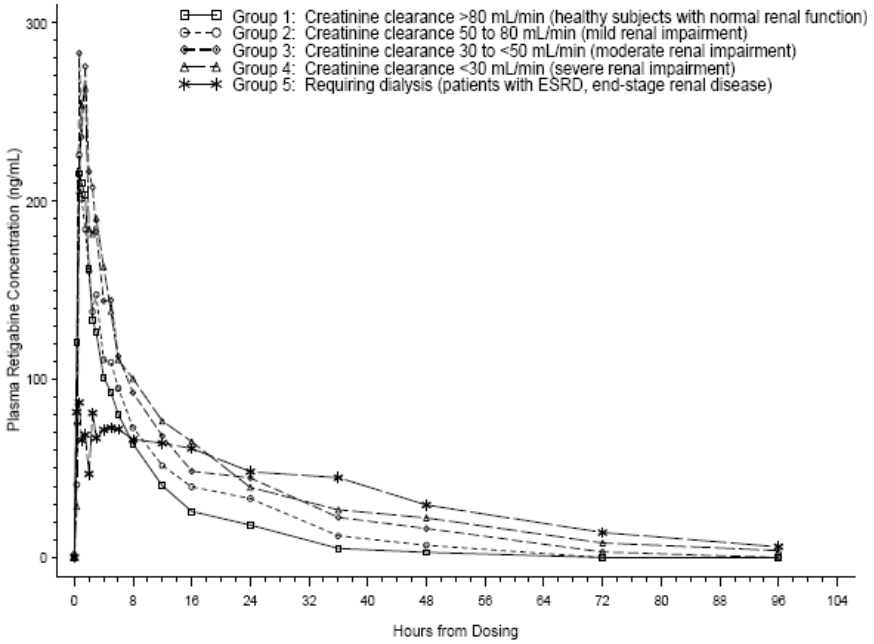


Figure 2. Mean Plasma N-acetyl Metabolite of Retigabine Concentration-Time Profiles Following Administration of a Single 100 mg Retigabine Tablet in Healthy Subjects and in Patients with Renal Impairment

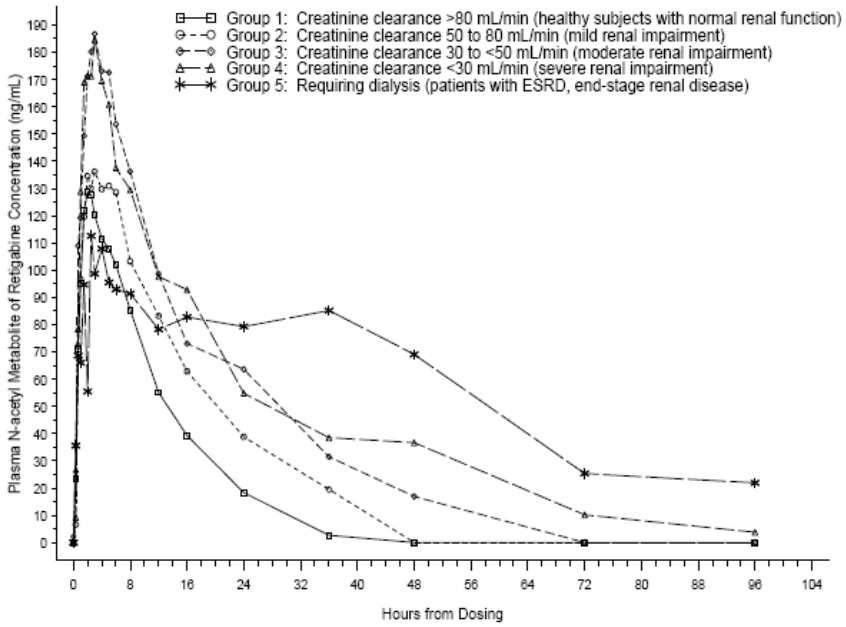


Table 1. Pharmacokinetic Parameters of Retigabine and NAMR following Administration of a Single 100 mg Retigabine Tablet in Healthy and Renally Impaired Subjects

Analyte / Parameter	Mean ± SD				
	Group 1 (Healthy, N=6)	Group 2 (Mild, N=6)	Group 3 (Moderate, N=8)	Group 4 (Severe, N=5)	Group 5 (ESRD, N=6)
RTG					
$AUC_{0\text{-}inf}$ (ng*h/mL)	1700 ± 514	2166 ± 420	4888 ± 4868	3533 ± 1078	3557 ± 478
C_{max} (ng/mL)	269 ± 106	271 ± 142	434 ± 268	256 ± 127	127 ± 63.0
t_{max} (h)[a]	1.00 (0.67, 1.50)	0.83 (0.67, 3.00)	0.83 (0.67, 5.00)	1.00 (1.00, 1.50)	0.83 (0.33, 36.0)
$t_{1/2}$ (h)	8.21 ± 3.82	11.1 ± 1.26	15.6 ± 3.89	19.9 ± 7.09	22.8 ± 5.12
CL/F (L/h)	65.1 ± 26.0	47.5 ± 8.27	28.9 ± 10.3	30.6 ± 9.40	28.5 ± 3.48
CL_R (L/h)	13.5 ± 7.56	10.3 ± 2.75	5.68 ± 2.61	4.37 ± 2.12	0.058
%Dose Excreted	21.9 ± 15.1	20.8 ± 5.16	18.6 ± 4.51	12.9 ± 5.13	0.18
NAMR					
$AUC_{0\text{-}inf}$ (ng*h/mL)	1792 ± 394	2702 ± 636	4620 ± 1948	4896 ± 1576	6774 ± 1653
C_{max} (ng/mL)	137 ± 29.1	158 ± 17.8	235 ± 67.0	186 ± 40.3	142 ± 41.6
t_{max} (h)[a]	2.25 (1.00, 3.00)	2.75 (2.00, 6.00)	2.75 (0.67, 6.10)	2.50 (1.50, 3.00)	3.25 (1.50, 36.0)
$t_{1/2}$ (h)	8.74 ± 3.51	12.3 ± 2.84	15.3 ± 5.90	21.8 ± 9.12	30.8 ± 10.6
CL_R (L/h)	5.59 ± 3.87	5.83 ± 0.99	3.68 ± 1.66	2.78 ± 1.05	0.058
%Dose Excreted	9.40 ± 6.50	14.6 ± 3.71	14.0 ± 3.46	13.0 ± 5.68	0.40

a Tmax: median (minimum, maximum). Group 5: PK dosing was on a dialysis-free day. N=1 for CL_R.

Table 2. Summary of exposure measures (AUC0-t, AUC0-inf, and Cmax) for plasma retigabine and the N-acetyl metabolite of retigabine for each renal-impaired group and the normal renal function group are summarized below:

Pharmacokinetic Parameters	Mean ± SD				
	Group 1 N = 6	Group 2 N = 5	Group 3 N = 5	Group 4 N = 4	Group 5 N = 6
Retigabine					
$AUC_{0\text{-}t}$ (ng*hr/mL)	1578 ± 516.7	2049 ± 457.6	2980 ± 625.5	3417 ± 1145	3304 ± 428.4
$AUC_{0\text{-}inf}$ (ng*hr/mL)	1700 ± 513.5	2160 ± 469.6	3172 ± 640.4	3657 ± 1203	3557 ± 477.5
C_{max} (ng/mL)	269 ± 106	277 ± 158	339 ± 207	283 ± 130	127 ± 63.0
N-Acetyl Metabolite					
$AUC_{0\text{-}t}$ (ng*hr/mL)	1529 ± 407.0	2315 ± 556.3	3377 ± 912.1	4021 ± 1172	5730 ± 1099
$AUC_{0\text{-}inf}$ (ng*hr/mL)	1792 ± 393.8	2761 ± 692.5	4164 ± 1662	4372 ± 1440	6774 ± 1653
C_{max} (ng/mL)	137 ± 29.1	157 ± 19.8	215 ± 66.9	192 ± 43.8	142 ± 41.6

Table 3. Statistical Analysis on Effect of Renal Impairment on the Single-Dose Pharmacokinetics of Retigabine

Pharmacokinetic Parameters	% MR (90% CI)[b]			
	Group 2 vs Group 1	Group 3 vs Group 1	Group 4 vs Group 1	Group 5 vs Group 1
$AUC_{0\text{-}t}$ (ng*hr/mL)	134.31 (101.76, 177.28)	195.70 (148.27, 258.31)	217.63 (161.89, 292.57)	219.13 (168.17, 285.52)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	130.70 (100.11, 170.65)	192.42 (147.37, 251.23)	215.48 (162.16, 286.34)	217.52 (168.68, 280.50)
C_{max} (ng/mL)	98.95 (56.02, 174.77)	111.84 (63.32, 197.55)	100.98 (55.06, 185.18)	46.65 (27.12, 80.25)

[a] Tmax: Median (min, max)

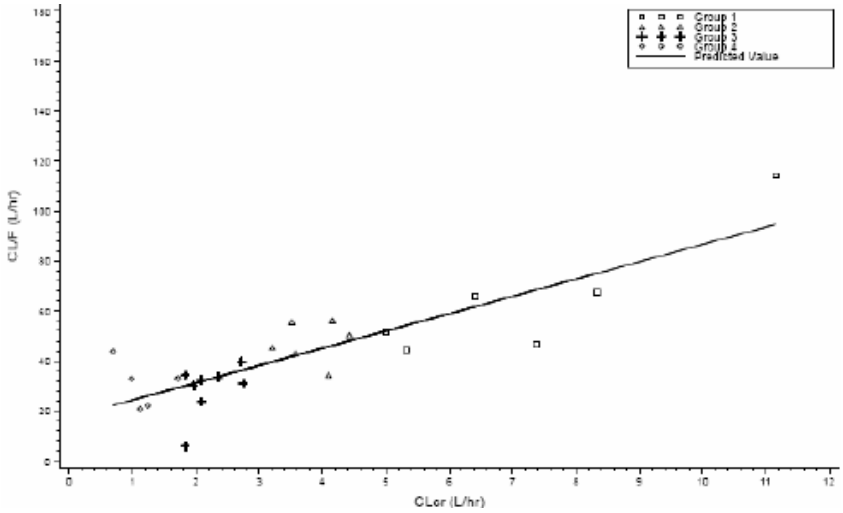
Table 4. Impact of Various Degrees of Renal Impairment on Retigabine and NAMR Exposure

Degree of Renal Impairment	Fold Increase (RTG)	
	AUC	Cmax
Mild	1.3	1.0
Moderate	1.9	1.1

Severe	2.2	1.0
ESRD	2.2	0.5

Degree of Renal Impairment	Fold Increase (NAMR)	
	AUC	Cmax
Mild	1.5	1.2
Moderate	2.2	1.5
Severe	2.4	1.4
ESRD	3.8	1.0

Figure 3. Relationship between Retigabine Oral Clearance and Creatinine Clearance in Healthy Subjects and Subjects with Varying Degrees of Renal Impairment



Urine data:

Table 5. Summary of Urinary Pharmacokinetic Parameters for Retigabine Following Administration of a Single 100 mg Retigabine Tablet in Healthy Subjects and in Patients with Renal Impairment

	Mean ± SD				
Pharmacokinetic Parameters	**Group 1 N=6**	**Group 2 N=5**	**Group 3 N=5**	**Group 4 N=4**	**Group 5 N=1**
Cum.Ae (µg)	21891.60 ± 15051.37	19925.35 ± 5281.59	19091.90 ± 5519.79	12108.94 ± 5535.46	179.00
Cum. %Dose Excr.	21.89 ± 15.05	19.93 ± 5.28	19.09 ± 5.52	12.11 ± 5.54	0.18

For Group 5: Only 1 patient was able to produce urine for PK analysis

Dialysate:

- Limited amount of retigabine was recovered in dialysate samples that was collected over a 5-hour period (F_D ~0.022; CL_D <32.5 mL/min or 2 L/h).
- Only 2 patients had detectable N-acetyl metabolite. CL_D and F_D were not calculated for the metabolite.

Safety Summary:

A total of 8 reported AEs by 5 (18%) subjects, including 3 subjects in Group 1, 1 patient in Group 2, and 1 patient in Group 4. One AE was reported as moderate in severity and all others were mild. No deaths or treatment-emergent SAEs reported and no subjects discontinued from the study. Dizziness, which was reported by 2 subjects overall. No abnormal laboratory findings.

CONCLUSION:

- This study demonstrated that pharmacokinetics of retigabine are dependent on degrees of renal function. As the severity of the renal impairment increased in patients relative to healthy subjects (Group 1), retigabine exposure parameters AUC0-t and AUC0-inf increased exposure was 34% higher for patients with mild renal impairment (Group 2) and approximately 96~116% higher for patients with moderate impairment (Group 3) to ESRD (Group 5).
- Peak plasma levels (Tmax) of retigabine were reached at similar time among groups, but mean t1/2 increased as the severity of the renal impairment increased in patients.
- Plasma and renal clearance of retigabine decreased in renal-impaired patients compared to healthy subjects.
- CL/F decreased as the severity of the renal impairment increased (i.e., CLcr decreased) in patients, compared to that in healthy subjects. The amount of retigabine excreted in urine over 96 hours postdose was similar for Groups 1, 2, and 3, with Group 4 excreted less.
- Similar to the exposure increases for RTG, there was a trend for increasing accumulation of NAMR metabolite with highest accumulation observed in patients with ESRD (see Table 4).
- The anticipated accumulation for the major N2-glucuronide-RTG metabolite was not monitored in this study. Therefore, the changes of magnitude of the systemic exposure of the major glucuronide metabolites cannot be clearly predicted in patients with various degrees of renal functions, in particularly with the moderate~severe impairment and or with ESRD on dialysis, following chronic repeated dosing.
- Results from accumulative amounts of analytes in 5-hour dialysate samples suggest a limited contribution from the dialysis procedure to elimination of RTG or NAMR metabolites.
- Given the more modest changes in retigabine PK (i.e., fold changes in exposure for both RTG and NAMR) observed in patients with mild renal dysfunction, we agree with the sponsor that dosage adjustment is not be necessary for patients with mild renal impairment.
- For patients with renal impairment for severe than moderate, the sponsor proposed a 50% decrease in the initial and maintenance dose of retigabine. Such proposal for the labeling recommendation may be reasonable, considering the observed fold changes in exposure for both RTG and NAMR and the lack of clarity regarding any safety concern for the potential accumulation (significant or not) of the glucuronides conjugates in these patients groups.

Study 3065A1-200/201

Title: Effect Of Age And Sex On The Pharmacokinetics Of Retigabine

Objectives: To evaluate the pharmacokinetics of retigabine and its acetylated metabolite, AWD21-360, in young and elderly men and women after administration of a single 200 mg oral dose of retigabine.

Dose and Drug Products:

- Retigabine: 100-mg capsules, oral, batch number VV 97/06. The 200-mg dose was administered as 2 x 100-mg retagabine capsules.

Study Population:
Young healthy subjects (18-40 y.o.): 24 (12M/12F) planned, 24 enrolled, 24 completed, and 24 analyzed for safety and pharmacokinetics.
Elderly subjects (≥66 y.o.): 24 (12M/12F) planned, 24 enrolled, 24 completed, and 24 analyzed for safety and pharmacokinetics.

Study Design:
This was an open-label, 1-period, in-patient study to evaluate the PK of retigabine after single dosing in healthy young and elderly subjects of either gender who were enrolled and received a single oral dose of 200 mg retigabine. Routine safety assessments were performed. Plasma levels of retigabine (RTG) and its acetyl-metabolite (AWD21-360) were collected for 72 hours postdose.

Pharmacokinetic Sampling:
Plasma samples: predose, and 0.3, 0.6, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 , 16, 20, 24, 36, 48, 60, and 72 h postodse.

Pharmacokinetic Assessments:
The following PK parameters of retigabine and acetyl-metabolite (AWD21-360) were estimated from plasma data using noncompartmental methods: Cmax, Tmax, AUC0-12, t1/2, MRT, and CL/F, Vz/F. Potential PK differences between ages and genders were assessed on these PK parameters using a 2-factor ANOVA with factors for age, sex, and age*sex.

Bioanalytical Method:
Plasma and urine samples were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method. The assay was linear between 1-1000 ng/mL for retigabine and between 2.5-1000 ng/mL for AWD21-360. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-105

		Retigabine (plasma)	AWD21-360 (plasma)
Method:		HPLC/MS/MS	HPLC/MS/MS
Standard Curve:	Range:	1.0-1000 ng/mL	2.5-1000 ng/mL

	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 20%	< ± 20%
LOQ:		1.0 ng/mL	2.5 ng/mL
QC:		3, 15, 150, 750 ng/mL	3, 15, 150, 750 ng/mL
	Precision:	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

RESULTS

Demographics:

Characteristics	Young Men (n = 12)	Young Women (n = 12)	Elderly Men (n = 12)	Elderly Women (n = 12)
Age, yr				
Mean ± SD	33 ± 5	32 ± 4	73 ± 5	71 ± 4
Range	(21 - 40)	(25 - 39)	(67 - 82)	(66 – 81)
Weight, kg				
Mean ± SD	80.2 ± 5.4	64.6 10 ± 8.9	80.0 ± 6.3	65.0 ± 7.2
Range	(71 - 90)	(57 - 80)	(69 - 86)	(48 - 74)
Ethnic Origin				
White	11	12	12	12
Asian	1	-	-	-

Pharmacokinetics:

Retigabine:

Figure 1. Mean (±SE) Plasma-time Concentration profiles of Retigabine (Left) and AWD21-360 (Right) Following Oral Administration of 200 mg Single Oral Dose

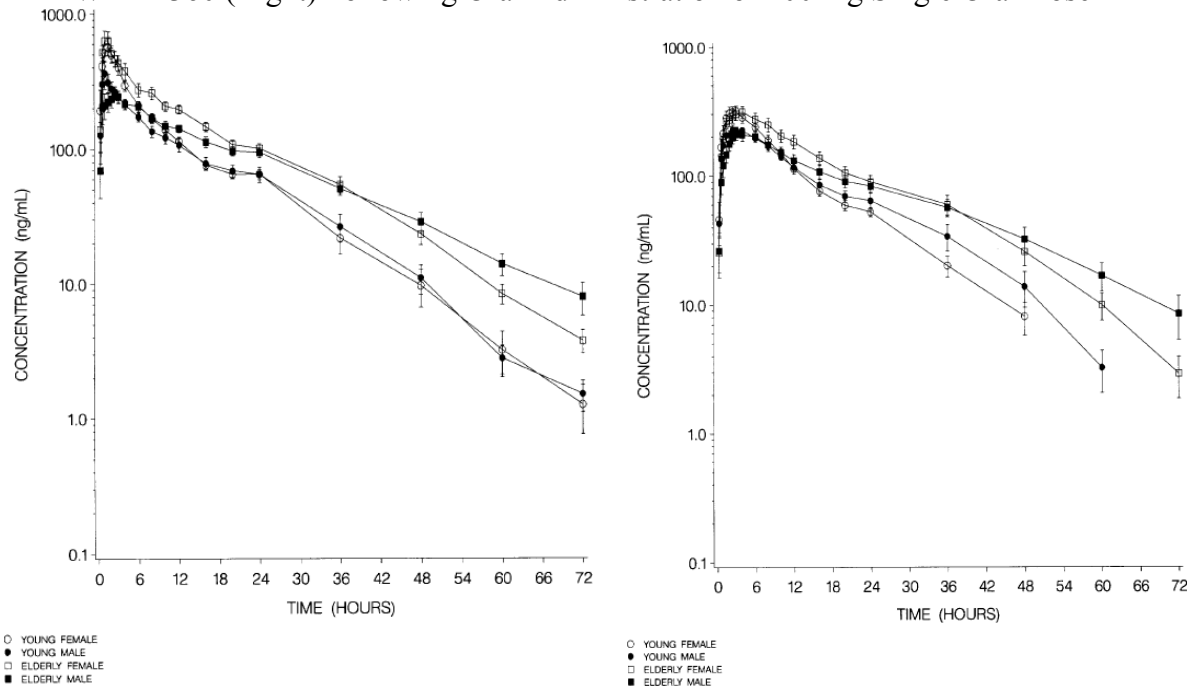


Figure 2. Mean Plasma Retigabine Concentration-Time Profiles following Administration of Retigabine 200 mg to Young Males and Young Females (x-axis truncated at 24 h)

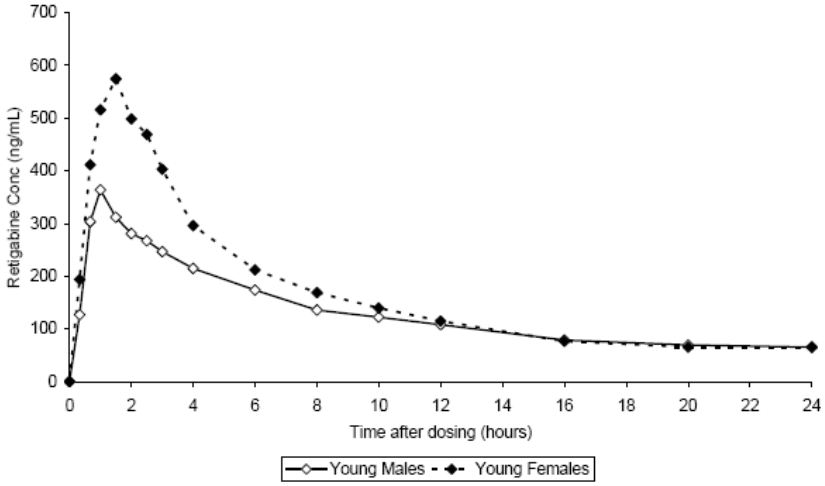


Figure 2. Mean Plasma Retigabine Concentration-Time Profiles Following Administration of Retigabine 200 mg to Elderly Males and Elderly Females (x-axis truncated at 24 h)

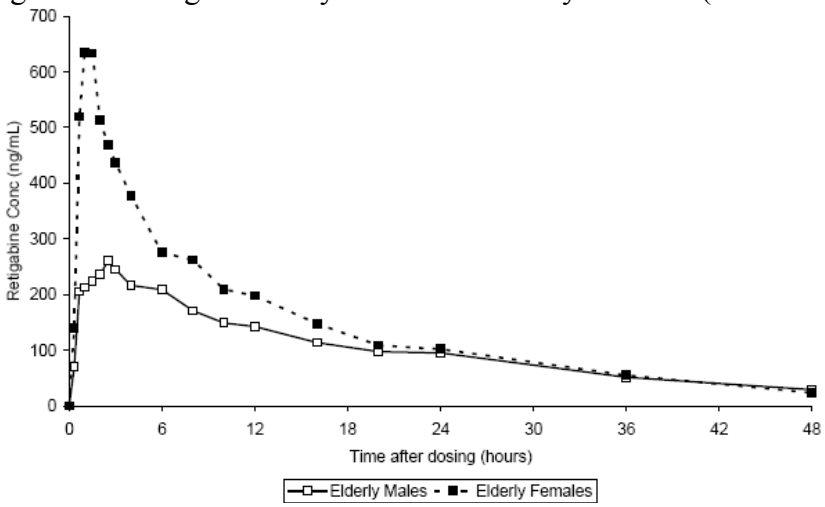


Figure 4. Retigabine Mean (±SD) Individual Cmax (Top Left), AUC (Top Right), CL/F (Bottom Left), and t1/2 (Bottom Right) Values Following Oral Administration of 200 mg Single Oral Dose

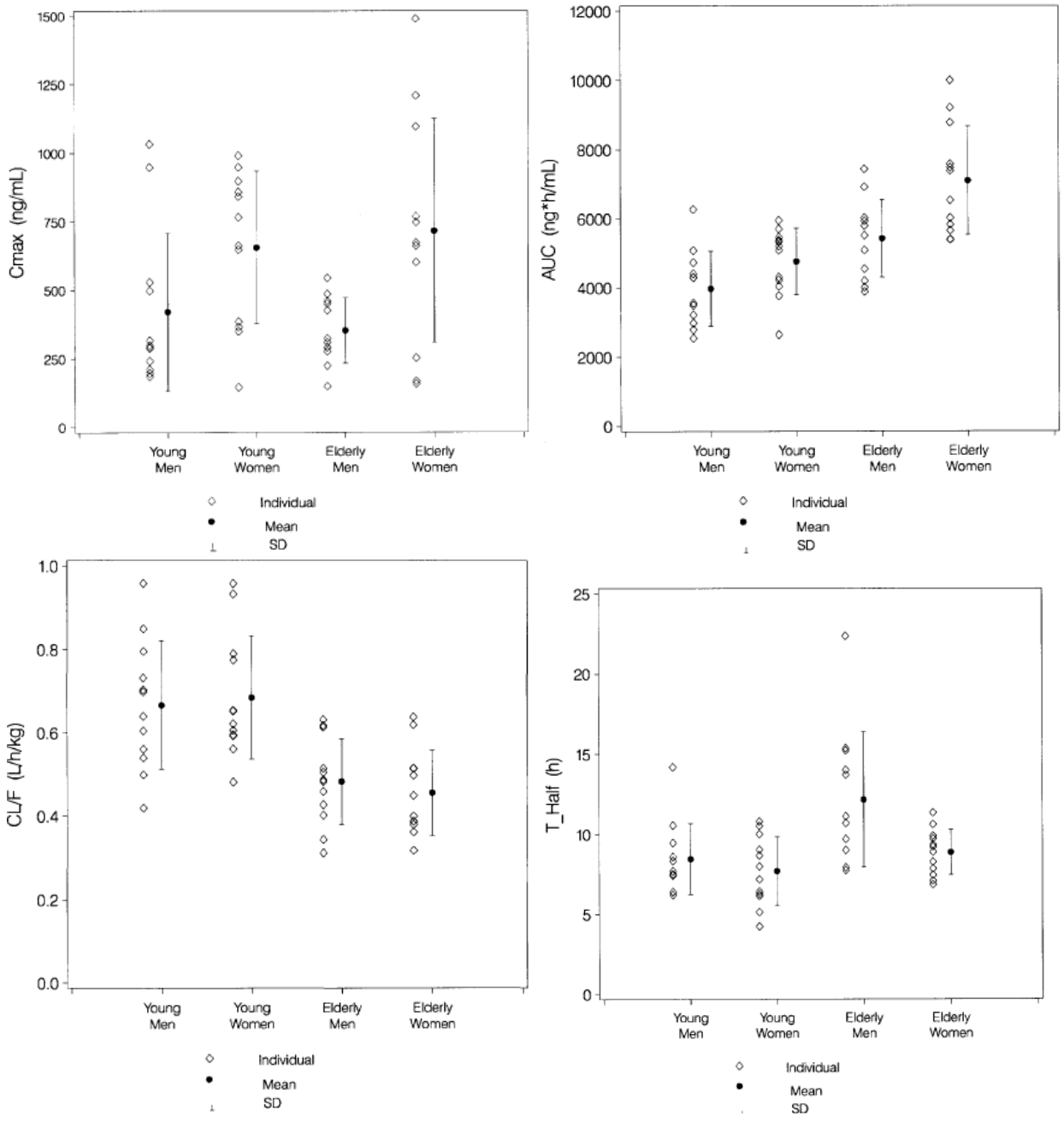


Figure 5. AWD21-360 Mean (±SD) Individual max (Top Left), AUC (Top Right), CL/F (Bottom Left), and t1/2 (Bottom Right) Values Following Oral Administration of 200 mg Single Oral Dose

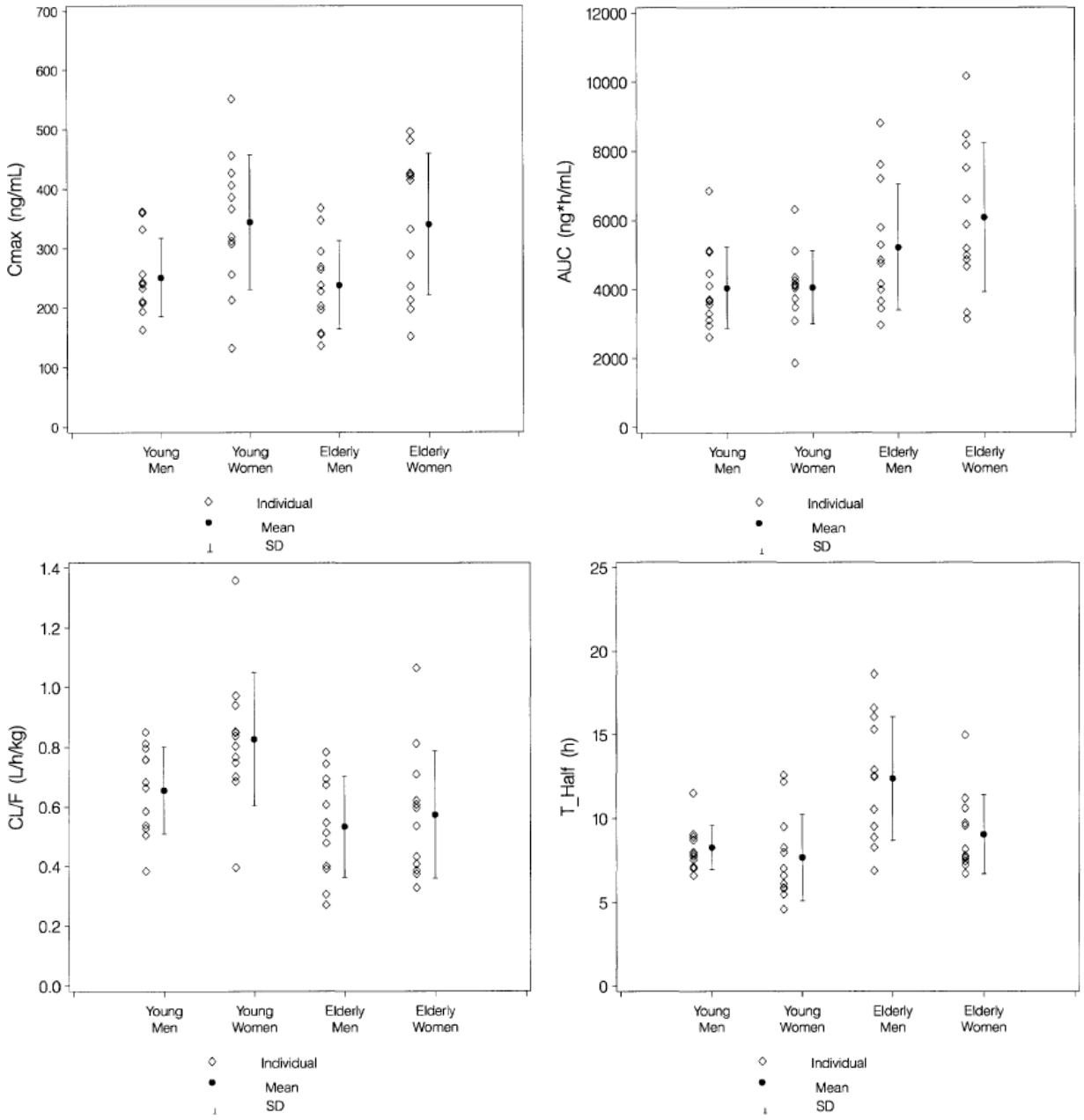


Table 1. Summary of Pharmacokinetic Parameters of Retigabine

Subject Group	C_{max} (ng/mL)	t_{max} (h)	AUC (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)
Young men	421 ± 288	2.0 ± 1.5	3970 ± 1083	8.5 ± 2.2	0.67 ± 0.15
Young women	656 ± 279	1.2 ± 0.7	4753 ± 968	7.7 ± 2.2	0.68 ± 0.15
Elderly men	354 ± 119	3.1 ± 2.7	5425 ± 1132	12.2 ± 4.2	0.48 ± 0.10
Elderly women	717 ± 409	2.7 ± 3.1	7108 ± 1573	8.9 ± 1.4	0.46 ± 0.10
p-values from the ANOVA on untransformed values associated with difference for:					
Sex	0.001	0.338	0.001	0.014	0.900
Age	0.971	0.048	0.001	0.003	0.001
Sex * age	0.451	0.754	0.204	0.113	0.550

a: Values represent mean±sd, n=12 per group

Table 2. Summary of Pharmacokinetic Parameters of AWD21-360

Subject Group	C_{max} (ng/mL)	t_{max} (h)	AUC (ng•h/mL)	$t_{1/2}$ (h)	CLm/(F•f_m) (L/h/kg)
Young men	251 ± 66	3.2 ± 1.2	4048 ± 1188	8.3 ± 1.3	0.66 ± 0.15
Young women	345 ± 113	2.6 ± 0.9	4055 ± 1069	7.7 ± 2.6	0.83 ± 0.22
Elderly men	238 ± 74	4.6 ± 4.1	5222 ± 1824	12.4 ± 3.7	0.53 ± 0.17
Elderly women	340 ± 119	3.0 ± 1.0	6083 ± 2156	9.1 ± 2.3	0.57 ± 0.21
p-values from the ANOVA on untransformed values associated with difference for:					
Sex	0.001	0.096	0.359	0.013	0.065
Age	0.757	0.174	0.001	0.001	0.001
Sex * age	0.876	0.426	0.367	0.077	0.243

a: Values represent mean±sd, n=12 per group

Table 3. Pharmacokinetic Parameters (Mean± SD) of Retigabine after Administration of a Single Oral Dose of 200 mg Retigabine to Healthy Young and Elderly Men and Women (N=12 per group)

Parameter	Younger Subjects		Elderly Subjects		p-Values [a]	
	Men	Women	Men	Women	Age	Sex
C_{max} (ng/mL)	421 ± 288	656 ± 279	354 ± 119	717 ± 409	0.971	0.001
AUC (ng*h/mL)	3970 ± 1083	4753 ± 968	5425 ± 1132	7108 ± 1573	0.001	0.001
t_{max} (h)	2.0 ± 1.5	1.2 ± 0.7	3.1 ± 2.7	2.7 ± 3.1	0.048	0.338
$t_{1/2}$ (h)	8.5 ± 2.2	7.7 ± 2.2	12.2 ± 4.2	8.9 ± 1.4	0.003	0.014
CL/F (L/h/kg)	0.67 ± 0.15	0.68 ± 0.15	0.48 ± 0.10	0.46 ± 0.10	0.001	0.900

A: *p*-Values from the ANOVA of untransformed values

Safety: There was no death, no SAE, no withdrawal, and well-tolerated. The most frequent AEs were asthenia, headache, thrombophlebitis, dizziness, and local reaction to procedure.

CONCLUSION:

- There were statistical differences in retigabine pharmacokinetics between men and women, with higher exposure measures and shorter t1/2 in women. There were statistical differences in retigabine pharmacokinetics between young and elderly subjects, with higher AUC and longer t1/2 values and corresponding lower CL/F values in the elderly in general. The Cmax values were similar between elderly and young subjects. Similar trends were observed for AWD21-360.
- The AUC values were approximately ~20% higher in young females compared to young males and ~30% in elderly females compared to elderly males. These differences in AUC are likely to be attributable to differences in body weight because there were no differences in weight-normalized CL/F of retigabine between genders.
- The Cmax values were approximately ~50% higher in young females compared to young males and ~100% higher in elderly females compared to elderly males. However, AUC values were ~40-50% higher in elderly subjects compared to young subjects and half-life was ~30% longer in elderly compared to young subjects of either gender.
- No dosage adjustment was recommended by the sponsor based on sex or age. However, the Agency reanalyzed the data and the percent probability of coordination abnormal (an AE of interest) was found to significantly increase with the increase of age across the proposed doses, probably due to increased sensitivity to retigabine levels in the elderly.

- Considering the ~40-50% increases in AUCs and ~30% longer t1/2 in the elderly, and increased probability of coordination abnormal (a safely concern) in the elderly subjects vs. young subjects, we recommend that a dose reduction to approximately two-thirds of the target dose should be considered for the elderly patients.

Report of Meta-Analysis for Comparison of Race

Title: A Meta-Analysis of Phase I Clinical Studies to Compare the Clearance of Retigabine in Black and Caucasian Subjects

Objective: To compare the apparent clearance (CL/F) of retigabine between Black and Caucasian subjects

Post-Hoc Analysis Approach:
Data was pooled from 195 healthy subjects in 8 Phase 1 clinical studies (3065A1-102, 3065A1-105, 3065A1-106, 3065A1-107, 3065A1-109, 3065A1- 110, 3065A1-113, and VRX-RET-E22-105). Among them, 36 were female (all Caucasian), and 159 were male (110 Caucasian, 43 Black, 3 Hispanic, and 3 Asian). As stated by the Sponsor, to mitigate potentially undue influence, Caucasian females and Asian and Hispanic males were excluded from statistical analysis. Using the Mixed procedure (SAS version 8.2), a linear mixed-effects model, with age, race (black vs. Caucasian), weight and dose as the fixed effects and subject as the random effect, was employed to analyze natural logarithmic transformed CL/F values from Black vs. Caucasian. The geometric LS mean ratio and the 90% confidence interval (CI) were constructed based on ln-transformed least-squares (LS) mean CL/F ratios between Black and Caucasian.

RESULTS

Pharmacokinetics Summary:
As shown in Table below, retigabine CL/F differed significantly between Black and Caucasian subjects, and significantly affected by the subject's age and administered dose level (p-values <0.01). The geometric mean CL/F value was approximately 20.0% lower in Black subjects than in Caucasian subjects, with a 90% confidence interval for the Black/Caucasian mean ratio overlapping the equivalence limits of 80-125%

Table. Statistical Comparison of Retigabine Apparent Clearance Following a Single Oral Dose to Between Black and Caucasian Healthy Subjects

	Geometric LS Mean		Black/Caucasian	90% Confidence Interval	
Parameter	Caucasian	Black	Mean Ratio	Lower	Upper
CL/F (L/h)	52.73	42.33	80.27%	73.73%	87.39%

CONCLUSION:
- The approximately 20% lower CL/F in Black subjects corresponds to higher systemic exposure than Caucasian subjects at the same dose.
- Though statistically significant, the difference in systemic clearance alone between Black and Caucasian subjects may not be clinically significant or warrant a dose

adjustment. Therefore, no dosage adjustment is recommended for labeling based solely on the CL/F difference between Black and Caucasian subjects

4.4.3 Extrinsic Factors

Study 3065A1-109

Title: An Open-Label, Drug Interaction Study Of Retigabine (GkE-841, D-23129) And Lamotrigine In Healthy Male Subjects

Objectives: (1) To evaluate the effect of multiple doses of retigabine at steady state on the metabolism and the pharmacokinetics of a single dose of lamotrigine, (2) to assess the effect of multiple, low doses of lamotrigine at steady-state on the metabolism and pharmacokinetics of a single dose of retigabine, and (3) to evaluate the safety of multiple doses of retigabine

Dose and Drug Products:
Retigabine: 25-mg capsules (batch number: VV 97/05) and 100-mg capsules (batch number: VV 97/04) taken orally
The daily dose of retigabine: 200 mg in group A; 400~600 mg in group B

Study Population:
30 planned, 29 enrolled, 29 completed, and 29 analyzed; N=14 assigned to receive multiple doses of lamotrigine (treatment group A) and N=15 assigned to receive multiple doses of retigabine (treatment group B)

Study Design:
This was an open-label, parallel-group study to evaluate the effect of multiple-doses of lamotrigine on the single-dose PK of retigabine and the effect of multiple-dose retigabine on the single-dose PK of lamotrigine. Twenty-nine (29) healthy male subjects were enrolled and assigned to the following two treatment groups:

Group A: Lamotrigine (perpetrator) was administered orally at 25 mg daily on Days 3 through 8. Retigabine was administered orally as a single 200-mg dose alone on Day 1 and concurrently with lamotrigine on Day 7 (N=14).

Group B: Retigabine (perpetrator) was administered orally at 200 mg BID (400 mg/day) titrating up to 300 mg BID (600 mg/day) on Days 6~20. Lamotrigine was administered orally as a single 200-mg dose alone on Day 1 and concurrently with retigabine on Day 17 (N=15).

PK Blood samples were collected pre-dose up to 48 hours after each single dose of retigabine and pre-dose, and up to 96 hours after each single dose of lamotrigine. Trough blood samples for lamotrigine concentrations were collected prior to lamotrigine dosing on Days 6, 7, and 8 in Group A and prior to retigabine dosing on Days 15, 16 and 17 for determination of retigabine and acetyl-metabolite (AWD21-360) in Group B..

Pharmacokinetic Sampling:

Group A: plasma samples at predose, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, and 48 h postodse for RTG; predose on Days 6~8 for LTG.

Group B: plasma samples at predose, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, and 96 h postodse for RTG; predose on Days 15~17 for LTG

Pharmacokinetic Assessments:

The following PK parameters of retigabine and acetyl-metabolite (AWD21-360), and lamotrigine were estimated from plasma data using noncompartmental methods: Cmax, Tmax, AUC0-t, AUC0-inf, t1/2, MRT, and CL/F, Vz/F. Plasma concentrations and PK parameters of the analytes were compared between treatment groups by using 2-factor ANOVA with factors for treatment. Point estimates and 90% CIs were calculated for ln-transformed PK parameters (with vs. without co-med), judged by strictly defined 80-125% BE limits.

Bioanalytical Method:

Plasma and urine samples were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method. The assay was linear between 1-1000 ng/mL for retigabine and between 2.5-1000 ng/mL for AWD21-360. A HPLC/MS/MS analytical method was used to determine the lamotrigine concentrations in human plasma.The limit of quantitation was 100 ng/mL and the assay was linear up to 25000 ng/mL. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-109

		Retigabine (plasma)	AWD21-360 (plasma)	Lamotrigine
Method:		HPLC/MS/MS	HPLC/MS/MS	HPLC/MS/MS
Standard Curve:	Range:	1.0-1000 ng/mL	2.5-1000 ng/mL	100-25000 ng/mL
	Precision:	< ± 15%	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%	< ± 15%
LOQ:		1.0 ng/mL	2.5 ng/mL	100 ng/mL
QC:		3, 15, 150, 750 ng/mL	3, 15, 150, 750 ng/mL	300, 6980, 18000 ng/mL
	Precision:	< ± 15%	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%	< ± 15%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

RESULTS

Demographics:

29 subjects completed the study.

Characteristic	Group A	Group B	Total
Age, years			
n	14	15	29
Mean	28.6	27.8	28.2
Standard deviation	7.0	8.1	7.4
Range	20-42	18-45	18-45
Sex, n (%)			
Male	14 (100)	15 (100)	29 (100)
Ethnic origin, n (%)			
White	11 (79)	9 (60)	20 (69)
Black	2 (14)	6 (40)	8 (28)
Hispanic	1 (7)		1 (3)
Height (cm)			
n	14	15	29
Mean	174.7	175.1	174.9
Standard deviation	6.4	7.3	6.8
Range	165-184	164-188	164-188
Weight (kg)			
n	14	15	29
Mean	72.1	72.7	72.4
Standard deviation	8.0	9.0	8.4
Range	61-90	60-89	60-90

Pharmacokinetics:

Group A:

Figure 1. Individual Mean (± Se) Retigabine (Left) and AWD21-360 (Right) Plasma Concentrations-time Profiles After Single Oral Retigabine (200 mg) Administration Alone (Open Circles) And At Steady-State Concentrations Of Lamotrigine (Closed Circles) In 14 Subjects (Treatment Group A)

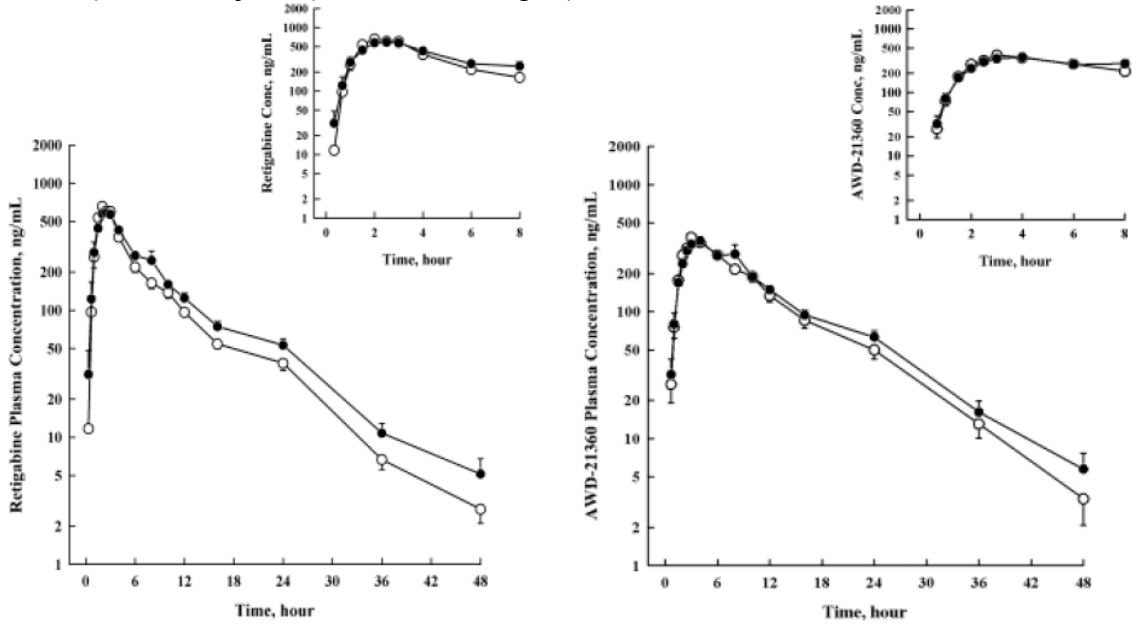


Table 1. Pharmacokinetic Parameters of Retigabine With and Without Lamotrigine Co-Administration (N=14, Mean±SD)

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (ng*h/mL)	CL/F (L/h/kg)
RTG alone	741 ± 172	2.2 ± 0.6	6.3 ± 1.1	4227 ± 892	0.69 ± 0.14
RTG with lamotrigine	663 ± 142	2.2 ± 0.6	6.8 ± 1.5	4881 ± 1021	0.60 ± 0.13
Statistical analysis					
$Mean_{geo}$ (90% CI)	90 (86-94)	--	107 (104-110)	115 (111-120)	87 (83-90)

Table 2. Pharmacokinetic Parameters of AWD21-360 With and Without Lamotrigine Co-Administration (N=14, Mean±SD)

Treatment	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng.hr/mL)	$t_{1/2}$ (hr)
Alone	392 ± 50	3.2 ± 0.4	4248 ± 1309	6.6 ± 1.4
With lamotrigine	378 ± 52	3.6 ± 0.7	4452 ± 988	7.2 ± 1.4
p-Values from the ANOVA associated with treatment difference				
	0.16	0.096	0.13	0.027
90% Confidence Limits – Reference is retigabine alone (Unit = %)[b]				
	96	--	110	109
	94 - 99	--	106 - 114	103 - 114

- Lamotrigine Steady-State Concentrations, measured on days 6~8, were reached on day 7

Group B:

Figure 2. Mean (± Se) Lamotrigine Plasma Concentrations As A Function Of Time After Single Oral Lamotrigine (200 Mg) Administration Alone (Open Circles) And At Steady-State Concentrations Of Retigabine (Closed Circles) In 15 Subjects (Treatment Group B)

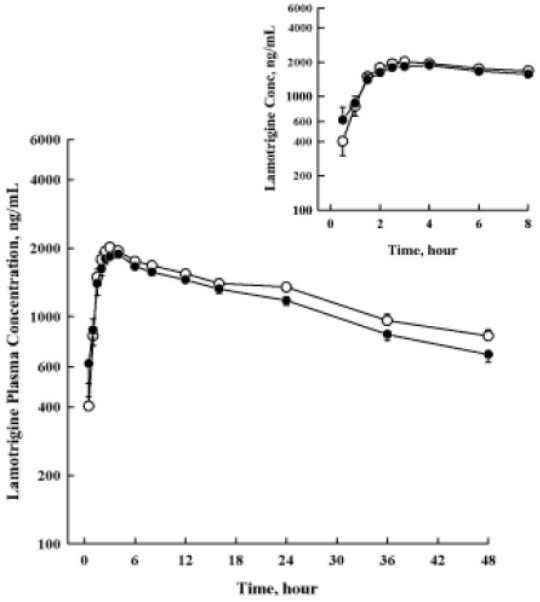


Table 3. Pharmacokinetic Parameters of Lamotrigine With and Without Retigabine Co-Administration (N=15, Mean ± SD)

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (µg*h/mL)	CL/F (L/h/kg)
Lamotrigine alone	2121 ± 213	3.0 ± 1.1	37.4 ± 10.4	106.8 ± 33.9	0.028 ± 0.007
Lamotrigine with RTG	2037 ± 349	3.0 ± 1.1	31.7 ± 7.5	87.5 ± 25.4	0.034 ± 0.009
Statistical analysis					
$Mean_{geo}$ (90% CI)	95 (91-99)	--	85 (81-87)	82 (80.1-84.0)	122 (119-125)

- Retigabine and AWD21-360 Steady-State Concentrations, measured on days 15, 16, and 17, were achieved on Day 17.

Safety: There was no death, no SAE. One (1) or more AEs were reported by 4 (24%) subjects in treatment group A and 12 (80%) subjects in treatment group B. Most frequent drug related AE was dizziness reported by 5 (40%) subjects while receiving titrated Retigabine. One subject (subject 10905-0018) was withdrawn from the study on the last study day (day 20) before receiving a final dose of retigabine because of a moderate maculopapular rash (erythematous papular rash; self-limiting, resolved within 2 days).

CONCLUSION:
- Results showed that co-administered retigabine did not significantly alter the PK profile of lamotrigine based on the acceptance criteria of 80-125% limits. However, concomitant retigabine seemed to result in an increase in apparent clearance (~22%), decrease in AUC (~18%) and a shortened t1/2 (from 37.4 h to 31.7 h), suggesting a potential metabolic-inducing effect by retigabine.
- Results showed that co-administered lamotrigine did not significantly alter the PK profile of retigabine and AWD21-360 based on the acceptance criteria of 80-125% limits.
- Since lamotrigine was studied at a lower dose, rather than typical therapeutic doses used in clinical practice, the magnitude of this drug interaction with higher lamotrigine doses is not known.

Study 3065A1-113

Title: An open-label drug interaction study of retigabine (GKE841, D-23129) and phenobarbital in healthy male subjects

Objectives: (1) To evaluate evaluate a possible drug-drug interaction between retigabine and phenobarbital at steady-state, and (2) to assess the safety of the association of retigabine with phenobarbital

Dose and Drug Products:
Retigabine: 50-mg, 100-mg, and 200-mg capsules (Batch numbers: VV 98/23, VV 98111, and VV 98/15, respectively). Phenobarbital: 30-mg tablets (batch number: 8K58PE).

Study Population: 15 enrolled; 15 planned; 13 completed; 15 included analysis
Study Design:
This was an open-label, non-randomized study to evaluate the effect of phenobarbital on the PK of retigabine and NAMR, and the effect of retigabine on the PK of phenobarbital in 3 sequential treatment periods:
- Period 1: Retigabine administered as a single oral dose of 200 mg on Day 1;

- Period 2: Phenobarbital 90 mg in the evening once-daily on Days 4–25;
- Period 3: Retigabine 100 TID to 200 TID (300 to 600 mg/day) coadministered with phenobarbital 90 mg daily dosing on Days 26–35.

PK blood samples for pharmacokinetic analysis were collected up to 72 hours after retigabine dosing on Days 1 and 32; and up to 24 hours after phenobarbital dosing on Days 24 and 31.

Pharmacokinetic Sampling:

Plasma samples: at predose, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, and 72 h postodse for RTG; at predose, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h postdose for phenobarbital

Pharmacokinetic Assessments:

The following PK parameters of retigabine and acetyl-metabolite (AWD21-360), and lamotrigine were estimated from plasma data using noncompartmental methods: Cmax, Tmax, AUC0-t, AUC0-inf, t1/2, MRT, and CL/F, Vz/F. Plasma concentrations and PK parameters of the analytes were compared between treatment groups by using 2-factor ANOVA with factors for treatment. Point estimates and 90% CIs were calculated for ln-transformed PK parameters (with vs. without co-med), judged by strictly defined 80-125% BE limits.

Bioanalytical Method:

Plasma and urine samples were analyzed using a validated Liquid chromatography- mass spectroscopy (LC-MS/MS) analytical method. The assay was linear between 1-1000 ng/mL for retigabine and between 2.5-1000 ng/mL for AWD21-360. A reversed phase HPLC procedure with ultraviolet (UV) detection was used to determine the phenobarbital concentrations in human plasma. The assay was linear between 1000~50000 ng/mL. The performance of the assay during sample analysis is summarized in the table below.

Table. Assay performance for Study 3065A1-113

		Retigabine (plasma)	AWD21-360 (plasma)	Pheno(plasma) barbital
Method:		LC-MS/MS	LC-MS/MS	HPLC/UV
Standard Curve:	Range:	1.0-1000 ng/mL	2.5-1000 ng/mL	1000-50000 ng/mL
	Precision:	< ± 15%	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%	< ± 15%
LOQ:		1.0 ng/mL	2.5 ng/mL	1000 ng/mL
QC:		7.5, 50, 150, 750 ng/mL	3, 15, 150, 750 ng/mL	0.1, 8.32, 24.96, 49.9 µg/mL
	Precision:	< ± 15%	< ± 15%	< ± 15%
	Accuracy:	< ± 15%	< ± 15%	< ± 15%

Comment: The bioanalytical methods were found acceptable, with inter-day and intra-day accuracy and precision being <15%.

RESULTS

Demographics:

A total of 15 healthy male subjects enrolled, aged from 22-45 years (mean, 30 years), weighed from 63-85 kg (mean 71 kg), 11 (73%) White, 3 (20%) Black, and 1 (7%) Asian.

Pharmacokinetics:

Figure 1. Mean (± SE) Retigabine (Left) and AWD21-360 (Right) Plasma Concentrations-time Profiles After Single Oral Retigabine Administration Alone (Open Circles) And At Steady-State Concentrations Of Phenobarbital (Closed Circles)

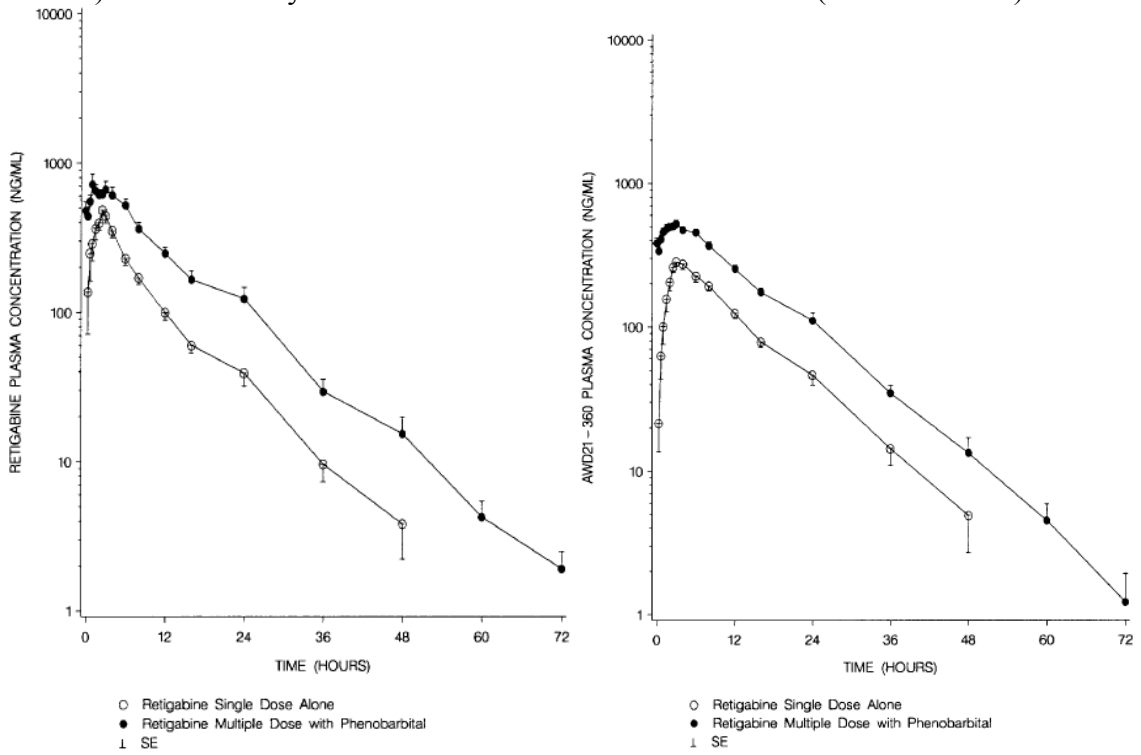


Table 1. Pharmacokinetic Parameters of Retigabine With and Without Phenobarbital Co-Administration (Mean±SD)

Subject Group	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	CL/F (L/h/kg)	Vz/F (L/kg)
Alone[a]						
Mean ± SD	639 ± 192	2.0 ± 1.1	6.7 ± 1.8	3936 ± 976	0.76 ± 0.19	7.2 ± 1.7
Geometric Mean	611	1.6	6.5	3823	0.74	7.0
With Phenobarbital[a]						
Mean ± SD	931 ± 434	1.6 ± 0.9	8.5 ± 2.1	4433 ± 1455	0.70 ± 0.21	8.5 ± 2.9
Geometric Mean	852	1.5	8.3	4226	0.67	8.1
p-values for transformed analysis of variance with factor for						
Treatment	NA[b]	0.43	0.02	0.20	0.20	0.32
Statistical power, %	NA	12	58	56	56	44
Geometric Mean Ratio	NA	--	123	111	90	--
90% Confidence Limits	NA	--	107 - 141	97 - 128	78 - 103	--

a comparison of single-dose AUC0-inf and multiple-dose AUCτ
b NA= not applicable due to comparison of single- and multiple-dose Cmax values
n = 15 for retigabine alone and n = 13 for retigabine with phenobarbital treatment

Table 2. Pharmacokinetic Parameters of AWD21-360 With and Without Phenobarbital Co-Administration (N=13, Mean±SD)

Subject Group	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	CLm/(F•fm) (L/h/kg)
Alone[a]					
Mean ± SD	318 ± 71	3.5 ± 1.0	6.8 ± 1.5	3638 ± 802	0.81 ± 0.17
Geometric Mean	311	3.3	6.6	3562	0.80
With Phenobarbital[a]					
Mean ± SD	586 ± 99	2.6 ± 1.8	7.7 ± 1.9	3622 ± 628	0.81 ± 0.16
Geometric Mean	579	2.5	7.5	3572	0.80
p-values for transformed analysis of variance with factor for					
Treatment	NA[b]	0.14	0.05	0.90	0.90
Statistical Power, %	NA	17	98	59	59
Geometric Mean Ratio	NA	--	110	101	99
90% Confidence Limits	NA	--	102 - 118	88 - 116	86 - 114

n = 15 for retigabine alone and n = 13 for retigabine with phenobarbital treatment
b NA= not applicable due to comparison of single- and multiple-dose Cmax values

- Lamotrigine Steady-State Concentrations, measured on days 6~8, were reached on day 7

Figure 2. Mean (± Se) Lamotrigine Plasma Concentrations As A Function Of Time for Phenobarbital Administered Alone (Open Circles) And Under Steady-State Concentrations Of Retigabine (Closed Circles)

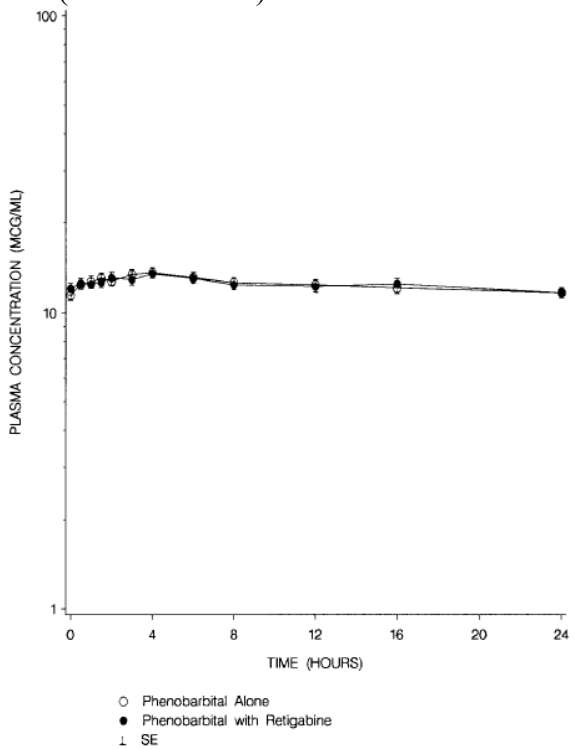


Table 3. Pharmacokinetic Parameters of Phenobarbital With and Without Retigabine Co-Administration (N=13, Mean ± SD)

Subject Group	C_{max} (µg/mL)	t_{max} (h)	AUC (µg•h/mL)	CL/F (mL/h/kg)
Alone				
Mean ± SD	14.6 ± 1.9	3.6 ± 2.4	298 ± 38	4.35 ± 0.37
Geometric Mean	14.4	2.7	296	4.34
With Retigabine				
Mean ± SD	15.4 ± 5.0	5.7 ± 4.6	311 ± 59	4.23 ± 0.60
Geometric Mean	14.9	4.4	307	4.18
p-values for log- transformed analysis of variance with factor for:				
Treatment	0.65	0.12	0.40	0.40
Geometric Mean Ratio	103	--	104	97
90% Confidence Limits	92 - 116	--	96 - 111	90 - 104

Safety: There was no death, no SAE. One or more TEAEs were reported by 8 (53%) subjects who took phenobarbital 90 mg, 6 (46%) subjects who took phenobarbital with retigabine, and 4 (27%) subjects who took a single dose of retigabine 200 mg. Most TEAEs were of mild or moderate severity. Overall, the most frequent TEAE was headache reported by 4 (27%) subjects who took phenobarbital 90 mg, 3 (23%) subjects who took phenobarbital with retigabine, and 1 (7%) subject who took retigabine 200 mg. No subjects died or reported any serious AEs during the study. One (1) subject was withdrawn from the study during period 2 after repeated administration of phenobarbital for severe abdominal pain. There were no clinically important changes in laboratory tests, vital signs, or ECG data.

CONCLUSION:

- There was an approximately 11% increase in retigabine AUC, with a longer t1/2, with concomitant phenobarbital, which is not inline with the potential AUC reduction as a result of induction for metabolic enzymes (i.e., UDPGT1A4, 1A1, and 1A9) responsible for retigabine metabolism.
- Although the upper limit of the 90% CI was slightly outside the bioequivalence acceptance limits of 80-125%, we agree with the sponsor that an insignificant interaction between retigabine and repeated once-daily dosing of 90 mg phenobarbital (an enzyme inducer) can be concluded.
- There was no significant effects of retigabine on phenobarbital exposure (Cmax and AUC) on the basis of 90% being within the with the acceptance limits of 80-125%.
- Results suggest that dose adjustments of either drug are not required for concomitant administration.

Study 3065A1-112-US

Title: A study of the potential effect of retigabine (GKE-841, D-23129) on the pharmacokinetics of an oral contraceptive containing norgestrel and ethinyl estradiol (LO-OVRAL) in healthy female subjects

Objectives: **To** evaluate the potential effects of multiple doses of retigabine on the

pharmacokinetics of norgestrel/ethinyl estradiol following coadministration

Dose and Drug Products:
Retigabine: 5 mg capsules (Batch number W 97/05); 100 mg capsules (VV 98/05)
Norgestrel/ethinyl estradiol: (0.3 mg/0.03 mg) oral

Study Design:
This was an open-label, non-randomized, cross-over study to evaluate the effect of retigabine on the PK of the oral contraceptive steroids ethinyl estradiol and norgestrel. Eligible 21 healthy female subjects 18-45 years of age, inclusive, were enrolled into 2 treatment Periods:

Period 1: Norgestrel/ethinyl estradiol (0.3 mg/0.03 mg) administered as an oral contraceptive tablet daily on Days 1-21 followed by a placebo tablet daily on Days 22

Period 2: Norgestrel/ethinyl estradiol (0.3 mg/0.03 mg) as an oral contraceptive tablet daily on Days 1-21 followed by a placebo tablet daily on Days 22-28, and retigabine 150 mg TID concomitantly with oral contraceptive dosing on Days 10-13.

PK Blood samples were collected pre-dose up to 48 hours after each single dose of retigabine and pre-dose, and up to 96 hours after each single dose of lamotrigine. Trough blood samples for lamotrigine concentrations were collected prior to lamotrigine dosing on Days 6, 7, and 8 in Group A and prior to retigabine dosing on Days 15, 16 and 17 for determination of retigabine and acetyl-metabolite (AWD21-360) in Group B..

Pharmacokinetic Assessments:
- Ethinyl estradiol and norgestrel: plasma samples at predose, 0.67, 1, 1.5, 2, 3, 5, 7, 8, 12, 14, and 24 hours postdose
- Retigabine and AWD21-360: trough concentrations on Days 11~13 of cycle 2

The PK analysis of ethinyl estradiol and norgestrel plasma concentrations was performed by noncompartmental methods. PK parameters include Tmax, Cmax, AUC, terminal t1/2, CL/F, Vz/F. The potential effect of retigabine on the PK of ethinyl estradiol and norgestrel was assessed using ANOVA and confidence limits. Point estimates and 90% CIs were calculated for ln-transformed PK parameters (with vs. without co-med), judged by strictly defined 80-125% BE limits.

Bioanalytical Method:
Plasma samples were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method. The assay was linear between 1-1000 ng/mL for retigabine and between 2.5-1000 ng/mL for AWD21-360. A GC/MS analytical method was used to determine the Ethinyl estradiol and norgestrel concentrations in plasma. The assay was linear between 2-1000 pg/mL for ethinyl estradiol and between 0.050-25.0 ng/mL for norgestrel. The performance of the assay during sample analysis and was found acceptable, as summarized below.

Analytes	First QC[a] Conc	CV%	bias%	Second QC Conc	CV%	bias%	Third QC Conc	CV%	bias%	Fourth QC Conc	CV%	bias%
Retigabine, ng/mL	3.0	4.52	8.67	15.01	2.73	2.50	149.9	3.24	3.81	749.4	4.67	5.91
AWD21-360, ng/mL	3.0	10.17	-15.58	14.99	6.77	-0.58	149.9	5.91	5.32	749.4	9.27	3.10
Ethinyl Estradiol, pg/mL	6.00	7.75	-2.30	40.0	2.93	-3.31	400	4.30	-3.46			
Norgestrel, ng/mL	0.15	7.87	2.40	1.00	3.54	-2.27	10.0	4.60	-3.48			

a: quality control.

RESULTS

Demographics: 20 subjects planned, 21 enrolled (aged 18~41 years (mean, 28.8 years), weighed 47~89 kg (mean, 64 kg), with mean BMI of 24.1 kg/m^2), 20 completed, and 20 analyzed; Black N=2, Hispanic N=17, White N=2

Pharmacokinetics:

Ethinyl Estradiol and Norgestrel:

Figure 1. Individual Mean (± SE) Ethinyl Estradiol (Left) and Norgestrel (Right) Plasma Concentrations-time Profiles With or Without Co-administered Oral Retigabine

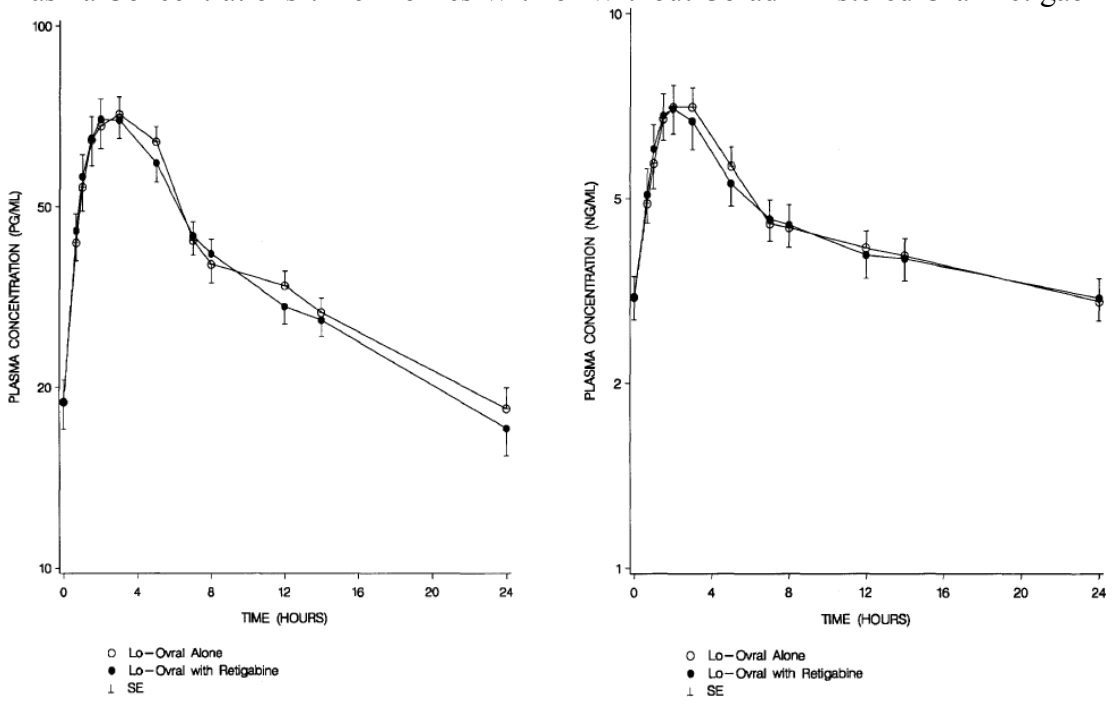


Table 1. Pharmacokinetic Parameters of Ethinyl Estradiol With or Without Co-administered Oral Retigabine

Treatment	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (pg*h/mL)	CL/F (L/h/kg)
Ethinyl Estradiol without RTG	79.0 ± 24.4	3.1 ± 1.5	14.2 ± 2.5	887 ± 267	0.59 ± 0.20
Ethinyl Estradiol with RTG	75.9 ± 21.9	2.8 ± 1.3	13.9 ± 3.8	858 ± 274	0.62 ± 0.22
Statistical analysis					
$Mean_{geo}$ (90% CI)	96 (90-103)	--	--	96 (92-101)	--

Table 2. Pharmacokinetic Parameters of Norgestrel With or Without Co-administered Oral Retigabine

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (ng*h/mL)	CL/F (L/h/kg)
Norgestrel without RTG	7.80 ± 2.44	2.2 ± 0.8	30.9 ± 10.3	103 ± 36	0.052 ± 0.019
Norgestrel with RTG	7.78 ± 2.85	2.2 ± 1.0	38.9 ± 25.8	102 ± 44	0.056 ± 0.026
Statistical analysis					
$Mean_{geo}$ (90% CI) [a]	98 (89-109)	--	--	96 (89-103)	--

Retigabine and AWD21-360:
On days 12, 13, and 14 of cycle 2, the steady-state plasma concentrations of regitabine and AWD21-360 were 221.9 ± 82.2 ng/mL and 269.5 ± 80.7 ng/mL, respectively.

Safety: There was no death, no SAE. The most frequently reported AEs were headache reported by 10 subjects, somnolence reported by 7 subjects, and constipation reported by 5 subjects. All these AEs were mild in intensity. There were no clinically important changes in laboratory tests, vital signs, or ECG results during the study.

CONCLUSION:
- Results showed that the three-day course of co-administered retigabine 150 mg TID did not significantly alter the PK profiles of either contraceptive steroid based on the acceptance criteria of 80-125% limits. No dose adjustment is necessary when female subjects are on LO-OVRAL and concomitant retigabine.
- Although no direct effect of retigabine on contraceptive steroid PK was observed with short-term dosing, the retigabine dosing duration in this study may not be long enough to result in any enzyme induction.

Study VRX-RET-E22-106

Title: A pharmacokinetic interaction study evaluating the effect of repeated retigabine dosing on the pharmacokinetics of oral contraceptives in healthy adult female volunteers

Objectives:
- To assess the effect of a multiple-dose regimen of retigabine 250 mg three times daily (TID) on the steady-state plasma pharmacokinetics of 1 mg norethindrone and 0.035 mg ethinyl estradiol in healthy adult female subjects
- To assess the safety and tolerability of coadministration of multiple doses of retigabine and norethindrone/ethinyl estradiol in healthy adult female subjects
- To assess the steady-state pharmacokinetics of retigabine with and without multiple dose administration of norethindrone and ethinyl estradiol in healthy adult female subjects

Dose and Drug Products:
Retigabine: 50 mg VV06/20; 100 mg Lot: VV06/09; 300 mg VV06/15

Ortho® 1/35: 1 mg norethindrone/0.035 mg ethinyl estradiol, Lot 7ASK000, Janssen-Ortho Inc.

Study Design:
This was an open-label, non-randomized, multiple-dose, two-treatment study to assess the effect of a prolonged repeat-dose retigabine regimen on the PK of norethindrone and ethinyl estradiol. Thirty (30) healthy female subjects aged 18 and 55 years, with body weight ≥52 kg, body mass index (BMI) of 18.00–28.00 kg/m^2 and experiencing regular menstrual cycles were enrolled in the study enrolled into the following three sequent treatment periods:

Period 1: OC was administered daily on Days 1 to 21.

Period 2: Placebo oral contraceptive tablet administered for 7 days on Days 22 to 28 with an escalating retigabine TID dose. The retigabine dose was started at 100 mg TID on Day 22, titrating up at 50 mg TID every 3 days to a planned dose of 300 mg TID (amended to 250 mg TID or 750 mg/day).

Period 3: OC was administered daily on Days 29 to 49 with an escalating retigabine TID dose (continuing from Period 2).

Pharmacokinetic Assessments:
- Plasma samples for ethinyl estradiol and norgestrel:
  Days 21 and 49: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours
  Days 1, 19, 20, 21, 29, 47-49: trough (Cmin) samples
- Plasma samples for retigabine and N-acetyl metabolite:
  Days 28 and 49: 0, 20, 40, and 60 minutes and 1.5, 2, 2.5, 3, 4, 6, and 8 hours
  Days 22, 26, 27, 47-49: trough (Cmin) samples

The PK analysis of ethinyl estradiol and norgestrel plasma concentrations was performed by noncompartmental methods. PK parameters include Tmax, Tmax,ss, Cmax,ss, Cmin,ss, AUC0-τ, terminal t1/2, CL/F. The potential effect of retigabine on the PK of ethinyl estradiol and norgestrel was assessed using ANOVA and confidence limits. Point estimates and 90% CIs were calculated for ln-transformed exposure parameters Cmax,ss and AUC0-τ (Day 49 with retigabine vs. Day 28 alone), judged by strictly defined 80-125% BE limits.

Bioanalytical Method:
Plasma samples for retigabine and the N-acetyl metabolite were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method at (b) (4) The assay was linear between 5-2000 ng/mL for retigabine and between 15-2000 ng/mL for N-acetyl metabolite. Plasma samples for norethindrone and ethinyl estradiol were analyzed using a validated LC-MS/MS analytical method by (b) (4) . The assay performance of during sample analysis is summarized in the Table below. The bioanalytical methods were found acceptable.

RESULTS

Demographics:

Variable	Total (N = 30)
Age (years, mean ± SD)	40.6 ± 7.71
Race (n[%])	
Caucasian	28 (93.3)
Black	2 (6.7)
Height (cm, mean ± SD)	163.3 ± 7.02
Weight (kg, mean ± SD)	65.0 ± 5.94
BMI (kg/m^2, mean ± SD)	24.4 ± 2.24

Pharmacokinetics:

Ethinyl Estradiol and Norethindrone:

In Period 1, steady state was achieved by Day 19 for norethindrone and by Day 20 for ethinyl estradiol. Both analytes reached steady state by Day 47 in Period 3. Plasma concentration-time profiles and PK parameters of both analytes are shown in the Figures below.

Figure 1. Mean Plasma Norethindrone Concentrations-time Profiles With or Without Co-administered Oral Retigabine 250 mg TID

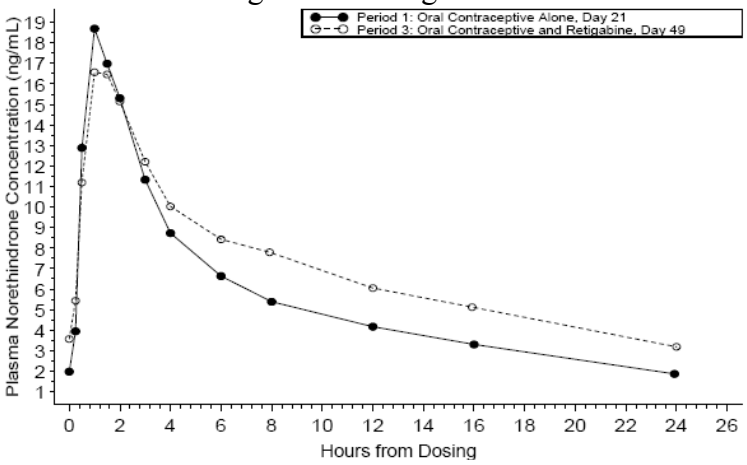


Figure 2. Mean Plasma Ethinyl Estradiol Concentrations-time Profiles With or Without Co-administered Oral Retigabine 250 mg TID

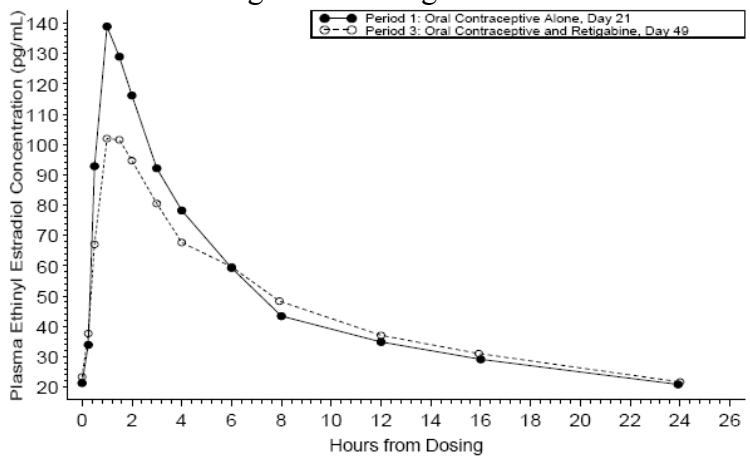


Table 1. Pharmacokinetic Parameters of Ethinyl Estradiol With or Without Co-administered Oral Retigabine 250 mg TID

	Mean ± SD		Mean Ratio (%)[a]
	Without RTG (Day 21)	With RTG (Day 49)	(90% CI)
Norethindrone			
C_{max} (pg/mL)	19.8 ± 4.72	18.8 ± 4.01	96.0 (88.9, 104)
C_{min} (pg/mL)	1.83 ± 0.634	3.57 ± 1.24	
t_{max} (h) [b]	1.00 (1.00, 3.00)	1.14 (0.607, 3.05)	
$AUC_{0-\tau}$ (pg*h/mL)	133 ± 34.3	169 ± 40.9	128 (120, 135)
CL/F (L/h)	8.06 ± 2.30	6.31 ± 1.83	
Ethinyl Estradiol			
C_{max} (pg/mL)	141 ± 44.7	114 ± 43.7	79.2 (71.8 , 87.4)
C_{min} (pg/mL)	20.3 ± 6.20	23.3 ± 7.86	
t_{max} (h) [b]	1.00 (0.618, 2.00)	1.51 (0.607, 6.01)	
$AUC_{0-\tau}$ (pg*h/mL)	1122 ± 243	1078 ± 265	95.5 (90.9, 100)
CL/F (L/h)	32.9 ± 8.48	34.7 ± 9.76	

a. Mean ratios were calculated on ln-transformed parameters
b. Tmax: median (minimum, maximum)

Retigabine and N-acetyl metabolite of retigabine:
Plasma concentration-time profiles and PK parameters of both analytes are shown in the Figures below. Statistical analyses were performed with dose-normalized exposure measures.

Figure 3. Mean Plasma Retigabine Plasma Concentrations-time Profiles With or Without Co-administered Oral Contraceptive

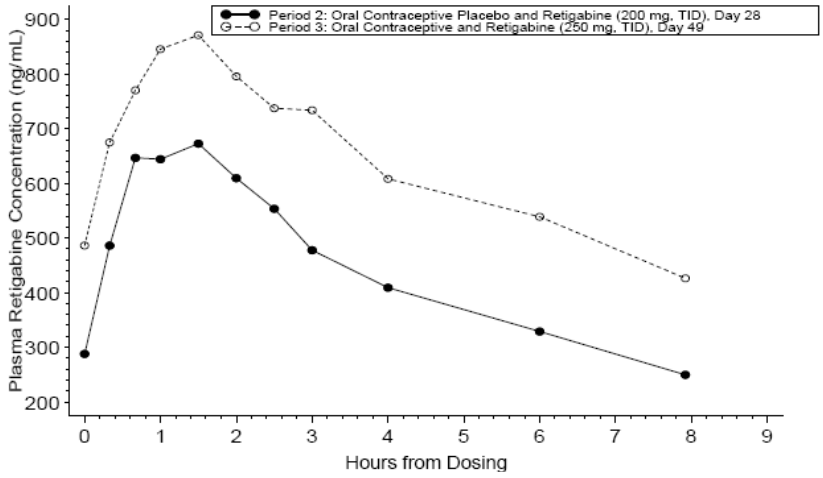


Figure 4. Mean Plasma N-acetyl Metabolite Concentrations-time Profiles With or Without Co-administered Oral Contraceptive

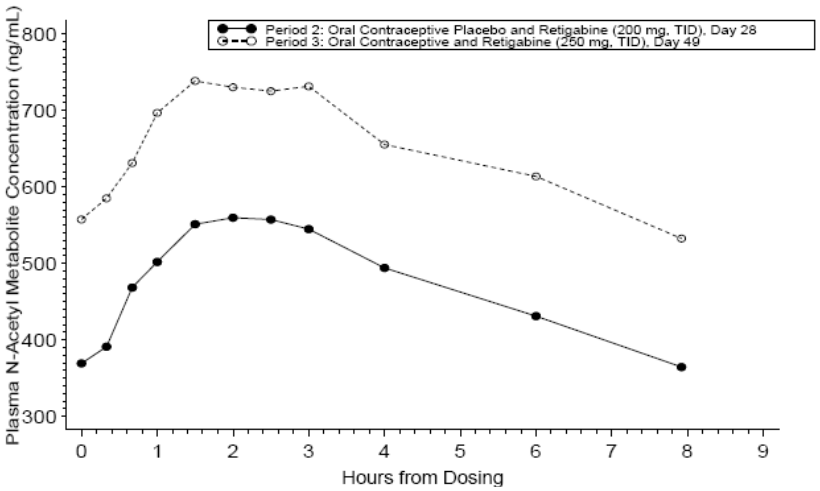


Table 2. Pharmacokinetic Parameters of Retigabine With or Without Co-administered Oral Contraceptives

	Mean ± SD		Mean Ratio (%)[a] (90% CI)
	Without OC (Day 28) RTG 200 mg TID	With OC (Day 49) RTG 250 mg TID	
C_{max} (ng/mL)	827 ± 243	1054 ± 286	102 (94.3, 111)
C_{min} (ng/mL)	236 ± 49.1	390 ± 96.5	
t_{max} (h) [b]	1.00 (0.336, 4.00)	1.50 (0.375, 3.08)	
$AUC_{0-\tau}$ (ng*h/mL)	3472 ± 635	5053 ± 973	116 (110, 123)
CL/F (L/h)	59.5 ± 11.2	51.2 ± 9.40	

a. Mean ratios were calculated on ln-transformed parameters
b. Tmax: median (minimum, maximum)

Table 3. Pharmacokinetic Parameters of N-acetyl Metabolite With or Without Co-administered Oral Contraceptives

	Period 2 (Day 28)	Period 3 (Day 49)	
Pharmacokinetic parameters	**Mean ± SD**	**Mean ± SD**	**% MR (90% CI)[a]**
$C_{max,ss}$ (pg/mL)	610.940 ± 155.162	824.344 ± 156.043	109.14 (102.74, 115.93)
$C_{min,ss}$ (pg/mL)	321.164 ± 129.264	490.388 ± 157.140	
$T_{max,ss}$ (h)[b]	2.00 (0.693, 6.00)	2.00 (0.675, 4.05)	
$AUC_{0-\tau}$ (pg*h/mL)	3741.6 ± 1079.8	5141.8 ± 1292.9	110.60 (105.61, 115.82)

a. Mean ratios were calculated on ln-transformed parameters
b. Tmax: median (minimum, maximum)

Safety: There was no death, no SAE. Most AEs were reported after administration of retigabine following a rapid-titration regimen. The most common AEs were gastrointestinal disorders and nervous system disorders. Six psychiatric disorder AEs of at least moderate severity were reported after receiving retigabine 300 mg TID where were subsequently reduced to 250 mg TID.

CONCLUSION:

- Mean plasma norethindrone Cmax values following oral contraceptive dosing were similar with or without retigabine. However, AUC was increased 28% with retigabine (133 p·gh/mL vs. 169 pg·h/mL). The 90% CIs of the geometric means for

Cmax (88.92, 103.58) fell within the limits of bioequivalence, while those of AUC0-τ (120.25, 135.30) exceeded the upper limit of BE acceptance criteria.

- Mean plasma ethinyl estradiol Cmax values were 21% lower following oral contraceptive dosing with retigabine, while AUC0-τ values remain similar. The 90% CIs of the geometric means for Cmax (71.79, 87.43) fell outside of the lower limit of BE acceptance criteria.
- Daily oral contraceptives had no effect on the pharmacokinetics of retigabine or the N-acetyl metabolite of retigabine.
- No dosage adjustment is recommended for either drug.

Study VRX-RET-E22-107

Title: A randomized, partially double-blind, four-way crossover study to determine the effects of a single dose of retigabine combined with a single dose of alcohol

Objectives: To determine the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects when retigabine 200 mg is combined with an intoxicating dose of ethanol (1.0 g/kg)

Dose and Drug Products:
Retigabine: 100 mg tablets (batch number: W06/09) or retigabine placebo tablets (batch number: W06/03)
Ethanol: 1 g/kg BW (Absolut® Vodka, 40% ethanol; Lot numbers: L47TY and L47R8)

Study Design:
This was a partially double-blind, randomized, 4-way cross-over study including a screening/qualifying (ethanol beverage or ethanol placebo beverage) period, a treatment period, and a post-treatment follow-up period. Twenty-four (24) healthy male and female subjects (moderate alcohol drinkers), aged 19-55 years, were enrolled after their tolerability of ethanol 1 g/kg beverage was demonstrated in a qualifying period. Enrolled subjects were randomized to receive the following treatments under fasted conditions, with a washout period of 5 to 21 days between doses:

- Treatment A: Retigabine 200 mg + ethanol placebo
- Treatment B: Retigabine placebo + ethanol 1 g/kg beverage
- Treatment C: Retigabine 200 mg + ethanol 1 g/kg beverage
- Treatment D**:** Retigabine placebo + ethanol placebo

There was a 5 to 21 day period between treatments. Serial PK blood samples for PK analysis were collected up to 24 hours after each retigabine/placebo dosing, and up to 12 hours after each ethanol/placebo dosing. PD blood samples were collected up to 24 hours.

Pharmacokinetic Assessments:

- Retigabine and its N-acetyl metabolite (NAMR): at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose in each treatment session

- Ethanol: at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose during the qualifying period and in each treatment session

Plasma samples were analyzed using a validated HPLC-MS/MS analytical method at (b) (4) The assay was linear between 5-2000 ng/mL for retigabine and between 15-2000 ng/mL for NAMR. The performance of the assay during sample analysis was found acceptable.

The PK analysis of plasma retigabine and its NAMR concentrations was performed by noncompartmental methods. PK parameters include Tmax, Cmax, AUC0-t, AUC0-8hr, AUC0-∞, terminal t1/2, CL/F, V/F. The potential effect of ethanol on PK of retigabine was assessed using ANOVA and confidence limits. Point estimates and 90% CI were calculated for ln-transformed PK parameters, judged by 80-125% BE limits.

Pharmacodynamic Assessments:

- Qualifying period: at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose
- Treatment period: at predose and at approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose

PD endpoints: visual analog scales VAS (Attention Span Good, Dizziness, Feel Sick, Intoxication, Nausea and Vision Clear/Crisp), balance platform, choice reaction time (CRT), and divided attention test (DA).

RESULTS

Demographics:

Twenty-four subjects who passed the qualifying period were enrolled and 19 subjects completed the treatment period. Seventeen subjects were included in the PK/PD population. Most subjects were male (83.3%) and White (66.7%) or Black (20.8%), either non-smokers (91.7%) or ex-smokers (8.3%), aged 24-55 years with a BMI range of 22-29 kg/m^2.

Pharmacokinetics:

This review focuses mostly on PK results of the effects of ethanol on retigabine and NAMR.

Figure 1. Retigabine Plasma Concentration-Time Profiles for Retigabine (Left) 200 mg and NAMR (Right) Administered With or Without Ethanol (1 g/kg) in Healthy Subjects

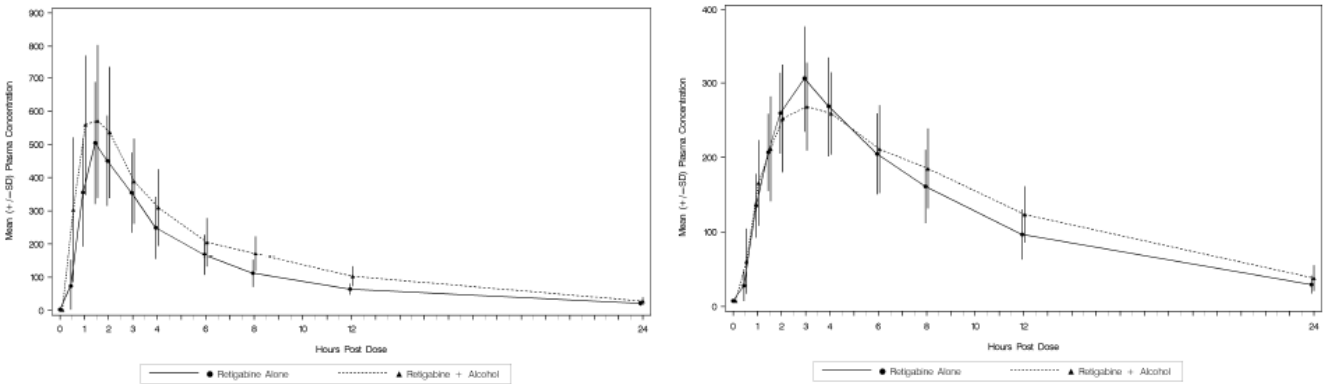


Table 1. Retigabine Pharmacokinetic Parameters after Retigabine 200 mg Administration with and without Ethanol 1 g/kg in Healthy Subjects

Table 14.2.2.1 Summary of PK Parameters of Retigabine (ng/mL) PK Population Retigabine Alone									
	Cmax (ng/mL)	Tmax (h)	AUC(0-8h) (h*ng/mL)	AUC(0-t) (h*ng/mL)	Lz (1/h)	AUC(0-inf) (h*ng/mL)	T1/2 (h)	CL/F (L/h)	V/F (L)
Mean	554.8	1.803	1957.0	2766.9	0.1057	2995.4	6.856	69.237	689.1
SD	169.89	0.6063	553.35	664.15	0.02244	651.06	1.5513	12.7297	194.11
Minimum	307	0.95	1352	1972	0.067	2104	4.37	39.57	249
Median	523.2	1.450	1794.7	2733.7	0.1056	2886.2	6.564	69.294	705.2
Maximum	843	2.95	3530	4908	0.159	5054	10.39	95.07	1040
Geo Mean	530.3	1.719	1894.0	2705.4	0.1034	2938.6	6.702	68.060	658.1
% CV	32.1%	31.9%	26.0%	21.2%	22.0%	19.8%	22.0%	19.8%	34.4%

Table 14.2.2.1 Summary of PK Parameters of Retigabine (ng/mL) PK Population Retigabine + Alcohol									
	Cmax (ng/mL)	Tmax (h)	AUC(0-8h) (h*ng/mL)	AUC(0-t) (h*ng/mL)	Lz (1/h)	AUC(0-inf) (h*ng/mL)	T1/2 (h)	CL/F (L/h)	V/F (L)
N	17	17	17	17	17	17	17	17	17
Mean	660.9	1.685	2527.5	3744.0	0.1167	4045.1	6.639	52.202	497.3
SD	188.18	0.7729	732.23	971.27	0.02986	981.83	3.3143	12.7637	266.96
Minimum	426	0.95	1469	2320	0.037	2432	4.30	30.57	243
Median	659.6	1.450	2481.8	3702.2	0.1129	3991.2	6.142	50.111	456.9
Maximum	966	3.95	4206	6108	0.161	6542	18.88	82.24	1434
Geo Mean	635.8	1.567	2432.9	3630.1	0.1118	3937.0	6.202	50.800	464.5
% CV	29.4%	41.0%	29.0%	26.0%	34.6%	24.4%	34.6%	24.4%	42.3%

Table 2. Statistical Analyses of Retigabine PK Parameters after Retigabine 200 mg Administration with and without Ethanol 1 g/kg in Healthy Subjects

PK Parameter (Unit)	Least Squares Mean (90% Confidence Interval)		Ratio of RTG + Ethanol to RTG Alone
	Retigabine Alone	Retigabine + Ethanol	
C_{max} (ng/mL)	531.9 (467.5, 605.2)	652.5 (573.4, 742.4)	1.23 (1.02, 1.47)
AUC_{0-t} (h*ng/mL)	2727.6 (2480.5, 2999.4)	3726.3 (3388.7, 4097.5)	1.37 (1.27, 1.47)
AUC_{0-8h} (h*ng/mL)	1914.0 (1713.2, 2138.3)	2508.2 (2245.0, 2802.1)	1.31 (1.18, 1.46)
AUC_{0-inf} (h*ng/mL)	2957.2 (2703.8, 3234.3)	4017.9 (3673.6, 4394.4)	1.36 (1.29, 1.43)

Table 3. Statistical Analyses of NAMR PK Parameters after Retigabine 200 mg Administration with and without Ethanol 1 g/kg in Healthy Subjects

PK Parameter (Unit)	Least Squares Mean (90% Confidence Interval)		
	Retigabine Alone	Retigabine + Ethanol	Ratio of RTG + Ethanol to RTG Alone
C_{max} (ng/mL)	312.9 (284.1, 344.5)	287.8 (261.3, 316.9)	0.92 (0.85, 1.00)
AUC_{0-t} (h*ng/mL)	2802.1 (2532.4, 3100.5)	3125.1 (2824.3, 3457.9)	1.12 (1.04, 1.20)
AUC_{0-8h} (h*ng/mL)	1642.7 (1497.2, 1802.5)	1662.8 (1515.4, 1824.4)	1.01 (0.93, 1.10)
AUC_{0-inf} (h*ng/mL)	3075.2 (2759.3, 3427.2)	3513.2 (3152.3, 3915.3)	1.14 (1.08, 1.21)

Pharmacodynamics:

Table 4. Summary of PD Results

PD Parameter	Ethanol Alone vs Placebo	RTG Alone vs Placebo	RTG + Ethanol vs Ethanol Alone
VASs			
Attention Span Good	↓	NS	NS
Dizziness	↑	NS	NS
Feel Sick	NS	NS	NS
Intoxication	↑	NS	NS
Nausea	NS	NS	NS
Vision Clear, Crisp	↓ (AUE_{0-2h}, AUE_{0-8h} only)	↓ (E_{min} only)	↓ (AUE_{0-24h} only)
Balance platform			
95% confidence ellipse, eyes closed	↑	NS	NS
95% confidence ellipse, eyes open	↑	NS	NS
COP velocity, eyes closed	↑	NS	NS
COP velocity, eyes open	↑	NS	NS
COP path length, eyes closed	↑	NS	NS
COP path length, eyes open	↑	NS	NS
Choice Reaction Time			
Motor Reaction Time	↑	NS	NS
Recognition Reaction Time	↑	NS	NS
Total Reaction Time	↑	NS	NS
% Correct responses	↓ (AUE_{0-2h}, AUE_{0-8h} only)	NS	NS
Divided Attention			
Hit latency	↑	NS	NS
Greatest distance (from road)	↑	NS	NS
% Over road	↓	NS	NS
RMS distance	↑	NS	NS
% Target hits	↓	NS	NS
# False alarms	↑ (E_{max} only)	NS	NS

NS = Not substantially different (95% confidence interval of difference includes zero)
↑ = Both arms of 95% confidence interval of difference greater than zero
↓ = Both arms of 95% confidence interval of difference less than zero
AUE0-th = Area under the effect curve from zero to t hours; COP = Center of pressure; Emax = Mean maximum effect; Emin = Mean minimum effect; PD = Pharmacodynamic; RMS = Root mean square;

Safety: There was no death or SAE. The highest incidence of AEs was observed following retigabine with ethanol, followed by ethanol alone. The most common AE was feeling drunk, followed by headache, somnolence, dizziness, and euphoric mood. The addition of retigabine 200 mg was reported to not substantially add to the negative effects of ethanol (such as subjective dizziness, intoxication, or attention span), but did modestly decreased visual clarity.

CONCLUSION:

- Consumption of a 1 g/kg dose of ethanol resulted in increases of retigabine AUC and C_{max} value by 23% and 37%, respectively.
- Retigabine 200 mg did not significantly affect the PK of ethanol.

- Retigabine administered in combination with the ethanol dose studied resulted in an increase in visual blurring. This finding should be described in label and patients should be advised of this effect on vision.

Study 3065A1-202-US

Title: A multicenter, open-label, safety, tolerability, and preliminary efficacy study of GKE-841 (retigabine, D-23129) administered as add-on therapy to patients with epilepsy currently receiving monotherapy with an established anticonvulsive agent

Objectives:
- To determine the highest tolerated dose and to evaluate the safety and tolerability of ascending doses of retigabine administered first as add-on therapy and then as monotherapy to patients with epilepsy
- To evaluate the PK interaction of retigabine at steady-state with an established antiepileptic drug (AED), valproic acid, carbamazepine, phenytoin, or topiramate
- To evaluate the preliminary efficacy of retigabine administered first as add-on therapy and then as monotherapy

Drug Products:

Study Medication	Dosage Form (capsule)	Lot Number	Formulation Number	Source
Retigabine	25 mg	VV 97/05	0930836D	AWD[a], Dresden, Germany
	25 mg	VV 98/02	0930999D	AWD, Dresden, Germany
	25 mg	VV 98/04	0930999D	AWD, Dresden, Germany
	100 mg	VV 97/04	0930837D	AWD, Dresden, Germany
	100 mg	VV 97/06	0930837D	AWD, Dresden, Germany
	100 mg	VV 97/07	0930837D	AWD, Dresden, Germany
	100 mg	VV 98/03	0930837D	AWD, Dresden, Germany
	100 mg	VV 98/05	0930837D	AWD, Dresden, Germany

a: AWD: Arzneimittelwerk.

Study Design:
This was an open-label safety, tolerability, and preliminary efficacy add-on study in patients with epilepsy currently treated with valproic acid, carbamazepine, phenytoin, or topiramate monotherapy. Sixty (60) patients were enrolled into the following four background anti-epileptic drug (AED) treatment groups:
- N=8 receiving valproic acid 750–2250 mg/day
- N=22 receiving carbamazepine 600–2400 mg/day
- N=19 receiving phenytoin 120–600 mg/day
- N=11 receiving topiramate 250–1200 mg/day

Enrolled patients underwent 4 treatment phases, as shown below. Retigabine was administered BID in the initial phases of the study. However TID regimen was allowed in later parts of the study, if required for tolerability.

1. Retigabine titration phase (Day 1 to 70): retigabine dose was started and titrated up to the maximum tolerated dose (MTD) in the presence of the AED background monotherapy;
2. AED tapering phase (Day 77 to 84): the background AED dose was reduced to 0 or the lowest clinically-acceptable level in the presence of retigabine at MTD;
3. Retigabine maintenance phase (Day 91 to 105): the MTD of retigabine was maintained alone or concurrently with the lowest clinically-acceptable background AED dose for 2 weeks;
4. Retigabine tapering phase (Day 112 to 126): the retigabine dose was reduced to 0 and the established AED was re-introduced.

Pharmacokinetic Assessments:
Serial blood samples for PK analysis were collected up to 12 hours (BID only) after morning dosing on Days -1 (AEDs only), 14 (retigabine and AED), 28 (retigabine and AED), 42 (retigabine and AED) and 105 (target retigabine alone). Trough blood samples were collected on Days -1 (AEDs only), 77, 84 and 91. In addition, the preliminary efficacy of retigabine as add-on therapy and then as monotherapy was evaluated.

Plasma samples for retigabine and the N-acetyl metabolite were analyzed using a validated high performance liquid chromatography (HPLC)/MS/MS analytical method at (b) (4). The assay was linear between 1-1000 ng/mL for retigabine and between 2.5-1000 ng/mL for N-acetyl metabolite. Plasma samples for valproic acid were analyzed using a validated GC analytical method at (b) (4) The limit of quantitation was 2.0 µg/mL and the assay was linear up to 150 µg/mL. Plasma samples for topiramate were analyzed using a validated GC analytical method at (b) (4) . The limit of quantitation was 0.1 µg/mL and the assay was linear up to 50.0 µg/mL. Plasma samples for phenytoin were analyzed using a validated GC analytical method at (b) (4). The limit of quantitation was 0.05 µg/mL and the assay was linear up to 25.0 µg/mL. A HPLC analytical method was used to determine the plasma concentrations of carbamazepine and carbamazepine-10,11 epoxide. The limit of quantitation was 0.05 µg/mL, and the assay was linear up to 20.0 µg/mL. The assay performance during the sample analysis, as shown in Table below, was found acceptable, with accuracy and precision being <15%.

Analytes	----- First QC -----			---- Second QC ----			----- Third QC -----			---- Fourth QC ----		
	QC	CV%	bias%	QC	CV%	bias%	QC	CV%	bias%	QC	CV%	bias%
Retigabine, ng/mL	3.0	8.71	6.53	15.0	9.41	3.13	150	11.36	1.46	750	10.52	7.54
	3.0	6.68	7.93	15.0	6.04	3.58	150	4.54	5.52	750	5.62	9.38
AWD21-360, ng/mL	3.0	11.34	-0.06	15.0	8.40	3.64	150	7.85	4.91	750	7.92	10.16
	3.0	12.05	-2.08	15.0	7.99	3.91	150	10.29	6.59	750	10.73	6.05
Valproic acid, µg/mL	5.0	2.26	-0.72	25.0	1.48	1.76	125	1.58	0.15	NA	NA	NA
Topiramate, µg/mL	0.25	8.80	0.0	3.0	5.10	2.7	40.0	12.62	0.3	NA	NA	NA
Phenytoin, µg/mL	0.10	12.7	-0.98	1.0	3.61	1.64	16.0	4.10	-0.86	NA	NA	NA
Carbamazepine, µg/mL	0.15	7.33	0	6.0	3.38	-2.3	16.0	5.96	-2.5	NA	NA	NA
Carbamazepine-10,11 epoxide, µg/mL	0.15	8.13	6.7	6.0	4.93	0.7	16.0	4.53	0.6	NA	NA	NA

Pharmacokinetic Analysis:
Statistical comparisons of retigabine PK parameters, with and without AED coadministration, and of AED PK parameters with and without retigabine coadministration were performed using ANOVA for each treatment group. PK parameters were compared across subjects and across retigabine and concomitant AED dose levels.

RESULTS

Pharmacokinetics Summary:

- Fifty-eight (58) of the 60 enrolled patients were included in the PK evaluation.

Effects of AEDs on PK of Retigabine:
Retigabine PK parameters for 4 treatment groups are summarized in Table below.

Table 1. Dose-Normalised Retigabine Pharmacokinetic Parameters after Oral Administration With and Without Background AED Therapies

Treatment	Cmax (ng/mL) a	Tmax (h)	t½ (h)	AUCss (ng*h/mL) a
Effect of Valproic Acid on RTG Parameters:				
AED close to full dose				
Mean ± SD (N=8)	1320 ± 517	1.4 ± 0.5	5.80 ± 1.77	7079 ± 2852
AED reduced dose				
Mean ± SD (N=2)	868 ± 124	1.3 ± 1.1	10.71 ± 7.00	5108 ± 2460
RTG alone				
Mean ± SD (N)	1473 ± 181 (3)	1.8 ± 0.5 (4)	5.56 ± 4.93 (2)	8508 ± 1509 (4)
p-value from the respective ANOVA	0.72	0.60	0.06	0.98
Effect of Topiramate on RTG Parameters:				
AED close to full dose				
Mean ± SD (N=10)	1108 ± 541 b	1.6 ± 0.6	11.51 ± 8.71	6456 ± 2436

AED reduced dose				
Mean (N=1)	1127 b	1.0	nd	6684
RTG alone				
Mean ± SD (N)	809 ± 209 (4) b	3.4 ± 3.9 (7)	6.87 ± 4.47 (4)	6017 ± 2050 (5)
p-value from the respective ANOVA				
	0.89	0.17	0.67	0.91
Effect of Phenytoin on RTG Parameters:				
AED close to full dose				
Mean ± SD (N)	768 ± 194 (13) b	1.8 ± 1.0 (18)	9.49 ± 6.15 (13)	5323 ± 1847 (18)
AED reduced dose				
Mean ± SD (N=4)	1138 ± 517 b	1.8 ± 0.5	8.09 ± 3.36	8392 ± 3391
RTG alone				
Mean ± SD (N)	1231 ± 533 (7) b	1.8 ± 1.0 (9)	10.65 ± 9.59 (7)	8128 ± 5497 (9)
p-value from the respective ANOVA				
	0.001	0.43	0.52	0.001
Effect of Carbamazepine on RTG Parameters:				
AED close to full dose				
Mean ± SD (N)	879 ± 293 (17) b	1.2 ± 0.4 (21)	6.37 ± 2.08 (17)	4979 ± 1618 (21)
AED reduced dose				
Mean ± SD (N)	1094 ± 552 (7) b	2.0 ± 1.2 (9)	6.27 ± 2.14 (7)	6998 ± 3390 (9)
RTG alone				
Mean ± SD (N)	1031 ± 863 (6) b	2.0 ± 1.3 (8)	8.31 ± 3.86 (5)	7447 ± 5561 (8)
p-value from the respective ANOVA				
	0.41	0.033	0.44	0.001

a. Cmax and AUC were normalized to a 200 mg BID dose of RTG (400 mg/day);
b. Cmax included only data from patients receiving RTG in a BID regimen; nd=no data

Effects of Retigabine on PK of AEDs:

The PK parameters of valproic acid, topiramate, phenytoin, and carbamazepine with and without retigabine coadministration are summarized in Table below.

Table 2. Pharmacokinetic Parameters of Valproic Acid, Topiramate, Phenytoin or Carbamazepine after Oral Administration With and Without RTG Co-Administration

Treatment	**C_{max} (ng/mL) [a]**	**T_{max} (h)**	**$t_{½}$ (h)**	**AUC_{ss} (ng*h/mL) [a]**
Effect of Valproic Acid on RTG Parameters:				
AED close to full dose				
Mean ± SD (N=8)	1320 ± 517	1.4 ± 0.5	5.80 ± 1.77	7079 ± 2852
AED reduced dose				
Mean ± SD (N=2)	868 ± 124	1.3 ± 1.1	10.71 ± 7.00	5108 ± 2460
RTG alone				
Mean ± SD (N)	1473 ± 181 (3)	1.8 ± 0.5 (4)	5.56 ± 4.93 (2)	8508 ± 1509 (4)
p-value from the respective ANOVA				
	0.72	0.60	0.06	0.98
Effect of Topiramate on RTG Parameters:				
AED close to full dose				

Mean ± SD (N=10)	1108 ± 541 [b]	1.6 ± 0.6	11.51 ± 8.71	6456 ± 2436
AED reduced dose				
Mean (N=1)	1127 [b]	1.0	nd	6684
RTG alone				
Mean ± SD (N)	809 ± 209 (4) [b]	3.4 ± 3.9 (7)	6.87 ± 4.47 (4)	6017 ± 2050 (5)
p-value from the respective ANOVA				
	0.89	0.17	0.67	0.91
Effect of Phenytoin on RTG Parameters:				
AED close to full dose				
Mean ± SD (N)	768 ± 194 (13) [b]	1.8 ± 1.0 (18)	9.49 ± 6.15 (13)	5323 ± 1847 (18)
AED reduced dose				
Mean ± SD (N=4)	1138 ± 517 [b]	1.8 ± 0.5	8.09 ± 3.36	8392 ± 3391
RTG alone				
Mean ± SD (N)	1231 ± 533 (7) [b]	1.8 ± 1.0 (9)	10.65 ± 9.59 (7)	8128 ± 5497 (9)
p-value from the respective ANOVA				
	0.001	0.43	0.52	0.001
Effect of Carbamazepine on RTG Parameters:				
AED close to full dose				
Mean ± SD (N)	879 ± 293 (17) [b]	1.2 ± 0.4 (21)	6.37 ± 2.08 (17)	4979 ± 1618 (21)
AED reduced dose				
Mean ± SD (N)	1094 ± 552 (7) [b]	2.0 ± 1.2 (9)	6.27 ± 2.14 (7)	6998 ± 3390 (9)
RTG alone				
Mean ± SD (N)	1031 ± 863 (6) [b]	2.0 ± 1.3 (8)	8.31 ± 3.86 (5)	7447 ± 5561 (8)
p-value from the respective ANOVA				
	0.41	0.033	0.44	0.001

a. Cmax and AUC were normalized to a 200 mg BID dose of RTG (400 mg/day);
b. Cmax included only data from patients receiving RTG in a BID regimen; nd=no data

Preliminary Efficacy Results:

Preliminary observations from this study suggest that retigabine reduced the median percentage of seizures. A dose-dependent decrease in the median percentage of seizures was observed during the retigabine add-on therapy phases. The median percentage decrease in seizure rate was 19% during the titration phase, 38% during the titration phase, and 41% during the background taper phase. An increase in the number of responders was correlated with increasing retigabine doses. The percent of responders was reported to be 44% at MTD of retigabine with AED add-on therapy.

Safety Summary:

The most common TEAEs were dizziness (53%), asthenia (42%), somnolence (33%), nausea (27%), speech disorder (27%), and tremors (27%). The TID dose regimen had a slightly lower incidence of TEAEs than in BID dose regimen (91% and 100%, respectively). Patients in the TID dose group also reported fewer CNS TEAEs than patient in the BID dose group (64% versus 98%, respectively). AEs were the cause for discontinuation of treatment for 2 (25%), 2 (9%), 2 (11%), and 2 (18%) patients in the

valproic acid, carbamazepine, phenytoin, and topiramate background AED groups, respectively. Five patients had serious adverse events but not discontinued from the study.

CONCLUSION:

- Retigabine BID or TID dosing at 300-1200 mg daily did not significantly alter the PK parameters the concomitant AEDs.
- Valproic acid or topiramate did not significantly affect the retigabine PK.
- Dose-normalized retigabine exposure measure (AUC values) were approximately 20~30% higher in patients taking retigabine alone compared to patients taking concomitant phenytoin or carbamazepine. Data suggest that retigabine clearance may be increased by approximately 30% with concomitant phenytoin or carbamazepine.
- Based on the study results and the adverse events profile, retigabine 1200 mg daily as BID dosing regimen was determined to be the MTD in epileptic patients.

Report D-23129/9321030001 (Study 202/205)

Title: An evaluation of plasma data from clinical studies 202 and 205 for potential mutual pharmacokinetic interactions between retigabine and other antiepileptic drugs (AEDs)

Objective:
To assess the potential PK interactions between retigabine and concomitant AEDs using an accepted confidence interval approach in a post-hoc analysis for the intra-individual comparisons of CL/F among retigabine, carbamazepine, phenytoin, valproic acid, and topiramate

Post-Hoc Analysis Approach:
The PK dataset from Study 3065A1-202 and -205 was further evaluated to assess the potential PK interactions between retigabine and concomitant AEDs, focusing on comparisons of CL/F. This post-hoc analysis was restricted to only those patients for whom data was available at the same dose with and without the potential interacting AED medication. The point estimates and 90% CIs were constructed for the log-transformed CL/F values and were evaluated based on the 80%-125% bioequivalence limits.

RESULTS

Pharmacokinetics Summary:
Statistical comparisons of AED CL/F with and without concomitant retigabine are presented in Table 1 blow. Statistical comparisons of retigabine CL/F with and without concomitant carbamazepine, phenytoin, valproic acid, or topiramate are presented in Table 2 blow

Table 1. Effects of Retigabine Co-Administration on Apparent Oral Clearance of Carbamazepine, Phenytoin, Valproic Acid and Topiramate

AED	90% CI of (AED+RTG/AED) Ratio of $Mean_{geo}$ AED CL/F	p-Value (ANOVA)
Carbamazepine (N=21)	0.98 (0.93-1.03)	0.4728
Phenytoin (N=17)	1.04 (0.92-1.18)	0.5844
Valproic acid (N=8)	0.99 (0.80-1.23)	0.9257
Topiramate (N=9)	1.04 (0.99-1.09)	0.1585

Table 2. Effects of Carbamazepine, Phenytoin, Valproic Acid and Topiramate Co-Administration on Apparent Oral Clearance of Retigabine

AED	90% CI of (AED+RTG/REG) Ratio of $Mean_{geo}$ REG CL/F	p-Value (ANOVA)
Carbamazepine (N=8)	1.27 (0.96-1.70)	0.1553
Phenytoin (N=9)	1.36 (1.11-1.67)	0.0239
Valproic acid (N=4)	1.04 (0.69-1.56)	0.8519
Topiramate (N=5)	0.83 (0.45-1.52)	0.5437

CONCLUSION:

- For all the concomitant AEDs, the ratios of geometric mean CL/F with and without concomitant retigabine were close to unity and the corresponding 90% confidence intervals were within the 80-125% BE limits (the criteria proposed by the Sponsor). Noted that the Agency does not recommend the use of BE criteria for the PK measures other than the exposure (AUC and Cmax).
- The Retigabine plasma levels were lowered by co-administered Phenytoin and Carbamazepine. The retigabine CL/F geometric mean ratio was increased by 36% and 27% with Concomitant phenytoin and carbamazepine resulted in increases of retigabine CL/F by 36% and 27%, respectively.
- There did not appear to be significant effects of concomitant valproic acid or topiramate of retigabine CL/F values based on the geometric mean ratios. The sample sizes were relatively small for cases of valproic acid or topiramate.

4.4.4 *In-Vitro* Studies

Study PR2005-029: In Vitro Induction of Human CYP Enzymes by Five NCEs

Objective: To investigate the effect of five new chemical entities (NCEs) on the expression of cytochrome P450 enzymes in primary cultures of human hepatocytes

Methods:
Three preparations of cultured human hepatocytes (2~3 days in culture) from three separate human livers (H575, H576 and H577) were treated with dimethyl sulfoxide (vehicle, 0.1% [v/v]), one of three concentrations of NCE 1 (VRX480773: 1, 10 and 100 □M), NCE 2 (VRX 481806: 1, 10 or 50 μM), NCE 3 (VRX 494859: 1, 10 or 50 μM), NCE 4 (Retigabine: 1, 10 or 100 μM) and NCE 5 (N-acetyl Retigabine: 1, 10 or 100 μM) or known human cytochrome P450 enzyme inducers as positive controls, namely omeprazole (100 μM) or rifampin (10 μM), once daily for 3 consecutive days. After treatment, cells were harvested to prepare microsomes for the analysis of 7-ethoxyresorufin *O*-dealkylation (marker for CYP1A2) and testosterone 6β-hydroxylation (marker for CYP3A4/5), as shown in Table below.

Enzyme	Substrate	Substrate Concentration (μM)	Quantity of Protein (mg)	Final Volume (mL)	Time (min)
CYP1A2	7-Ethoxyresorufin	10	0.05 and 0.1	1.0	60 and 120
CYP3A4/5	Testosterone	250	0.05	0.5	40

The effectiveness of the test article was calculated by dividing the difference in activity between the test article and the vehicle control by the difference in activity between the positive controls and the vehicle control, and then multiplying by 100%.

Results:
Figure. The effect of treating culture human hepatocytes with five NCEs on markers of cytochrome P450: expressed as average fold-increase

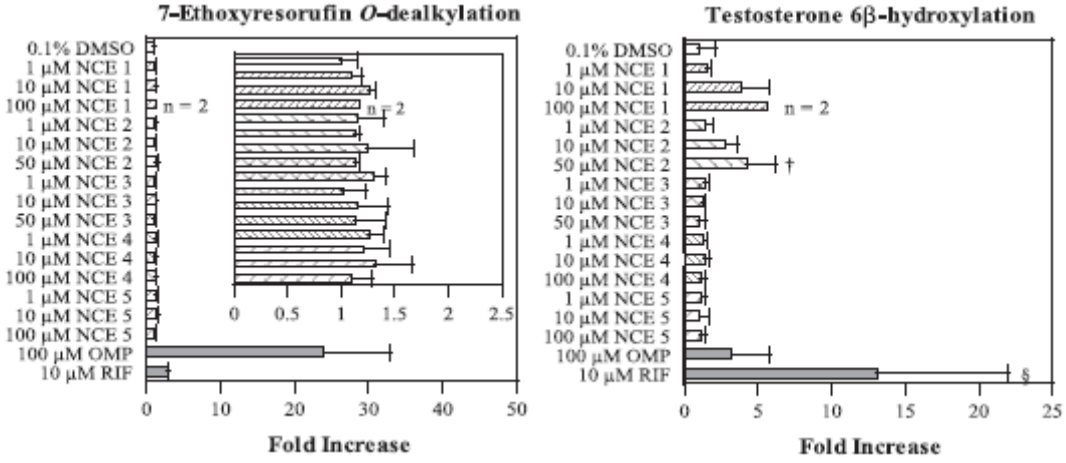


Table. Effects of treating cultured human hepatocytes with five NCEs or prototypical inducers on the fold induction of cytochrome P450 enzymes

Treatment	Concentration	7-Ethoxyresorufin *O*-dealkylation (CYP1A2)	Testosterone 6ß-hydroxylation (CYP3A4/5)
		Fold Induction [a]	
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.14	1.00 ± 1.11
NCE 1	1 µM	1.10 ± 0.09	1.55 ± 0.23
NCE 1	10 µM	1.26 ± 0.05	3.91 ± 1.82
NCE 1	100 µM	1.18 (n = 2)	5.70 (n = 2)
NCE 2	1 µM	1.16 ± 0.24	1.44 ± 0.51
NCE 2	10 µM	1.13 ± 0.04	2.81 ± 0.80
NCE 2	50 µM	1.24 ± 0.43	4.27 ± 1.92†
NCE 3	1 µM	1.13 ± 0.04	1.42 ± 0.25
NCE 3	10 µM	1.30 ± 0.12	1.26 ± 0.12
NCE 3	50 µM	1.01 ± 0.22	0.959 ± 0.469
NCE 4	1 µM	1.16 ± 0.28	1.32 ± 0.20
NCE 4	10 µM	1.13 ± 0.28	1.40 ± 0.31
NCE 4	100 µM	1.26 ± 0.13	1.15 ± 0.32
NCE 5	1 µM	1.21 ± 0.24	1.17 ± 0.31
NCE 5	10 µM	1.31 ± 0.35	1.03 ± 0.64
NCE 5	100 µM	1.10 ± 0.18	1.09 ± 0.35
Omeprazole	100 µM	23.9 ± 9.0	3.21 ± 2.60
Rifampin	10 µM	2.82 ± 0.13	13.1 ± 8.9§

Conclusions:

- Treatment with omeprazole resulted in a 16.7~34 fold induction of 7-ethoxyresorufin O-dealkylase activity. None of the NCEs studied caused more than a 2-fold increase in 7-ethoxyresorufin O-dealkylase activity.
- Treatment with rifampin caused a 13.1-fold increase in testosterone 6β-hydroxylase activity. Treatment of cultured human hepatocytes with the NCE 3, NCE 4 or NCE 5 had little or no effect on testosterone 6β-hydroxylase activity.
- Treatment of cultured human hepatocytes with NCE 1 or NCE 2 resulted in concentration-dependent increases up to 5.70 fold and 4.27 fold, respectively in testosterone 6β-hydroxylase activity.
- Results of the study indicate that neither Retigabine (NCE 4) and N-acetyl Retigabine (NCE 5) induces CYP1A2 and CYP3A4/5.
- The lack of significant induction for CYP1A2 and CYP3A4/5 suggests a lack of significant induction for P-glycoprotein and CYP2C isozymes in view of the similar mechanism of induction among them.

Study PR2006-016: Evaluation of *in vitro* Metabolism of Retigabine and N-Acetyl Retigabine in Rat, Rabbit, Dog, Monkey and Human Liver Microsomes and Hepatocytes

Objective: To aid the selection of a non-rodent species for toxicology studies, the metabolic profiles of retigabine and N-acetyl retigabine were studied in rat, rabbit, dog, monkey and human liver microsomes and hepatocytes.

Methods:

Microsomal Incubations: [14C]retigabine or [14C]N-acetyl retigabine (20 µM) was incubated with rat, rabbit, dog, cynomolgus monkey and human liver microsomes (1 mg

protein/mL). The reaction was initiated by the addition of NADPH (final concentration of 1 mM) and incubated for 60 minutes at 37°C. The reaction was terminated by the addition of 500 µL of acetonitrile. After centrifugation at 10,000 rpm for 10 minutes, the supernatant was transferred to clean vials and analyzed by HPLC with ß-Ram detection.

Hepatocyte incubations: The Krebs-Henseleit (KH) buffer was added to the suspension of the hepatocytes pellet to make a final density of 2 million cells/mL. Incubation was carried out at a final retigabine or N-acetyl retigabine concentration of 20 µM for cryopreserved hepatocytes. The culture plate was incubated at 37 °C under 5% carbon dioxide and 95% air atmosphere for 4 hr. The metabolic reaction was terminated by transferring the contents of the well into a centrifuge tube containing 1 mL of methanol and then vortexing. After centrifugation, an aliquot of supernatant was injected onto HPLC for the metabolite profiling.

Results:

Metabolic profile of retigabine:

- Incubation of [14C]retigabine with human, monkey, dog, rabbit, and rat liver microsomes in the presence of NADPH did not produce any Phase I metabolites, indicating cytochrome P450 was not involved in the metabolism of retigabine.
- Following incubation of retigabine with human, monkey, dog, rabbit, and rat hepatocytes, the relative amount (%) of metabolites are summarized as follows:

Species	M1	M2	M3	M4	M5	M6	Retigabine	Total
Human	-	-	10.9	24.3	1.8	14.6	48.4	100.0
Monkey	-	-	22.8	44.3	4.5	-	26.5	98.0
Dog	-	-	-	53.3	4.7	-	42.1	100.1
Rabbit	-	-	24.6	44.0	-	2.9	25.5	97.0
Rat	-	-	2.8	1.2	-	3.6	91.3	99.1

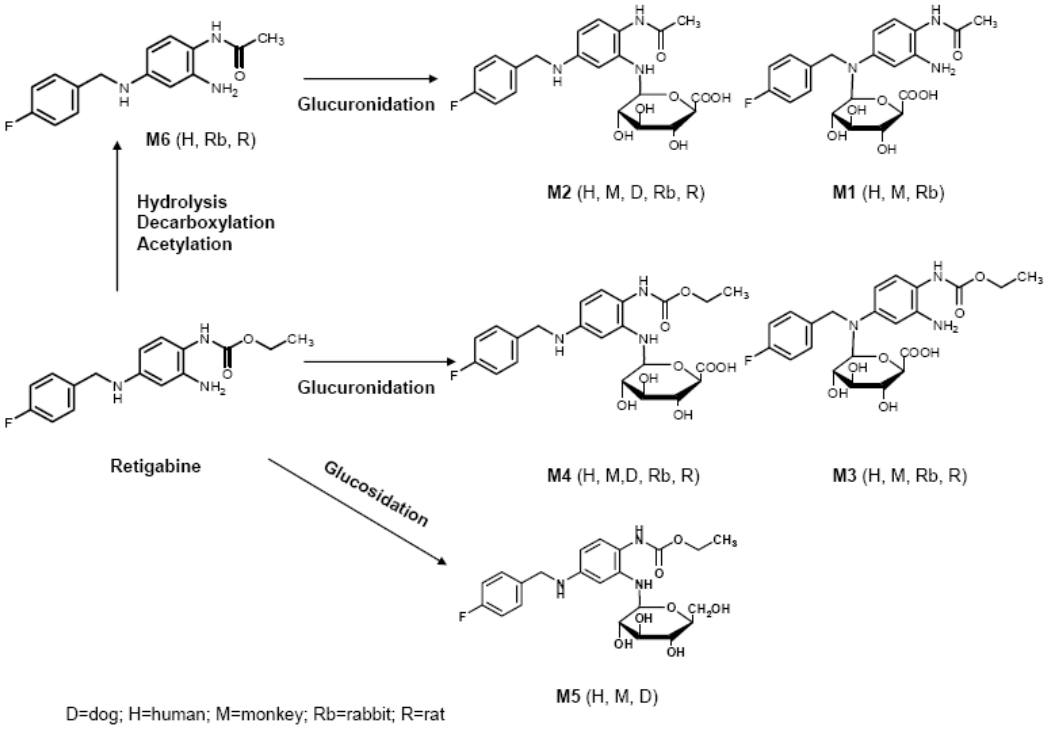
Metabolic profile of N-acetyl retigabine:

- There were no Phase I metabolites formed following incubation of N-acetyl retigabine with human, monkey, dog, rabbit, and rat microsomes in the presence of NADPH, indicating cytochrome P450 was not involved in the metabolism of retigabine.
- Following incubation of N-acetyl retigabine with human, monkey, dog, rabbit, and rat hepatocytes, the relative amount (%) of metabolites are summarized as follows:

Species	M1	M2	N-acetyl retigabine	Total
Human	4.0	2.0	93.9	99.9
Monkey	6.9	7.3	85.8	100
Dog	-	23.9	76.1	100
Rabbit	4.6	16.2	76.3	97.1
Rat	-	1.6	98.4	100

- N-acetyl retigabine is much more stable than retigabine in hepatocytes of all species except the rat.
- Similar metabolic profiles were observed amongst human, monkey, and rabbit.
- Metabolic profiles in the dog and rat were different from other species due to the lack of formation of M1.

Metabolic pathways of retigabine are presented as follows:



D=dog; H=human; M=monkey; Rb=rabbit; R=rat

- Retigabine was metabolized through glucuronidation, acetylation, or glucosidation reaction.
- Metabolic profile in dog was different from human, due to the lack of metabolite M3.
- Similar metabolic profiles amongst human, rabbit, and rat were obtained, except metabolite M5 was only detected in human.
- Similar metabolic profiles were obtained between human and monkey except, metabolite M6 was not detected in monkey.

Conclusions:

- Incubation of [14C]retigabine or N-acetyl retigabine with human, monkey, dog, rabbit, and rat liver microsomes in the presence of NADPH did not produce any oxidative metabolites.
- Retigabine was metabolized mainly through glucuronidation in hepatocytes from rats, rabbits, dogs, monkeys, and humans.
- Incubation of [14C]retigabine with human hepatocytes indicated that both acetylation and glucuronidation are the major metabolic pathways of retigabine in humans.

- Retigabine-N2-glucuronide (M4) is the dominant metabolite in human hepatocytes, followed by the N-acetyl retigabine (M5), retigabine-N4-glucuronide (M3), and a small amount of glucoside metabolite (M6).
- The formation of N-glucoside conjugates, which is not a common drug metabolite, were detected in the human, monkey and dog, indicating that N-glucosidation of retigabine seems to be a minor metabolic pathway. The dog is also specific in the metabolism of retigabine among other species because it does not form secondary amino-N-glucuronide (M3) or N-acetyl glucuronide (M1) metabolite.
- Qualitatively, the metabolite profile of retigabine in human hepatocytes is similar to those of the rabbit and monkey. However, no single species can fully represent human.
- Incubation of N-acetyl retigabine with rat, rabbit, dog, monkey, and human hepatocytes produced M1 (secondary amino acetyl retigabine-N-glucuronide) and/or M2 (primary amino acetyl retigabine N-glucuronide).
- The amount of metabolites produced by N-acetyl retigabine was significantly lower than those of retigabine. The amount of metabolites produced by incubation with human or rat hepatocytes was less than 7%.

Study PR2006-081: In Vitro Protein Binding Determination of N-acetyl Metabolite of Retigabine in CD-1 Mouse, Sprague-Dawley Rat, New Zealand White Rabbit, Beagle Dog, and Human Plasma by Equilibrium Dialysis

Objective:
- To determine the extent of protein binding of the N-acetyl metabolite of retigabine across species at 37°C using an equilibrium dialysis method

Methods:
- The spiked nominal concentrations of the N-acetyl metabolite of retigabine in plasma were 0.5, 5, and 50 μM, analyzed by a validated LC/MS/MS method with the assay range of 5–3000 nM (1.37–820 μg/mL). The spiked plasma and blank phosphate buffer were placed into opposite sides of the assembled dialysis cells which were rotated slowly in a 37^{o}C water bath for 4 hours.
- Stability of the N-acetyl metabolite of retigabine was evaluated at 37°C at 2, 3, 4, and 6 hours in phosphate buffer (pH 7.4), with equilibrium being achieved after approximately 4 hours of dialysis.

Results:
- The mean percent unbound [bound] of the N-acetyl metabolite of retigabine was 45.2 [54.8] ± 0.8% in human plasma at the tested concentration range of 0.5~50 μM (136.7 – 13665.5 ng/mL), as summarized in the Table below. Results were similar to that from the stability testing.
- Concentration dependency of the plasma protein binding was not observed under the test conditions.

Nominal Concentration (μM)	Percent Unbound[Bound] (Mean ± SD) [a]				
	Species				
	Mouse	Rat	Rabbit	Dog	Human
0.5	48.3[51.7] ± 2.3	45.7[54.3] ± 0.7	41.0[59.0] ± 1.3	42.5[57.5] ± 1.1	44.8[55.2] ± 3.3
5	45.7[54.3] ± 1.3	44.3[55.7] ± 1.7	38.6[61.4] ± 1.7	41.3[58.7] ± 1.1	44.6[55.4] ± 2.6
50	48.7[51.3] ± 3.5	47.0[53.0] ± 2.2	41.2[58.8] ± 1.0	41.8[58.2] ± 0.8	46.1[53.9] ± 1.2
Overall Mean	47.6[52.4] ± 1.7	45.7[54.3] ± 1.4	40.3[59.7] ± 1.5	41.9[58.1] ± 0.6	45.2[54.8] ± 0.8

[a] Mean and SD represent N=3.

Study PR2008-010: *In Vitro* Evaluation of Retigabine and *N*-Acetyl metabolite of Retigabine as Inhibitors of Human CYP2C8

Objective: To evaluate the ability of Retigabine and N-Acetyl metabolite of Retigabine (N-AMR) to inhibit CYP2C8 in human liver microsomes.

Methods: Human liver microsomes from a pool of 16 individuals of mixed gender were incubated with amodiaquine, a known substrate of CYP2C8, at a concentration approximately equal to its apparent *K*m, in the presence or absence of Retigabine and *N*-AMR. The target concentrations of Retigabine and *N*-AMR ranged from 30.33 to 30330 ng/mL and 27.331 to 27331 ng/mL (0.1 to 100 μM), respectively. In addition, Retigabine and *N*-AMR were evaluated for their ability to function as time-dependent inhibitors at the same concentrations mentioned above, in which case Retigabine and *N*-AMR were pre-incubated with human liver microsomes and an NADPH-generating system for 30 minutes to allow for the generation of metabolites that might inhibit CYP2C8 activity. Known direct and metabolism-dependent inhibitors of CYP2C8 were included as positive controls. The experimental conditions are described in the table below.

Table 1: Summary of experimental conditions for enzyme assays: Direct and time-dependent inhibition of CYP2C8 by Retigabine and *N*-Acetyl metabolite of Retigabine (*N*-AMR) (IC_{50} determinations)

Enzyme	CYP Reaction	SOP followed	Substrate concentration (μM)	Incubation volume (μL)	Protein [a] (μg/mL)	Incubation time (min)	Pre-incubation time (min)	Test article	Test article target concentrations (ng/mL)	Solvent volume [b] (μL)
CYP2C8	Amodiaquine *N*-dealkylation	L3250.06	7	400	100	5	30	Retigabine	0, 30.33, 90.99, 303.3, 909.9, 3033, 9099, 30330	4
CYP2C8	Amodiaquine *N*-dealkylation	L3250.06	7	400	100	5	30	*N*-AMR	0, 27.331, 81.993, 273.31, 891.93, 2733.1, 8199.3, 27331	4

a The human liver microsomal sample used for these experiments was a pool of 16 individuals (samples 286, 290, 312, 313, 315, 333, 334, 335, 336, 339, 348, 359, 364, 383, 389 and 390).

b Methanol (1% final incubation concentration) was the vehicle used to dissolve the test article.

N-AMR *N*-Acetyl metabolite of Retigabine

Results: Retigabine and *N*-AMR caused little to no direct inhibition of CYP2C8 at incubation concentrations up to 30330 ng/mL and 27331 ng/mL (100 μM) respectively. Therefore the IC50 values for these enzymes were reported as greater than 30330 ng/mL and 27331 ng/mL (100 μM), respectively. No time-dependent inhibition for CYP2C8 by either Retigabine or *N*-AMR was observed. Data are summarized in the table below.

Table 3: Summary of results: *In vitro* evaluation of Retigabine and *N*-Acetyl metabolite of Retigabine (*N*-AMR) as inhibitors of human CYP2C8

			Direct inhibition		Time-dependent inhibition		
			Zero-minute preincubation		30-minute preincubation		
Enzyme	CYP Reaction	Test article	IC_{50} (ng/mL)	Maximum inhibition (%) [a]	IC_{50} (ng/mL)	Maximum inhibition (%) [a]	Potential for time-dependent inhibition [b]
CYP2C8	Amodiaquine *N*-dealkylation	Retigabine	>30330	1.6	>30330	1.6	Little or no
CYP2C8	Amodiaquine *N*-dealkylation	*N*-AMR	>27331	1.6	>27331	NA	Little or no

Notes: Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values. IC_{50} values were calculated with XLFit.

a Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (30330 ng/mL Retigabine, 27331 ng/mL *N*-AMR; results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent solvent control.

b Time-dependent inhibition was determined by comparison of IC_{50} values with and without preincubation, by comparison of the maximum inhibition (%) with and without preincubation and by visual inspection of the IC_{50} plot.

NA Not applicable. No value was obtained as the rate at the highest concentration of *N*-Acetyl metabolite of Retigabine evaluated (27331 ng/mL) was higher than the control rate.

Conclusions: Retigabine and *N*-AMR caused little to no direct inhibition of CYP2C8. There was no evidence of time-dependent inhibition for CYP2C8 by either Retigabine or *N*-AMR.

Study PR2008-017: EVALUATION OF THE POTENTIAL FOR RETIGABINE AND N-ACETYL METABOLITE OF RETIGABINE TO INHIBIT P-GLYCOPROTEIN IN LLC-PK1 CELL MONOLAYERS

Objective: To assess the P-gp inhibition potential of retigabine and N-acetyl metabolite of retigabine (N-AMR) in the MDR1-LLC-PK1 cell model.

Methods: The porcine kidney-derived, (b) (4) MDR1 LLC-PK1 cell line, expressing human P-gp cDNA (designated as 22L1, (b) (4) Cat #450211) and the control LLC-PK1 cell line containing the vector without human P-gp cDNA (designated as CLD, (b) (4) Cat #450216) were used. The cells were cultured in (b) (4) 24-well, 1 µm culture inserts in a humidified incubator at 37°C, with 5% CO2 for 7 days, with medium change at 3-4 days.

The assays were performed in the A to B and B to A directions in the P-gp transfected (22L1) and the vector carrying (CLD) LLC-PK1 cell lines. Positive controls were included in each assay with a test article. The assay conditions are described in the table below.

Table 2 Cell Monolayer Assay Conditions

Probe Substrate	Inhibitor	Incubation	Direction of Transport	Purpose
5 µM [^{3}H]-Digoxin	none	90 min, 37°C	A to B, B to A[2]	Positive control P-gp substrate
5 µM [^{3}H]-Digoxin	25 µM ketoconazole	90 min, 37°C	A to B, B to A	Positive control P-gp substrate with control inhibitor
5 µM [^{3}H]-Digoxin	retigabine at 1.0 µM (302 ng/mL), 10 µM (3018 ng/mL) or 100 µM (30178 ng/mL)	90 min, 37°C	A to B, B to A	Assessment of Retigabine as an inhibitor of P-gp
5 µM [^{3}H]-Digoxin	N-AMR[1] at 1.0 µM (264 ng/mL), 10 µM (2643 ng/mL) or 100 µM (26434 ng/mL)	90 min, 37°C	A to B, B to A	Assessment of N-AMR as an inhibitor of P-gp

[1] N-AMR: N-acetyl Metabolite of retigabine
[2] A to B (apical to basolateral), B to A (basolateral to apical)

Each test article was assayed at three concentrations, and was present in the donor side and receiver side of a monolayer, with probe substrate digoxin present in the donor side. The donor and receiver solutions were added to the apical or basolateral chambers of the monolayers (depending on the direction of transport to be measured). The monolayers were incubated on an orbital shaker (50 rpm) at 37°C, with ambient humidity and CO2 for the duration of the transport assay. Samples from the donor and receiver chambers were taken at the specified time point.

Results:

Controls-The TEER and lucifer yellow flux values confirmed acceptable monolayer integrity. Digoxin data measured in the absence of control inhibitor demonstrated functional P-gp activity in the test system. The digoxin transport results confirmed the activity of 5 µM [3H]-digoxin as the positive control substrate of P-gp. Inhibition of digoxin transport by 25 µM ketoconazole resulted in a 97% (Assay 1) and a 100% (Assay 2) decrease in polarization ratio (PR), and a 95% (Assay 1) and 100% (Assay 2) decrease in net flux ratio (NFR). These values confirmed the activity of 25 µM ketoconazole as the positive control inhibitor of P-gp. The recovery of digoxin (mass balance) ranged from 87%-110%

Test articles-Transport of digoxin was measured in the presence of retigabine at concentrations of 1.0 µM (302 ng/mL), 10 µM (3018 ng/mL) or 100 µM (30178 ng/mL). The results demonstrate that retigabine did not significantly inhibit digoxin transport. Data are shown in the table below.

Table 6 Inhibition Results Summary with Retigabine

Assay 1 - CLD (control) cells

Probe Substrate	Inhibitor	Digoxin A to B Papp[1] (x 10^{-6} cm/sec)	Digoxin B to A Papp[2] (x 10^{-6} cm/sec)	Digoxin Polarization Ratio[3] (PR)	Inhibition of Digoxin PR[4]
5 µM [^{3}H]-Digoxin	none	2.1	5.6	2.6	-
5 µM [^{3}H]-Digoxin	1 µM (302 ng/mL) Retigabine	2.3	5.7	2.4	12%
5 µM [^{3}H]-Digoxin	10 µM (3018 ng/mL) Retigabine	2.2	5.1	2.3	20%
5 µM [^{3}H]-Digoxin	100 µM (30178 ng/mL) Retigabine	2.6	5.4	2.1	34%

Assay 1 - 22L1 (P-gp) cells

Probe Substrate	Inhibitor	Digoxin A to B Papp[1] (x 10^{-6} cm/sec)	Digoxin B to A Papp[2] (x 10^{-6} cm/sec)	Digoxin Polarization Ratio[3] (PR)	Inhibition of Digoxin PR[4]	Digoxin Net Flux Ratio (NFR)[5]	Inhibition of Digoxin NFR[6]
5 µM [^{3}H]-Digoxin	none	0.69	11	16	-	6.1	-
5 µM [^{3}H]-Digoxin	1 µM (302 ng/mL) Retigabine	0.84	13	15	4.0%	6.3	-4.6%
5 µM [^{3}H]-Digoxin	10 µM (3018 ng/mL) Retigabine	0.72	11	15	8.7%	6.4	-5.8%
5 µM [^{3}H]-Digoxin	100 µM (30178 ng/mL) Retigabine	0.88	11	12	25%	5.9	2.8%

[1] Apical to basolateral Papp (apparent permeability) value is the mean of three replicates
[2] Basolateral to apical Papp (apparent permeability) value is the mean of three replicates
[3] PR: $Papp_{B\ to\ A}$ / $Papp_{A\ to\ B}$
[4] Inhibition of PR: % Inhibition = (1 - (PR_{+I} - 1) / (PR_{-I} -1))*100
Where: PR_{+I} = PR in the presence of inhibitor, PR_{-I} = PR in the absence of inhibitor
[5] NFR: (PR 22L1 cells) / (PR CLD cells)
[6] Inhibition of NFR: % Inhibition = (1 - (NFR_{+I} - 1) / (NFR_{-I} - 1)*100
Where: NFR_{+I} = NFR in the presence of inhibitor, NFR_{-I} = NFR in the absence of inhibitor

Retigabine was assayed in Assay 1 performed on February 8, 2008

Transport of digoxin was measured in the presence of N-AMR at concentrations of 1.0 µM (264 ng/mL), 10 µM (2643 ng/mL) or 100 µM (26434 ng/mL). The results demonstrate that N-AMR significantly inhibited digoxin transport in a concentration dependent manner. The inhibition observed with N-AMR did not reach the level of inhibition obtained with the positive control, ketoconazole. Data are shown in the table below.

Table 7 Inhibition Results Summary with N-Acetyl Metabolite of Retigabine

Assay 2 - CLD (control) cells							
Probe Substrate	Inhibitor	Digoxin A to B Papp[1] ($\times 10^{-6}$ cm/sec)	Digoxin B to A Papp[2] ($\times 10^{-6}$ cm/sec)	Digoxin Polarization Ratio[3] (PR)	Inhibition of Digoxin PR[4]		
5 µM [^{3}H]-Digoxin	none	2.5	5.7	2.3	-		
5 µM [^{3}H]-Digoxin	1 µM (264 ng/mL) N-AMR[8]	2.9	7.3	2.5	-12%		
5 µM [^{3}H]-Digoxin	10 µM (2643 ng/mL) N-AMR	2.7	6.2	2.3	2.2%		
5 µM [^{3}H]-Digoxin	100 µM (26434 ng/mL) N-AMR	3.0	6.3	2.1	18%		
Assay 2 - 22L1 (P-gp) cells							
Probe Substrate	Inhibitor	Digoxin A to B Papp[1] ($\times 10^{-6}$ cm/sec)	Digoxin B to A Papp[2] ($\times 10^{-6}$ cm/sec)	Digoxin Polarization Ratio[3] (PR)	Inhibition of Digoxin PR[4]	Digoxin Net Flux Ratio (NFR)[5]	Inhibition of Digoxin NFR[6]
5 µM [^{3}H]-Digoxin	none	0.72	14	20	-	8.4	-
5 µM [^{3}H]-Digoxin	1 µM (264 ng/mL) N-AMR	1.1	16	15	26%	5.9	33%
5 µM [^{3}H]-Digoxin	10 µM (2643 ng/mL) N-AMR	1.5	15[7]	9.7	53%	4.2	56%
5 µM [^{3}H]-Digoxin	100 µM (26434 ng/mL) N-AMR	2.2	15	6.8	69%	3.2	70%

[1] Apical to basolateral Papp (apparent permeability) value is the mean of three replicates
[2] Basolateral to apical Papp (apparent permeability) value is the mean of three replicates
[3] PR: $Papp_{B\ to\ A}$ / $Papp_{A\ to\ B}$
[4] Inhibition of PR: % Inhibition = (1 - (PR_{+I} - 1) / (PR_{-I} -1))*100
Where: PR_{+I} = PR in the presence of inhibitor, PR_{-I} = PR in the absence of inhibitor
[5] NFR: (PR 22L1 cells) / (PR CLD cells)
[6] Inhibition of NFR: % Inhibition = (1 - (NFR_{+I} - 1) / (NFR_{-I} - 1)*100
Where: NFR_{+I} = NFR in the presence of inhibitor, NFR_{-I} = NFR in the absence of inhibitor
[7] mean of two replicates
[8] N-AMR: N-acetyl metabolite of Retigabine

N-Acetyl metabolite of Retigabine was assayed in Assay 2 performed on February 11, 2008

The recovery of digoxin (mass balance) ranged from 79%-108%.

Conclusions: The monolayer QC and positive control substrate and inhibitor results demonstrated a properly functioning model for measuring P-gp transport and inhibition. Retigabine did not significantly inhibit the P-gp mediated transport of digoxin, suggesting that retigabine is not an inhibitor of P-gp. N-AMR significantly inhibited the P-gp mediated transport of digoxin in a concentration-dependent manner which suggests that N-AMR is an inhibitor of P-gp.

Study 7096020004: [Aniline ring-U-14C]D-23129: In vitro protein binding to human serum albumin and human plasma proteins

Objective: To determine the protein binding to human serum albumin and human plasma proteins.

Methods: [Aniline ring-U-14C]0-23129 was dissolved in 4 % human serum albumin solution in a concentration range of 0.1 - 8 µg/ml and human plasma (EDTA was used as anti-coagulant) in a concentration range of 0.1 – 2 µg/ml. The samples were incubated at 37 °C for 15 min and subsequently centrifuged at 250 000 x g for 16 h. The radioactivity of the supernatant without proteins was measured.

Results:

- Stability: No decay of the test compound could be observed in human plasma after incubation of 16 h at 37 °C.
- Protein binding to human serum albumin (human plasma) was investigated using four (three) increasing concentrations (0.1; 0.5; 5 and 8 µg/ml respectively (0.1; 0.5; 2 µg/ml)). Data are shown in the tables below.

Table 1 Protein binding of [Aniline ring-U-^{14}C]D-23129 to human serum albumin. The mean values determined from all the values are listed in the following table.

Concentr. µg/ml	Experiment 1 protein binding (%)	Experiment 2 protein binding (%)	Experiment 3 protein binding (%)	Experiment 4 protein binding (%)	mean (%)
0.1	79.0	78.4	72.3	70.51	75.1
0.5	77.4	78.2	77.8	77.6	74.6
5.0	77,8	77.6	-	-	77.7
8.0	-	-	77.9	79.0	78.4
mean					75.9

Table 2 Protein binding of [Aniline ring-U-^{14}C]D-23129 to human plasma. The mean values determined from all the values are listed in the following table.

Concentr. µg/ml	Experiment 1 protein binding (%)	Experiment 2 protein binding (%)	Experiment 3 protein binding (%)	Experiment 4 protein binding (%)	mean (%)
0.1	77.8	80.5	79.9	80.1	79.6
0.5	79.6	77.9	79.4	79.1	79.0
2.0	78.8	80.2	80.2	81.3	80.1
mean					79.6

- No concentration-dependent protein binding was observed to human serum albumin at concentrations of 0.1 - 8 µg/ml or in human plasma at concentrations of 0.1 - 2 µg/ml.

Conclusions: Protein binding to human serum albumin and human plasma proteins is ≤ 80 % at therapeutic concentrations.

Study 9321030009: GKE-841: The Preliminary Evaluation of GKE-841 as a Reversible Inhibitor of Human P450 Enzymes

Objective: To evaluate the ability or potential of GKE–841 to inhibit the major P450 enzymes in human liver microsomes

Methods: Human liver microsomes were pooled from 7 individuals. Human liver microsomes (100 mg) were incubated in duplicate for 1 to 10 min at 37 ± 1°C in 1-mL (final volume) incubation mixtures containing potassium phosphate buffer (50 mM, pH 7.4), MgCl2 (3 mM), EDTA (1 mM), NADP (1 mM), glucose-6-phosphate (5 mM), glucose-6-phosphate dehydrogenase (1 Unit/mL), marker substrate and GKE–841 (0, 0.1, 0.25, 1, 2.5, 10, 25, 100 and 250 µM) at the final concentrations indicated. GKE–841 was added to the 1-mL incubation mixtures dissolved in methanol (0.5%). Methanol was evaporated prior to the incubation in the CYP2E1 assay. Reactions were initiated by the addition of an NADPH regenerating system. After the designated incubation period, reactions were stopped by the addition of an appropriate stop reagent. A summary of the experimental conditions is provided below.

Enzyme	P450 Activity	[Substrate][a] (µM)	Incubation Volume (µL)	Protein[b] (µg/mL)	Incubation Time (min)
CYP1A2	7-Ethoxyresorufin *O*-dealkylase	0.30	1000	100	10
CYP2A6	Coumarin 7-hydroxylase	0.50	1000	100	1.0
CYP2C9	Diclofenac 4′-hydroxylase	5.0	1000	100	5.0
CYP2C19	*S*-Mephenytoin 4′-hydroxylase	24	200	1000	10 or 30[c]
CYP2D6	Dextromethorphan *O*-demethylase	4.0	1000	100	10
CYP2E1	Chlorzoxazone 6-hydroxylase	30	1000	100	10
CYP3A4/5	Testosterone 6β-hydroxylase	50	1000	100	10

a The substrate concentration was based on the kinetic constants shown in Appendix 1.

b Human liver microsomal sample used for these experiments was a pool of 7 individuals (samples 16, 17, 21, 23, 28, 29 and 30)

c The incubation time was increased for one of the two experiments to improve sensitivity of the assay.

Results: GKE–841 caused a concentration-dependent inhibition of CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 activity with IC50 values of 25, 300, 670, 210, 550 and 110 mM, respectively. GKE–841 did not inhibit the activity of CYP1A2. (see Table 1 below). The IC50 value for GKE–841 as an inhibitor of CYP1A2 is >250 µM, the highest concentration studied. A summary of the results is provided in Table 2 below.

Table 1. Direct inhibition of human P450 enzymes by GKE-841

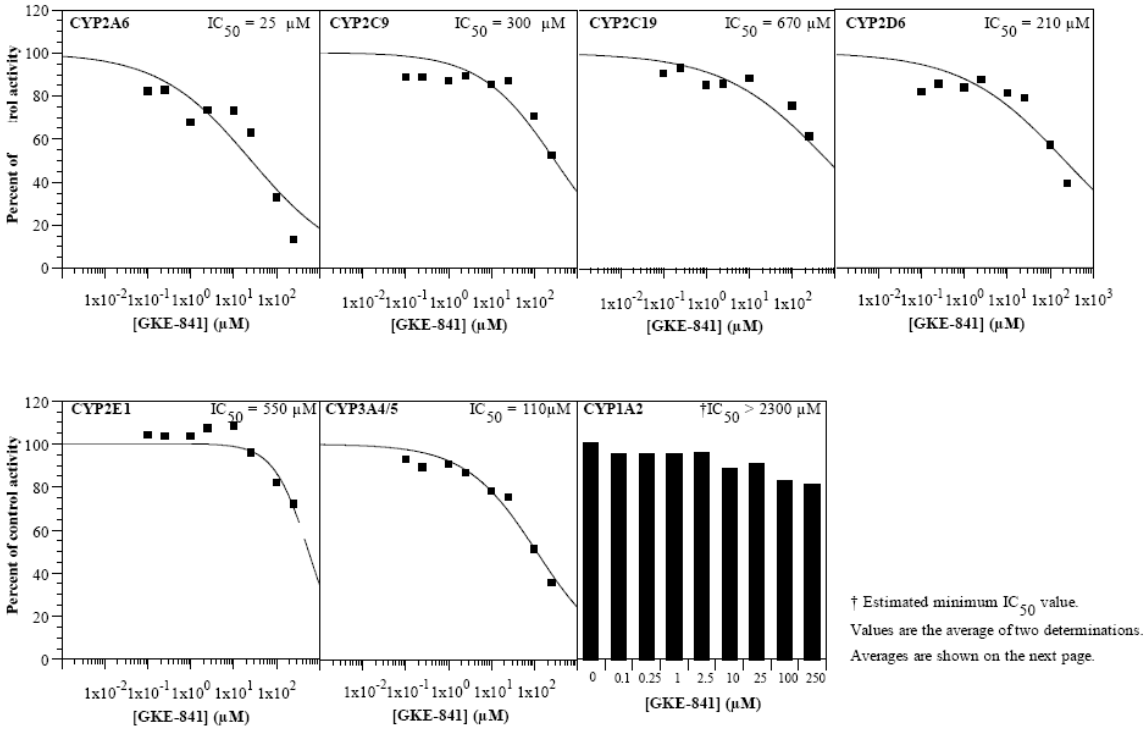


Table 2: Summary of Results: Evaluation of GKE–841 as an inhibitor of human P450 enzymes

Concentrations of GKE–841 studied: 0, 0.1, 0.25, 1, 2.5, 10, 25, 100, 250 µM

Enzyme	P450 Activity	Metabolism-independent IC_{50} (µM)
CYP1A2	7-Ethoxyresorufin *O*-dealkylase	>2300*
CYP2A6	Coumarin 7-hydroxylase	25
CYP2C9	Diclofenac 4′-hydroxylase	300
CYP2C19	*S*-Mephenytoin 4′-hydroxylase	670
CYP2D6	Dextromethorphan *O*-demethylase	210
CYP2E1	Chlorzoxazone 6-hydroxylase	550
CYP3A4/5	Testosterone 6β-hydroxylase	110

* Under the conditions examined, GKE-841 did not inhibit these P450 enzymes. Therefore, the IC_{50} value for inhibition of these P450 enzymes by GKE-841 is greater than 250 µM, which is the highest concentration of GKE-841 examined. Based on the conservative assumption that 10% inhibition of P450 activity by 250 µM GKE-841 could have been masked by experimental error, the IC_{50} value for GKE-841 could be as low as 2300 µM.

- Under similar experimental conditions, the positive controls caused a marked inhibition of the corresponding P450 enzymes.

Conclusions: Under the conditions examined, GKE–841 inhibited CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 activity with IC50 values of 25, 300, 670, 210, 550 and 110 µM, respectively. Little or no inhibition of CYP1A2 was observed at 250 µM GKE–841.

Study FB23000: Retigabine N-glucuronidation and its Potential Role in Enterohepatic Circulation

– This review focused on human results.

Objective:

- To characterize the enzyme kinetics of retigabine N-glucuronide formation in liver microsomes
- To determine the interindividual variability of retigabine N-glucuronide formation *in vitro* in a panel of 16 human livers
- To characterize UGT-glucuronosyltransferases (UGTs) contributing to retigabine N-glucuronidation by inhibition studies and by investigations with heterologously expressed enzymes

Methods:

Liver microsomes: Human liver samples (protein concentration of 10 mg/ml) were from livers of kidney transplant donors or from livers obtained from the (b) (4) .

Human Recombinant UGTs: Insect S19 cell extracts containing expressed UGT1A1, UGT1A3, UGT1A7, UGT1A9 and UGT1A10, UGT1A4, UGT1A6, UGT2B4 and UGT2B7, and UGT2B15. 400 µM of Retigabine was incubated with mixtures containing 100 µg of total protein for 90 minutes at 37°C.

Glucuronidation Assays: 80-400 µM Retigabine dissolved in methanol, incubated with human liver microsomes (protein contents of 40 µg) for 40~80 min at 37°C, stopped by 2 min. For inhibition studies, 330 µM bilirubin was added to the mixture containing 360 µM Retigabine, while 4 mM lamotrigine was added to the mixture containing 40 µM Retigabine.

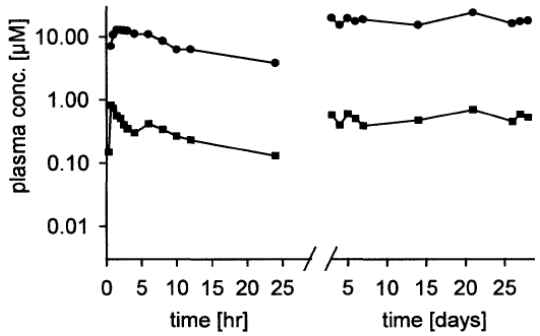
Assay: Formation of Retigabine N-glucuronide *in vitro* in microsomal incubates and *in vivo* in plasma and urine we developed a HPLC method for the simultaneous determination of Retigabine and Retigabine N-glucuronide.

Human plasma: Samples were obtained from Phase 1 study.

Data analysis: Apparent Km and Vmax values were determined with a non-linear least squares fitting program KINETIK 2.4.

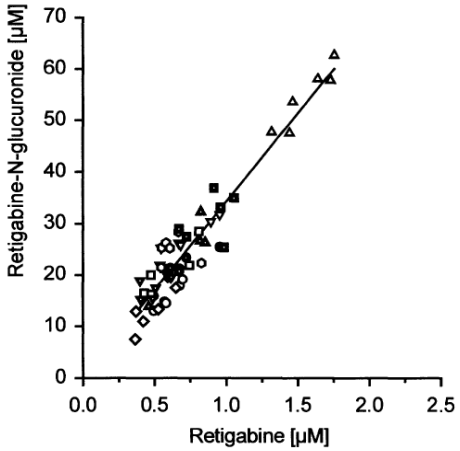
Results and Conclusions:

- Rapid and extensive N-glucuronide formation in human plasama as ear1y as 20 minutes after dosing
- Retigabine and Retigabine N-glucuronide reached the Cmax at 40 min and 1.5 hours, respectively. N-glucuronide concentrations exceeded those of Retigabine by a factor of 24±10 fold, as shown in Figure and Table below.

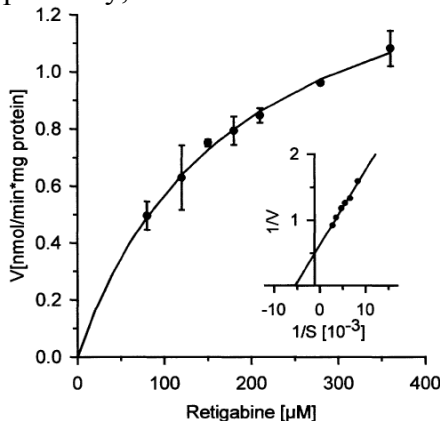


Subject	dose [mg]	Retigabine		Retigabine N-glucuronide		f
		AUC [µM*hr]	$t_{1/2}$ [hr]	AUC [µM*hr]	$t_{1/2}$ [hr]	
1	200	9.8	11.4	238	12.3	24.4
2	600	43.9	10.7	710	8.3	16.2
3	600	39.2	8.0	607	9.9	15.5

- Parallel decline of plasma levels suggested a constant ratio between Retigabine and its N-glucuronide, as shown in Figure below.



- The apparent kinetic constants Km and Vmax for the N-glucuronidation of Retigabine in human liver microsomes were 145±39 µM and 1.2±0.3 nmol*min-1*mg-1protein respectively, as shown in the Lineweaver-Burk plot below.



- The enzyme efficiency (Vmax/Km) was decreasing from dog to human to rat.
- Large interindividual variations in retigabine glucuronidation (up to 5 fold) were observed in human liver microsomes, similar to that in vivo.

- Among 10 different isoenzymes, UGT1A1, UGT1A3, UGT1A4 and UGT1A9 produced Retigabine N-glucuronide, as shown in Table below. UGT1A6, UGT1A7, UGT1A10, UGT2B4, UGT2B7 and UGT2B15 did not catalyze Retigabine-N-glucuronidation.

UGT	Retigabine-N-glucuronidation activity [pmol*min^{-1}*mg protein^{-1}]
UGT1A1	26
UGT1A3	5
UGT1A4	17
UGT1A9	4

- 4 mM Lamotrigine (substrate for UGT1A4) decreased the formation of Retigabine-N-glucuronide in liver microsomes to 21±3 % of control values. Results suggest that UGT1A4 is a major Retigabine N-glucuronosyltransferase *in vivo* and significantly contributes to the enterohepatic cycling of the drug in man.
- 330 µM bilirubin (substrate for UGT1A1 and UGT1A4) decreased the formation of Retigabine N-glucuronide to about 75±7% of control values.
- The apparent Km of Retigabine N-glucuronidation in human UGT1A1 and UGT1A4 was 460 µM and 322 µM, respectively.

Study FB20100: The Effect of Valproic Acid on Retigabine Glucuronidation in Human Liver Microsomes

Objective: To evaluate the effect of valproic acid on retigabine glucuronidation.

Methods: The influence on retigabine metabolism was investigated using incubations of retigabine with human liver microsomes and cofactors for glucuronidation reactions (UDP-glucuronic acid). Microsomal incubations were carried out in 0.1 M TRIS buffer supplemented with 10 mM ascorbic acid and 7 mM $MgCI_2$ at pH 8.0 and 37^{o}C in a shaking incubator. Experiments were started by incubating microsomal protein (200 µg) with varying concentrations of valproic acid (0, 1, 10, 100, 1000 µM), followed by the addition of retigabine (3, 10, 30, 100 µM). Enzymatic reactions were stopped by addition of an equal volume of ice-cold methanol after an incubation time of 40 min. After the denatured protein being removed, supernatants were kept at -25°C until the analysis of retigabine glucuronides. Incubations without valproic acid served as controls. Glucuronides formed from retigabine were quantified by HPLC.

Results: Valproic acid up to 1 mM slightly inhibited the formation of both retigabine glucuronides (RT38 and RT45) (see figure below). Apparent inhibitory constants (Ki) were calculated as 3.5 and 6.6 mM for the inhibition of RT45 and RT38 formation, respectively. These values are at least 5 fold higher than the recommended therapeutic plasma levels of valproic acid (50-100 µg/ml or 350-700 µM).

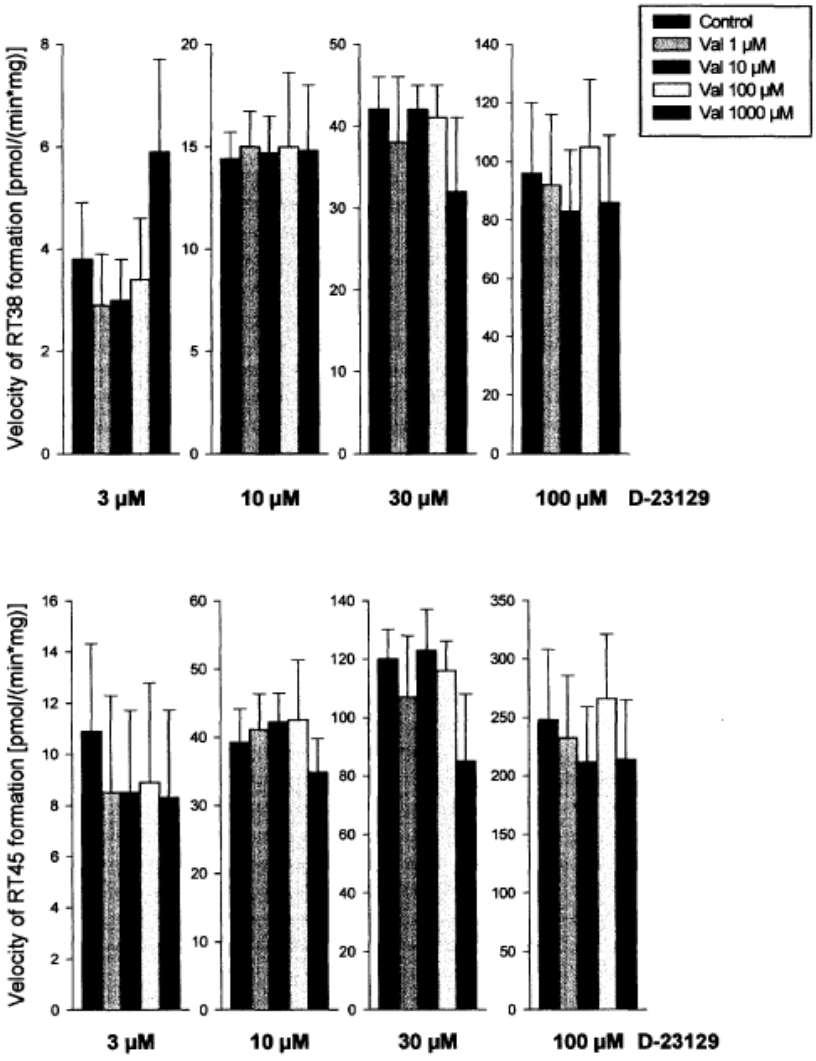


Figure 2: Influence of valproic acid (Val) on the glucuronidation of D-23129 to RT38 (top) or RT45 (bottom) by human liver microsomes (HGW13).

Conclusions: Data generated in this study indicates a weak potential for interactions of valproic acid with retigabine metabolism. However, because of a 5-fold factor between the determined Ki and the therapeutic plasma levels of valproic acid, clinically relevant interactions between these two compounds are not expected to occur.

Study FB20396: *In Vitro* and *In Vivo* Metabolism of D-23129 in Man

Objective: To investigate the main metabolic pathways of D-23129 in man

Methods: The metabolism of D-23129 in healthy volunteers was investigated after single (600 mg) or repeated (400 mg) oral administration in clinical phase I studies and compared with incubation of [14C]D-23129 with human liver slices. Metabolite profiles

were obtained by HPLC. Metabolites from human urine were isolated and characterized by MS, MS/MS and NMR.

Results: The metabolite profiles obtained showed no substantial differences between single and repeated administration. In both cases in urine and plasma samples two metabolites at retention times 112 min (M1) and 123 min (M2) were detected in addition to D-23129. M1 and M2 from human urine were isolated by semipreparative HPLC and characterized by electrospray MS, MS/MS and H-NMR. For metabolite M1 an N-glucuronide structure of the unchanged D-23129 was confirmed. The primary amino group is the site of glucuronidation. The structure of M2 was found to be identical to the reference substance AWD21-360 (acetyl-derivative). M2 is probably formed by decarboxylation of the urethane structure in D-23129 and subsequent acetylation of the retaining aromatic amino group. Based on NMR results, it is suggested that M2 exists in two conformational forms at room temperature. The approximate ratio between these was estimated to be 90:10 at room temperature. *In vitro* incubations of [14C]D-23129 with human liver slices predicted chromatographically the same metabolites as indeed were later found *in vivo* in man. Results from *in vitro* and *in vivo* studies clearly indicate that N-glucuronidation and N-acetylation are the major metabolic pathways of D-23129 in man. Results reported here revealed that man is more similar to rats than to dogs as regards metabolism of D-23129. But no reliable indications were found in human samples for the appearance of N-dealkylation of the benzylic side chain, which is a further major metabolic pathway in rats. A summary of the proposed metabolic pathways of D-23129 in rats, dogs and man is shown below.

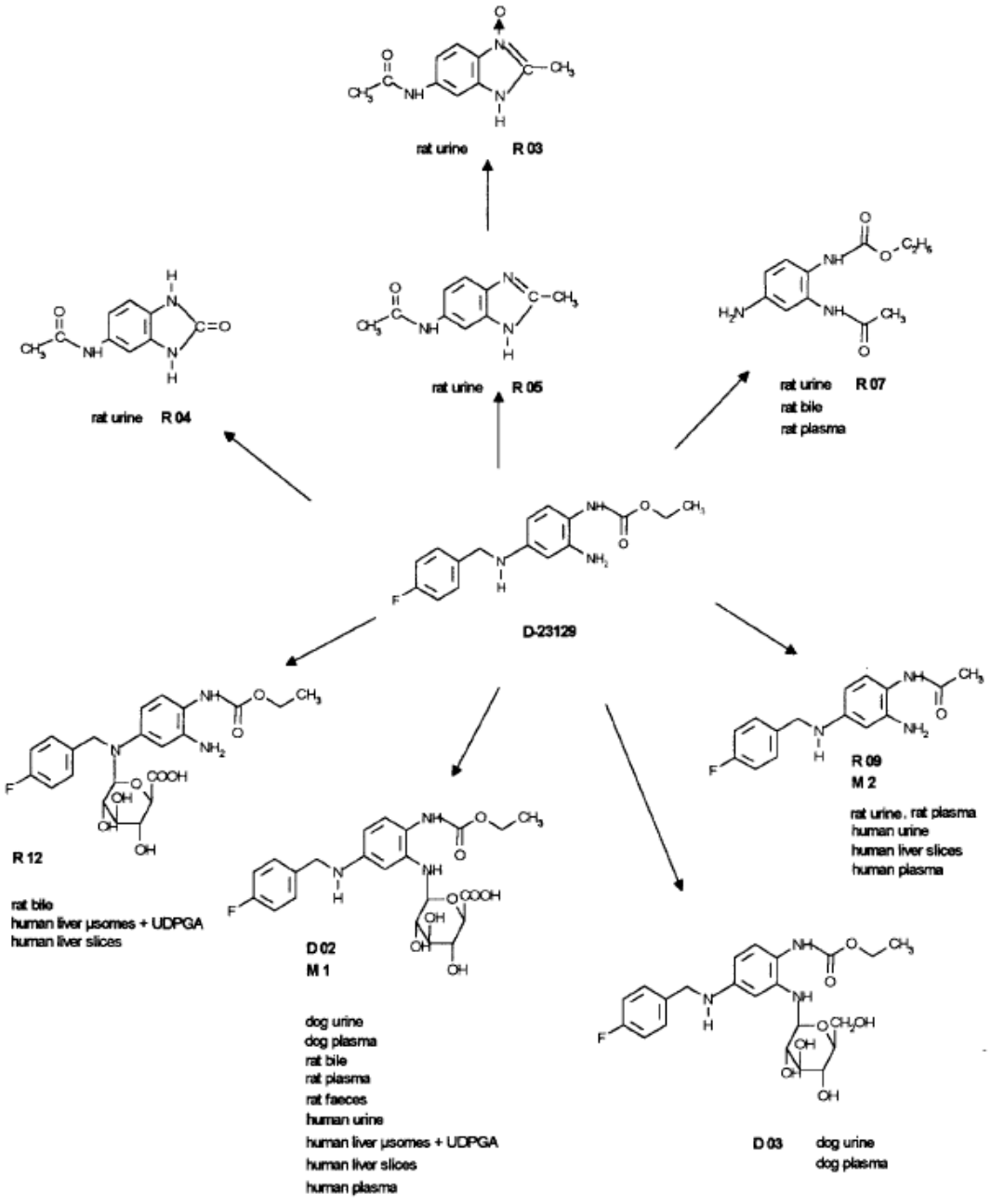


Figure 17: Synoptic representation of metabolic pathways of D-23129, which were proposed for rats (R), dogs (D) and man (M). The structure of metabolite R 04 is valid and was confirmed by comparison with the identical compound. The tentative structures for R 03, D 02, M 1 and M 2 are supported by MS, MS/MS and NMR findings. All other structures are proposed on the basis of MS and MS/MS results.

Conclusions: D-23129 is extensively metabolized in man after oral dosing. The major metabolic pathways are N-glucuronidation and N-acetylation. Preliminary investigations did not show the involvement of the N-acetyltransferase type genetic polymorphism of drug metabolism.

Study FB20399: The Effect of Imipramine or Lamotrigine on Retigabine Glucuronidation in Human Liver Microsomes

Objective: To investigate the effects of imipramine or lamotrigine on retigabine glucuronidation and estimate the metabolic interaction potential of these substances *in vivo*

Methods: Biotransformation of retigabine was studied in incubations with human liver microsomes and cofactors for glucuronidation reactions in dependence of increasing lamotrigine or imipramine concentrations. Incubations without an inhibitor served as controls. Experimental procedures are described below.

Retigabine Glucuronidation:
Microsomal incubations were carried out in 0.1 M TRIS buffer supplemented with 10 mM ascorbic acid and 7 mM MgCI2 at pH 8.0 and 37°C in a shaking incubator. Retigabine (final concentrations 3-360 µM) was added to 40 µg or 200 µg microsomal protein in a final volume of 200 µl. (b) (4) Formation of both metabolites (RT38 and RT45) in assays with 360 µM retigabine was linear for protein concentrations up to 1.0 *mg/ml* and for incubation times from 10 to 60 min.

Inhibition Assays:
Inhibition of retigabine glucuronidation by lamotrigine was investigated in two parallel incubations at varying substrate concentrations (50, 100, 300 µM) as well as varying inhibitor concentrations (0, 1, 10, 100,250,500 µM). Lamotrigine could be used only in concentrations up to 500 µM because of interference at higher concentrations with the retigabine metabolites in assay. The inhibition potential of imipramine at 0, 1, 10, 100 and 1000 µM was investigated in a first experiment with 50, 100 and 300 µM retigabine and two parallel incubations for each concentration. A second experiment was performed using retigabine concentrations of 3, 10, 30 and 100 µM. Experiments were performed by incubating microsomal protein (40 µg or 200 µg) with cofactors and UDPGA for 5 min at *37*°C in the presence of inhibitor. The reaction was stopped after the incubation time of 40 min. Apparent inhibitory constants (Ki) were calculated using KINETIK 2.4, a nonlinear regression data analysis program.

Results: In the presence of UDP-glucuronic acid human liver microsomes metabolized retigabine to two distinct glucuronides (RT38 and RT45). The mean apparent metabolic constants Vmax and Km of 0.200 nmol/(min*mg) and 492 µM, respectively, were

estimated for the formation of RT38. RT45 was formed with a mean Vmax of 0.645 nmol/(min*mg) and the mean Km for this reaction was calculated as 333 µM.

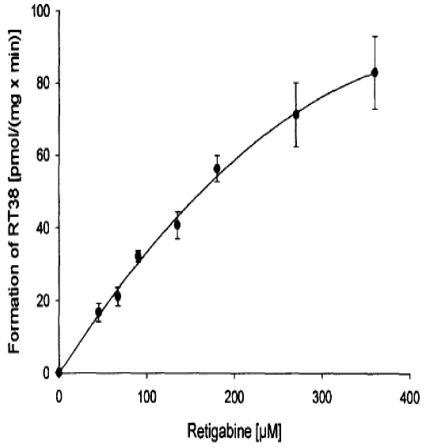


Figure 2: Michaelis-Menten plot for the formation of the retigabine glucuronide RT38 by human liver microsomes (HGW13).

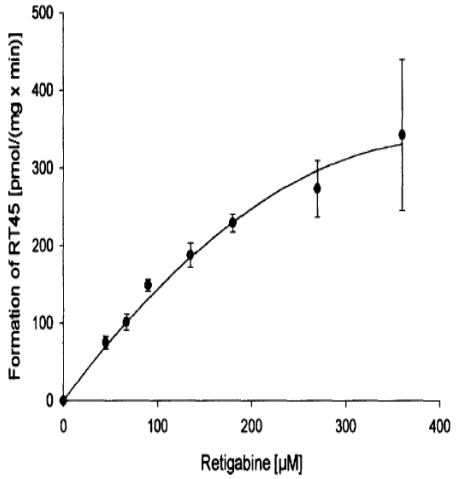


Figure 4: Michaelis-Menten plot for the formation of the retigabine glucuronide RT45 by human liver microsomes (HGW13).

- Lamotrigine in concentrations up to 500 µM (approximately 50-fold therapeutic plasma level) exhibited no inhibitory effect on the formation of both retigabine glucuronides.
- Imipramine caused a slight depression of RT38 as well as RT45 formation with calculated Ki values of 2.4 mM and 1.6 mM, respectively. These values are over 1000 fold higher than imipramine plasma levels in clinically effective doses (100-300 ng/ml, Benet 1996).

Conclusions: From these *in vitro* data it can be assumed that no clinically relevant interactions occur between retigabine and either imipramine or lamotrigine.

Study FB21999: In Vitro Permeability of Retigabine (D-23129) through Caco-2 Monolayers (Part 1)

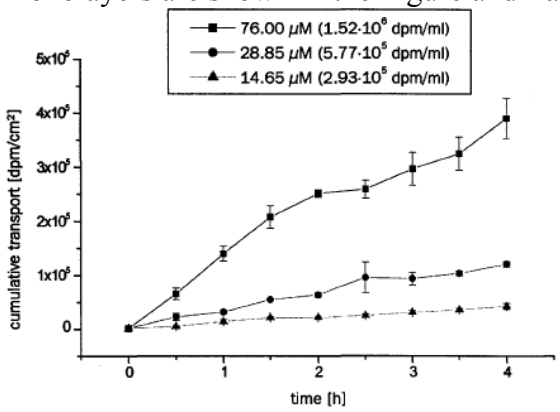
Objective:
- To investigate the permeability of D-23129 (retigabine) through Caco-2 monolayers used as an in vitro model for intestinal drug absorption
- To obtain basic information about retigabine transport from apical to basolateral side and the suitability of the Caco-2 cell monolayers

Methods: Caco-2 cells were cultivated in DMEM (pH 7.4) and were subsequently seeded into culture plates at a density of $6\text{-}10^4$ cells/m2 and were used for the transport studies with 14C-retigabine after 3 weeks to form confluent differentiated monolayers. The transport data obtained for retigabine were compared with the well characterized transport marker [3H]-mannitol and 3 standard transport markers, fluorescein, atenolol, and propranolol, for the quality control. The TEER values were documented during three

weeks of cultivation in Transwell™ plates and before each sampling. Three sets of experiments were conducted in triplicates under 37 °C and at pH 7.4 for KRB solution. Retigabine was applied to apical side of Caco-2 cells in 3 different concentrations (76.00, 28.85, and 14.65 μM). Studies were conducted in triplicates.

Results:

1. Results of concentration-dependent AP->BL transport of retigabine across Caco-2 monolayers are shown in the Figure and Table below.



Conc. [μM]	P_{app} [cm/s]
76.00	$1.64 \cdot 10^{-5}$
28.85	$1.43 \cdot 10^{-5}$
14.65	$9.45 \cdot 10^{-6}$

2. Similar cumulative transport values (0.95×10^{-5} cm/s - 1.64×10^{-5} cm/s) compared with that (1.24×10^{-5} cm/s - 2.01×10^{-5} cm/s) using cell-free filter suggest a rapid transport of retigabine across the Caco-2 cell monolayer.
3. Retigabine recoveries after the transport study were ≥80% of the initial doses.

Conclusions:

- Transport of retigabine across Caco-2 cell monolayers was rapid, suggesting that intestinal absorption is not likely the limiting factor in retigabine uptake.
- Based on the concentration-dependent AP->BL transport, it cannot be conclude whether the transport of retigabine involves an active or passive mechanism or a mixture of both.

Study FB22999: Mechanistic Investigations of ^{14}C-Retigabine Transport through Caco-2 Monolayers

Objective: To investigate the influence of active transport mechanisms on the permeability of D-23129 (retigabine) through Caco-2 monolayers

Methods:

Caco-2 cells were cultivated in DMEM (pH 7.4) and were subsequently seeded into culture plates at a density of $6\text{-}10^4$ cells/m2. Cell passages 16 and 19 were used for the transport studies with 14C-retigabine. Quality control of the cell passage included TEER documentation during three weeks of cultivation in Transwell™ plates as well as transport of three standard markers (fluorescein, atenolol and propranolol) across the

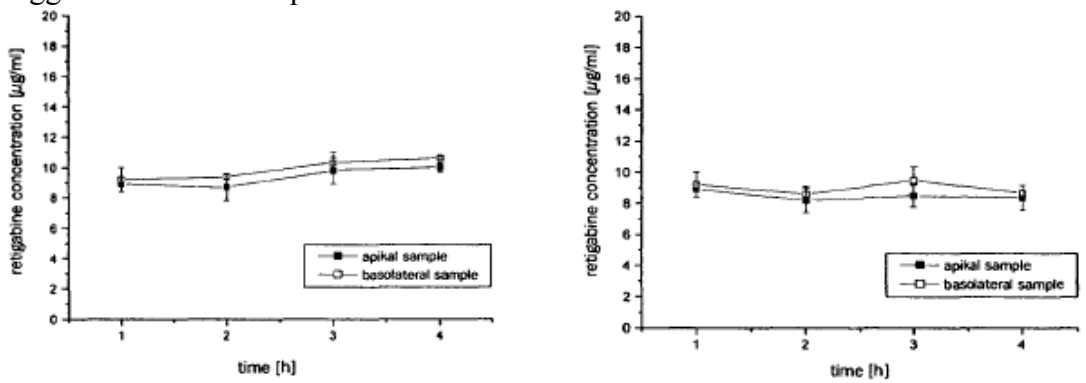
confluent monolayers. Three sets of experiments were conducted in triplicates under 37 °C and at pH 7.4, with TEER measured before each sampling.

- Bidirectional transport of regitabine (30 µL) from the apical (0.5mL) to the basolateral side (1.5mL) and vice versa of Caco-2 monolayers
- Bidirectional transport of regitabine with both compartments (apical and basolateral) were filled with retigabine solutions of the same concentration.
- The effect of verapamil (100 µL) and doxorubicin (172 µL), inhibitors of P-glycoprotein

Results:

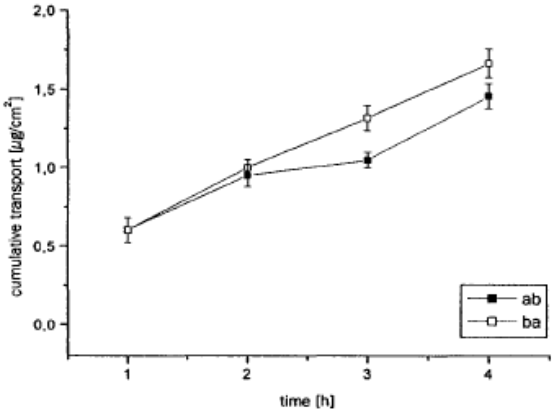
1. Transport of retigabine across Caco-2 monolayers:

As shown in the Figure below, the retigabine concentration in the apical and basolateral compartment remained constant during the entire experiment. The results thus do not suggest an active transport mechanism.



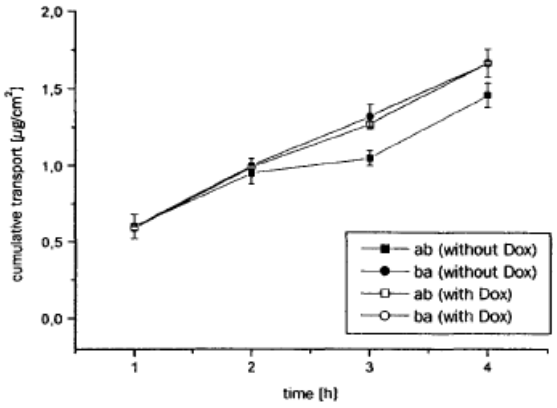
2. Retigabine applied to one compartment:

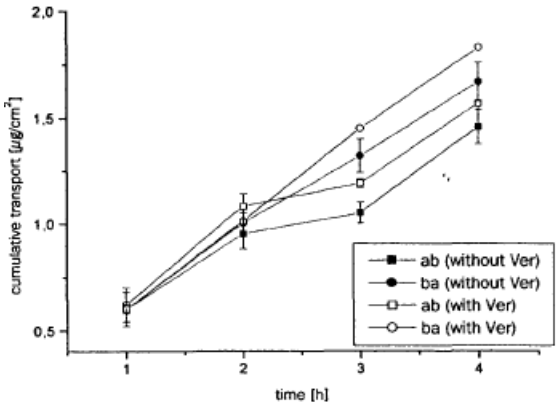
Results of retigabine transport across Caco-2 monolayer are shown in the Figure (expressed as mean ± SD) and Table below.



Transport direction	P_{app} [cm/s]	c_0 [µg/ml]	c_0 [µM]
apical-basolateral	$1.0 \cdot 10^{-5}$	7.3	24.1
basolateral-apical	$1.4 \cdot 10^{-5}$	7.4	24.4

3. Results of inhibition of retigabine transport with doxorubicin (a P-gp substrate) and verapamil (a P-gp inhibitor) are shown in the Figures and Table below:





Transport direction	P_{app} [cm/s]	c_0 [µg/ml]	c_0 [µM]	Inhibitor	c_0 (Inhibitor) [µM]
apical-basolateral	$1.0 \cdot 10^{-5}$	7.3	24.1	-	-
basolateral-apical	$1.3 \cdot 10^{-5}$	7.4	24.4	-	-
apical-basolateral	$1.2 \cdot 10^{-5}$	7.7	25.2	doxorubicin	172
basolateral-apical	$1.2 \cdot 10^{-5}$	8.0	26.3	doxorubicin	172
apical-basolateral	$1.1 \cdot 10^{-5}$	7.4	24.4	verapamil	100
basolateral-apical	$1.4 \cdot 10^{-5}$	8.0	26.2	verapamil	100

Conclusions:

- The results obtained from the study do not suggest an active carrier interfering with retigabine ermeation through Caco-2 monolayers. Passive diffusion was shown to be the primary driving force for retigabine permeation.
- Neither doxorubicin nor verapamil showed an inhibitory effect on retigabine transport.
- Doxorubicin transport from the basolateral to the apical side, however, decreased in the presence of retigabine, while its transport in the opposite direction was not influenced. The higher transport velocity of doxorubicin when co-applied with retigabine might, however, correlate with a decreased integrity of the monolayer indicated by the decrease of TEER.

Study FB23099: *In vitro* Metabolism of [14C] Retigabine ([^{14}C] D-23129) in Caco-2 Cell Cultures

Objective: To obtain basic information about the metabolic stability of D-23129 in assays with Caco-2 cell monolayers.

Methods: The *in vitro* metabolism of retigabine (D-23129) was investigated in assays with Caco-2 cell monolayers. These cells grew on filter supports which were placed between an apical and basolateral chamber. The compound was applied to the apical chamber and permeated through the Caco-2 monolayer to the basolateral chamber driven by concentration gradient. In the control assay no cells grew on the filter support.

Samples were taken from the chambers after an incubation time of four hours and were analyzed by radio HPLC.

Results: No metabolism of D-23129 was found in incubations over 4 hours with Caco-2 cells (Table 1). The same pattern of peaks was seen in all samples from assays with and without Caco-2 cells. The sponsor checked the stability of the radio active compound in Krebs-Ringer buffer (KBR). A decrease of the radiolabeled parent compound to 85 % after an incubation time of 24 hours was observed (Table 2). Mass spectroscopic investigations suggest the formation of (b) (4) under these conditions, which would most likely account for the loss of parent compound.

Comment: Caco-2 cell model is not known to be a good model for studying the in vitro metabolism in view of its limited expression in metabolic enzymes. Results of this study are expected.

Table 1: Results from *in vitro* incubations of D-23129 (90 µM) with Caco-2 cell monolayers. Incubation time 4 hours.

	Rel. Peak area [%] *)						
Retention times [min]	RT55	RT85	RT131	D-23129 RT149	RT153	RT168	Sum of others
Apical chamber with Caco-2 cells (n = 2)	1.5	0.4	1.9	95.5	0.4	0.3	0
Basolateral chamber with Caco-2 cells (n = 3)	2.3	1.0	2.3	91.0	0.7	1.0	1.7
Apical chamber without cells (n = 3)	0.9	0.9	1.4	94.4	0.3	1.1	1.0
Basolateral chamber without cells (n = 3)	3.1	0.9	1.7	90.2	1.4	1.8	0.9

*) 100 % equals the sum of all peak areas in the respective radio chromatogram.

Table 2: Results from incubations of D-23129 (90 µM) in Krebs-Ringer Buffer without Caco-2 cells for different incubation times.

	Rel. Peak area [%] *)						
Retention times [min]	RT55	RT85	RT131	D-23129 RT149	RT153	RT168	Sum of others
Incubation time 0 hours	0	0	0	100	0	0	0
Incubation time 24 hours	8.7	1.2	2.1	84.9	2.1	0	1.0

*) 100 % equals the sum of all peak areas in the respective radio chromatogram.

4.4.5 General Biopharmaceutics

4.4.5.1 Bioavailability and Bioequivalence Studies

306A1-123: Absolute and Relative Bioavailability of Retigabine IR Capsules in Healthy Male Subjects

Objectives:
To investigate absolute and relative bioavailability of retigabine immediate release (RGB IR) capsules

Study Design	Single-center, single-dose, open label, randomized, crossover study of 3 different dosage forms under fasting conditions
Study Population	N=12 Healthy male subjects Age: 18-45 years Gender: 12 males Race: 12 Caucasian
Treatment Group	crossover study (1 trt group, 3 trt periods)
Dosage and Administration*	1. RGB IV (50 mg retigabine diluted in 50 ml 0.9%saline)* 2. RGB IR (Retigabine 100 mg IR capsule, 2x100mg) 3. RGB OS (oral solution of retigabine in 200 ml of apple juice)
PK Sampling: plasma	1. RGB IV: pre-dose, 5 and 10 min after start of infusion, end of infusion, and 1, 3, 5, 10, 15, 20, 30, 45 min, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48 h post inf. 2. RGB IR and RGB OS: pre-dose; 20, 40 min, 1 h, 80 min, 100 min, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72 h post dose
PK Sampling: Urine	0-2, 2-4, 4-8, 8-12, 12-24, 24-48 h post dose
PK Sampling: Feces	none
Analysis	Solid phase extraction, HPLC- MS/MS method LOQ in plasma for retigabine 1 ng/ml LOQ in plasma for monoacetyl metabolite 2.5 ng/ml
PK Assessment	**In plasma**: Retigabine: AUC_{0-t}, AUC_{0-inf}, $C_{max,}$ $t_{max,}$ Vz, Vss, $t_{1/2}$, MRT, $F_{abs,}$ F_{rel} (bioavailability of the solid dosage form relative to the oral solution) Monoacetyl metabolite AWD 21-360: AUC_{0-t}, AUC_{0-inf}, $C_{max,}$ $t_{max,}$ $t_{1/2}$, MRT **In urine**: cumulative amount and renal clearance (if possible) of parent retigabine and its monoacetyl metabolite AWD 21-360
Safety Assessment	Vital signs, adverse events, ECG, laboratory tests
PD Assessment	None

* RGB IV: infusion rate 200 ml/min
RGB IR: 2 capsules retigabine IR with 200 ml tap water of room temperature
RGB OS: 200 ml oral solution of (180 mg) retigabine

Pharmacokinetic Results:

Assay Performance during the analysis of the samples:
The quality control samples for 2 of the 18 analytical batches for retigabine in plasma (batches 014 and 019) and 1 of the 18 analytical batches for AWD 21-360 in plasma (batch 023) did not meet the following acceptance criteria outlined in the Bioanalytical Method Validation Guidance:
The QC samples in duplicate at three concentrations should be incorporated in each assay run At least four of every six QC samples should be within 15% of their respective nominal value. Two of the six QC samples may be outside the 15% of their respective nominal value, but not both at the same concentration.
Two QC samples both at the same concentration (near the LLOQ) were more than 15% of their respective nominal value.
The QC samples of 2 of the 6 analytical batches for urine did not meet the above acceptance criteria for both analytes (batches 001 and 002). Two QC samples both at the same concentration at two or even three concentration levels were outside the 15% of their respective nominal value. Analyses for these batches were not repeated.
Therefore, the urine PK results are considered unreliable and will not be reviewed.

Mean (95% CI) plasma pharmacokinetics of retigabine and its monoacetyl metabolite AWD 21-360 are presented below:

Pharmacokinetic Parameters of Retigabine (D-23129) in Plasma

Trtm (n=12)	$Mean_{geo}$ (95% CI_{ln} LL - UL)						
	C_{max} [ng/ml]	AUC [ng·h/ml]	$AUC_{tlast-inf}$ [%]	CL [ml/min/kg]	V_z [l/kg]	V_{ss} [l/kg]	$MRT_{(IV\ or\ oral)}$ [h]
RGB IV	975 (771-1233)	1102 (1022-1188)	3.25 (1.96-5.39)	9.49 (8.67-10.4)	7.85 (6.33-9.74)	2.96 (2.61-3.36)	5.20 (4.55-5.94)
RGB OS	612 (514-729)	2313 (2026-2642)	0.69 (0.54-0.87)	-	-	-	7.72 (6.96-8.57)
RGB IR	499 (361-688)	2661 (2080-3404)	0.94 (0.57-1.56)	-	-	-	11.2 (9.71-12.9)

	Median (min - max)	
	t_{max} [h]	$t_{1/2}$ [h]
RGB IV	0.25 (0.17-0.33)	9.41 (6.10-18.1)
RGB OS	0.50 (0.33-1.00)	7.19 (5.67-10.11)
RGB IR	0.67 (0.33-4.00)	8.72 (7.02-13.4)

Pharmacokinetic Parameters of AWD21-360 in Plasma							
Trtm (n=12)	$Mean_{geo}$ (95% CI_{ln} LL - UL)					Median (min - max)	
	C_{max} [ng/ml]	AUC [ng·h/ml]	$AUC_{tlast-inf}$ [%]	HVD [h]	MR	t_{max} [h]	$t_{1/2}$ [h]
RGB IV	66.7 (59.0-75.4)	745 (632-880)	5.70 (4.33-7.50)	8.38 (7.11-9.88)	1.48 (1.30-1.69)	1.75 (0.42-2.25)	7.16 (5.42-8.80)
RGB OS	280 (248-317)	2899 (2421-3471)	1.96 (1.38-2.79)	7.16 (5.90-8.68)	0.80 (0.74-0.86)	2.25 (1.00-3.00)	7.10 (5.38-8.42)
RGB IR	236 (189-296)	3316 (2626-4187)	2.01 (1.44-2.82)	9.70 (8.38-11.2)	0.80 (0.74-0.87)	2.50 (0.67-4.00)	8.16 (6.60-10.5)

Bioavailabilities (absolute and relative) of retigabine and AWD21-306 were calculated for the different dosage forms on an intra-subject basis. The results are summarized in the table below. Due to the different single doses administered the calculation of bioavailabilities required dose-normalization. For RGB OS an adjusted dose of 180 mg was taken, to account for a (b) (4) degradation in apple juice between preparation of the oral solution and administration, demonstrated by an investigation of the stability of a solution of retigabine lyophilized in apple juice (200mg in 200 ml).
Dose- normalization was possible because dose-proportional kinetics has been demonstrated for oral doses of retigabine from 25 – 600 mg.

Absolute and Relative Bioavailability $Mean_{geo}$ (95% CI_{ln} LL - UL)			
Retigabine (D-23129)			AWD21-360
$F_{abs, OS}$	$F_{abs, IR}$	$F_{rel, IR}$*	$F_{rel, IR}$*
58.3* (51.7-65.8)	60.4 (48.6-75.0)	104 (81.0-132)	103 (84.1-126)

*: relative to RGB OS

- The mean absolute bioavailability was about 60% for both oral solution and the immediate release capsule.
- The exposure to retigabine and the monoacetyl metabolite AWD21-360, based on AUC comparison, was nearly the same after the oral solution and after the immediate release capsule. Relative bioavailability of the immediate release capsule was about 100% relative to the oral solution.
- Average apparent terminal plasma half-lives of retigabine and AWD21-360 were both 7-9 h.
- Terminal plasma half-life for retigabine was in the same order of magnitude after intravenous and oral administration. This means that the terminal part of the plasma concentration-time profile is not absorption rate limited.

Safety Results:

- Single dose of 200 mg retigabine as immediate release capsules or as an oral solution were well tolerated in healthy men.
- An intravenous dose of 50 mg retigabine administered as a 15 min infusion was considered to be close to the maximum tolerated dose in healthy male subjects. There were 3 AEs with a 'severe' intensity: vertigo in 2 subjects followed by

fatigue in one of them lasting for more than one hour. These AEs occurred with RGB IV treatment. Vertigo was related to peak plasma concentrations.

306A1-106-GE: Food Interaction Study Of Retigabine (D-23129) In Healthy Volunteers Of Both Sexes

Objectives:
To determine the effects of fasting and a high fat breakfast on bioavailability and pharmacokinetics of oral single doses; to investigate sex-related differences regarding safety, tolerability, and pharmacokinetics.

Study Design	Single-center, single-dose, open label, randomized, 2-period, 2-sequence cross-over
Study Population	N=24 Healthy male and female subjects Age: 18-40 years Gender: 12 males, 12 females Race: no information
Treatment Group	crossover study (1 trt group, 2 trt periods)
Dosage and Administration*	2 capsules (2x100 mg) on two occasions (fasting or fed) separated by a wash-out period of at least 7 days
PK Sampling: plasma	predose and 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36 and 48 h post dose
PK Sampling: Urine	none
PK Sampling: Feces	none
Genotyping	For the determination of the individual pNAT and CYP 2 D6 genotypes (pNat for acetylation, CYP 2D6 for oxidative metabolic pathways) of the subjects whole blood samples were drawn.
Analysis	Solid phase extraction, HPLC- MS/MS method LOQ in plasma for retigabine 1 ng/ml LOQ in plasma for monoacetyl metabolite 2.5 ng/ml
PK Assessment	Retigabine and metabolite AWD 21-360: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, $t_{1/2}$
Safety Assessment	Vital signs, adverse events, ECG, laboratory tests
PD Assessment	None

*Fasted, after a 10 hr fast
Fed, within 3 min after a high fat breakfast

Pharmacokinetic Results:

Assay Performance during the analysis of the samples:
The quality control samples for 2 of the 7 analytical batches for retigabine in plasma (batches B02 and B08) and 4 of the 7 analytical batches for AWD 21-360 in plasma (batches B02, B03, B04 and B08) did not meet the following acceptance criteria outlined in the Bioanalytical Method Validation Guidance:
The QC samples in duplicate at three concentrations should be incorporated in each assay run. At least four of every six QC samples should be within 15% of their respective nominal value. Two of the six QC samples may be outside the 15% of their respective nominal value, but not both at the same concentration.

In this study QC samples at 4 concentration levels were injected in some of the analytical batches in duplicate, while in other analytical batches the QC samples were injected in triplicate or quadruplicate.
For retigabine: in batch B02 all four QC samples at one concentration level (highest) were more than 15% of their respective nominal value. For batch B08 three out of four QC samples at one concentration level (lowest) were more than 15% of their respective nominal value.
For AWD 21-360 in batch B02 three to four (out of four) QC samples at all concentration levels were more than 15% of their respective nominal value. This batch should have been re-run. In batches B03 and B04 three to four (out of four) QC samples at two concentration levels did not meet the acceptance criteria. In B08 three (out of four) QC samples at one concentration level did not meet the acceptance criteria. – Although the assay performance was not entirely satisfactory, results of this study will provide only the supportive information for the pivotal food effect study VRX-RET-E22-104.

The results of genotyping (number of subjects for the predicted phenotype) are summarized in the following table:

Males				**Females**			
Nat 2		Cyp2 D6		Nat 2		Cyp2 D6	
fast	slow	extensive	poor	fast	slow	extensive	poor
6	6	12	--	7	5	11	1

The PK results of retigabine and AWD 21-360 are summarized below:

			AUC [ng·h·ml^{-1}]					
Sex	Statistics		D-23129			AWD21-360		
n			fed	fasted	ratio	fed	fasted	ratio
Males	$Mean_{geo}$		4032.3	4293.2	0.94	5698.3	5853.0	0.97
n = 12	CI_{ln} 95%:	lower	3406.2	3645.4	0.86	4780.3	4958.7	0.88
		upper	4773.6	5056.2	1.02	6792.6	6908.7	1.07
Females	$Mean_{geo}$		3913.6	4496.7	0.87	5135.1	5162.9	0.99
n = 12	CI_{ln} 95%:	lower	3331.4	3773.1	0.79	4529.7	4450.1	0.93
		upper	4597.7	5359.2	0.96	5821.4	5989.8	1.06
All	$Mean_{geo}$		3972.5	4393.8	0.90	5409.4	5497.1	0.98
n = 24	CI_{ln} 95%:	lower	3567.9	3933.3	0.85	4886.2	4945.0	0.93
		upper	4423.0	4908.2	0.96	5988.6	6110.9	1.04

C_{max} [ng/ml]							
Sex	Statistics		D-23129			AWD21-360	
n			fed	fasted	ratio	fed	fasted	ratio
Males	$Mean_{geo}$		620.2	543.8	1.14	474.2	364.8	1.30
n = 12	CI_{ln} 95%:	lower	494.7	407.3	0.88	425.3	305.1	1.11
		upper	777.5	726.0	1.48	528.7	436.3	1.52
Females	$Mean_{geo}$		491.1	578.8	0.85	465.2	399.5	1.16
n = 12	CI_{ln} 95%:	lower	418.2	440.3	0.62	412.7	323.6	0.96
		upper	576.7	760.9	1.17	524.3	493.2	1.41
All	$Mean_{geo}$		551.9	561.0	0.98	469.6	381.8	1.23
n = 24	CI_{ln} 95%:	lower	481.2	467.0	0.81	435.9	335.7	1.10
		upper	633.0	674.0	1.20	506.0	434.1	1.38

The fed/fasted ratios for the pharmacokinetic parameters AUC and Cmax were approximately 1, thus excluding a relevant effect of a high fat meal on these parameters when the two groups (male and female) were combined. However the 95%CI suggests a food effect when these groups were considered separately.
tmax was significantly delayed by about 2 hours under fed conditions.

t_{max} [h]							
Sex	Statistics	D-23129			AWD21-360		
n		fed	fasted	Δt_{max}	fed	fasted	Δt_{max}
Males	Median	2.25	0.83	1.42	3.54	2.50	1.00
n = 12	Min	0.33	0.33	-0.33	2.00	1.00	-3.00
	Max	6.00	2.50	5.33	6.00	6.00	5.00
Females	Median	4.00	1.25	3.00	6.00	2.25	2.50
n = 12	Min	2.50	0.33	1.50	3.00	1.00	0.50
	Max	6.00	3.00	5.33	6.00	4.00	5.00
All	Median	4.00	1.25	2.00	4.00	2.50	1.25
n = 24	Min	0.33	0.33	-0.33	2.00	1.00	-3.00
	Max	6.00	3.00	5.33	6.00	6.00	5.00

An ANOVA was performed for an investigation of a possible meal-effect or sex-effect on pharmacokinetics: logarithmic model (ratios) incl. factors SEQ (sequence: fed/fasted or fasted/fed), PER, SEX, TRT (treatrnent: fed or fasted), SEX TRT, SUB(SEQ SEX) as random factor.
For AUC and Cmax, the 90%-CI_{ANOVA} was calculated and summarized below:

Parameter	CI lower	Point estimate 1)	CI upper
AUC D-23129	85.8%	90.4%	95.3%
AUC AWD21-360	94.1%	98.4%	102.9%
C_{max} D-23129	83.5%	98.4%	115.9%
C_{max} AWD21-360	111.7%	123.0%	135.4%

1) ratios for AUC and C_{max}

Note: It is not clear which AUC (AUC_{0-t} or AUC_{0-inf}) was used for the comparisons.

The 90% confidence intervals were included within the boundaries of 80% - 125% for AUC and 70% - 143% for Cmax.
Note: It appears that there is a food effect based on Cmax of the metabolite. Cmax of the metabolite was increased 23% after high fat meal.

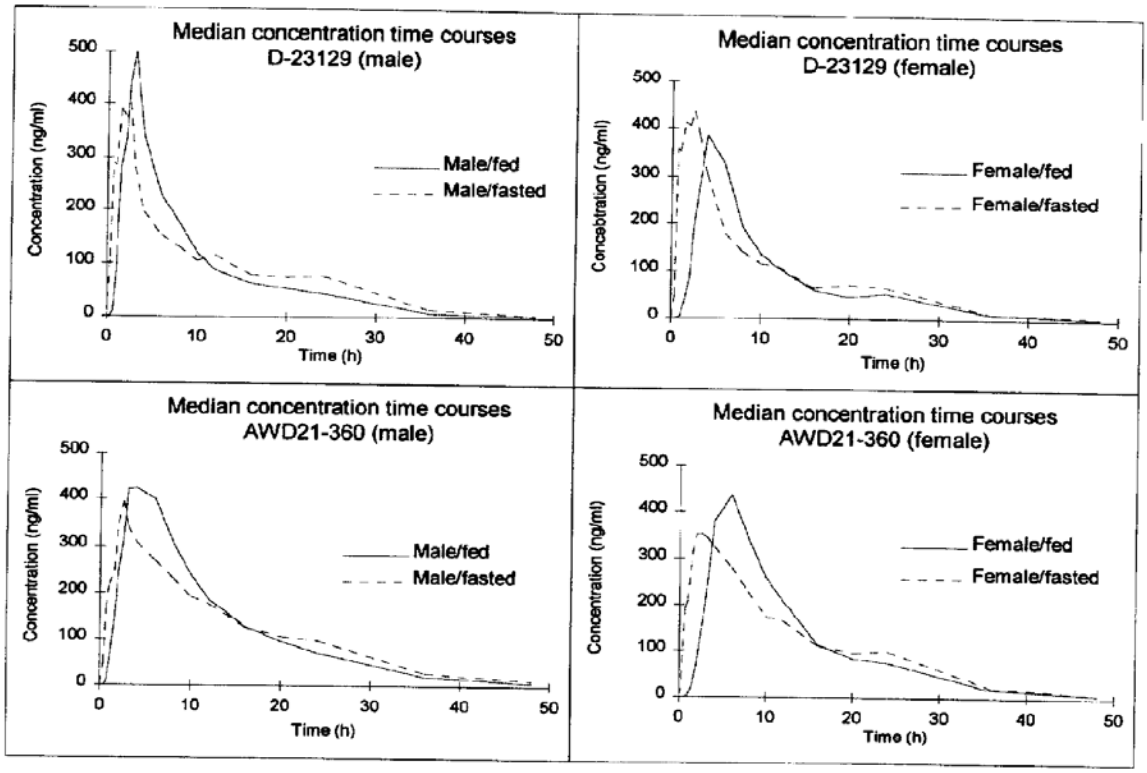


Fig PK 2: Median concentration time courses of D-23129 and AWD21-360 (fed / fasted)

Median plasma concentrations in males and females after single oral administration of 200 mg retigabine

No slow acetylator effect was detected in this study.

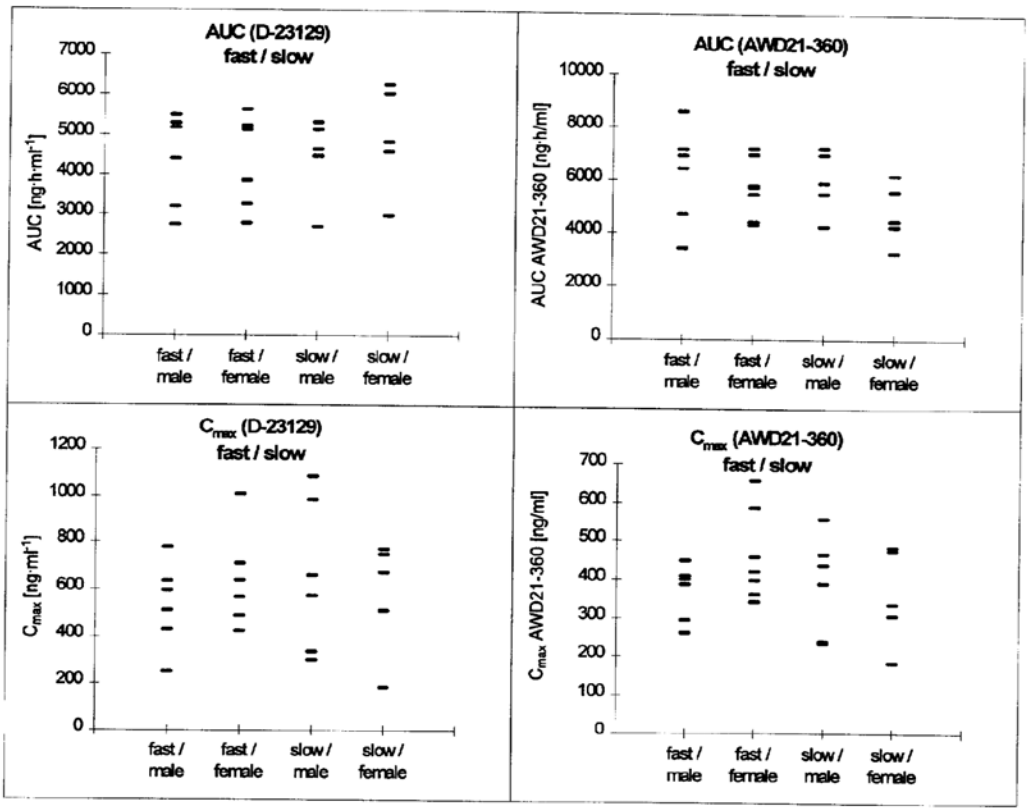


Fig PK 4: Values of AUC and C_{max} with acetylator phenotype predicted from genotyping results

Safety Results:

- Single oral dose of 200 mg retigabine as immediate release capsules were well tolerated in healthy men and women. No serious or unexpected adverse reaction occurred.
- The most common adverse events were fatigue and headache. All subjects completed the study as planned.

VRX-RET-E22-104: Comparative, Randomized, Open-Label, Single-Dose, 2-way Crossover Food Effect, Safety and Tolerability Study of a 400-mg Dose of the Retigabine Market Image Tablet in Healthy Adult Male Subjects

Objectives:

Primary:

To assess the effect of food on the pharmacokinetics of the retigabine 400-mg Market Image tablet formulation, following a single dose in healthy adult male subjects.

Secondary:

To assess the safety and tolerability of the retigabine 400-mg Market Image tablet formulation after a single dose in healthy adult male subjects.

Study Design	Single dose, open-label, single-center, randomized, 2-way crossover, 2-sequence, food-effect, safety, and tolerability study

Study Population	N=24 Healthy male subjects Age: 18-55 years Gender: 24 males Race: 24 Caucasians
Treatment Group	Treatment A (fed) or Treatment B (fasted)
Dosage and Administration*	1 tablet of 400-mg Market Image (Lot 0703847) on two occasions (fasting or fed) separated by a wash-out period of at least 7 days
PK Sampling: plasma	predose and 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 h post dose
PK Sampling: Urine	none
PK Sampling: Feces	none
Analysis	Solid phase extraction, HPLC- MS/MS method LOQ in plasma for retigabine 5 ng/ml LOQ in plasma for monoacetyl metabolite 15 ng/ml
PK Assessment	Retigabine and the N-acetyl metabolite of retigabine: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, $t_{1/2}$ and AUC_R (ratio of AUC_{0-t} to AUC_{0-inf}).
Safety Assessment	Vital signs, adverse events, ECG, laboratory tests
PD Assessment	None

*Fasted, after a 10 hr fast
Fed, 30 minutes after administration of a standard high-fat breakfast

Pharmacokinetic Results:

Assay Performance during the analysis of the samples

Samples were analyzed using a previously validated LC-MS/MS method. Samples were assayed in 15 batches. All batches passed acceptance criteria except for batch SA006. All samples from this batch were successfully re-analyzed. Across the successful batch analyses, the accuracy values for calibration standards and the QC control samples were within ± 15 % and the CV values for calibration standards and the QC samples were less than 15 %, with at least one acceptable value at each QC concentration within each batch. Results are acceptable.

A total of 24 subjects were enrolled in the study and 22 subjects completed both treatments. Subjects 2 and 5 were only administered study drug in Period 1 and were excluded from the PK summary statistics.

Absorption of retigabine was rapid under both fed and fasted conditions. The mean peak plasma concentration under fed conditions was 711.86 ng/mL at 3 hours postdose and 560.97 ng/mL at 2 hours postdose under fasted conditions, indicating that food delayed the time to the peak plasma retigabine concentration and increased Cmax.

Summary of Pharmacokinetic Parameters for Plasma Retigabine Following Administration of a Single 400 mg Retigabine Dose Under Fed or Fasted Conditions

Pharmacokinetic Parameters	Treatment A Fed Mean ± SD	Treatment B Fasted Mean ± SD	% MR (90% CI)[a]
AUC_{0-t} (ng*hr/mL)	7814.6 ± 1349.6	7145.0 ± 1619.0	110.52 (102.51, 119.14)
AUC_{0-inf} (ng*hr/mL)	7895.9 ± 1356.1	7355.9 ± 1643.9	107.92 (100.42, 115.98)
AUC_R	0.990 ± 0.00387	0.980 ± 0.0197	NA
C_{max} (ng/mL)	938.7 ± 219.2	728.8 ± 301.4	137.63 (114.50, 165.42)
t_{max} (hr)	2.50 (1.00, 6.02)[b]	1.75 (0.333, 6.02)[b]	NA
k_{el} (1/hr)	0.113 ± 0.0168	0.0973 ± 0.0229	NA
$t_{1/2}$ (hr)	6.28 ± 0.938	7.57 ± 2.09	NA

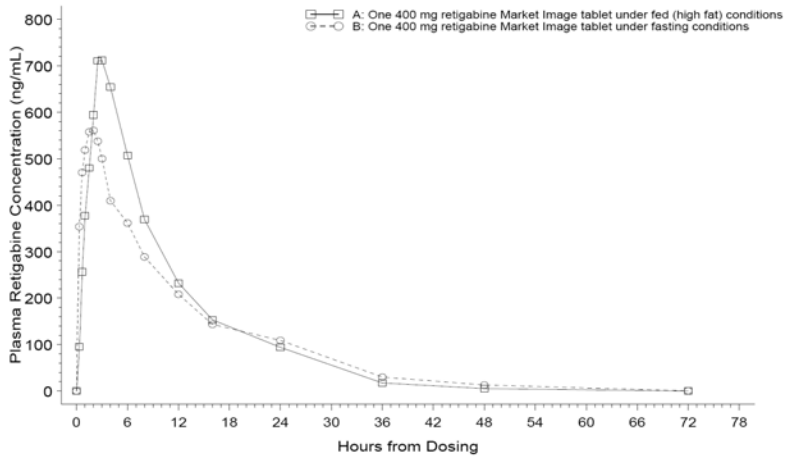
[a] 90% CI and % mean ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as median (minimum, maximum)
MR = mean ratio, SD = standard deviation, CI = confidence interval, AUC = area under the curve, AUC_R = AUC ratio, C_{max} = maximum concentration, t_{max} = time of maximum concentration, k_{el} = elimination rate constant, $t_{1/2}$ = half-life, NA = not applicable.

Summary of Pharmacokinetic Parameters for Plasma N-acetyl Metabolite of Retigabine Following Administration of a Single 400-mg Retigabine Dose under Fed or Fasted Conditions

Pharmacokinetic Parameters	Treatment A Fed Mean ± SD	Treatment B Fasted Mean ± SD	% MR (90% CI)[a]
AUC_{0-t} (ng*hr/mL)	8785.9 ± 1697.6	7840.1 ± 1998.3	113.40 (106.18, 121.11)
AUC_{0-inf} (ng*hr/mL)	9085.9 ± 1684.0	8313.5 ± 2031.4	109.76 (103.36, 116.56)
AUC_R	0.966 ± 0.0195	0.946 ± 0.0236	NA
C_{max} (ng/mL)	645.3 ± 104.7	462.3 ± 143.5	144.72 (128.72, 162.72)
t_{max} (hr)	4.00 (2.50, 8.00)[b]	4.00 (3.00, 12.0)[b]	NA
k_{el} (1/hr)	0.101 ± 0.0143	0.0855 ± 0.0181	NA
$t_{1/2}$ (hr)	7.05 ± 1.19	8.51 ± 2.06	NA

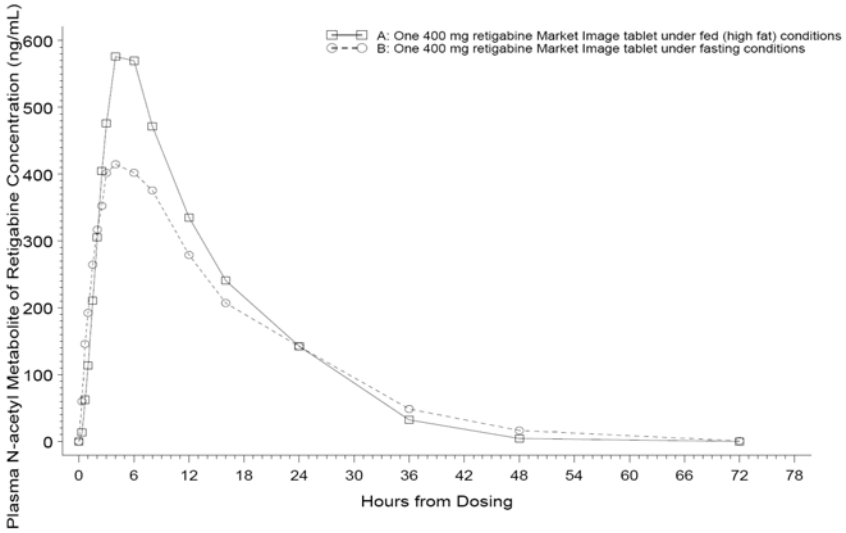
[a] 90% CI and % mean ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as median (minimum, maximum)

Plasma Retigabine Concentration-time Profiles Following Administration of a Single 400-mg Retigabine Dose under Fed or Fasted Conditions



Plasma N-acetyl metabolite of Retigabine Concentration-time Profiles

Following Administration of a Single 400-mg Retigabine Dose under Fed or Fasted Conditions



- The results of this study demonstrate that food did not affect the extent of absorption of retigabine (8% increase in AUC with the 90% CI remaining well within the 80–125% boundary).
- However, there was a 38% higher peak plasma retigabine concentration under fed versus fasted conditions, and time to peak concentration was delayed.

Safety Results:
Adverse events reported by the most subjects were dizziness (33%), somnolence (22%), and euphoric mood (21%). The adverse reaction profile noted in previous studies of retigabine includes CNS disorders. The proportions of subjects with AEs were similar between treatment groups and treatment sequences. Overall, there were no clinically important or unexpected safety results.

Reviewer's comment:
The sponsor's claim of no food effect is not justified since Cmax of both retigabine and its N-acetyl metabolite was increased (by 38% and 45%, respectively) after high fat meal. Food effect needs to be addressed in the label.

3065A1-110: A Comparative Bioavailability Study Of Three Oral Dose Formulations Of Retigabine In Healthy Adult Subjects

Objectives:
The primary objective of this study was to assess the comparative bioavailability of three oral solid dose immediate-release formulations, two capsules (reference) and one tablet (test), of retigabine given under fasting conditions. The secondary objective was to determine the effect of a high-fat meal on the relative bioavailability of the test tablet formulation.

Study Design	Single-center, single-dose, open label, randomized, 4-period, cross-over
Study Population	N=23 Healthy male subjects Age: 26-45 years Race: Black 17, White 4, Hispanic 2
Treatment Group	A) 4x50 mg reference capsules of retigabine (01998P1612), fasting; B) 200 mg reference capsule retigabine (1998P1S90), fasting; C) 200 mg test tablet of retigabine (1998P1S89), fasting; D) 200 mg test tablet of retigabine (1998P1S89) following a standard high-fat meal.
Dosage and Administration*	200 mg retigabine (see above) on four occasions separated by a wash-out period of 3 days
PK Sampling: plasma	predose and 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, and 48 h post dose
PK Sampling: Urine	none
PK Sampling: Feces	none
Analysis	HPLC- MS/MS method LOQ in plasma for retigabine 1 ng/ml LOQ in plasma for monoacetyl metabolite (AWD 21-360) 2.5 ng/ml
PK Assessment	Retigabine and metabolite AWD 21-360: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, $t_{1/2}$
Safety Assessment	Vital signs, adverse events, ECG, laboratory tests
PD Assessment	None

*Fasted, after a 10 hr fast
Fed, within 3 min after a high fat breakfast

Pharmacokinetic Results:

Assay Performance during the analysis of the samples:

Samples were analyzed using a previously validated LC/MS/MS method over the concentration ranges 1 ng/mL to 1000 ng/mL for retigabine and 2.5 ng/mL to 1000 ng/mL for AWD21-360.

The assays were linear between 1 and 1000 ng/mL for retigabine and between 2.5 and 1000 ng/rnL for AWD21-360. The Relative Standard Deviations (precision) of the quality control samples were ≤ 15% at each concentration levels for both retigabine and AWD21-360. The Percentages of Difference of the Mean (accuracy) were ≤ 13% at each concentration levels for both retigabine and AWD21-360. The overall CV% were equal to 8.48% for retigabine and 9.06% for AWD21-360. Results are acceptable.

A total of 23 subjects were enrolled and completed the study.

The statistical analyses of the effect of treatment on retigabine pharmacokinetics are presented below.

SUMMARY OF RETIGABINE PHARMACOKINETICS

Formulation Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
4x50-mg Capsule[a]				
Mean ± SD	864 ± 293	1.9 ± 1.5	7.0 ± 1.0	5482 ± 1022
Geometric Mean	793	1.6	7.0	5387
200-mg Capsule				
Mean ± SD	818 ± 311	2.3 ± 2.4	7.3 ± 1.1	5388 ± 1064
Geometric Mean	736	1.7	7.3	5286
200-mg Tablet				
Mean ± SD	823 ± 344	1.8 ± 0.9	7.2 ± 1.0	5294 ± 1219
Geometric Mean	727	1.5	7.2	5158
200-mg Tablet, Fed				
Mean ± SD	849 ± 197	2.3 ± 0.9	6.7 ± 0.8	4991 ± 1045
Geometric Mean	828	2.1	6.7	4885
Intrasubject Variability	26.3%	--	--	14.4%
4x50-mg / 200-mg Capsule				
Geometric Mean ratio	107	--	--	101
90% Confidence Limits	92 - 125	--	--	95 - 108
200-mg Tablet / 200-mg Capsule				
Geometric Mean ratio	99	--	--	97
90% Confidence Limits	85 - 115	--	--	91 - 104
200-mg Tablet Fed / Fasted				
Geometric Mean ratio	114	--	--	95
90% Confidence Limits	98 - 132	--	--	89 - 101

a: n = 23.

SUMMARY OF AWD 21-360 PHARMACOKINETICS

Formulation Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
4x50-mg Capsule				
Mean ± SD	356 ± 110	3.3 ± 1.0	7.2 ± 1.1	4434 ± 1458
Geometric Mean	338	3.2	7.2	4261
200-mg Capsule				
Mean ± SD	341 ± 113	3.8 ± 2.2	7.7 ± 1.3	4307 ± 1292
Geometric Mean	320	3.4	7.6	4137
200-mg Tablet				
Mean ± SD	356 ± 119	3.1 ± 1.1	7.4 ± 1.5	4457 ± 1469
Geometric Mean	333	3.0	7.3	4269
200-mg Tablet, Fed				
Mean ± SD	431 ± 138	3.7 ± 0.9	6.3 ± 0.9	4678 ± 1842
Geometric Mean	413	3.6	6.2	4411
Intrasubject Variability	22.0%	--	--	17.8%
4x50-mg / 200-mg Capsule				
Geometric Mean ratio	105	--	--	102
90% Confidence Limits	93 - 118	--	--	96 – 110
200-mg Tablet / 200 mg Capsule				
Geometric Mean ratio	104	--	--	103
90% Confidence Limits	93 - 117	--	--	96 – 110
200-mg Tablet Fed / Fasted				
Geometric Mean ratio	124	--	--	103
90% Confidence Limits	110 - 139	--	--	97 - 111

a: n = 23

- The 4x50-mg capsules and 200-mg capsule are considered to be bioequivalent on the basis of the 90% confidence limits for C_{max} and AUC, which were within the standard bioequivalence range.
- The 200-mg capsule and 200-mg tablet are considered to be bioequivalent on the basis of the 90% confidence limits for C_{max} and AUC.
- Administration of a high-fat breakfast with the tablet produces 14% higher retigabine C_{max} but the retigabine AUC was not modified.

Safety Results:

Overall, the single 200-mg dose of retigabine was safe and well tolerated. The most common events were dizziness (60.9%), abnormal thinking (34.8%), headache (34%), somnolence (21.7%), euphoria (26%), and asthenia (17.4%). All adverse events were mild and most resolved spontaneously without treatment. No clinically important laboratory or vital signs changes were observed.

Reviewer's comment:

The sponsor's claim of no food effect is not justified (C_{max} of retigabine and its metabolite were outside the standard bioequivalence range).

VRX-RET-E22-105 Comparative, randomized, open-label, single-dose, 2-way crossover bioavailability, safety and tolerability study of a 400 mg dose of retigabine administered as the clinical trials formulation and the market image formulation in healthy adult male subjects

Objectives:

Primary:

To assess the single-dose relative bioavailability of the retigabine Market Image tablet formulation to the retigabine clinical trials formulation tablets, under fasting conditions.

Secondary:

To assess the safety and tolerability of the retigabine formulations after a single dosing of 400 mg in healthy adult male subjects.

Study Design	Single-center, single-dose, open label, randomized, 2-way crossover, 2-sequence, comparative bioavailability study
Study Population	N=36 Healthy male subjects enrolled, 34 completed Age: 18-55 years Race: Caucasian 34, Black 1, Asian 1
Treatment Group	Treatment A: 1 retigabine 400-mg Market Image tablet Treatment B: 1 retigabine 300-mg clinical trials tablet and 2 retigabine 50-mg clinical trials tablets (total 400mg)
Dosage and Administration*	400 mg retigabine Market Image tablet or clinical trials tablets (total 400mg) separated by a wash-out period of 7 days
PK Sampling: plasma	predose and 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 h post dose
PK Sampling: Urine	none
PK Sampling: Feces	none
Analysis	HPLC- MS/MS method LOQ in plasma for retigabine 5 ng/ml LOQ in plasma for monoacetyl metabolite (AWD 21-360) 15 ng/ml
PK Assessment	Retigabine and the N-acetyl metabolite of retigabine: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, $t_{1/2}$ and AUC_R (ratio of AUC_{0-t} to AUC_{0-inf}).
Safety Assessment	Vital signs, adverse events, ECG, laboratory tests
PD Assessment	None

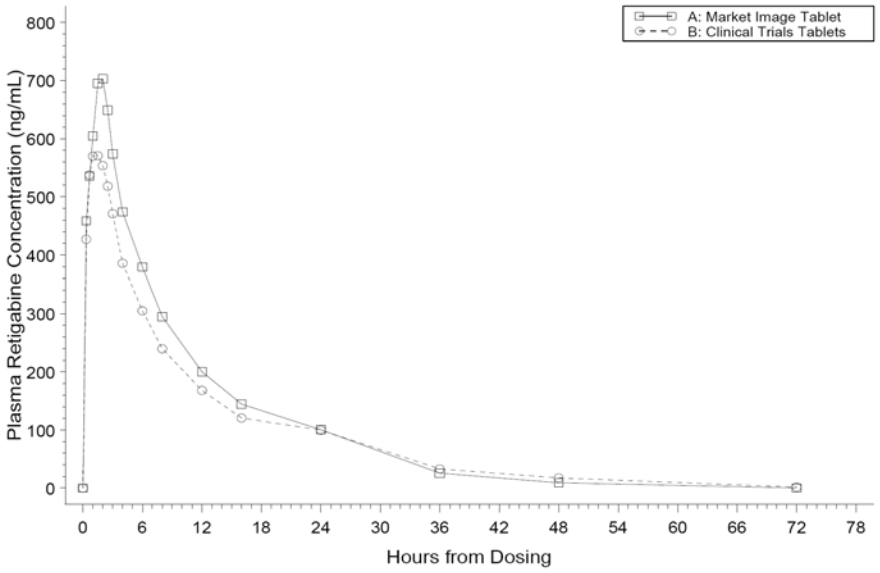
*Fasted, after a 10 hr fast for both treatments

Pharmacokinetic Results:

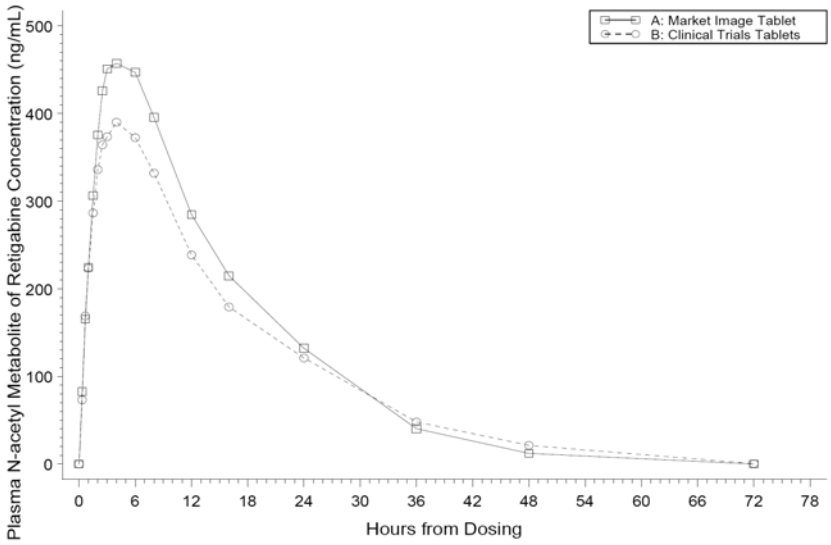
Assay Performance during the analysis of the samples:

Samples were analyzed using a previously validated LC-MS/MS method. The accuracy values for calibration standards and the QC control samples were within ±15% (± 20% at LLOQ) and the CV values for calibration standards and the QC samples were less than 15%, with at least one acceptable value at each QC concentration within each batch.

The mean plasma concentrations of retigabine and its metabolite following a single oral 400-mg retigabine dose as a Market Image formulation or a clinical trials formulation are presented below.



Mean Plasma Retigabine Concentration-time Profiles Following Administration of a Single 400-mg Retigabine Dose as a Market Image Formulation or a Clinical Trials Formulation



Mean Plasma N-acetyl Metabolite of Retigabine Concentration-time Profiles Following Administration of a Single 400-mg Retigabine Dose as a Market Image or a Clinical Trials Formulation

Mean PK parameters and statistical analysis for plasma retigabine following a dose of Market Image formulation or clinical trials formulations are presented in table below.

	Market Image Formulation (Test)	Clinical Trials Formulation (Reference)	
Pharmacokinetic Parameters	**Mean ± SD**	**Mean ± SD**	**% MR (90% CI)[a]**
AUC_{0-t} (ng*hr/mL)	7424.4 ± 2220.6	6636.2 ± 1921.1	111.39 (106.03, 117.01)
AUC_{0-inf} (ng*hr/mL)	7547.3 ± 2261.1	6880.9 ± 1914.8	108.90 (103.26, 114.85)
AUCR	0.984 ± 0.00755	0.963 ± 0.0518	.NA
C_{max} (ng/mL)	834.200 ± 286.564	753.933 ± 340.299	115.98 (101.23, 132.87)
t_{max} (hr)	1.51 (0.334, 6.00)[b]	1.00 (0.334, 12.1)[b]	.NA
k_{el} (1/hr)	0.103 ± 0.0191	0.0744 ± 0.0238	.NA
$t_{1/2}$ (hr)	6.97 ± 1.41	10.5 ± 4.27	.NA

[a] 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as Median (Minimum, Maximum)
MR = mean ratio, SD = standard deviation, CI = confidence interval, AUC = area under the curve, AUCR = AUC ratio, C_{max} = maximum concentration, t_{max} = time of maximum concentration, k_el = elimination rate constant, $t_{1/2}$ = half-life, NA = not applicable

Pharmacokinetic results summary:

- The retigabine Market Image formulation was bioequivalent to the clinical trials formulation on the basis of systemic exposure (AUC), but not C_{max}.
- C_{max} was greater by approximately 16% and AUC_{0-t} and AUC_{0-inf} by 11% and 9% following the Market Image versus the clinical trials formulations.
- The 90% CIs of the ratios of the geometric means for plasma retigabine Cmax, AUC0-t, and AUC0-inf were 101.23%–132.87%, 106.03%–117.01%, and 103.26%–114.85%, respectively.

- Median t_{max} was delayed approximately 30 minutes after administration of the Market Image formulation compared to the clinical trials formulation.
- Retigabine $t_{1/2}$ was significantly shorter (6.97 hours) after administration of the Market Image tablet than after the Clinical trials tablet (10.5 hours). Note: retigabine mean $t_{1/2}$ is about 10 hours, based on previous phase 1 single dose studies.
- The 90% CIs of the ratios of the geometric means for the plasma N-acetyl metabolite of retigabine C_{max}, AUC_{0-t} and AUC_{0-inf} were 110.54%–126.83%, 106.69%–115.44%, and 104.90%–112.94%, respectively.

Safety results:

• A total of 27 (75%) subjects reported treatment-emergent AEs in this study; 17 (49%) following a dose of the Market Image formulation and 20 (57%) following a dose of the clinical trials formulation. No important sequence effects were noted.
• The preferred term AEs reported by the highest proportion of subjects were dizziness (44%), somnolence (22%), headache (14%), oral hypoaesthesia (14%), euphoric mood (11%), and blurred vision (11%).
• Of 106 AEs, 100 (94%) were mild in severity and 6 (6%) were moderate.
• No deaths or serious AEs were reported in this study and there were no AEs leading to discontinuation.

Reviewer's comments:

The results from this study indicated that the Market Image formulation was bioequivalent to the clinical trials formulation on the basis of systemic exposure (AUC), but not Cmax. However, since Cmax was not substantially greater (approximately 16%) following the Market Image than following the clinical trials formulations and the safety profiles were similar following the Market Image formulation and the clinical trials formulation, the difference in Cmax is not expected to be of clinical significance. A pivotal BE study (RTG113287) was later submitted during the review cycle, which demonstrated the bioequivalence between the Market Image formulation and the clinical trials formulation with respect to Cmax and AUC.

RTG113287: An open-label, single-centre, randomised, 2-way crossover study to evaluate the bioequivalence of retigabine given as the Market Image tablet compared to retigabine clinical trial tablets.

Objectives:

Primary:
To demonstrate the bioequivalence of the retigabine Market Image immediate release (IR) tablet (400 mg) relative to the Clinical Trial IR tablets (1 x 300 mg + 2 x 50 mg).
Secondary
To assess the safety and tolerability of single doses of retigabine Market Image IR tablet (400mg) and Clinical Trial IR tablets (1 x 300 mg + 2 x 50 mg).

Study Design	Single-center, single-dose, open label, randomized, 2-way crossover, 2-sequence, comparative bioavailability study
Study Population	N=82 Healthy male and female subjects between 18 and 65 years of age, inclusive
Treatment Group	Treatment A: 1 retigabine 400-mg Market Image tablet Treatment B: 1 retigabine 300-mg clinical trials tablet and 2 retigabine 50-mg clinical trials tablets (total 400mg)
Dosage and Administration*	400 mg retigabine Market Image tablet or clinical trials tablets (total 400mg) separated by a wash-out period of 7 days
PK Sampling: plasma	predose and 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 h post dose
PK Sampling: Urine	none
PK Sampling: Feces	none
Analysis	HPLC- MS/MS method LOQ in plasma for retigabine 5 ng/ml LOQ in plasma for monoacetyl metabolite (AWD 21-360) 15 ng/ml
PK Assessment	Retigabine and the N-acetyl metabolite of retigabine: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, $t_{1/2}$ and AUC_R (ratio of AUC_{0-t} to AUC_{0-inf}).
Safety Assessment	Vital signs, adverse events, ECG, laboratory tests
PD Assessment	None

*Fasted, after a 10 hr fast for both treatments

An interim analysis was planned to be conducted after the first cohort of approximately 72 subjects completed the last PK sampling in order to assess the bioequivalence. Dosing for subjects in the second cohort was planned to commence if the results of the interim analysis indicated that the study should proceed as described in the decision tree listed below.

Interim Analysis Decision Tree

Outcome	Action
Adjusted 90% CIs for Cmax and AUC are within the BE range 0.80 to 1.25.	Stop the trial and conclude bioequivalence
The ratio of Cmax or AUC is outside the BE range 0.80 to 1.25 therefore addition of a second cohort will not result in successful demonstration of bioequivalence.	Stop the trial and conclude that we are not able to demonstrate bioequivalence
The adjusted 90% CI for Cmax or AUC extend beyond the BE range 0.80 to 1.25 due to a slight deviation in sample size assumptions (CVw=34% and true difference assumed to be 5%).	A second cohort may be recruited to account for the deviation in sample size assumptions and is not expected to exceed the number of subjects required in the first cohort
The adjusted 90% CI for Cmax or AUC extend beyond the BE range 0.80 to 1.25 due to a significant deviation in sample size assumptions therefore addition of a second cohort will result in a significantly large number of subjects	Stop the trial and conclude that we are not able to demonstrate bioequivalence

AUC= Area under curve
BE= Bio-equivalence
CI= Confidence interval

Reviewer's Comments

The results from this study are not acceptable due to the following:

1. Our preliminary calculations show that less than 60 subjects should be enough to demonstrate BE based the Guidance Statistical Approaches to Establish BE and on the intra-subject variability of this drug.
2. Even if this drug was highly variable, the above Guidance recommends replicate design rather than increasing the number of subjects for establishing BE for highly variable drugs.
3. The sponsor's initial target sample size was 76 subjects in the first cohort in order to obtain evaluable data from 72 subjects.
4. The sponsor enrolled 2 cohorts (82 subjects) and used interim analysis. Subsequently, they adjusted the 90% CIs for AUC(0-∞) and Cmax to account for interim analysis.
5. It is not clear what Clinical Trials tablets batch was used. In Study Rationale the sponsor claims: "A batch of Clinical Trials tablets that was more representative in terms of particle size of the batches of drug substance used in Studies 301 and 303 was compared with Retigabine Market Image". How does this relate to the Clinical Trials tablets batch used in the first BE study (VRX-RET-E22-105)?

4.4.5.2 Bioanalytical and Analytical Methods for Human Studies

Report D-23129/7095850003: Validation of the determination of D-23129 in human plasma by column-switching-HPLC with fluorescence detection

Note: D-23129 refers to retigabine

Method: direct injection of plasma into a HPLC system with an on- line clean-up and sample enrichment by a column-switching technique. (b) (4)

Detection of D-23129: fluorescence at excitation 254 nm and emission 372 nm.

Internal standard: (b) (4)
Range and Linearity: linear over the range of 1.5 and 800 ng/ml for D-23129
Recovery for D-23129 after the on-line solid phase extraction was calculated in the range of 80 to 86% and for (b) (4) 74 to 77%.
Within-day accuracy: between 1.7 and 12.8%
Within-day precision: 1.3 to 1.8%
Inter-day accuracy: assessed with three concentration levels on 8 different days.
The mean RME was between 5.2 and 8.2%
Inter-day precision: between 3.8 and 6.0%

Stability of analyte: loss of no more than 5% of D-23129 after two cycles of freezing and thawing in spiked plasma samples and also for storage at 4ºC or 15ºC for 15 h after preparation of the diluted plasma samples.

Note: This method was validated in 1996 (before Bioanalytical Method Validation Guidance 2001) and was used for quantitation of samples in study 3065A1-100.
The results for the 100 mg dose group from study 3065A1-100 should be interpreted with caution because, according to Table 50 of the Review Aid, the precision for QC samples in was ≤35.1% during the analysis of the samples for this dose group, which is not acceptable.

Report D-23129/7096430006: Validation of the HPLC-assay for the determination of D-23129 in human urine by on-line sample preparation with column-switching and fluorescence detection

Note: D-23129 refers to retigabine

Method: direct injection of plasma into a HPLC system with an on- line clean-up and sample enrichment by a column-switching technique. (b) (4)

Detection of D-23129 and the internal standard: fluorescence at excitation 254 nm and emission 372 nm.
Internal standard: (b) (4)

Range and Linearity: linear over the range of 12.5 and 2000 ng/ml for D-23129
Recovery for D-23129 after the on-line solid phase extraction was calculated in the range of 86 to 103% and for [redacted] (b) (4) 80 to 82%.
Within-day accuracy: between -5.8 and -8.6%
Within-day precision: 1.2 to 2.9%
Inter-day accuracy: assessed with three concentration levels on 10 different days: between -3.2 and -7.0%
Inter-day precision: between 0.8 and 5.1

Stability of analyte
The stability of D-23129 was investigated after "spiking" human urine with three different concentrations (50, 200 and 800 ng/ml) and determination of the concentrations freshly and after storing the samples at 15ºC in the autosampler for 20 hours.
[redacted] (b) (4) This assay was used for quantitation of D-23129 in urine samples from study 3065A1-100. In Table 51 (page 90, Review Aid) the sponsor reports good short term stability in urine, this needs to be confirmed by the reviewer of this study.

Report D-23129/7096051007: Validation of the HPLC-method for the determination of D-23129 and the metabolite AWD21-360 in human plasma by column-switching and fluorescence detection

Note: D-23129 refers to retigabine
AWD21-360 refers to the N-acetyl metabolite of retigabine

Method: direct injection of plasma into a HPLC system with an on- line clean-up and sample enrichment by a column-switching technique. [redacted] (b) (4)
Detection of D-23129 and AWD21-360: fluorescence at excitation 254 nm and emission 372 nm.

Range and Linearity: linear over the range of 6.25 and 2000 ng/ml for D-23129 and 12.5 and 2000 ng/ml for the metabolite AWD21-360.
Recovery of D-23129: in the range of 93.7 to 105.7% and between 87.0 and 91.1% for AWD21-360.
Within-day accuracy: for D-23129 between -0.9 and 5.0% and between -3.3 and 1.6% for AWD21-360
Within-day precision: for D-23129: 1.5 to 2.9% and 1.7 to 3.0% for AWD21-360
Inter-day accuracy: assessed with three concentration levels on 10 different days.

For D-23129 the mean RME was between -4.7 and 0.7% and for AWD21-360 between -5.7 and -11.5%.
Inter-day precision: for D-23129: between 6.5 and 9.8% and for AWD21-360 between7.0 and 8.5 %.
Stability of analyte: loss no more than 3.7% of AWD21-360 and 1.4% of D-23129 after two cycles of freezing and thawing in spiked plasma samples and also for storage at 15ºC for 20 h after preparation of the diluted plasma samples.

Internal standard: none
Calculations were done using external standard methods because of an unknown peak co-eluting with the internal standard (b) (4).

Note: This method was validated in 1998 (before Bioanalytical Method Validation Guidance 2001) and was used for quantitation of samples in one study only (3065A1-101). The results from this study should be interpreted with caution because of the following:

- Lack of internal standard
- The precision for QC samples in study 3065A1-101 was ≤32.9% during the analysis of the samples for D-23129 according to Table 54 of the Review Aid

Report D-23129/9321020113: Implementation and Validation of an LC-MS/MS Method for the Determination of Retigabine (D-23129) and its Metabolite (AWD21-360) in Human Plasma

Method: HPLC atmospheric pressure chemical ionisation – mass spectrometry/mass spectrometry (HPLC-APCI-MS/MS).
(b) (4)
The MRM transitions for D-23129 at m/z 304 to 230; for the metabolite AWD21-360 at m/z 274 to 256 and for the internal standard at m/z 329 and 133.
Internal standard: (b) (4)
Range and Linearity: linear over the range of 1 and 1000 ng/ml for D-23129 and 2.5 and 1000 ng/ml for the metabolite AWD21-360.
Recovery of D-23129: about 80 % and 88 % at concentrations of 10 and 1000 ng and between 84.62 and 94.19% for AWD21-360 at concentrations of 10 and 1000 ng in plasma.

D-23129
The mean intra-assay precisions (CV within-day) for five calibration curves ranged from 0.78 to 5.84 % with the mean accuracies ranging from -8.01 to 8.94 %. The mean inter-assay precisions (CV between-day) for the standards ranged from 1.76 to 10.20 % with the mean accuracies ranging from – 12.20 to 11.60 %.

The mean intra-assay precisions (CV within-day) for QC's analysed together with five curves were 4.95 % (QC3), 4.45 % (QC15), 2.59 % (QC150) and 9.05 % (QC750) with the mean accuracies of 1.81 % (QC3), 6.44 % (QC15), 3.25 % (QC150) and 0.16 % (QC750), respectively.
The mean inter-assay precisions (CV between-day) for QC's analysed in duplicate at different occasions were 19.66 % (QC3), 4.17 % (QC15), 4.03 % (QC150) and 4.33 % (QC750) with the mean accuracies of 4.95 % (QC3), 10.67 % (QC15), 5.35 % (QC150) and 6.87 % (QC750), respectively.

AWD21-360
The mean intra-assay precisions (CV within-day) for five calibration curves ranged frorn 1.83 to 5.27 % with the mean accuracies ranging frorn – 5.04 to 3.38 %. The mean inter-assay precisions (CV between-day) for the standards ranged from 1.11 to 6.00 % with the mean accuracies ranging from – 5.59 to 4.90 %.
The mean intra-assay precisions (CV within-day) for QC's analysed together with five curves were 7.73 % (QC3), 3.38 % (QC15), 2.79 % (QC150) and 9.42 % (QC750) with the mean accuracies of 0.31 % (QC3), -2.01 % (QC15), -3.01 % (QC150) and – 6.20 % (QC750), respectively.
The mean inter-assay precision (CV between-day) for QC's analysed in duplicate at different occasions were 16.03 % (QC3), 6.67 %o (QC15), 2.97 % (QC150) and 2.89 % (QC750) with the mean accuracies of 6.03 % (QC3), -0. 98 % (QC15), -6.80 % (QC150) and – 7.93 % (QC750), respectively.
The stability of D-23129 and AWD 21-360 under storage conditions in human plasma at -18°C as well as the stability in the autosampler at room temperature had been demonstrated earlier (note: the sponsor did not specify where and this report could not be verified).

Note: This method was used for quantitation of samples from studies 3065A1-110, 3065A1-113 and 3065A1-205.
The reviewer should assess the reliability of the standard curves during the analysis of the samples for D-23129 in these studies, since at the time of the validation, the regression line seems to be missing the highest standards (see representative calibration line for D-23129 below):

Report D-23129/7099022032: D-23129: Development and validation of an HPLC-assay for the determination of D-23129 and the metabolite AWD 21-360 in human plasma by column-switching and UV-detection

Note: D-23129 refers to retigabine
AWD21-360 refers to the N-acetyl metabolite of retigabine

Method: direct injection of plasma into an HPLC system with an on-line clean-up and analyte enrichment by a column-switching technique. The method was used for the quantitative determination of D-23129 and its metabolite AWD 21-360 in human plasma samples obtained from study 3065A1-108 after dosing of [^{14}C]D-23219 .

(b) (4)

HPLC and detected by UV detection at 220 nm as radio-detection proved to be less sensitive.
Internal standard: none (quantification was performed with D-23129 and AWD 21-360 as external standards).
Range and Linearity: linear over the range of 25 and 1000 ng/ml for both D-23129 and AWD21-360.
Recovery of D-23129: in the range of 92.3 and 100.7 %, and between 88.8 and 96.5% for AWD21-360.

D-23129
The intra-assay precision (CV within-day) for six quality control samples was ± 5.40 % (QC 50), ± 4.15 % (QC 250) and ± 1.29 % (QC 750) with mean accuracies of 95.42 % (QC 50), 101.05 % (QC 250) and 104.09 % (QC 750).
The inter-day precision (CV between-day) for five quality samples was ± 3.44 % (QC50), ± 5.27 % (QC 250) and ± 1.78 % (QC 750) with mean accuracies of 99.22 % (QC 50), 97.72 % (QC 250) and 103.09 % (QC 750).
AWD 21-360
The intra-assay precision (CV within-day) for six quality samples was ±5.08 % (QC 50), ± 1.82 % (QC 250) and ± 1.32 % (QC 750) with mean accuracies of 99.12 % (QC 50), 91.59 % (QC 250) and 99.38 % (QC 750).
The inter-assay precision (CV between-day) for five quality samples was ± 2.61 % (QC 50), ± 2.41 % (QC 250) and ± 2.07 % (QC 750) with mean accuracies of 102.29 % (QC 50), 93.22 % (QC 250) and 97.44 % (QC 750).

The stability of D-23129 and AWD 21-360 under storage conditions in human plasma at -18°C had been demonstrated earlier (note: the sponsor did not specify where and this report could not be verified) and as well as the stability in the autosampler at +15^{0}C and at room temperature.

This method was successfully validated and used for the quantitation of samples from study 3065A1-108.

Report D-23129/7097077013: Validation of an HPLC-APCI-MS/MS method in combination with online solid phase extraction (column-switching) for the determination of retigabine (D-23129) and the metabolite, AWD21-360, in human, rat, and dog plasma

Method: uses an on-line solid phase extraction procedure (column switching) on C2 stationary phase to isolate D- 3129, the metabolite (AWD21-360), (b) (4) (internal standard). The plasma sample work up procedure is performed by a column-switching technique (b) (4)

Validation was performed in human plasma and subsequently cross-validation of human plasma versus dog and rat plasma.
Internal standard: (b) (4)
Range and Linearity: linear over the range of 1.0 to 1000 ng/ml for D-23129 and 2.5 to 1000 ng/ml for AWD21-360
Recovery of D-23129 estimated from 77.3% to 100.2% and from 84.9% to 108.2 % for AWD21-360.

D-23129
The mean inter-assay precision (CV between-day) for the QC's analysed together with five calibration curves were +7.0 (QC15), t4.2 (QC150), and +6.9% (QC750) with mean accuracies ranging from -9.1% to +11.0% (QC15), -2.4% to +12.9% (QC150), and -11.1% to 14.1% (QC750), respectively. The mean intra-assay precisions (CV within-day) for the QC's were +12.2 (QC15), +0.2% (QC150), and +7.2% (QC750) with mean accuracies of -3.5 % (QC15), -7.6% (QC150), and -1.2% (QC750), respectively.
AWD21-360
The mean inter-assay precision (CV between-day) for the QC's analysed together with five calibration curves were +10.0 (QC15), +7.1 (QC150), and +9.2% (QC750) with relative errors ranging from -2.5% to +29.4% (QC15), -1.7% to +25.7% (QC150), and -4.2% to 24.9% (QC750), respectively. Note: accuracy for AWD21-360 not acceptable!
The mean intra-assay precisions (CV within-day) for the QC's were +7.4 (QC15), +6.9% (QC150), and +7.5% (QC750) with mean accuracies of -10.5 % (QC15), -7.9% (QC150), and -3.9% (QC750), respectively.

Autosampler stability: Diluted human plasma samples were stable at +15ºC for at least 24 hours. Long term storage stability of human QC plasrna samples containing D-23129 and ADW21- 360 frozen at approximately -20 C according to the sponsor was guaranteed for one year. Stability studies are reported in a separate report (Viertel, 1997), which is not available for review.
The Freeze/Thaw stability in human QC plasma samples 'spiked' with D-23129 and AWD21-360 was assessed over 4 cycles and the reported deviation from the nominal value was <20%.

Cross-Validation: HPLC-MS/MS versus HPLC with fluorescence detection

Note: D-23129 refers to retigabine
AWD21-360 refers to the N-acetyl metabolite of retigabine

Analyses of 48 quality control plasma samples 'spiked' with D-23129 and AWD21-360 at three different concentration levels (15 ng/ml, 150 ng/ml, and 750 ng/ml) were performed with the above described HPLC-MS/MS method and the earlier described HPLC-fluorescence detection method (Viertel, 1996).
The results from both the HPLC-MS/MS and the HPLC-fluorescence detection were in good agreement with the nominal values (overall deviations < +15 %) for D-23129. Values for D-23129 and AWD21-360 (at the 150 ng/ml and 750 ng/ml level only) analyzed by both HPLC-MS/MS and HPLC-fluorescence detection showed overall negative biases between -4.35% to -9.2%. For AWD21-360 the samples at the low concentrations (15 ng/ml) showed a high positive bias of +36.9% which, according to the sponsor, was due to interferences from the plasma matrix at the retention time of AWD21-360 when analyzed by HPLC/fluorescence detection. Therefore, integrations could not be performed reliably for the metabolite, AWD21-360, at the 15 ng/ml concentration level.

Cross-validation of human versus dog and rat plasma

QC samples at three different concentration levels (15, 150 and 750 ng/ml) were prepared in plasma of three different species (human, rat (NH_4-heparinised) and dog (Na-heparinised) and measured with a calibration curve from human (Na-heparinised) plasma. The back-calculated values for the metabolite, AWD21-360, prepared in dog and rat plasma showed higher positive, relative deviations (accuracies ranging from +22.8 % to +26.9%). All other accuracies and precisions for both analytes showed accuracies ranging from -0.8% to +14.1% and were considered to be acceptable.

Report D-23129/7097004008: Stability of D-23129 and the metabolites AWD21460 (acetyl metabolite) and N-glucuronide of D-23129 in spiked quality control samples and plasma samples from clinical studies stored at ≤-18°C

Note: D-23129 refers to retigabine

The storage stability of D-23129 and the acetyl metabolite AWD21-360 in spiked quality control samples and human plasma samples was investigated. The samples were stored at ≤-18 ºC up to one year. Further investigations were done concerning the stability of the N-glucuronide of D-23129 present in (real) human plasma samples to demonstrate the validity and specificity of the HPLC-assay.
Two validated HPLC methods (D-23129/7095850003 and D-23129/7096051007) were applied for the determination of D-23129. The second method included also the determination of the metabolite AWD21-360 in human plasma. Determination of the N-

glucuronide retigabine metabolite concentrations was performed indirectly by determining retigabine concentrations prior to and following cleaving the glucuronide conjugate with HCl, and calculating the differential. To demonstrate the independence of the HPLC-eluent pH on the quantification of D-23129 the eluent pH was increased from pH 3.9 (routinely used) to pH 7.2 and real plasma samples were re-analyzed under this condition.

Results:

- The spiked quality control samples showed no loss of D-23129 after storage up to one year. The mean accuracy of the spiked quality control samples for the different concentration levels was within -14.1 and 14.7%. For the real plasma samples the rnean accuracy was between 10.5 and 16.2% and no loss of D-23129 was observed after storage up to one year.
- In the spiked quality control samples no loss of AWD21-360 was observed at least up to one year. The mean accuracy for the different concentration levels was found to be within -13.6 and 1.1%. The stability of the acetyl metabolite AWD21-360 in real plasma sarnples was investigated up to six months storage. Results from one year stability were not obtained because of analytical problems and insufficient sample material for replicate analysis. During the half year storing period the real plasma samples showed no loss of AWD21-360. The mean accuracy was 5.3%. Storage stability of AWD21-360 in real plasma samples is given at least up to six months after storage.
- No increase of D-23129 concentration values in real plasma sarnples was observed which indicates that there was no decomposition of the D-23129-glucuronide during storage at ≤-18 ºC. If the real plasma samples were acidified to pH 3 the glucuronide bonding was splitted and D-23129 was released. Plasma concentrations increased to a factor of about 8 to 23 depending on sampling time. The check on the influence of the routinely used acidic HPLC eluent in comparison to a neutral eluent showed no increase of the D-23129 concentration, indicating that there is no interference from D-23129 which might be liberated from D-23129-N-glucuronide.

Report SWA5003: Validation of an HPLC Method with Mass Spectrometric Detection to Quantify Retigabine and N-acetyl Retigabine in Human Plasma

This method was validated but never applied to the analysis of any clinical study samples and will not be reviewed. The method was changed to allow for use of a different chromatographic column. A cross-validation was conducted (SWA5015).

Report SWA5015: Validation and Cross-Validation of an HPLC Method with Mass Spectrometric Detection to Quantify Retigabine and N-acetyl Retigabine in Human Plasma

The objective of this study was to validate a previously validated method for the determination of Retigabine and N-acetyl Retigabine in human plasma using solid phase extraction followed by high performance liquid chromatography analysis with tandem mass spectrometric detection following a change in the chromatography column.
Internal standard: [$^{13}C_6$] Retigabine and [$^{13}C_6$] N-acetyl Retigabine

Results: The Retigabine and N-acetyl Retigabine assay in human plasma was successfully validated over the concentration range of 5 to 2000 ng/mL for Retigabine and 15 to 2000 ng/mL for N-acetyl Retigabine using a 200 µL aliquot of plasma.
In the cross validation experiment, more than 80 % of the total % difference results for Retigabine and N-acetyl Retigabine were within ± 30 % and results were acceptable.
A summary of the validation results is given below:

Assay	Retigabine in human plasma	N-acetyl Retigabine in human plasma
Calibration model	Linear $1/x^2$	Linear $1/x^2$
Validated range	5 to 2000 ng/mL	15 to 2000 ng/mL
Precision (CV) (intra-batch)	2.97 % to 6.32 % (2.24 % for dilution QC)	4.25 % to 8.32 % (2.64 % for dilution QC)
Precision (CV) (inter-batch)	3.23 % to 9.28 % (5.28 % for dilution QC)	4.69 % to 7.00 % (3.70 % for dilution QC)
Accuracy (intra-batch)	97.7 % to 112 % (99.9 % for dilution QC)	94.8 % to 104 % (101 % for dilution QC)
Accuracy (inter-batch)	97.2 % to 107 % (105 % for dilution QC)	95.7 % to 103 % (101 % for dilution QC)
Maximum dilution	10-fold	10-fold
Selectivity	No significant interference with the analytes or internal standards	

The method validation fulfils all the requirements outlined in the 2001 Bioanalytical Method Validation Guidance.

Report SWA5008: Validation of an HPLC Method with Mass Spectrometric Detection to Quantify Retigabine and N-acetyl Retigabine in Human Urine

Method: HPLC method with tandem mass spectrometric detection following solid phase extraction.
Internal standards: [$^{13}C_6$] Retigabine and [$^{13}C_6$] N-acetyl Retigabine.
Range and Linearity: 5.00 to 2000 ng/mL for Retigabine and 15.0 to 2000 ng/mL for N-acetyl Retigabine.
The method was fully validated by assessment of precision, accuracy, sensitivity and selectivity of Retigabine and N-acetyl Retigabine. Urine stability, freeze / thaw stability, extract stability, recovery, matrix effect on ionisation and carryover were also determined.
Initially the validation was carried out using a [redacted]$^{(b)(4)}$ HPLC column [redacted]$^{(b)(4)}$). During the course of sample analysis, this column was seen to lack robustness and a new column [redacted]$^{(b)(4)}$ was used

and partially validated for use. Two inter-batch accuracy and precision batches were extracted with the inclusion of carryover, selectivity and matrix effect.
The overall inter-batch accuracy and CV values were within 15% across the calibration range. Extraction recovery was low but consistent over the concentration range (did not differ by more than 15% over the concentration range) and no matrix effect was observed. No significant carryover was evident in human urine samples.
The method validation fulfils all the requirements outlined in the 2001 Bioanalytical Method Validation Guidance. A summary of the validation results is given below:

Assay	Retigabine in human urine	N-acetyl Retigabine in human urine
Calibration model	Linear $1/x^2$	
Validated range	5.00 to 2000 ng/mL	15.0 to 2000 ng/mL
Precision (CV) (intra-batch)	4.60 % to 12.4 % (7.76 % for dilution QC)	6.03 % to 8.73 % (8.07 % for dilution QC)
Precision (CV) (inter-batch)	6.36 % to 10.9 % (9.41 % for dilution QC)	5.88 % to 13.4 % (7.33 % for dilution QC)
Accuracy (intra-batch)	99.5 % to 113 % (94.9 % for dilution QC)	89.3 % to 104 % (92.2 % for dilution QC)
Accuracy (inter-batch)	102 % to 112 % (101 % for dilution QC)	91.7 % to 103 % (96.9 % for dilution QC)
Maximum dilution	10-fold	
Selectivity	No significant interference with the analyte or internal standard	
Biological matrix stability	Up to 24 h at room temperature and at 4 °C and up to 3 months at -20 °C and -80 °C	
Freeze / thaw stability	Up to 3 cycles	
Processed extract stability	Up to 24 h at 4 °C	

Report SWA5012: Full Validation of an HPLC Method with Mass Spectrometric Detection to Quantify Retigabine and N-acetyl Retigabine in Tris Buffered Krebs Ringers Solution

Tis method was developed to support analysis of retigabine and N-acetyl retigabine in human dialysate for Study VRX-RET-E22-101.
Method: LC-MS/MS method to quantify retigabine and N-acetyl retigabine in buffered Krebs Ringers solution.
Internal standards: [$^{13}C_6$] Retigabine and [$^{13}C_6$] N-acetyl Retigabine
Range and Linearity: 5.00 to 2000 ng/mL for Retigabine and 15.0 to 2000 ng/mL for N-acetyl Retigabine.

A summary of the method validation parameters is provided in the table below.

Assay	Retigabine in Tris buffered Krebs Ringers solution	N-acetyl Retigabine in Tris buffered Krebs Ringers solution
Calibration model	Linear $1/x^2$	Linear $1/x^2$
Validated range	5 to 2000 ng/mL	15 to 2000 ng/mL
Precision (intra-assay)	0.982 % to 7.02 % (≤ 12.6 % for dilution QC)	0.840 % to 2.92 % (≤ 10.2 % for dilution QC)
Precision (inter-assay)	2.26 % to 7.00 % (≤ 7.54 % for dilution QC)	2.17 % to 6.51 % (≤ 5.88 % for dilution QC)
Accuracy (intra-assay)	90.8 % to 106 % (± 98.2 % for dilution QC)	101 % to 108 % (± 100 % for dilution QC)
Accuracy (inter-assay)	92.8 % to 109 % (± 100 % for dilution QC)	102 % to 108 % (± 103 % for dilution QC)
Maximum dilution	10-fold	
Biological matrix stability	Up to 4 h at room temperature and up to 1 month at -80 °C	
Freeze / thaw stability	Up to 2 cycles	
Processed extract stability	Up to 24 h at 4 °C	

During the course of the validation the three freeze / thaw stability batch did not meet the acceptance criteria for Retigabine. The stability batch was repeated for two freeze /thaw cycles, which did meet the acceptance criteria.
The 24 h room temperature stability also failed the acceptance criteria; however, 4 h room temperature stability was achieved. There was no impact on the integrity of the data according to the sponsor.

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/s/

TA-CHEN WU
01/25/2011

YUXIN MEN
01/25/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-345
Brand Name:	Potiga™
Generic Name:	Retigabine (Ezogabine)
Sponsor:	Valeant Pharmaceuticals & GlaxoSmithKline
Type of Dosage Form:	Immediate release film-coated tablet
Strengths:	50, (b) (4) 200, 300, and 400 mg
Indications:	Adjunctive treatment of partial onset seizures
OCP Reviewers:	Ta-Chen Wu, Ph.D., Kristina Dimova, Ph.D.
OCP Team Leader:	Angela Yuxin Men, M.D., Ph.D.
Pharmacometrics Reviewers/ Secondary Review	Joo-Yeon Lee, Ph.D., Yaning Wang, Ph.D.
Pharmacogenomics Reviewers/Secondary Review	Li Zhang, Ph.D., Issam Zineh, Pharm.D. M.P.H.
OCP Division:	DCP-1 HFD-860
OND Division:	Division of Neurology Drug Products HFD-120
Submission Date:	October 30, 2009, November 29, 2009, February 26, 2010, March 11, 2010, April 9, 2010, May 11, 2010, June 4, 2010
Type of Submission:	New, Standard NDA

Table of Contents

1 Executive Summary

In this original NDA 22-345 submission, the sponsor seeks approval of Potiga™ (retigabine) as adjunctive treatment of partial onset seizures (POS) with or without secondary generalization in patients 18 years of age and older with epilepsy. Retigabine was later renamed as "ezogabine"; however, retigabine will be used throughout this review while ezogabine will be used in the proposed labeling. The proposed commercial dosage form is immediate release film-coated tablet, with proposed 5 strengths being 50, 100, 200, 300, and 400 mg. The recommended dosing regimen for Potiga™ is 600~1200 mg/day, tid, with starting dose being 100 mg tid (300 mg/day) and increased at weekly intervals by a maximum of 150 mg/day (3 divided doses or 50 mg tid) up to recommended doses based on individual patient response and tolerability.

Retigabine (RTG) is a first in class neuronal potassium channel opener for the treatment of partial-onset seizures. Mechanism of action contributing to its anti-epileptic activity is mediated through its ability to enhance the neuronal K+ current mediated by the Kv7 subfamily of voltage-gated potassium (KCNQ) channels, predominantly KCNQ2 and KCNQ3. Retigabine can enhance the native M-current and therefore provide a stabilizing effect on excitable, particularly hyperexcitable, neurons.

Retigabine is extensively metabolized in humans and is converted to inactive N-glucuronides. Retigabine is also metabolized to an N-acetyl metabolite (NAMR) that is also subsequently glucuronidated. The N-acetyl metabolite of retigabine has antiepileptic activity, but is less potent than retigabine in animal seizure models. There is no evidence for hepatic oxidative metabolism of retigabine or NAMR by cytochrome P450 enzymes.

The current NDA submission consists of 44 studies, including 28 Phase 1 studies, 5 completed Phase 2 studies, 2 completed Phase 3 studies, and 6 long-term, open-label extension studies (of which, extensions to two Phase 3 studies remain ongoing). Three additional studies, including two Phase 2 studies in bipolar disorder and in post-herpetic neuralgia (PHN), and a second bioequivalence study (RTG113287) were submitted as part of the 120-day safety submission. To support the efficacy and safety of retigabine as adjunctive therapy for treating POS, this NDA contains results from three adequate and well-controlled studies in patients with partial-onset epilepsy: a Phase 2b study (Study 3065A1-205 or Study 205) and two Phase 3 studies (Study VRX-RET-E22-301 or Study 301; Study VRXRET-E22-302 or Study 302) conducted in >17 countries. Dosing regimens of these studies ranged from 600mg/day up to 1200 mg/day.

Exposure-Response was performed to evaluate the relationship between systemic exposure of retigabine and efficacy/safety endpoints from the Phase 3 studies, 301 and 302. For efficacy, two PD endpoints were evaluated - (i) the percent change from baseline in seizure frequency, and (ii) a binary outcome analysis (responder / non responder), where a responder was defined as a subject having a ≥50% reduction from baseline in total partial seizure. For safety, 6 most frequently observed adverse events were evaluated. Population PK analysis was performed using sparse PK data from the

Phase 3 program in refractory epilepsy patients with POS and healthy subjects for retigabine and its N-acetyl metabolite. In addition, impact of genetic polymorphism (UGT and NTA2) on pharmacokinetics of retigabine, as well as the need for any dose adjustment, was assessed.

The primary aim of this review is to assess the quality and the acceptability of Clinical Pharmacology data of retigabine submitted by the applicant for the proposed indication, and to provide the necessary dosing and labeling recommendations.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 22-345 acceptable from an OCP perspective provided that the Sponsor agrees with the Phase IV commitments. In addition, agreement on the labeling language should be reached between the Sponsor and the Agency.

Comments to be conveyed to the Medical Officer:

- In view of the fold increase in AUC of moderate hepatic impairment, as well as potential impact of age and gender on retigabine exposure, a dose reduction (by 1/3) may be considered for patients with moderate hepatic impairment based on PK property.
- Based on the results of the study in patients with renal impairment, we agree with the Sponsor's proposal that for patients with renal impairment CL_{Cr}<50 ml/min, a 50% decrease in the initial and maintenance dose of retigabine is recommended. Such proposal for the dose adjustment is based on AUC changes of retigabine. Having 50% dose deduction, Cmax will be reduced to 50% in moderate~severe renal impaired patients and to 25% in ESRD patients. Therefore, the impact of lower Cmax as a result of dose reduction on the efficacy should be considered.
- The Sponsor proposes no dose adjustment based on age or gender. However, in view of the magnitude of increases in systemic exposure (AUC) in the elderly subjects vs. young subjects, we recommend that a dose reduction (by 1/3) or a starting dose at the low end of the dosing range for the elderly patients should be considered.
- While the sponsor studied some variants in UGT1A1 and NAT2, variants exist in other genes may also be important in retigabine metabolism (e.g., UGT1A3, 1A4, and 1A9). The sponsor concluded that glucuronidation compensates for impaired acetylation and vice-versa could not be substantiated in this study. No further pharmacogenetic studies of PK are required at this time given the clinically insignificant differences in PK seen to date.

1.2 Phase IV Commitments

- The Sponsor should follow the Agency's Guidance to screen the inhibition potential of retigabine on CYP2B6 activity using recommended probe substrates for this CYP isozyme.

- The sponsor should conduct an *in vitro* study to investigate ezogabine as a potential substrate for major transporters in kidney.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings of the review on clinical pharmacology, biopharmaceutics, and *in vitro* investigations are summarized below

General Pharmacokinetic Properties:

Single-Dose:

- The pharmacokinetics and systemic exposure of retigabine and its NAMR metabolite were characterized to be linear, dose-proportional, and dose-independent across the dose range 25-600 mg studied.
- Retigabine was fast absorbed with Tmax of the first peak ranging 0.67~1.5 h and a terminal t1/2 values ranging 9~14 h.
- The second peak phenomenon was observed, with Tmax at approximately 1.75~4 h postdose, suggests potential enterohepatic re-circulation of the drug-derived material.

BID Regimen:

- Steady-state exposure (Cmax and AUC) of retigabine increased linearly with increasing dose up to 350 mg BID.
- Similar PK profiles to those observed following single doses.
- Accumulation ratios at the steady state ranged 1.5~2.7 in healthy subjects.
- Similar steady-state PK profiles of retigabine and NAMR metabolite following repeated retigabine 50, 100 and 200 mg BID oral doses in patients with epilepsy were similar to those observed in healthy subjects, with median Tmax being approximately 1 h postdose.

TID Regimen:

- Steady-state exposure (Cmax and AUC) of retigabine increased dose-proportionally and linearly with increasing dose up to 400 mg TID (1200 mg/day).
- Similar PK properties were obtained compared to the BID dosing regimen.
- Both CL/F and apparent elimination t1/2 were dose-independent, suggesting that retigabine does not inhibit or induce its own clearance.
- The predicted exposures to retigabine from the final population PK model showed approximately linear increases in systemic exposure to retigabine over the dose range studied in the primary efficacy trials (200~400 mg TID).

Absorption:

- Retigabine is generally rapidly absorbed after single or multiple oral dosing, with short Tmax values of 0.5~2.0 hours.
- The absolute bioavailability of retigabine from oral capsule is approximately 60% (~68.5% estimated by population PK analysis).

- Retigabine is well absorbed following oral administration based on results of mass-balance study (i.e., 84% urinary recovery of drug related material). Retigabine was also shown to be highly permeable in Caco-2 cell test systems.

Distribution:
- Steady-state volume of distribution of retigabine of 2-3 L/kg suggests that retigabine is well distributed in body.
- Plasma protein binding, mainly to albumin, of both retigabine and its N-acetyl metabolite (NAMR) are approximately 80% and 45%, respectively.
- The whole blood-to-plasma ratio for the radioactivity ranged 0.55~0.68, indicating that retigabine does not significantly partition into cellular components of blood.
- The binding of retigabine to plasma proteins was not measured in studies in subjects with renal or hepatic impairment.

Metabolism and Excretion:
- Retigabine is metabolized extensively through formation of NAMR and through N-glucuronidation of both retigabine and NAMR.
- The N-acetylation of retigabine was primarily carried out by NAT2, while glucuronidation was primarily carried out by UGT1A4, followed by UGT1A1, and then UGT1A3 and UGT1A9.
- There was a lack of evidence for oxidative metabolism of retigabine via CYP450 enzymes.
- Results of mass balance study suggest that renal is the major route of elimination for retigabine and NAMR, with ~98% of the radiolabeled dose recovered: 84% was recovered in the urine with unchanged parent drug accounting for 36% of the administered dose, along with 7 other metabolites; another 13.5% of the radioactivity was recovered in the feces with unchanged retigabine accounting for 3% of the total dose.
- Retigabine metabolites accounted for more than 90% of total radioactivity in the plasma, The N2- glucuronide of retigabine was the predominant circulating metabolite in plasma among 7 metabolites found in human plasma, followed by retigabine and NAMR. The contribution of retigabine and NAMR to the AUC of total radioactivity ranged 3.3~8.4% (5.18% based on mean values) and 3.5~6.5% (4.21% based on mean values), respectively, suggesting the extensive metabolism.
- The CL of retigabine following iv dosing was approximatley 0.4-0.6 L/h/kg. Retigabine CL/F is predominantly affected by renal function and body size (BSA).
- Retigabine and NAMR have similar terminal t1/2 ranging approximately 7-11 hours.

Variability of PK parameters:
- The between-subject variability of retigabine AUC and Cmax were generally in the range 20-30% (~40% in one study) and 20-45% (~54% in one study), following oral dosing of tablets and capsule formulation, respectively.
- The population PK analysis identified the creatinine clearance (CR_{CL}), body surface area (BSA), dose and the use of lamotrigine on clearance (CL), and age on volume of distribution (V) as the statistically significant covariates. For NAMR, CR_{CL} and

SGPT were the significant covariates on CL and dose on V. However, the effects didn't appear to be clinically meaningful.

Exposure-Relationship:

1. The evidence of effectiveness of retigabine was demonstrated in three placebo-controlled studies; a Phase 2b study conducted by Wyeth, study 3065A1-205 (Placebo, 200mg TID, 300mg TID, 400mg TID) and two Phase 3 studies conducted by Valeant, study VRX-RET-E22-301 (Placebo, 400mg TID) and study VRX-RETE22-302 (Placebo, 200mg TID, 300mg TID).
   - Two primary endpoints were evaluated in order to support international registration of retigabine: percent change from baseline to the double-blind period, in total partial seizure frequency per 4 weeks (FDA requirement), proportion of responders experiencing a ≥50% reduction from baseline to the maintenance phase, in total partial seizure frequency per 4 weeks (EMEA requirement)
   - The results on the percent change in total partial seizure frequency showed that 900 mg/day (300mg TID) and 1200 mg/day (400mg TID) doses were statistically superior to placebo in the studies of 205 and 302 ($p<0.05$)
   - 600 mg/day (200mg TID) dose was statistically superior to placebo in the study of 302 ($p=0.007$) but not the study of 205 ($p=0.156$).
   - The results from responder analyses showed similar trend.

2. For the exposure-response analyses, two Phase 3 studies (301 and 302) were included for both efficacy and safety evaluation related to the retigabine exposure (AUC μg·h/mL)
   - E-R relationship based on percent change in seizure frequency during double-blind phase from the baseline and AUC appears to be clearly significant and seems to reach a plateau at 1200mg/day
   - Based on the reviewer's assessment, the percent reduction during double-blind phase from baseline in total partial seizure frequency ranged from approximately 17% at placebo to the maximum of 50% reduction with active treatment.
   - AUC was found to be significant predictors for the probability of responder, meaning that the probability of responder tends to go up as the exposure is increased.

3. In terms of exposure-safety relationship, six adverse events of interest including coordination abnormal, dizziness, dysarthria, somnolence, tremor, and blurred vision were evaluated in the correlation with retigabine predicted AUC based on the sponsor's logistic regression and all six endpoints showed exposure-dependent relationship.

Intrinsic Factors:

Age and Gender: The impact of age and gender on the pharmacokinetics of retigabine was investigated in the same study following a single dose of retigabine to healthy young (21-40 years of age) and elderly (66-82 years of age). The AUC values were ~20% higher in young females compared to young males and ~30% higher in elderly females

compared to elderly males. Cmax values were ~50% higher in young females compared to young males and ~100% higher in elderly females compared to elderly males. However, AUC values were ~40-50% higher in elderly subjects compared to young subjects and half-life was ~30% longer in elderly compared to young subjects across males and females. Weight-normalized CL/F values of retigabine were similar between male and female subjects, but were lower in elderly subjects. In view of the magnitude of increases in systemic exposure and the likelihood of increased adverse events in the elderly subjects, we recommend a dose reduction to approximately two-thirds of the target dose for the elderly patients.

Race/Ethnicity: No clinical pharmacology study was conducted to assess the impact of race on the PK. A meta-analysis was conducted to compare retigabine CL/F parameters between healthy Black and Caucasian subjects pooling from 6 Phase 1 studies. The rretigabine CL/F was approximately 19% lower than that for Caucasian subjects (43.3 L/hr vs. 53.6 L/hr).

Renal Impairment:

Degree of Renal Impairment	Fold Increase (RTG)	
	AUC	Cmax
Mild	1.3	1.0
Moderate	1.9	1.1
Severe	2.2	1.0
ESRD	2.2	0.5

Degree of Renal Impairment	Fold Increase (NAMR)	
	AUC	Cmax
Mild	1.5	1.2
Moderate	2.2	1.5
Severe	2.4	1.4
ESRD	3.8	1.0

- A dose reduction to one-half was proposed for patients with CLcr<50ml/min (Moderate, Severe, and ESRD), while no dose adjustment is needed for mild renal impairment.

Hepatic Impairment:

Degree of Hepatic Impairment	Fold Increase (RTG)	
	AUC	Cmax
Mild	0.91	0.73
Moderate	1.5	1.3
Severe	2.1	1.3

- A 50% dose reduction for severe hepatic impairment, while no dose adjustment is needed for mild or moderate hepatic impairment.
- However, in view of the fold increase in AUC of moderate hepatic impairment, as well as potential impact of age and gender on retigabine exposure, a dose reduction to two-thirds should be considered for patients with moderate hepatic impairment.

Genetic Polymorphism:

- After oral single (200 mg retigabine immediate release) and multiple dose retigabine treatment (200 mg retigabine immediate release BID), the AUC of the acetylated metabolite was higher in NAT2 fast acetylators versus slow acetylators, and higher in

subjects with UGT1A1*28 mutation versus subjects with UGT1A1 wildtype. The differences in PK parameters do not warrant dose change recommendations.
- There was no indication that serum bilirubin concentrations increase with single or multiple dose of retigabine in UGT1A1*28 mutation carriers.
- While the sponsor studied some variants in UGT1A1 and NAT2, variants exist in other genes may also be important in retigabine metabolism (e.g., UGT1A3, 1A4, and 1A9). The sponsor's conclusion that glucuronidation compensates for impaired acetylation and vice versa could not be substantiated in this study. No further pharmacogenetic studies of PK are required at this time given the clinically insignificant differences in PK seen to date.

Extrinsic Factors:

In-Vitro Investigations for Drug-Drug Interaction Potential:

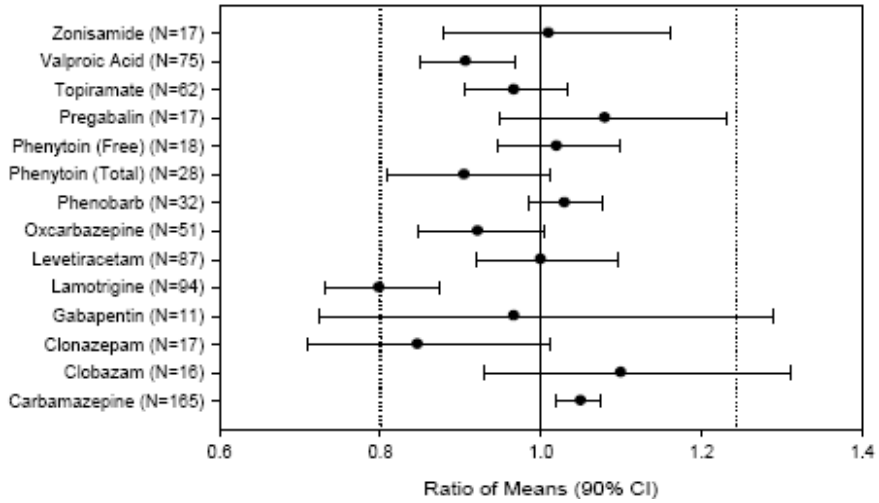
- Retigabine did not significantly inhibit the major CYP isoenzymes including CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. Interaction potential is low via inhibitory mechanism.
- Retigabine and NAMR did not induce CYP1A2 or CYP3A4/5.
- Retigabine was highly permeable in Caco-2 cells and was shown to be neither a substrate of P-glycoprotein (P-gp) nor significantly inhibit the P-gp mediated transport activity. The acetyl-metabolite NAMR may inhibit the P-gp mediated drug transport at much higher concentrations of ≥10 μM.

Effect of Coadministered Antiepileptic Drugs on PK of Retigabine:

- Repeat administration of lamotrigine (25 mg/day, a lower dose than clinical use) showed no impact on PK of single-dose retigabine.
- The apparent clearance of retigabine was increased by 33% with concomitant phenytoin in a Phase 2 study, leading to a 34% and 18% decreases in AUC and Cmax, respectively, and a 2.7-hour shortening in t1/2.
- The apparent clearance of retigabine was increased by 28% with concomitant carbamazepine in a Phase 2 study, leading to a 31% and 23% decreases in AUC and Cmax, respectively, and a 5.3-hour shortening in t1/2.
- Population PK analysis from Phase 3 clinical trials indicate that impact of concomitant retigabine on concomitant AEDs appears insignificant.

Effect of Retigabine on PK of Coadministered Antiepileptic Drugs:

- A 300 mg BID regimen of retigabine did not affect the PK of 200-mg lamotrigine.
- Retigabine (200 mg TID) with phenobarbital (90 mg daily) did not significantly alter the PK exposure of phenobarbital.
- In Phase 2 studies, no significant effects of retigabine were observed on the trough concentrations of these either carbamezepine (600-2400 mg/day), phenytoin (120-600 mg/day), valproic acid (750–2250 mg/day), or topiramate (250-1200 mg/day).
- Results of population PK analysis show 20% and 16% decreases in lamotrigine and clonazepam exposure, respectively (see Figure above).



Other Drug-Drug Interactions:

- At retigabine doses of up to 750 mg/day, there was no impact on exposure of the estrogen or progestogen components of oral contraceptives (LO-OVRAL and Ortho® 1/35).
- No significant effects of oral contraceptive steroids on retigabine PK were observed.
- The AUC and Cmax of retigabine are increased by 36% and 23%, respectively, after coadministration with a 1 g/kg dose of ethanol. Retigabine did not affect the PK parameters of ethanol.

General Biopharmaceutics:

Relative Bioavailability Study:

- The relative bioavailability was compared between clinical formulation IR Tablets (1x300mg + 2x50mg) and proposed to-be-marketed IR Tablets (400mg) in a single-dose, open label, randomized, 2-way crossover, 2-sequence, comparative bioavailability study in healthy male subjects.
- The BE was established between the proposed 400-mg IR Tablet formulation and clinical formulation (IR Tablets: 1x300mg + 2x50mg). The 90% CIs of Cmax, AUC0-∞, and AUC0-t were within 80-125% acceptance criteria for BE.

Retigabine Formulations	PK parameter	Ratio (90% CI)	%CVw
Market Image Vs. Clinical Trials	AUC(o-∞)	1.020 (0.98, 1.06)	13..6
	Cmax	0.999 (0.89, 1.12)	39.1
	AUC(o-t)	1.019 (0.98, 1.06)	13.8

Food Effect:

- High-fat food increases Cmax of retigabine by approximately 38%, while the 90% CI of Cmax was outside of the upper boundary of the 80-125% acceptance criteria. Food had no significant impact on the AUC of retigabine as the 90% CI of AUC0-∞ fell within 80-125% acceptance criteria.
- Tmax was prolonged by 0.75 hour, while t1/2 remains similar.
- Retigabine can be taken with or without food, as stated in proposed label.

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2 Question Based Review

2.1 General Attributes

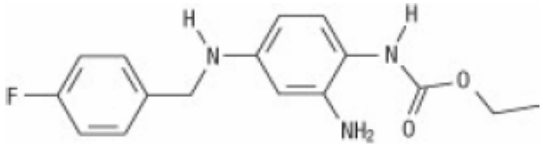
What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The clinical development program for retigabine in epilepsy was initiated under IND 53,950 with the Division of Neurology Products of FDA on 14 July 1997. The sponsorship of this program was changed from AstaMedica AG to Wyeth, to Viatris, to Xcel, and eventually to Valeant partnering with GSK. Most of the early clinical pharmacology studies were conducted by Wyeth or Viatris (Study number prefix 3065A1), with more recent clinical pharmacology studies being conducted by Valeant (Study number prefix VRX-E22).

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?

Regitabine (RTG), the active ingredient of POTIGA™, is chemically known as N-[2-amino-4(4 fluorobenzylamino)-phenyl] carbamic acid ethyl ester. Its molecular formula is $C_6H_{18}FN_3O_3$ and the molecular weight is 303.33. Retigabine is a white to slightly colored, odorless, tasteless, crystalline powder. At room temperature, retigabine is practically insoluble in aqueous media at pH values above 4, while the solubility is higher in polar organic solvents. At gastric pH, retigabine is sparingly soluble in water (about 16 g/L). The pKa is approximately 3.7 (mildly alkaline). The structure for retigabine drug substance is provided in the following Figure:

Figure. Chemical structure of regitabine



POTIGA™ is supplied as film-coated tablets for oral administration in 50, (b) (4) 200, 300, and 400 mg strengths. Each tablet contains the labeled amount of retigabine and the following inactive ingredients: carmine (50- and 400-mg tablets), croscarmellose sodium, FD&C Blue No. 2 (50-, (b) (4) 300-, and 400-mg tablets), hypromellose, iron oxide yellow (b) (4) 200-, 300-mg tablets), magnesium stearate, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide. The five strengths of retigabine tablets are differentiated by a combination of size, color and shape. Each market image tablet is debossed to identify and differentiate the unit dose strength.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

POTIGA™ is indicated as adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization.

The active ingredient, retigabine, belongs to the pharmacologic class of a novel potassium channel opener. Potassium channels are one of the voltage-gated ion channels found in neuronal cells and are important determinants of neuronal activity. In vitro studies indicate that mechanism of action contributing to its anti-epileptic activity is mediated through its ability to enhance the neuronal K+ current mediated by the Kv7 subfamily of voltage-gated potassium (KCNQ) channels, predominantly KCNQ2 and KCNQ3. Retigabine can enhance the native M-current and therefore provide a stabilizing effect on excitable, particularly hyperexcitable, neurons. In addition to its primary activity at KCNQ channels, retigabine's augmentation of GABA-mediated inhibitory currents may also contribute a stabilizing effect on neuronal excitability.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The applicant proposes that retigabine immediate release tables are to be administered orally in 3 divided doses daily with or without food. Dosing should begin at 300 mg/day (100 mg tid) for 1 week and then titrated to the recommended maintenance dose by increasing the dose 150 mg/day (50 mg tid) at weekly intervals based on individual patient response and tolerability. The effective dose should be optimized between 600 and 1200 mg/day.

2.2 General Clinical Pharmacology

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

The current NDA submission consists of 44 studies, including 28 Phase 1 studies, 5 completed Phase 2 studies, 2 completed Phase 3 studies, and 6 long-term, open-label extension studies (of which, extensions to two Phase 3 studies remain ongoing). Three additional studies, including two Phase 2 studies in bipolar disorder and in post-herpetic neuralgia (PHN), and a second comparative bioavailability study (RTG113287) were submitted as part of the 120-day safety submission.

To support the proposed indication, the clinical pharmacology program investigated the absorption, distribution, metabolism and elimination characteristics of retigabine following single dose mass-balance study. The impact of intrinsic factors (gender, age, renal impairment, hepatic impairment and race) on the pharmacokinetic of retigabine was investigated following single dose administration of retigabine. The impact of genetic polymorphisms of NAT2 and UGT1A1 on the pharmacokinetics of retigabine was examined following single and multiple dosing. For drug-drug interaction studies, the impact of concomitant retigabine and other drugs or AEDs on pharmacokinetic profiles was investigated. The pharmacokinetics of retigabine and was characterized in both healthy volunteers and epileptic patients. Initial repeat dose studies with retigabine were

conducted using a two times daily dosing regimen (BID), and was subsequently changed to a three times daily dosing regimen (TID). In addition, in-vitro studies using human biomaterial were carried out to investigate the distribution properties of retigabine, its metabolic profiles, and the drug-drug interaction potential involving metabolic enzymes or efflux transporter. Analysis for exposure-response was performed to explore the relationship between systemic exposure to retigabine and efficacy/safety endpoints from the Phase 3 studies, 301 and 302. Additional population analysis for pharmacokinetics and pharmacokinetics/pharmacodynamics were carried out using sparse pharmacokinetic data from the Phase 3 program in refractory epilepsy patients with POS and healthy subjects for retigabine and its N-acetyl metabolite.

The biopharmaceutical development program evaluated comparative bioavailability of various retigabine formulations used in different phases of the drug development, the bridging between various formulations and the dosage strength equivalence, potential effects of high-fat food on pharmacokinetic profile of regitabine from early formulations and from the to-be-marketed formulation of the highest strength. The applicant later submitted a new formulation bridging study between proposed commercial formulations and the clinical formulations used in the Phase 3 clinical trials.

To support the efficacy and safety of retigabine as adjunctive therapy for treating POS, three pivotal studies have been conducted to evaluate the efficacy and safety of retigabine versus placebo in patients with partial-onset seizures taking 1~3 AEDs: a Phase 2b study (Study 3065A1-205 or Study 205) and two Phase 3 studies (Study VRX-RET-E22-301 or Study 301; Study VRXRET-E22-302 or Study 302) conducted in >17 countries. The dosing regimens of retigabine studied in these placebo-controlled pivotal clinical trials are 600 mg/day, 900 mg/day, or 1200 mg/day in Study 3065A1-205, 1200 mg/day in Study VRX-RET-E22-301, and 600 mg/day or 900 mg/day in Study VRXRET-E22-302.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Analysis for exposure-response was performed to explore the relationship between systemic exposure to retigabine and efficacy/safety endpoints from the Phase 3 studies, 301 and 302. For efficacy, two PD endpoints were evaluated: i) the percent change from baseline in seizure frequency and ii) a binary outcome analysis (responder / non responder), where a responder was defined as a subject having a ≥50% reduction from baseline in total partial seizure.

In terms of exposure-safety relationship, six adverse events of interest including coordination abnormal, dizziness, dysarthria, somnolence, tremor, and blurred vision were evaluated in the correlation with retigabine predicted AUC based on the sponsor's logistic regression. All six endpoints showed exposure-dependent relationship.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Refer to Section 2.6 (Analytical Section)

2.2.4 Exposure-response

The sponsor conducted exposure-response analyses to evaluate the relationship between exposure (AUC, μg·h/mL) and two primary endpoints (percent change from baseline to the double-blind period, in total partial seizure frequency per 4 weeks: FDA requirement, proportion of responders experiencing a ≥50% reduction from baseline to the maintenance phase, in total partial seizure frequency per 4 weeks: EMEA requirement) and to support the effectiveness of retigabine in two pivotal studies.

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

There is a significant relationship between the primary endpoint (change in standardized seizure frequency from baseline) and retigabine exposures (AUC, μg·h/mL), which was also confirmed by responder analyses.

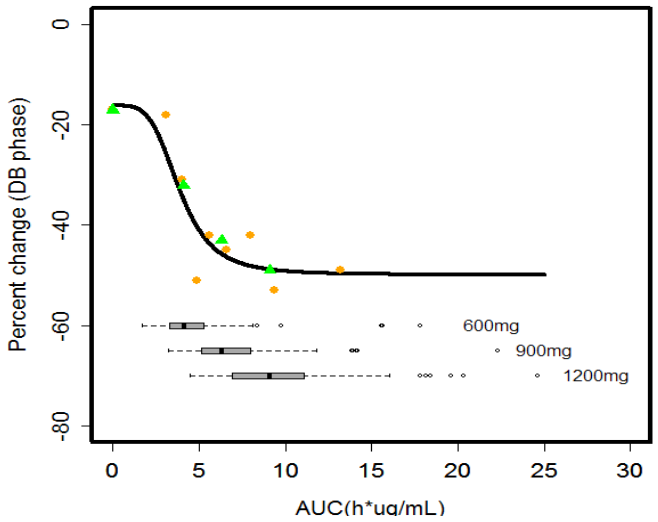
The applicant evaluated the relationship based on two primary endpoints in order to support international registration of retigabine as follows;

1. percent change from baseline to the double-blind period (titration through maintenance), in total partial seizure frequency per 4 weeks: FDA requirement.
2. proportion of responders experiencing a ≥50% reduction from baseline to the maintenance phase, in total partial seizure frequency per 4 weeks: EMEA requirement.

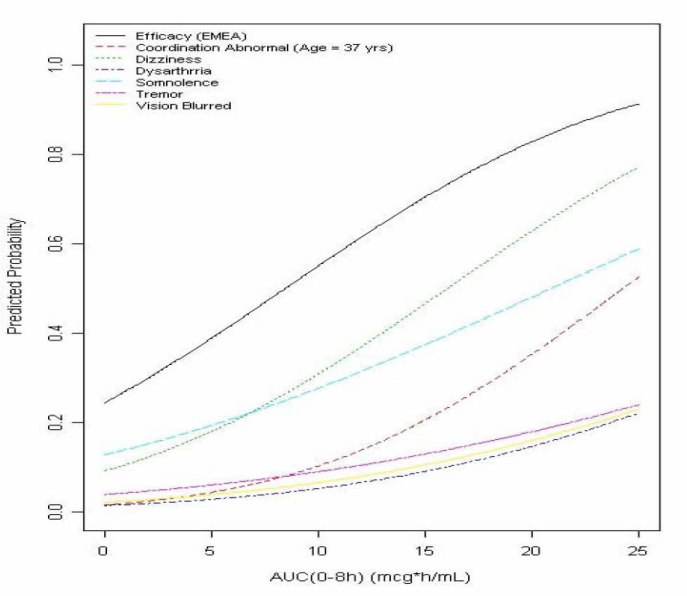
In the efficacy analyses three placebo-controlled studies (study 205, 301 and 302) were included. The results on the percent change in total partial seizure frequency showed that 900 mg/day (300mg TID) and 1200 mg/day (400mg TID) doses were statistically superior to placebo in the studies of 205 and 302 ($p<0.05$) but 600 mg/day (200mg TID) dose was statistically superior to placebo in the study of 302 ($p=0.007$) but not the study of 205 ($p=0.156$). The results from responder analyses showed similar trend.

For the exposure-response analyses, two Phase 3 studies (301 and 302) were included for both efficacy and safety evaluation related to the retigabine concentration.
The efficacy of retigabine was assessed based on both primary endpoints in the correlation with retigabine predicted area under the concentration-time curve (AUC, μg·h/mL). There appears a significant relationship and seems to reach a plateau at 1200mg/day. Based on the reviewer's assessment, the percent reduction during double-blind (DB) phase from baseline in total partial seizure frequency ranged from approximately 17% at placebo to the maximum of 50% reduction.

The Figure below demonstrates the relationship between percent change in seizure frequency during DB phase from the baseline and AUC (µg·h/mL) from the studies of 301 and 302. Then orange dots and green triangles indicate the observed percent reduction during DB phase at decile of AUC and at each dose group which were marked at the median exposure. The boxplots represent the distribution of exposure at three dose levels.



The Figure below displays the probability of responder (≥50% reduction in seizure frequency) along with the probability of six adverse events of interest including coordination abnormal, dizziness, dysarthria, somnolence, tremor, and blurred vision in the correlation with retigabine predicted AUC based on the sponsor's logistic regression. AUC was found to be significant predictors for the probability of responder, meaning that the probability of responder tends to go up as the exposure is increased. In terms of safety endpoints, all six endpoints showed exposure-dependent relationship. The slope of the exposure-response relationship for probability of responder was similar to that for dizziness and coordination abnormal whereas the slope of the exposure response relationship for dysarthria, somnolence, tremor and vision blurred were less steep, indicating that these latter AEs were less sensitive to changes in exposure.



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Refer to answer 2.2.4.1.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Yes, retigabine produced a QT-prolonging effect in healthy volunteers titrated to 400 mg TID. "The maximum mean (upper 1-sided, 95% CI) increase of baseline and placebo adjusted QTc interval based on Fridericia correction method (QTcF) was 7.7 ms (11.9 ms) and was observed at 3 hours after dosing." Therefore, the QT frequency should be monitored when POTIGA is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia. Details are available in Dr. of review for thorough QT study review conducted by Dr. Hao Zhu of the QT-IRT review team.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (In some cases, it may be possible to combine this with 2.2.4.2 and 2.2.4.3.)

Refer to answer 2.2.4.1. There is no unresolved dosing or administration issue.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Single-Dose in Healthy Volunteers:

The pharmacokinetics of retigabine increased linearly across a dose range of 25 to 600 mg after single oral dosing (Study 3065A1-100), as shown in Figures and Table below. Dose-proportionality and dose-independence were observed following single dose administration. The pharmacokinetics of retigabine were characterized as fast absorption with Tmax of the first peak ranging 0.67~1.5 h and a terminal t1/2 values ranging 9~14 h. The second peak phenomenon observed in plasma concentration-time profiles, with median Tmax at approximately 1.75~4 h postdose, suggests potential enterohepatic re-circulation of the drug or other unknown mechanisms.

Figure. Mean Plasma Concentration-Time Profiles of Retigabine after Single Oral Administration of 25 to 600 mg Retigabine

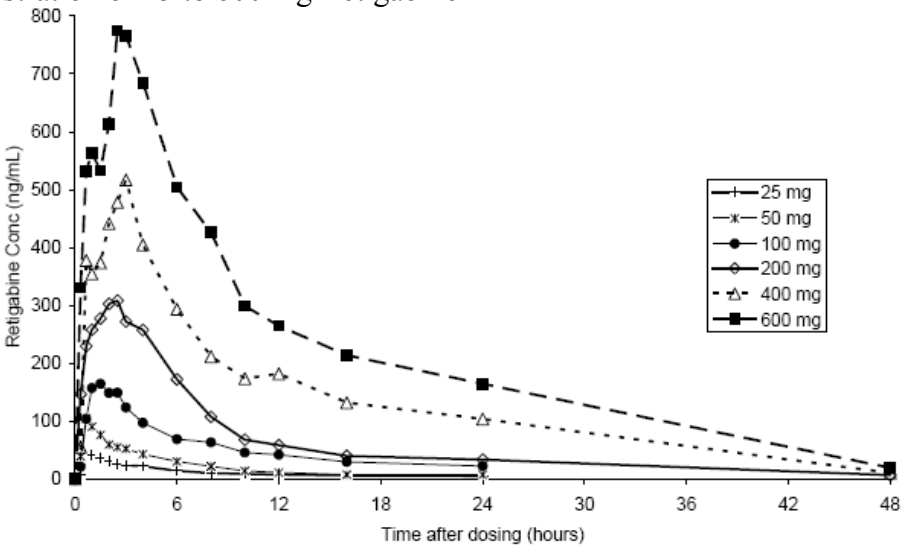
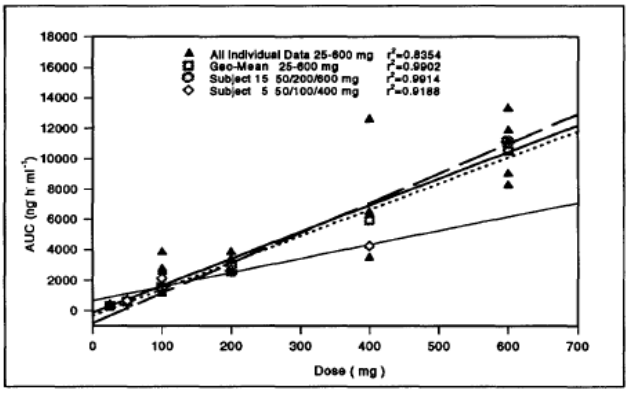
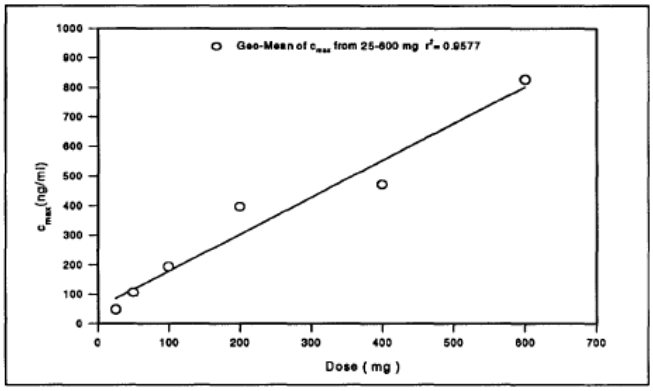


Table. Retigabine Pharmacokinetic Parameters after Administration of a Single Oral Dose in Healthy Male Subjects

Dose (mg)	C_{max} (ng/mL)	AUC (ng*h/mL)	t_{max} (h)	$t_{1/2}$ (h)
	Geometric Mean (CV_{in} %)	Geometric Mean (CV_{in} %)	Median (Min, Max)	Median (Min, Max)
25	47 (25.4)	313 (27.7)	0.66 (0.66, 1.0)	13.5 (5.3, 17.3)
50	104 (27.5)	584 (20.0)	0.66 (0.66, 1.0)	10.2 (3.2, 20.5)
100	192 (45.5)	1545 (33.8)	1.50 (0.66, 2.0)*	10.8 (6.4, 14.8)
200	396 (20.7)	2952 (18.8)	1.50 (0.33, 2.5)	10.1 (7.3, 15.5)
400	470 (58.5)	5945 (52.7)	0.66 (0.66, 2.0)	10.3 (7.1, 13.7)
600	825 (21.0)	10,552 (19.9)	0.66 (0.33, 4.0)	9.3 (7.3, 10.7)

Figure. Dose linearity: Regression of means of AUC (r^2= 0.9902) and Cmax (r^2= 0.9577)





BID Regimen in Healthy Volunteers:
Following repeated BID dosing, the steady-state exposure (Cmax and AUC) of retigabine increased linearly with increasing dose up to 350 mg BID. As shown in the Table below, the PK parameters obtained after repeated dosing are similar to those observed following single doses. The accumulation ratios at the steady state ranged 1.5~2.7. There was no significant accumulation of retigabine with the BID dosing regimens. Similar PK properties of NAMR following BID regimen were observed compared to single doses.

Table. Retigabine Pharmacokinetic Parameters (Mean ± SD) after Administration of Single (Day 1) or Multiple (Day 15) BID Oral Doses of Retigabine in Healthy Males

Parameter	Day	100 mg BID	200 mg BID	250 mg BID	300 mg BID/ 350 mg BID*
C_{max} (ng/mL)	1	414 ± 282	819 ± 202	842 ± 352	1071 ± 287
	15	498 ± 255	978 ± 169	993 ± 370	1593 ± 198
t_{max} (h)	1	1.5 ± 0.8	1.8 ± 0.5	1.7 ± 0.7	1.4 ± 0.7
	15	0.9 ± 0.3	1.5 ± 0.9	0.9 ± 0.3	2.1 ± 0.6
[a]AUC (ng*h/mL)	1	1831 ± 739	5134 ± 1663	5136 ± 994	7823 ± 884
	15	1914 ± 789	5279 ± 984	5184 ± 1665	9522 ± 874
$t_{1/2}$ (h)	1	8.4 ± 1.9	7.4 ± 2.9	7.9 ± 3.3	9.2 ± 3.0
	15	7.2 ± 1.0	7.0 ± 1.4	6.8 ± 1.0	7.0 ± 1.6
CL/F (L/h/kg)	1	0.72 ± 0.17	0.58 ± 0.20	0.62 ± 0.15	0.53 ± 0.07
	15	0.71 ± 0.24	0.51 ± 0.10	0.67 ± 0.28	0.51 ± 0.05
[b] Accumulation factor	15	2.7 ± 0.8	1.8 ± 0.6	1.8 ± 0.4	1.5 ± 0.3

BID Regimen in Epileptic Patients:
Steady-state PK parameters of retigabine following repeated retigabine 50, 100 and 200 mg BID oral doses were characterized in patients with epilepsy (Study 3065A1-101). As shown in Figure and Table below, overall the PK parameters and exposure measures are similar to those observed in healthy subjects, with median Tmax being approximately 1 hour postdose and a peak-to-trough ratio approximately 4~6.5-fold at steady state.

Figure. Median Plasma Concentration-Time Profiles for Retigabine and NAMR Metabolite After Repeated BID Dosing in Epileptic Patients

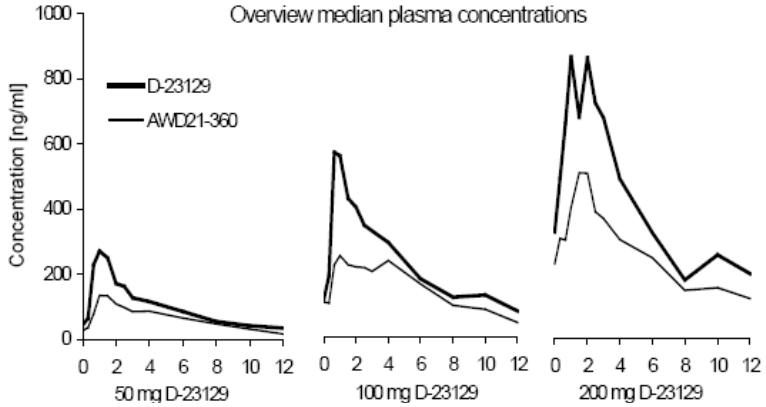


Table. Pharmacokinetic Parameters of Retigabine following Retigabine 50 mg, 100 mg, and 200 mg BID Dosing in Epileptic Patients with Partial-Onset Seizures

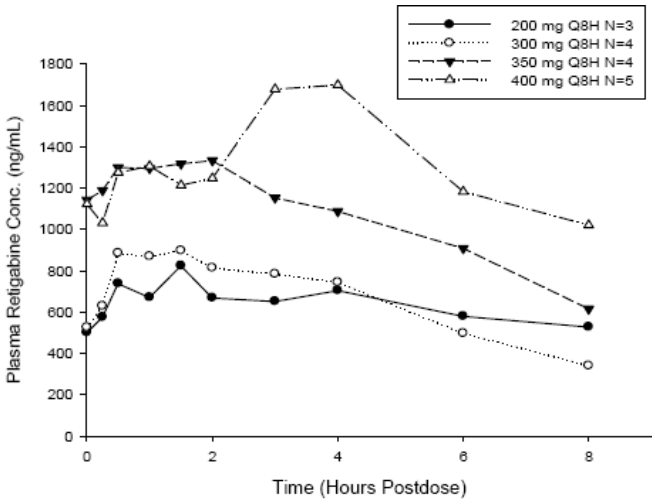
Parameter	50 mg BID	100 mg BID	200 mg BID
Cmax (ng/mL)	282 [287]	607 [625]	994 [1001]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(230 – 346)	(475 - 776)	(841 – 1174)
AUC0-12h (ng*h/mL)	1085[a] [1107]	2174[b] [2179]	5584[b] [5593]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(596 – 1975)	(1938 - 2440)	(5012 - 6221)
Tmax (h)	1.08[c]	1.05	1.08
Median (min, max)	(0.78, 1.49)	(0.67, 8.00)	(0.38, 2.53)
t1/2 (h)	6.00 [5.60][e]	5.53[d] [6.03]	4.78 [6.39]
Median (min, max)	(4.46, 112)	(3.99, 9.52)	(4.39, 9.20)
Ctrough (ng/mL)	43.3 [45.9]	143 [209]	289 [308]
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(29.2 - 64.3)	(65.1 - 315)	(174 - 479)
Ratio Cpeak/Ctrough	6.54[c]	4.24	3.44
$Mean_{geo}$ (95% CI_{ln}, LL-UL)	(4.02 - 10.6)	(2.28 - 7.87)	(1.85-6.40)

[a] N=3, [b] N=4, [c] N=5, [d] N=6; [e] Patient #1 excluded as outlier (N=5); values in [ ] represent arithmetic mean

TID Regimen in Epileptic Patients:

Following repeated TID dosing (Study VRX-RET-E22-301), the steady-state exposure (Cmax and AUC) of retigabine increased dose-proportionally linearly with increasing dose up to 400 mg TID (1200 mg/day). The PK parameters and exposure measures are similar to those observed in previous single or repeated dose studies. Lesser peak-to-trough ratios of approximately 2~3-fold for the TID dosing regimen were observed compared with the greater fluctuation after BID dosing. The PK profiles of retigabine and NAMR metabolite are presented in Figure and Tables below.

Figure. Mean Plasma Retigabine (Left) and Its N-acetyl Metabolite (Right) Concentration-Time Profiles following Administration of Retigabine 200-400 mg TID (Q8H) in Patients with Epilepsy



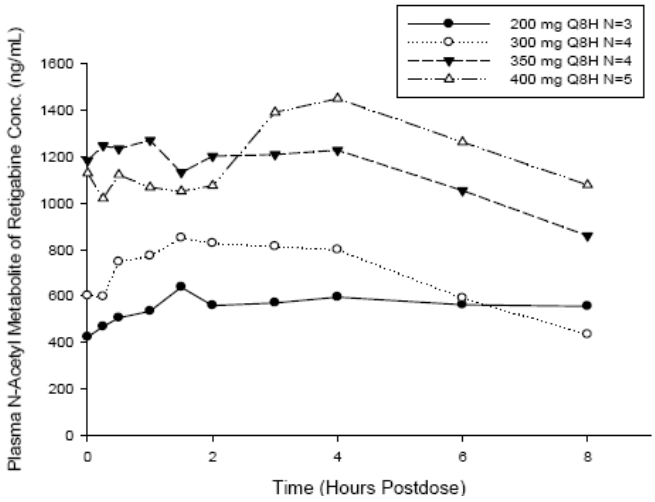


Table. Mean Retigabine Pharmacokinetic Parameters following Administration of Retigabine 200-400 mg TID in Epileptic Patients with Partial Onset Seizures

Parameter Mean ± SD	200 mg TID N=2	300 mg TID N=4	350 mg TID N=4	400 mg TID N=5
$AUC_{0-\tau}$ (ng•h/mL)	5445	5267 ± 2069	8548 ± 1806	10698 ± 5121
C_{max} (ng/mL)	940	1014 ± 366	1432 ± 325	1850 ± 1001
t_{max} (h)	1.0	1.0 ± 0.4	1.4 ± 0.8	2.3 ± 1.5
C_{min} (ng/mL)	507	339 ± 156	743 ± 277	891 ± 156
*Ratio C_{peak}/C_{trough}	1.85	3.28 ± 0.91	2.05 ± 0.67	2.01 ± 0.78

Table. Mean Pharmacokinetic Parameters of N-acetyl Metabolite of Retigabine following Administration of Retigabine 200-400 mg TID in Epileptic Patients

	200 mg TID (N=2)[a]	300 mg TID (N=4)	350 mg TID (N=4)	400 mg TID (N=5)
Pharmacokinetic Parameter	**Mean**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
C_{max} (ng/mL)	780	885 ± 419	1402 ± 544	1523 ± 612
t_{max} (hr)	2.92	1.66 ± 0.43	1.19 ± 0.63	2.20 ± 2.05
$AUC_{0-\tau}$ (ng·hr/mL)	4898	5551 ± 2788	9087 ± 2787	9847 ± 3141
C_{min} (ng/mL)	479	434 ± 242	854 ± 130	910 ± 139
C_{avg} (ng/mL)	612	694 ± 349	1136 ± 348	1231 ± 393
FI (%)	51.5	68.4 ± 26.3	44.0 ± 19.1	44.0 ± 24.6

[a] Patient 01403 was excluded from pharmacokinetic analysis.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics of retigabine have been studied in healthy subjects and in epilepsy patients following a twice daily dosing regimen. As shown in Table below, overall the PK properties of retigaine and NAMR appear to be comparable in healthy subjects and in epileptic patients. The representative PK parameters are seen in Sections 2.2.5.3~2.2.5.10.

In healthy volunteers, repeat dose PK data is available over the dose range of 50-200 mg bid (3065A1-101) and over the dose range of 100~350mg bid (3065A1-102). In epilepsy patients pharmacokinetic data is available over the dose range 50-200 mg bid (3065A1-200/201). The Cmax and AUC_{0-12} values of retigabine following bid administration (50, 100 or 200 mg) observed in the healthy subject study 3065A1-100 were generally lower than those observed in the healthy subject study 3065A1-102. However, the Cmax and AUC_{0-12} values of retigabine and its acetyl metabolite observed in the healthy subject study 3065A1-102 were similar to those observed in both the epilepsy subject studies.

Table. Geometric Mean Cmax and AUC_{0-12} values of Retigabine in Healthy Subjects and Patients with Epilepsy

Dose	Population	Study	Cmax (ng/mL)	AUC(0-12) (ng h/mL)
50mg BID	Healthy	3065A1-100	156	625
	Epilepsy	3065A1-200	266	1181
	Epilepsy	3065A1-201	282	1085
100mg BID	Healthy	3065A1-100	269	1331
	Healthy	3065A1-102	498	1914
	Epilepsy	3065A1-200	418	2247
	Epilepsy	3065A1-201	607	2174
200mg BID	Healthy	3065A1-100	581	2841
	Healthy	3065A1-102	978	5279
	Epilepsy	3065A1-200	925	5299
	Epilepsy	3065A1-201	994	5584

2.2.5.3 What are the characteristics of drug absorption?

Retigabine is generally rapidly absorbed after single or multiple oral dosing, with Tmax values ranging from approximately 0.5~2.0 hours. The absolute bioavailability of retigabine from oral capsule is approximately 60% (~68.5% estimated by population PK analysis). Mass balance studies show 84% urinary recovery of drug related material, suggesting that retigabine is well absorbed following oral administration.

Retigabine was shown to be highly permeable in Caco-2 cell test systems. Retigabine was shown to be neither a substrate of P-glycoprotein (P-gp) nor significantly inhibit the P-gp mediated transport activity. The acetyl-metabolite NAMR may inhibit the P-gp mediated drug transport at much higher concentrations of ≥10 μM, which is unlikely to result in clinically significant interaction with oral absorption of other drugs that are P-gp substrates via this efflux transport system.

2.2.5.4 What are the characteristics of drug distribution?

The steady-state volume of distribution (Vss) of retigabine was approximately 2-3 L/kg, suggesting that retigabine is well distributed in body. Data from *in-vitro* protein-binding studies suggests that the plasma protein binding of both retigabine and NAMR are approximately 80% and 45%, respectively, over the concentration range of 0.1~2 μg/mL. The clinically significant drug interactions via protein binding displacement with

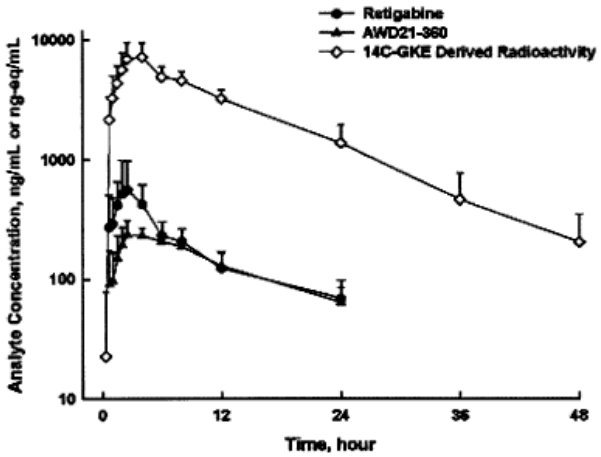
retigabine administration were not anticipated. Results from human mass-balance study indicate that the whole blood-to-plasma ratio for the radioactivity ranged 0.55~0.68, indicating that retigabine does not significantly partition into cellular components of blood.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Results of mass balance study following oral radiolabeled [^{14}C]-Retigabine suggest that renal is the major route of elimination for retigabine, as retigabine and its acetyl- and glucuronide-metabolites are mainly eliminated via the renal route into urine. Approximately 98% of the radiolabeled dose was recovered within 240 hours postdose, while majority (93%) of administered radiolabel was recovered within 72 hours postdose. Of the total recovery, 84% was recovered in the urine with unchanged parent drug accounting for 36% of the administered dose, along with 7 other metabolites (of which 6 were present in the plasma). Another 13.5% of the radioactivity was recovered in the feces with unchanged retigabine accounting for 3% of the total dose, along 3 new minor metabolites (possibly formed in gut).

A total of 7 metabolites were identified in human plasma, along with the parent drug. Results indicate that retigabine metabolites accounted for more than 90% of total radioactivity in the plasma, and suggest that retigabine N-glucuronide is the dominant metabolite. The contribution of retigabine and NAMR (AWD21-360) to the AUC of total radioactivity ranged 3.3~8.4% (5.18% based on mean values) and 3.5~6.5% (4.21% based on mean values), respectively. Based on the mean plasma concentrations of retigabine and total radioactivity, unchanged drug (retigabine) accounted for 3.9~11.0% of the total radioactivity at all time points, suggesting that retigabine is extensively metabolized. The plasma concentration-time profiles of major circulating moieties are presented in the Figure below.

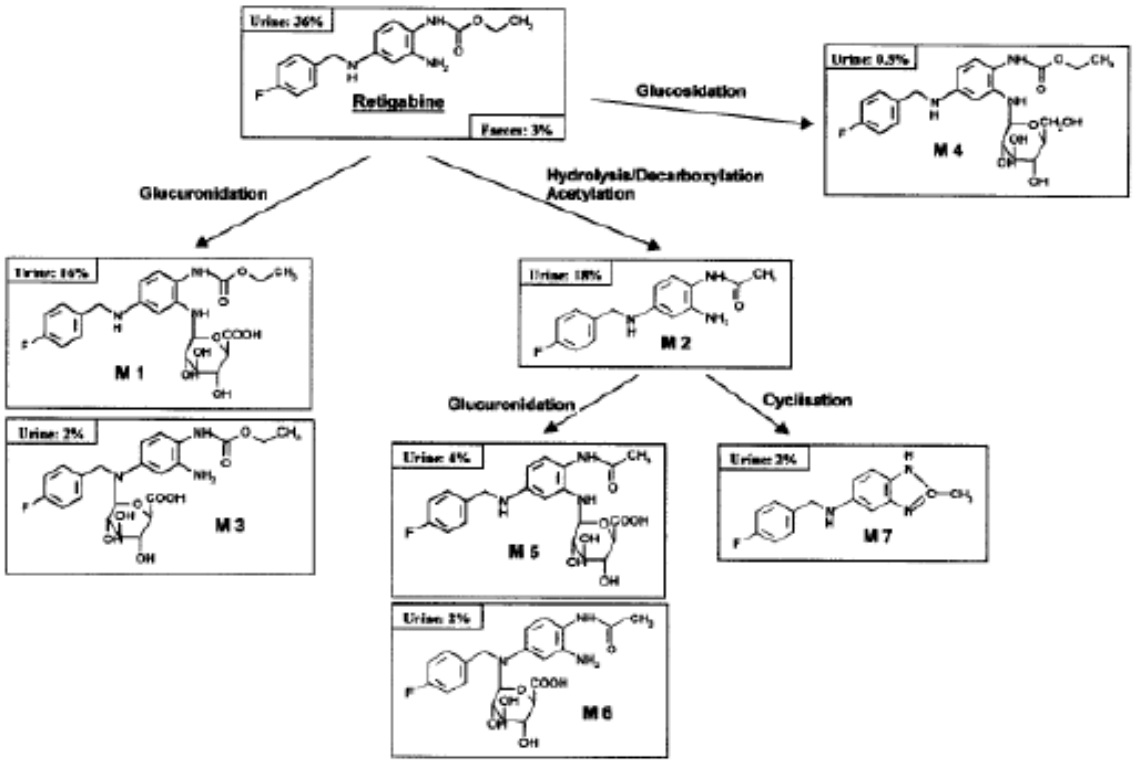
Figure. Retigabine, NAMR (AWD21-360) and [^{14}C]-Retigabine (^{14}C-GKE)-Derived Radioactivity Concentration-Time Profiles after Administration of a Single 200 mg Dose of [^{14}C]-Retigabine in Healthy Male Volunteer



2.2.5.6 What are the characteristics of drug metabolism?

Retigabine is metabolized extensively through formation of the NAMR metabolite and through N-glucuronidation of both retigabine and NAMR. In vitro studies using human biomaterials showed that the N-acetylation of retigabine was primarily carried out by NAT2, while glucuronidation was primarily carried out by UGT1A4, followed by UGT1A1, and then UGT1A3 and UGT1A9. Additional minor metabolites of retigabine are an N-glucoside of retigabine and a cyclized metabolite believed to be formed from NAMR. There is a lack of evidence for oxidative metabolism of retigabine via CYP450 enzymes. The proposed metabolic pathway is presented in the schematics below.

Figure. Proposed Metabolic Pathway for Retigabine



In human plasma, the N2- glucuronide of retigabine is the predominant metabolite. However, considering the generally low pharmacologic activity of glucuronide conjugates, the N-glucuronides of retigabine are not expected to contribute to the overall safety or activity profile of retigabine. NAMR, which had substantially less activity than retigabine in *in vitro* and *in vivo* pharmacology models (1/5~1/10), is also a circulating metabolite of retigabine.

2.2.5.7 What are the characteristics of drug excretion?

The CL of retigabine following intravenous dosing is typically 0.4-0.6 L/h/kg. Special population PK studies and the population PK analysis indicate that retigabine CL/F is predominantly affected by renal function and body size (BSA), with decreased CL/F

observed with decreasing CLcr and increased clearance observed with increasing BSA. Based on the renal clearance (CL_R) values in healthy volunteers, as presented in Sections 2.3.2.5 and Section 2.3.2.6, retigabine is actively secreted into urine. Retigabine and NAMR have similar terminal t1/2 ranging 7-11 hours.

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

The AUC and Cmax of retigabine increased linearly with increasing dose up to 600 mg after single oral dosing. The steady-state exposure of retigabine in subjects with epilepsy increased linearly with increasing dose up to 400 mg TID.

In the population PK analysis, dose was shown to be a statistically significant covariate on the retigabine clearance, with clearance values decreasing with increasing dose. However, this appears to have been mainly driven by higher clearance values in the 100 mg dose group rather than a true dose dependant change in clearance of retigabine.

The predicted exposures to retigabine from the final population PK model showed approximately linear increases in systemic exposure to retigabine over the dose range studied in the primary efficacy trials (200~400 mg TID).

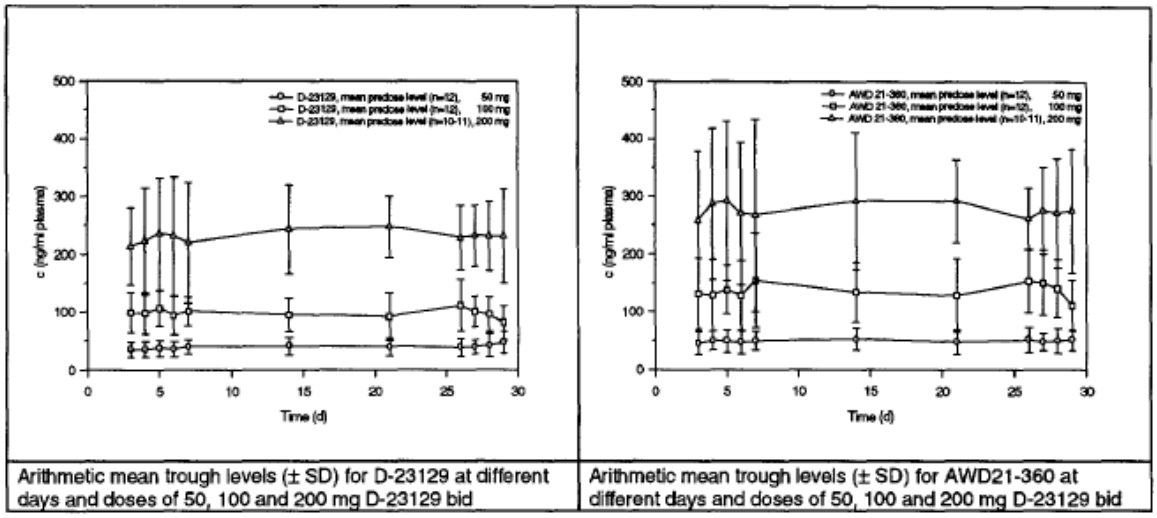
2.2.5.9 How do the PK parameters change with time following chronic dosing?

The PK profiles following repeated BID dosing in healthy subjects or epileptic patients (Study 3065A-200/201) are characterized by linearity and dose proportionality in systemic exposure (Cmax and AUC) of retigabine and NAMR metabolite. Both CL/F and estimated terminal t1/2 appear to be dose-independent.

The accumulation ratios of retigabine at steady state was 1.3~1.9 in Study 3065A-101 with 50-200 mg BID regimen for 29 days, and was approximately 1.5~2.7 in Study 3065A-102 with 100-350 mg BID regimen for 15 days. No clear evidence of auto-induction for retigabine was observed.

In an open-label extension to Study VRX-RET-E22-301, the multiple-dose PK of retigabine and NAMR was evaluated in epileptic patients who had maintained retigabine 200-400 mg TID (Q8h) dosing regimens (600–1200 mg/day) for at least 2 weeks. Similar PK characteristics were observed in epileptic patients vs. healthy subjects for the duration of the study (see Sections 2.2.5.1.~2.2.5.2.). In Study 3065A1-101 for PK of multiple BID doses in healthy subjects, mean trough levels of retigabine and its acetyl metabolite remained similar for the duration of 29 days, as presented in Figure below.

Figure. Mean trough levels of Retigabine and its metabolite AWD21-360 during exposure.



Arithmetic mean trough levels (± SD) for D-23129 at different days and doses of 50, 100 and 200 mg D-23129 bid

Arithmetic mean trough levels (± SD) for AWD21-360 at different days and doses of 50, 100 and 200 mg D-23129 bid

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Following single doses of retigabine to healthy subjects, the between-subject variability of retigabine AUC was generally in the range 20-30% (~40%) was observed in one study (3065A1-123) following oral administration of capsule formulation. For Cmax, between-subject variability was generally in the range 20-45%, although between subject variability as high as ~54% was observed in the same study 3065A1-123.

The population PK analysis for retigabine identified the creatinine clearance (CR_{CL}), body surface area (BSA), dose and the use of lamotrigine on clearance (CL) and age on volume of distribution (V) as the statistically significant covariates. For NAMR, CR_{CL} and SGPT were the significant covariates on CL and dose on V. However, the effects didn't appear to be clinically meaningful.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Intrinsic factors, such as age, gender, race, hepatic impairment, renal impairment, and genetic polymorphism were studied in Phase 1 trials and were shown to have impact on PK exposure of retigabine, as described in the following Sections.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The recommendations for potential dosage regimen adjustments are made on the basis of PK exposure alteration by the intrinsic factors. Details are delineated in the following Sections.

2.3.2.1 Age

The impact of age and gender on the pharmacokinetics of retigabine was investigated following a single dose of retigabine to healthy young (21-40 years of age) and elderly (66-82 years of age), male and female subjects. The mean plasma concentration-time profiles and mean PK parameters of retigabine are presented in the Figure and Table below. Similar trends of PK differences were observed for NAMR.

Figure. Mean Plasma Retigabine Concentration-Time Profiles Following Administration of Retigabine 200 mg to Healthy Young (left) And Elderly Subjects (right), (N=12 per group)

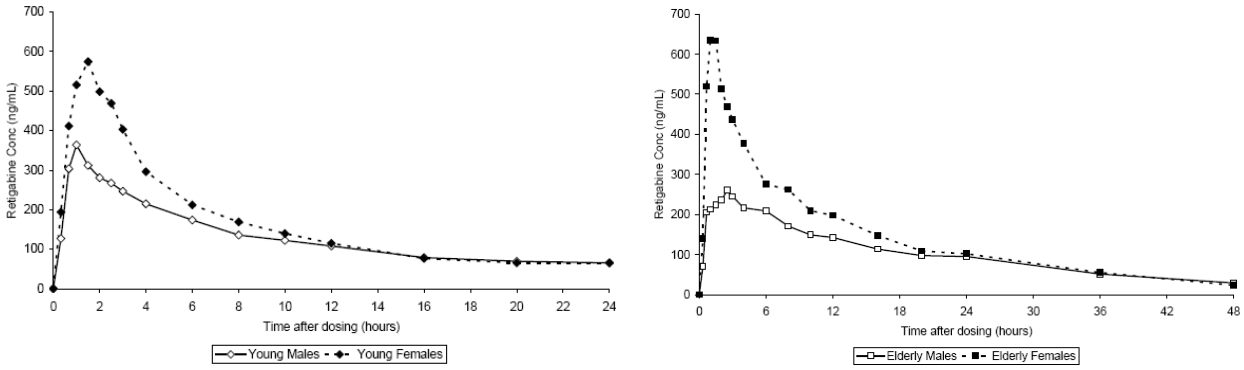


Table. Pharmacokinetic Parameters (Mean± SD) of Retigabine after Administration of a Single Oral Dose of 200 mg Retigabine to Healthy Young and Elderly Men and Women (N=12 per group)

Parameter	Younger Subjects		Elderly Subjects		p-Values [a]	
	Men	Women	Men	Women	Age	Sex
C_{max} (ng/mL)	421 ± 288	656 ± 279	354 ± 119	717 ± 409	0.971	0.001
AUC (ng*h/mL)	3970 ± 1083	4753 ± 968	5425 ± 1132	7108 ± 1573	0.001	0.001
t_{max} (h)	2.0 ± 1.5	1.2 ± 0.7	3.1 ± 2.7	2.7 ± 3.1	0.048	0.338
$t_{1/2}$ (h)	8.5 ± 2.2	7.7 ± 2.2	12.2 ± 4.2	8.9 ± 1.4	0.003	0.014
CL/F (L/h/kg)	0.67 ± 0.15	0.68 ± 0.15	0.48 ± 0.10	0.46 ± 0.10	0.001	0.900

a: *p*-Values from the ANOVA of untransformed values

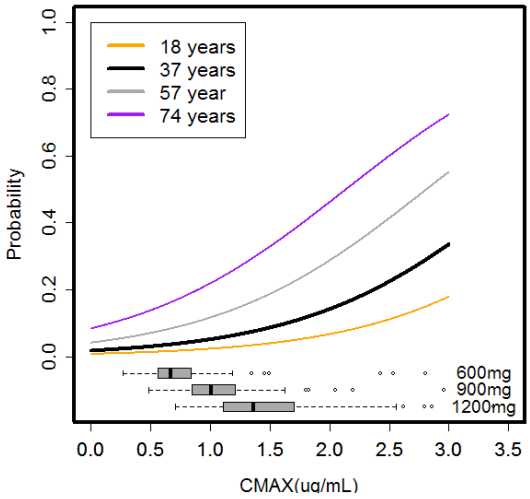
Statistically significant differences were observed between male and female subjects and between young and elderly subjects, with female subjects having a higher retigabine systemic exposure than males and elderly subjects having a higher systemic exposure than young subjects.

The AUC values were ~20% higher in young females compared to young males and ~30% higher in elderly females compared to elderly males. These differences in AUC are likely to be attributable to differences in body weight because there were no

differences in weight-normalized CL/F of retigabine between male and female subjects. However, Cmax values were ~50% higher in young females compared to young males and ~100% higher in elderly females compared to elderly males.

Cmax values in the elderly subjects were similar to those observed in young subjects. However, AUC values were ~40-50% higher in elderly subjects compared to young subjects and half-life was ~30% longer in elderly compared to young subjects across males and females. The weight-normalized CL/F of retigabine is lower in elderly subjects than in young subjects.

The applicant proposes no dose adjustment based on age or gender. However, the Agency reanalyzed the data and the percent probability of coordination abnormal (an adverse event of interest) was found to significantly increase with the increase of age across the proposed doses, probably due to increased sensitivity to retigabine levels in the elderly. Figure below illustrates the relationship between percent probability of coordination abnormal and peak plasma concentrations of retigabine across the proposed doses.



In view of the magnitude of increases in systemic exposure (Cmax and AUC) and in probability of coordination abnormal (a safely concern) in the elderly subjects vs. young subjects, we recommend that a dose reduction to approximately two-thirds of the target dose should be considered for the elderly patients.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The applicant has submitted the Proposed Pediatric Study Request (PPSR) for the study of retigabine in pediatric patients and requested a waiver for patients aged 0~1 year. The Agency placed the study on hold for patients under 12 years of age because of the urologic safety concern.

2.3.2.3 Gender

Referred to Section 2.3.2.1.

2.3.2.4 Race

No clinical pharmacology study was conducted to determine the impact of race on the pharmacokinetic profile of retigabine and its major metabolite. Instead, a meta-analysis was conducted to compare retigabine CL/F parameters between healthy Black and Caucasian subjects by pooling data from 6 single-dose clinical pharmacology studies (3065A1-102, 3065A1-107, 3065A1-109, 3065A1-110, 3065A1-113, and VRX-RET-E22-105). The analysis data set consisted of 118 male subjects (43 Black and 75 Caucasian) who received retigabine as a single oral dose of 100, 200, 250, 300 or 400 mg. A linear mixed-effects model, with race and dose as the fixed effects and subject as the random effect, was used to analyze natural-logarithmic transformed CL/F values. The geometric mean of retigabine CL/F was 43.3 L/hr for Black subjects and 53.6 L/hr for Caucasian subjects. The Black/Caucasian ratio of geometric LS means was 80.7% with a 90% confidence interval of (73.3%, 88.7%).

In population PK analysis to investigate the covariates (e.g., impact of race) that have potential impact on CL of retigabine, the covariate of race was coded as dichotomous, namely Caucasian vs. non-Caucasian, since 83.4% of the subjects were Caucasians. Race was found not to be a significant covariate. However, result is not considered conclusive because of the small sample size of non-Caucasian population.

2.3.2.5 Renal impairment

An open-label, single-dose, parallel-group study (VRX-RET-E22-101) was conducted in subjects with normal renal function (CLcr >80 mL/min), mild (CLcr ≥50 to ≤80 mL/min), moderate (CLcr ≥30 to <50 mL/min) or severe (CLcr <30 mL/min) renal impairment, and ESRD requiring hemodialysis following single-dose administration of retigabine 100 mg. This study demonstrated that pharmacokinetics of retigabine and the systemic exposure to retigabine and its NAMR metabolite are dependent on degrees of renal function, as shown in Tables below.

Table. Pharmacokinetic Parameters of Retigabine and NAMR following Administration of a Single 100 mg Retigabine Tablet in Healthy and Renally Impaired Subjects

Analyte / Parameter	Mean ± SD				
	Group 1 (Healthy, N=6)	Group 2 (Mild, N=6)	Group 3 (Moderate, N=8)	Group 4 (Severe, N=5)	Group 5 (ESRD, N=6)
RTG					
$AUC_{0\text{-}inf}$ (ng*h/mL)	1700 ± 514	2166 ± 420	4888 ± 4868	3533 ± 1078	3557 ± 478
C_{max} (ng/mL)	269 ± 106	271 ± 142	434 ± 268	256 ± 127	127 ± 63.0
t_{max} (h)[a]	1.00 (0.67, 1.50)	0.83 (0.67, 3.00)	0.83 (0.67, 5.00)	1.00 (1.00, 1.50)	0.83 (0.33, 36.0)
$t_{1/2}$ (h)	8.21 ± 3.82	11.1 ± 1.26	15.6 ± 3.89	19.9 ± 7.09	22.8 ± 5.12
CL/F (L/h)	65.1 ± 26.0	47.5 ± 8.27	28.9 ± 10.3	30.6 ± 9.40	28.5 ± 3.48
CL_R (L/h)	13.5 ± 7.56	10.3 ± 2.75	5.68 ± 2.61	4.37 ± 2.12	0.058
%Dose Excreted	21.9 ± 15.1	20.8 ± 5.16	18.6 ± 4.51	12.9 ± 5.13	0.18
NAMR					
$AUC_{0\text{-}inf}$ (ng*h/mL)	1792 ± 394	2702 ± 636	4620 ± 1948	4896 ± 1576	6774 ± 1653
C_{max} (ng/mL)	137 ± 29.1	158 ± 17.8	235 ± 67.0	186 ± 40.3	142 ± 41.6
t_{max} (h)[a]	2.25 (1.00, 3.00)	2.75 (2.00, 6.00)	2.75 (0.67, 6.10)	2.50 (1.50, 3.00)	3.25 (1.50, 36.0)
$t_{1/2}$ (h)	8.74 ± 3.51	12.3 ± 2.84	15.3 ± 5.90	21.8 ± 9.12	30.8 ± 10.6
CL_R (L/h)	5.59 ± 3.87	5.83 ± 0.99	3.68 ± 1.66	2.78 ± 1.05	0.058
%Dose Excreted	9.40 ± 6.50	14.6 ± 3.71	14.0 ± 3.46	13.0 ± 5.68	0.40

Table. Statistical Analysis on Effect of Renal Impairment on the Single-Dose Pharmacokinetics of Retigabine

Pharmacokinetic Parameters	% MR (90% CI)[b]			
	Group 2 vs Group 1	Group 3 vs Group 1	Group 4 vs Group 1	Group 5 vs Group 1
$AUC_{0\text{-}t}$ (ng*hr/mL)	134.31 (101.76, 177.28)	195.70 (148.27, 258.31)	217.63 (161.89, 292.57)	219.13 (168.17, 285.52)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	130.70 (100.11, 170.65)	192.42 (147.37, 251.23)	215.48 (162.16, 286.34)	217.52 (168.68, 280.50)
C_{max} (ng/mL)	98.95 (56.02, 174.77)	111.84 (63.32, 197.55)	100.98 (55.06, 185.18)	46.65 (27.12, 80.25)

Table. Impact of Various Degrees of Renal Impairment on Retigabine and NAMR Exposure

Degree of Renal Impairment	Fold Increase (RTG)	
	AUC	Cmax
Mild	1.3	1.0
Moderate	2.0	1.1
Severe	2.2	1.0
ESRD	2.2	0.5

Degree of Renal Impairment	Fold Increase (NAMR)	
	AUC	Cmax
Mild	1.5	1.2
Moderate	2.2	1.5
Severe	2.4	1.4
ESRD	3.8	1.0

The applicant proposed a 50% dose reduction in patients with CLcr<50ml/min (Moderate, Severe, and ESRD), while no dose adjustment is needed for mild renal impairment. We notice that the predominant glucuronide conjugate in systemic circulation was not monitored in this study, and thus the magnitude of accumulation is unknown in the presence of various degrees of renal dysfunction. The clinical significance of the magnitudes of the anticipated accumulation of the major glucuronides

is not known, and thus any concern for unwanted effects. Per communication with nonclinical and clinical review teams, glucuronides (other than acyl glucuronides), an inactive species, in general are of less concern for toxicity. From a clinical pharmacology perspective, given the above information, we concur with the sponsor's proposal regarding dosage adjustment for the use of retigabine in patients with CLcr<50ml/min.

Effect of dialysis for ESRD patients was not adequately evaluated in this study to allow clearly understanding for potential need for any dose adjustment in ESRD patients on hemodialysis.

2.3.2.6 Hepatic impairment

The plasma PK of retigabine following a single 100-mg dose of retigabine was evaluated in mild (Child-Pugh Score 5−6), moderate (Child-Pugh Score 7−9), and severe (Child-Pugh Score >9) hepatic impairment and compared to the PK in subjects with normal hepatic function (6 subjects in each cohort) (Study VRX-RET-E22-102). Retigabine AUC parameters and CL values were similar in subjects with mild hepatic impairment vs. healthy control group. However, impact of moderate or severe hepatic impairment on retigabine exposure was clearly observed, as shown in Tables below.

Table. Pharmacokinetic Parameters of Retigabine following Administration of a Single 100 mg Retigabine Dose in Healthy Subjects and Patients with Hepatic Impairment

Parameter	Mean ± SD			
	Group 1 (Healthy, N=6)	Group 2 (Mild, N=6)	Group 3 (Moderate, N=6)	Group 4 (Severe, N=6)
AUC_{0-t} (ng*h/mL)	1329 ± 578	1126 ± 137	2116 ± 924	2861 ± 1164
AUC_{0-inf} (ng*h/mL)	1458 ± 658	1231 ± 169	2218 ± 930	3019 ± 1179
C_{max} (ng/mL)	308 ± 174	207 ± 58.0	364 ± 63.6	396 ± 199
t_{max} (h) [a]	0.667 (0.667, 1.00)	1.25 (0.667, 4.00)	0.667 (0.333, 1.50)	1.50 (1.00, 3.00)
$t_{1/2}$ (h)	7.31 ± 1.89	8.17 ± 2.17	6.46 ± 1.36	7.43 ± 1.11
CL/F (L/h)	80.0 ± 31.2	82.7 ± 12.6	53.5 ± 24.9	38.4 ± 16.5
CL_R (L/h)	13.1 ± 5.90	14.2 ± 3.12	9.77 ± 5.84	5.66 ± 1.99

Table. Statistical Assessments of Retigabine Systemic Exposure in Patients with Hepatic Impairment vs. Healthy Subjects

Parameter	Geometric LS Mean Ratio (%) (90% Confidence Interval)		
	Mildly vs. Healthy	Moderate vs. Healthy	Severe vs. Healthy
AUC_{0-t} (ng*h/mL)	90.8 (61.3, 134)	157 (106, 233)	214 (145, 317)
AUC_{0-inf} (ng*h/mL)	90.8 (61.7, 134)	152 (103, 223)	209 (142, 307)
C_{max} (ng/mL)	72.5 (47.2, 111)	131 (85.3, 201)	127 (82.8, 196)

Table. Impact of Various Degrees of Hepatic Impairment on Retigabine and N-Acetyl Metabolite Exposure

Degree of Hepatic Impairment	Fold Increase (RTG)	
	AUC	Cmax
Mild	0.9	0.7

Moderate	1.5	1.3
Severe	2.1	1.3

Degree of Hepatic Impairment	Fold Increase (NAMR)	
	AUC	Cmax
Mild	0.77	0.83
Moderate	1.22	1.13
Severe	1.24	0.80

The applicant proposed a 50% dose reduction for severe hepatic impairment, while no dose adjustment is needed for mild or moderate hepatic impairment. However, in view of the fold increase in AUC of moderate hepatic impairment, as well as potential impact of age and gender on retigabine exposure (Section 2.3.2.1), a dose reduction to two-thirds of the target dose should be considered for patients with moderate hepatic impairment. For moderate and severe hepatic impaired patients, AUC will be similar to non-hepatic impaired patients upon reducing dose by half, thus a dose reduction to approximately one-half of the target dose should be considered.

2.3.2.7 Do UGT1A1 or NAT2 variants influence retigabine PK parameters?

This was an open, single-center, single dose and multiple dose, non-randomized study conducted in four parallel groups of healthy subjects with different genotypes. Thirty seven healthy Caucasians were included with predetermined information on their UGT1A1 and NAT2 genotype, as seen in Table below:

Group (number)	UGT1A1 Genotypes	NAT2 Genotypes
Group 1 (N=11)	6/6 genotype (normal wildtype)	either F1/S2 or F1/S1 kd (fast acetylators)
Group 2 (N=8)	7/7 genotype (Gilbert's Syndrome)	either F1/S2 or F1/S1 kd (fast acetylators)
Group 3 (N=11)	6/6 genotype (normal wildtype)	either S1kd/S2, S1kd/S1kd, S2/S2, S1kd/S1d, or S1k/S3 (slow acetylators)
Group 4 (N=7)	7/7 genotype (Gilbert's Syndrome)	either S1kd/S2, S1kd/S1kd, S2/S2, S1kd/S1d, or S1k/S3 (slow acetylators)

UGT1A1: UDP-Glucuronyl Transferase 1A1, NAT2: N-Acetyl Transferase 2

Instead of using sponsor's way to analyze the combination of metabolism biomarkers, the FDA genomics group reviewer analyzed the data separately for each gene, since it is unclear whether joint consideration of UGT1A1 and NAT2 genotypes is more informative than consideration of either gene alone. This allocates more individuals in each genotype group and allows for more power to detect differences of retigabine PK parameters (with geometric mean & 95% confidence interval), as presented in Tables below.

PK parameters of Retigabine after a single dose of 200mg retigabine					
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]	CL/F [ml/(min.kg)]
UGT1A1 ext (N=22)	378.1 (341.8, 515.1)	0.824 (0.680, 1.442)	9.455 (8.621, 10.842)	2811 (2560, 3225)	15.25 (14.18, 16.96)
UGT1A1 poor (N=15)	414.2 (335.8, 609.8)	0.942 (0.663, 2.092)	10.971 (9.347, 14.028)	2822 (2485, 3363)	14.94 (13.19, 17.68)
NAT2 fast	392.6	0.896	9.491	2875	15.20

(N=19)	(343.8, 525.5)	(0.741, 1.854)	(8.218,12.003)	(2579, 3361)	(13.85, 17.47)
NAT2 slow (N=18)	392.0 (336.4, 581.3)	0.843 (0.604, 1.545)	10.659 (9.577,12.344)	2753 (2483, 3190)	15.04 (13.73, 17.00)

PK parameters of AWD21-360 after a single dose of 200mg retigabine				
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]
UGT1A1 ext (N=22)	207.4 (187.9,248.8)	2.74 (2.28, 5.21)	10.75 (9.61, 12.84)	3476 (3092, 4178)
UGT1A1 poor (N=15)	231.2 (194.8, 311.6)	2.47 (1.94, 3.61)	12.79 (11.17, 15.48)	3932 (3435, 4837)
NAT2 fast (N=19)	241.1 (213.9, 294.2)	2.61 (1.94, 5.33)	12.28 (10.88, 14.92)	4168 (3709, 4987)
NAT2 slow (N=18)	193.7 (167.5, 251.9)	2.65 (2.26, 3.86)	10.80 (9.55, 12.87)	3300 (2842,3757)

PK parameters of Retigabine after multiple dose of 200mg retigabine BID					
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng h/ml]	CL/F [ml/(min.kg)]
UGT1A1 ext (N=21)	576.3 (503.7,773.8)	0.94 (0.73, 1.94)	7.80 (7.04, 8.98)	2604 (2386, 2961)	16.41 (15.23, 18.23)
UGT1A1 poor (N=15)	588.2 (486.7,817.7)	0.65 (4.26, 1.26)	8.44 (7.46, 9.97)	2658 (2380, 3059)	15.86 (14.43, 17.84)
NAT2 fast (N=19)	635.3 (553.4,828.8)	0.74 (0.60, 1.38)	8.16 (7.42, 9.34)	2746 (2502, 3128)	15.92 (14.72, 17.70)
NAT2 slow (N=17)	526.2 (437.0,747.2)	0.88 (0.55, 2.02)	7.95 (6.97, 9.48)	2499 (2266, 2846)	16.47 (15.07, 18.51)

PK parameters of AWD21-360 after multiple dose of 200mg retigabine BID				
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]
UGT1A1 ext (N=21)	414.5 (375.8,489.4)	1.91 (1.68, 2.92)	8.42 (7.26, 10.53)	3527 (3183, 4177)
UGT1A1 poor (N=15)	472.1 (418.5,552.1)	1.85 (1.51, 2.82)	8.61 (7.65, 10.07)	3925 (3417, 4770)
NAT2 fast (N=19)	480.6 (435.0,557.9)	1.99 (1.78, 2.88)	8.96 (7.73, 11.23)	4130 (3717, 4854)
NAT2 slow (N=17)	394.1 (353.8,461.8)	1.77 (1.41, 2.89)	8.00 (7.11, 9.31)	3249 (2893, 3844)

After single and multiple dose treatment, the AUCs of the acetylated metabolite (AWD21-360) were around 30% higher in the NAT2 fast groups relative to the NAT2 slow acetylator groups, whereas AUCs of Retigabine were around 10% higher in the NAT2 fast groups relative to the NAT2 slow acetylator groups. After single and multiple dose treatment, AUCs of the acetylated metabolite (AWD21-360) were around 13% higher in the poor UGT1A1 glucuronidator groups relative to the extensive UGT1A1 metabolizer groups, whereas systemic exposure to retigabine was about similar.

ANOVA analyses were performed for the pharmacokinetic parameters in plasma: AUC, Cmax, and $t_{1/2}$. Subject 22 (female, 35 years) was excluded from all analyses because she dropped out after the single dose part. There were no interactions UGT1A1*NAT2. No

statistically significant differences between the metabolizer groups were detected for parent drug retigabine for both ANOVA (Sponsor) and General Linear Model (FDA) analyses. However, there are statistically significant differences between the phenotypes UGT1A1 and NAT2 for the metabolite AWD21-360, which seem to become more pronounced in the multiple dose part of the study (steady state), as presented in Tables below.

Retigabine (D-23129) Parameter	Comparison	p (UGT)	p (NAT)	p (UGT*NAT)
AUC (log)	SD	0.4681	0.6919	0.7141
	MD1 (dose 9)	0.6271	0.6455	0.8863
	MD2 (dose 10)	0.8241	0.5494	0.0716
	MD1 versus SD accumulation	0.2563	0.8609	0.6065
C_{max} (log)	SD	0.5020	0.8841	0.8887
	MD1 (dose 9)	0.7846	0.5344	0.2656
	MD2 (dose 10)	0.2666	0.0996	0.6586
	MD1 versus SD accumulation	0.4170	0.7245	0.4709
$t_{1/2}$ (lin)	MD2	0.3768	0.8037	0.7222

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AWD21-360 Parameter	Comparison	p (UGT)	p (NAT)	p (UGT*NAT)
AUC (log)	SD	0.2168	0.1866	0.5541
	MD1 (dose 9)	0.1582	**0.0308**	0.7324
	MD2 (dose 10)	0.1009	0.0975	0.5105
	MD1 versus SD accumulation	**0.0071**	**0.0008**	0.3037
C_{max} (log)	SD	0.2813	0.1034	0.3682
	MD1 (dose 9)	0.0769	0.0996	0.7711
	MD2 (dose 10)	0.0734	**0.0166**	0.9810
	MD1 versus SD accumulation	**0.0174**	**0.0047**	0.4407
$t_{1/2}$ (lin)	MD2	0.9589	0.2268	0.8621

The reviewer concludes that after oral single (200 mg retigabine immediate release) and multiple dose retigabine treatment (200 mg retigabine immediate release BID), the AUC of the acetylated metabolite was 30% higher in NAT2 fast acetylators versus slow acetylators, and higher in subjects with UGT1A1*28 mutation versus subjects with UGT1A1 wildtype. The differences in PK parameters do not warrant dose change recommendations.

2.3.2.8 Does Retigabine affect 24h serum bilirubin concentration differentially by genetic subgroups?

UGT1A1 defines the genetic basis of Gilbert syndrome, which is the most common hereditary cause of increased bilirubin and is found in up to 5% of the population.

Similar to the strategy under Section 2.3.2.7, the reviewer looked into UGT1A1 and NAT2 subgroups respectively, holding more power to detect whether retigabine affect 24h serum bilirubin concentration differentially by genetic subgroups (with mean and 95% confidence interval).

	AUC [umol·l/h]		
Biomarker group	Screen	SD	MD
UGT1A1 ext (N=22)	385.5 (341.5, 429.5)	328.5 (284.8, 372.2)	347.5 (307.3, 387.7)
UGT1A1 poor (N=15)	747.9 (618.0, 877.7)	529.3 (432.6, 626.1)	513.3 (418.8, 607.9)
NAT2 fast (N=19)	532.4 (447.3, 617.5)	410.2 (370.1, 450.2)	426.2 (367.4, 484.9)
NAT2 slow (N=18)	532.4 (453.3, 611.6)	409.7 (323.3, 496.0)	402.7 (334.4, 470.9)

As shown in the Table above, baseline AUCs of the 24h serum bilirubin concentration were 94% higher in UGT1A1 poor metabolizers vs. wildtype group. There were no obvious differences in mean concentration-time courses after single and multiple dose treatment among the groups. In general, retigabine treatment did not cause elevations in bilirubin AUC in any subgroup.

No important differences were noted for 24h total bilirubin levels when comparing data (geometric mean and 95% confidence interval) from each biomarker group, with the exception that (consistent with expected) baseline 24h bilirubin level in UGT1A1 poor group was 97% higher relative to wildtype group (see Table below).

Biomarker Group	Screen [mg/dl]	Treated Period [mg/dl]
UGT1A1 ext (N=22)	18.6 (17.1, 21.2)	15.6 (14.3, 18.3)
UGT1A1 poor (N=15)	36.7 (30.8, 49.5)	23.8 (21.0, 28.6)
NAT2 fast (N=19)	24.9 (20.4, 35.5)	19.0 (17.1, 22.9)
NAT2 slow (N=18)	24.0 (19.7 34.9)	18.0 (15.6, 23.5)

2.3.2.9 Does retigabine have QT prolonging effects in genetic subgroups?

KCNQ2 and KCNQ3 subunits form heteromeric potassium channels that underlie slow, subthreshold M-type potassium currents in autonomic (and possibly central) neurons. They are related to KCNQ1 and KCNQ4 subunits, mutations of which produce one form of the cardiac long QT syndrome. For safety evaluation, sponsor screen QT variable. The heart rate corrected QTc interval was calculated by the system according to Bazett's formula.

Further data analysis for geometric mean and 95% confidence interval was performed for the QT difference between genotypes within each biomarker group (see Table below).

Biomarker Group	Screen [ms]	Treated Period [ms]	QT Changes [ms]	P-Value
UGT1A1 ext (N=22)	413.43 (399.81, 429.64)	416.71 (405.47, 429.61)	2.82 (-7.33, 12.97)	0.484
UGT1A1 poor (N=15)	402.99 (392.32, 414.61)	400.99 (387.79,415.67)	-1.73 (-10.73, 7.26)	
NAT2 fast (N=19)	408.54 (398.98, 419.12)	411.63 (401.48, 422.94)	3.16 (-6.52, 12.84)	0.510
NAT2 slow (N=18)	409.83 (393.18, 429.49)	408.83 (393.95,426.05)	-1.33 (-11.74, 9.07)	

There was no QT extreme case (eg. individual change in QTc ≥60 ms). The small mean QT changes are considered to be clinically not relevant. There were no statistically relevant changes in QT between genetic groups within each biomarker.

2.3.2.10 What pregnancy and lactation use information is there in the application?

In Highlight section of the proposed PLR label it states that "Pregnant patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry (1-888-233-2334)." The Section 8.1 of the proposed POTIGA label states that "There are no adequate and well-controlled studies in pregnant women. POTIGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." Additional information is available in the proposed POTIGA label.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Extrinsic factors regarding the drug-drug interaction with coadministered enzyme-inducing AEDs, enzyme inducer, valproate (inhibitor of UGT), oral contraceptives, and alcohol consumption were studied in Phase 1 trials. In most of these studies insignificant effects on retigabine were observed, except for alcohol which resulted in retigabine AUC and Cmax increases by 23% and 37%, respectively.

Population PK analysis examined the trough concentrations of AEDs prior to and after retigabine administration using pooled data from the Phase 3 clinical studies (Studies 301 and 302). Other than approximately 20% and 16% decreases in lamotrigine and clonazepam exposure, respectively, impact of concomitant retigabine on concomitant AEDs appear insignificant. Analysis shows a potential for carbamezepine and phenytoin to increase retigabine clearance by 27% and 36%, respectively.

2.4.2 Drug-drug interactions

2.4.2.1 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Refer to Section 2.2.5.6 and Section 2.3.2.7.

2.4.2.2 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Refer to Section 2.4.2.3.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes on an in vitro basis??

In vitro studies using human liver microsomes shows that retigabine did not significantly inhibit the major CYP isozymes including CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. In vitro screening for inhibition potential on CYP2B6 was not performed, and thus the inhibition potential is unknown and should be investigated.

In addition, results of in vitro studies using human primary hepatocytes show that retigabine and NAMR did not induce CYP1A2 or CYP3A4/5 (hence the CYP2C family and P-gp as well). On the basis of these in vitro invetigations using human biomaterials, retigabine is not expected to have significant impact on PK of concomitant medications that are substrates of the major CYP isoenzymes through inhibition or induction mechanism.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Refer to Section 2.2.5.3. Retigabine was shown to be highly permeable in Caco-2 cells. Retigabine was shown to be neither a substrate of P-glycoprotein (P-gp) nor significantly inhibit the P-gp mediated transport activity. The acetyl-metabolite NAMR may inhibit the P-gp mediated drug transport at much higher concentrations of $\geq$10 μM,

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Refer to Section 2.2.5.6. Retigabite was metabolized primarily via Phase II glucuronidation and N-acetylation, with little or no involvement of CYPs.

2.4.2.6 Is the drug an inhibitor and/or an inducer of CYP enzymes based on clinical study results?

Studies with Probe Drugs of CYPs:
No study was conducted using probe drugs of CYPs (Refer to Section 2.4.2.3).

Studies with Antiepileptic Drugs:

Both retigabine and NAMR are cleared via glucuronidation and renal excretion. The applicant conducted several drug-drug interaction studies, as well as population PK analysis in order to evaluate the impact of co-administration AEDs that are substrate (lamotrigine), inducers (phenobarbital, phenytoin and carbamezepine) or inhibitors (valproate) of glucuronidation.

Lamotrigine:
Co-administered retigabine did not significantly alter the PK profile of lamotrigine based on the acceptance criteria of 80-125% limits. However, concomitant retigabine seemed to result in an increase in apparent clearance (~22%), decrease in AUC (~18%) and a shortened t1/2 (from 37.4 h to 31.7 h), suggesting a potential metabolic-inducing effect by retigabine. No dose adjustment is necessary based on the ~18% changes in lamotrigine. Results are shown in the Table below.

Table. Pharmacokinetic Parameters (N=15, Mean ± SD) of Lamotrigine With and Without Co-Administration of Retigabine

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC (µg*h/mL)	CL/F (L/h/kg)
Lamotrigine alone	2121 ± 213	3.0 ± 1.1	37.4 ± 10.4	106.8 ± 33.9	0.028 ± 0.007
Lamotrigine with RTG	2037 ± 349	3.0 ± 1.1	31.7 ± 7.5	87.5 ± 25.4	0.034 ± 0.009
Statistical analysis					
$Mean_{geo}$ (90% CI)	95 (91-99)	--	85 (81-87)	82 (80.1-84.0)	122 (119-125)

In the same study, repeat administration of lamotrigine (25 mg/day) showed no impact on PK of single-dose retigabine. Since lamotrigine was studied at a lower dose, rather than typical therapeutic doses used in clinical practice, the magnitude of this drug interaction with higher lamotrigine doses is not known based on results of this study.

Phenobarbital:
Coadministration of retigabine (200 mg TID) with phenobarbital (90 mg daily) did not significantly alter the PK parameters of phenobarbital in healthy subjects based on point estimates and the acceptance criteria of 80-125% limits. There appears to be ~1.9 hours delay in reaching Cmax for phenobarbital with coadministered retigabine, though no considered as statistically insignificant in view of the large variable.

Repeat administration of phenobarbital did not appear to significantly alter the retigabine PK, although the 90%CI exceeded the upper boundary of 80-125% limits for AUC based on the BE acceptance criteria. There was an approximately 11% increase in retigabine AUC, corresponding with an approximately 10% decrease in CL/F value and a longer t1/2, which cannot be explained by the anticipated enzyme-inducing effect of phenobarbital on metabolism of retigabine.

Carbamazepine, Phenytoin, Valproic Acid and Topiramate:
The applicant investigated the impact of retigabine add-on to the existing AEDs in epileptic patients participating in the Phase 2 clinical study (Study 202). Patients were receiving either carbamezepine (n=22) (600-2400 mg/day), phenytoin (n=19) (120-600 mg/day), valproic acid (n=8) (750–2250 mg/day), or topiramate (n=11) (250-1200 mg/day).

Trough levels of carbamazepine, phenytoin, valproic acid, and topiramate were analyzed using point estimate and a 90% confidence interval approach, judged by the acceptance criteria of 80-125%. No significant effects of retigabine were observed on the trough concentrations of these four coadministered AEDs. As shown in Table below, the apparent clearance of retigabine was increased by 36% with concomitant phenytoin in a Phase 2 study, leading to 34% and 18% decreases in AUC and Cmax, respectively, and a 2.7-hour shortening in t1/2. The apparent clearance of retigabine was increased by 27% with concomitant carbamazepine in a Phase 2 study, leading to a 31% and 23% decreases in AUC and Cmax, respectively, and a 5.3-hour shortening in t1/2. An increase in POTIGA™ dosage may be considered to attain optimal efficacy when co-administered with inducers of drug metabolizing enzymes. In addition, retigabine plasma levels may increase if these concomitantly administered drugs are discontinued, and thus a decrease in dosage should be considered.

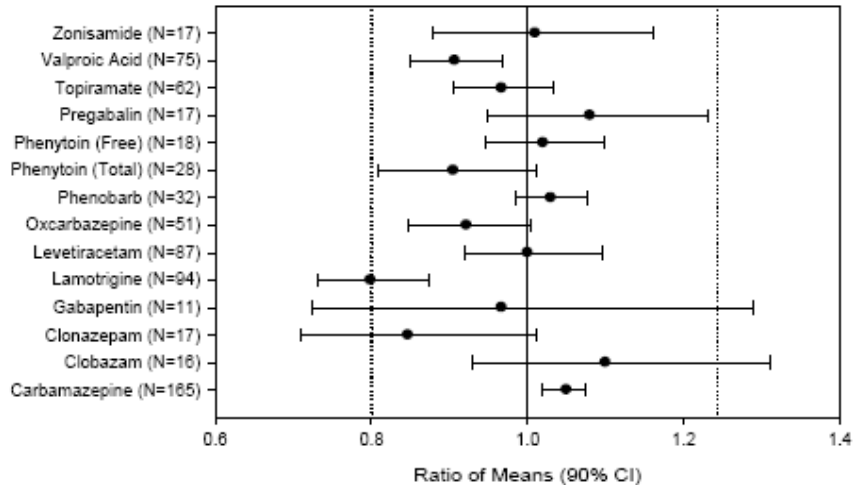
Table. Effects of Carbamazepine, Phenytoin, Valproic Acid and Topiramate Co-Administration on Apparent Oral Clearance of Retigabine

AED	RTG+AED/RTG Ratio of $Mean_{geo}$ RTG CL/F (90% CI)	p-Value (ANOVA)
Carbamazepine (N=8)	1.27 (0.96-1.70)	0.1553
Phenytoin (N=9)	1.36 (1.11-1.67)	0.0239
Valproic acid (N=4)	1.04 (0.69-1.56)	0.8519
Topiramate (N=5)	0.83 (0.45-1.52)	0.5437

Population PK Analysis:
Population PK analysis examined the trough concentrations of AEDs, including carbamazepine, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamid, prior to and after retigabine administration using pooled data from the Phase 3 clinical studies (Studies 301 and 302). Enrolled patients were on 1~3 AEDs, while regitabine was administered as add-on therapy. Results of the analysis demonstrated that subjects receiving lamotrigine had a 6.7% lower retigabine CL than those not receiving lamotrigine. None of the other concomitant AEDs were shown to have any significant impact on the CL of retigabine. In combination, the effects of CL_{Cr}, BSA, dose and lamotrigine co-administration reduced the inter-individual variability (CV) of retigabine CL from 22.1% (base model) to 21.7% (final model), indicating a small net impact on retigabine CL.

Other than approximately 20% and 16% decreases in lamotrigine and clonazepam exposure, respectively, impact of concomitant retigabine on PK of concomitant AEDs appear insignificant (see Figure below). Analysis shows a potential for carbamazepine and pheytoin to increase retigabine clearance by 27% and 36%, respectively.

Figure. Effects of Retigabine on Trough AED Concentrations in Epileptic Patients



Studies with Non-Antiepileptic Drugs:

Two studies (3065A1-112 and VRX-RET-E22-106) evaluated the effect of retigabine on the oral contraceptive steroid PK. At retigabine doses of up to 750 mg/day, there was no impact on the pharmacokinetics of the estrogen or progestogen components of oral contraceptive steroids. In addition, no effect of oral contraceptive steroids on retigabine PK was observed. Furthermore, given the lack of in-vitro activity of retigabine on human cytochrome P450s, no interactions are anticipated for retigabine doses greater than 750 mg/day. No dose adjustments are required for either retigabine or oral contraceptives when concomitantly administered

Oral Contraceptives:

1. LO-OVRAL contains norgestrel/ethinyl estradiol (0.3 mg/0.03mg). Co-administration of retigabine (150mg tid for 3 days) had no effects on the PK exposure of either ethinyl estradiol or norgestrel component in Study 3065A1-112. The geometric mean ratios between co-administration and administered without retigabine were close to 1 and the 90% CIs were within the acceptable criteria of 80-125%. Results of this study suggest that women on LO-OVRAL can take retigabine without the need for backup contraceptives.

2. Study VRX-RET-E22-106 was conducted evaluate the impact of a higher dose of retigabine (100 to 250 mg tid or 750 mg/day) for 28 days on the PK profiles of the norethindrone and ethinyl estradiol components of the oral contraceptive Ortho® 1/35 (norethindrone/ethinyl estradiol: 1 mg/0.035 mg). The effect of Ortho® 1/35 daily dosing on retigabine PK was also assessed.

   Norethindrone Cmax was unchanged and AUC0-τ was approximately 28% higher when administered concurrently with retigabine. There was no impact of retigabine on the AUC0-τ of ethinyl estradiol but Cmax was decreased by 21% and median tmax was delayed by one-half hour. Since the slight reduction in Cmax was not accompanied by any change in AUC0-τ or trough concentrations (Cmin), no effect on the oral contraceptive effectiveness is expected. There was no impact of norethindrone/ethinyl estradiol administration on the PK profile of retigabine or its

NAMR metabolite. In view of the metabolism of retigabine and results of in vitro investigations, therapeutic doses >750mg/day is not expected to have significant drug-drug interaction with oral contraceptive Ortho®.

Ethanol:
The impact of the co-administration of ethanol (1g/kg) with retigabine (200mg) on the safety, tolerability, PK, and PD endpoints (i.e., subjective effects, balance, and psychomotor and cognitive performance) was investigated in a single dose study with healthy subjects. As shown in the Table below, AUC and Cmax of retigabine are increased by 36% and 23%, respectively, after coadministration with a 1 g/kg dose of ethanol (VRX-RET-E22-107). Retigabine did not affect the PK parameters of ethanol.

Table. Retigabine Pharmacokinetic Parameters after Retigabine 200 mg Administration with and without Ethanol 1 g/kg in Healthy Subjects

Parameter	Geometric LS Mean (%Cofficient of Variation)		Mean Ratio of RTG+Ethanol/RTG Alone (90% CI)
	RTG Alone (N=17)	RTG+Ethanol (N=17)	
C_{max} (ng/mL)	530 (32.1%)	636 (29.4)	1.23 (1.02, 1.47)
$AUC_{0\text{-}inf}$ (ng*h/mL)	2939 (19.8%)	3937 (24.4%)	1.36 (1.29, 1.43)
T_{max} (h)	1.45 (0.95, 2.95)	1.45 (0.95, 3.95)	

Among PD endpoints assessed in this study, there was significant difference on visual blurring between co-administration of retigabine and ethanol vs. ethanol alone. It is recommended that patients are advised of the possible effects on vision if they take retigabine with alcohol.

2.4.2.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The proposed label states the potential co-administration with lamotrigine, other antiepileptic drugs (carbamazepine, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide), CYP enzyme inducer such as phenbarbital, and oral contraceptives. The interaction potential between these drugs has been evaluated in drug-drug interaction studies in humans (e.g., lamotrigine, phenobarbital, oral contraceptives) and via populations PK analysis.

2.4.2.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

NA

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

The in vitro screening for induction potential of retigabine on UGT and NAT enzymes as performed using hepatic preparations from rats, instead of human hepatic preparations as

recommended by the Agency. Consequently, its induction potential on UGT and NAT of human origins is not entirely clear. In clinical study and as shown in results of population PK analysis, concomitant retigabine and lamotrigine (a substrate of UGT) resulted in approximately 18% reduction in lamotrigine levels.

In addition, since AEDs may not be the only concomitant medications that the epileptic patients will be taking, the applicant should follow the Agency's Guidance to screen the inhibition potential of retigabine on CYP2B6 activity using recommended probe substrates for these CYP isozymes.

Further, renal elimination is the major route of elimination for retigabine and retigabine is active secreted in urine, which suggests the involvement of active transport system in kidney for retigabine. (Refer to Section 2.2.5.7.)

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None

2.5 General Biopharmaceutics

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

As proposed by the applicant, retigabine can be considered to be BCS Class 2 drug (i.e., high permeability, low solubility). Please refer to the review by ONDQA.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

A single-center, single-dose, open label, randomized, crossover study of 3 different dosage forms under fasting conditions (study 306A1-123) was conducted to investigate the absolute and relative bioavailability of retigabine immediate release capsules (used in early Phase 1 and 2, including the pivotal Phase 2b study). Twelve healthy male subjects age between 18-45 years were enrolled. Results of bioavailability are presented in the Table below.

Table. Mean PK parameters and statistical analysis for the parent drug and its acetyl metabolite

Absolute and Relative Bioavailability $Mean_{geo}$ (95% CI_{ln} LL - UL)			
Retigabine (D-23129)			**AWD21-360**
$F_{abs, OS}$	$F_{abs, IR}$	$F_{rel, IR}$*	$F_{rel, IR}$*
58.3* (51.7-65.8)	60.4 (48.6-75.0)	104 (81.0-132)	103 (84.1-126)

*: relative to RGB OS

The mean absolute bioavailability was about 60% for both oral solution and the immediate release capsule.

The sponsor further developed Clinical Trials Immediate Release Tablets (50, 100 and 300 mg) to be used in the pivotal Phase 3 studies and for Phase 1 studies conducted after initiation of the Phase 3 program and Market Image Immediate Release Tablets (50, 100, 200, 300 and 400 mg). A pivotal bioequivalence study (Study VRX-RET-E22-104) was conducted to compare the market image tablet (400 mg) with the clinical trial tablet used in the Phase 3 clinical studies i.e. 1x 300 mg + 2x 50mg. This was a single dose, open-label, single-center, randomized, 2-way crossover, 2-sequence, food-effect, safety, and tolerability study in 24 healthy male subjects.

The mean retigabine concentration-time profiles, PK parameters, and statistical analysis for plasma retigabine following a 400-mg dose of market image formulation or clinical trials formulations are presented in the Figures and Tables below.

Figure. Mean Plasma Retigabine (Left) and NAMR (Right) Concentration-time Profiles Following Administration of a Single 400-mg Retigabine Dose as a Market Image Formulation or a Clinical Trials Formulation

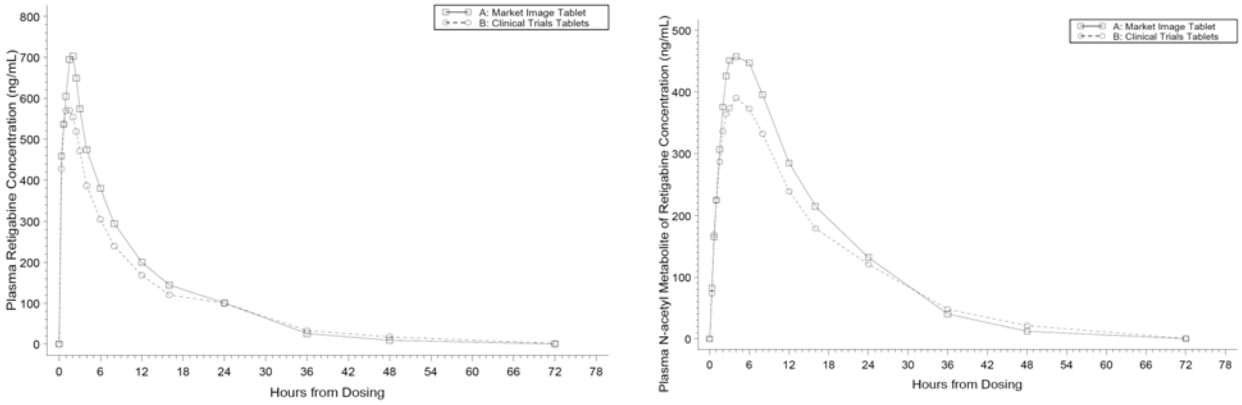


Table. Summary of Pharmacokinetic Parameters for the Plasma Retigabine (Top) And NAMR (Bottom) Following Administration of a Single 400-mg Retigabine Dose as a Market Image or Clinical Trials Formulation

Pharmacokinetic Parameters	Market Image Formulation (Test) Mean ± SD	Clinical Trials Formulation (Reference) Mean ± SD	% MR (90% CI)[a]
AUC_{0-t} (ng*hr/mL)	7424.4 ± 2220.6	6636.2 ± 1921.1	111.39 (106.03, 117.01)
AUC_{0-inf} (ng*hr/mL)	7547.3 ± 2261.1	6880.9 ± 1914.8	108.90 (103.26, 114.85)
AUCR	0.984 ± 0.00755	0.963 ± 0.0518	.NA
C_{max} (ng/mL)	834.200 ± 286.564	753.933 ± 340.299	115.98 (101.23, 132.87)
t_{max} (hr)	1.51 (0.334, 6.00)[b]	1.00 (0.334, 12.1)[b]	.NA
k_{el} (1/hr)	0.103 ± 0.0191	0.0744 ± 0.0238	.NA
$t_{1/2}$ (hr)	6.97 ± 1.41	10.5 ± 4.27	.NA

[a] 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as Median (Minimum, Maximum)
MR = mean ratio, SD = standard deviation, CI = confidence interval, AUC = area under the curve, AUCR = AUC ratio, C_{max} = maximum concentration, t_{max} = time of maximum concentration, k_el = elimination rate constant, $t_{1/2}$ = half-life, NA = not applicable

Pharmacokinetic Parameters	Market Image Formulation (Test) Mean ± SD	Clinical Trials Formulation (Reference) Mean ± SD	% MR (90% CI)[a]
AUC_{0-t} (ng*hr/mL)	7983.5 ± 2738.8	7138.6 ± 2381.7	110.98 (106.69, 115.44)
AUC_{0-inf} (ng*hr/mL)	8435.0 ± 2754.0	7732.1 ± 2429.7	108.85 (104.90, 112.94)
AUCR	0.941 ± 0.0369	0.920 ± 0.0460	NA
C_{max} (ng/mL)	494.707 ± 129.400	421.566 ± 123.579	118.41 (110.54, 126.83)
t_{max} (hr)	4.00 (1.44, 8.00)[b]	4.00 (2.00, 8.02)[b]	NA
k_{el} (1/hr)	0.0905 ± 0.0204	0.0719 ± 0.0237	NA
$t_{1/2}$ (hr)	8.05 ± 1.90	10.6 ± 3.12	NA

[a] 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as Median (Minimum, Maximum)\
MR = mean ratio, SD = standard deviation, CI = confidence interval, AUC = area under the curve, AUCR = AUC ratio, C_{max} = maximum concentration, t_{max} = time of maximum concentration, k_el = elimination rate constant, $t_{1/2}$ = half-life, NA = not applicable

The results from this study indicated that the Market Image formulation was bioequivalent to the clinical trials formulation on the basis of systemic exposure (AUC), but had $C_{max.}$value approximately 16% higher than that for the clinical trials formulations.

A second bioequivalence study (RTG113287) was submitted as part of the 120-day safety submission. This is a single-center, single-dose, open label, randomized, 2-way crossover, 2-sequence, comparative bioavailability study. A total of 82 healthy male and female subjects between 18 and 65 years of age, inclusive, were enrolled in this BE study.

An interim analysis was planned to be conducted after the first cohort of approximately 72 subjects completed the last PK sampling in order to assess the bioequivalence. Dosing for subjects in the second cohort was planned to commence if the results of the interim analysis indicated that the study should proceed as described in the decision tree, as listed in the Table below.

Outcome	Action
Adjusted 90% CIs for Cmax and AUC are within the BE range 0.80 to 1.25.	Stop the trial and conclude bioequivalence
The ratio of Cmax or AUC is outside the BE range 0.80 to 1.25 therefore addition of a second cohort will not result in successful demonstration of bioequivalence.	Stop the trial and conclude that we are not able to demonstrate bioequivalence
The adjusted 90% CI for Cmax or AUC extend beyond the BE range 0.80 to 1.25 due to a slight deviation in sample size assumptions (CVw=34% and true difference assumed to be 5%).	A second cohort may be recruited to account for the deviation in sample size assumptions and is not expected to exceed the number of subjects required in the first cohort
The adjusted 90% CI for Cmax or AUC extend beyond the BE range 0.80 to 1.25 due to a significant deviation in sample size assumptions therefore addition of a second cohort will result in a significantly large number of subjects	Stop the trial and conclude that we are not able to demonstrate bioequivalence

AUC= Area under curve
BE= Bio-equivalence
CI= Confidence interval

The mean retigabine concentration-time profiles, PK parameters, and statistical analysis for plasma retigabine following a 400-mg dose of market image formulation or clinical trials formulations are presented in the Tables below. Results of this study demonstrated that retigabine Market Image IR tablet (400 mg) and the Clinical Trial IR tablets (1x 300 mg + 2x 50 mg) are bioequivalent.

Table. Summary of Pharmacokinetic Parameters of Retigabine Market Image IR tablet (400 mg) and the Clinical Trial IR tablets (1x 300 mg + 2x 50 mg)

Parameter	Tablet	N	n	Geometric Mean	95% CI	CVb (%)
AUC(0-∞) (ng.h/mL)	Market Image	78	78	6690	(6180, 7240)	36
	Clinical Trial	80	80	6470	(6020, 6960)	34
AUC(0-t) (ng.h/mL)	Market Image	78	78	6630	(6120, 7180)	37
	Clinical Trial	80	80	6410	(5960, 6900)	34
Cmax (ng/mL)	Market Image	78	78	799	(702, 908)	62
	Clinical Trial	80	80	795	(710, 890)	54
t½ (h)	Market Image	78	78	8.0	(7.6, 8.4)	23
	Clinical Trial	80	80	8.0	(7.7, 8.3)	19
tmax (h)[1]	Market Image	78	78	1.50 (0.25-8.00)	NA	NA
	Clinical Trial	80	80	1.50 (0.25-8.00)	NA	NA

NA: Not Applicable
1. Median (range)

Table. Statistical Summary of Bioequivalence for Retigabine Primary and Secondary Endpoints

Comparison	PK Parameter	Ratio (90% CI)[1]	%CVw
Retigabine Market Image vs. Retigabine Clinical Trial	AUC(0-∞)	1.020 (0.98, 1.06)	13.6
	Cmax	0.999 (0.89, 1.12)	39.1
	AUC(0-t)	1.019 (0.98, 1.06)	13.8

1. Adjusted 90% CIs presented for AUC(0-∞) and Cmax to account for interim analysis. Adjusted 90% CI is equivalent to a 93% CI (i.e. an alpha of 0.035)

Reviewer's comment: It is not clear what Clinical Trials tablets batch was used. In Study Rationale the sponsor claims: "A batch of Clinical Trials tablets that was more representative in terms of particle size of the batches of drug substance used in Studies 301 and 303 was compared with Retigabine Market Image". How does this relate to the

Clinical Trials tablets batch used in the first BE study (VRX-RET-E22-105)? This request has been conveyed to the CMC reviewer and the sponsor.

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?

Not applicable.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A food effect study (VRX-RET-E22-104) was conducted with the Retigabine Market Image Tablet (400-mg). This was a single dose, open-label, single-center, randomized, 2-way crossover, 2-sequence, food-effect, safety, and tolerability study in 24 Healthy male subjects.

Table. Summary of Pharmacokinetic Parameters for Plasma Retigabine Following Administration of a Single 400 mg Retigabine Dose Under Fed or Fasted Conditions

	Treatment A Fed	Treatment B Fasted	
Pharmacokinetic Parameters	**Mean ± SD**	**Mean ± SD**	**% MR (90% CI)[a]**
AUC_{0-t} (ng*hr/mL)	7814.6 ± 1349.6	7145.0 ± 1619.0	110.52 (102.51, 119.14)
AUC_{0-inf} (ng*hr/mL)	7895.9 ± 1356.1	7355.9 ± 1643.9	107.92 (100.42, 115.98)
AUC_R	0.990 ± 0.00387	0.980 ± 0.0197	NA
C_{max} (ng/mL)	938.7 ± 219.2	728.8 ± 301.4	137.63 (114.50, 165.42)
t_{max} (hr)	2.50 (1.00, 6.02)[b]	1.75 (0.333, 6.02)[b]	NA
k_{el} (1/hr)	0.113 ± 0.0168	0.0973 ± 0.0229	NA
$t_{1/2}$ (hr)	6.28 ± 0.938	7.57 ± 2.09	NA

[a] 90% CI and % mean ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as median (minimum, maximum)
MR = mean ratio, SD = standard deviation, CI = confidence interval, AUC = area under the curve, AUC_R = AUC ratio, C_{max} = maximum concentration, t_{max} = time of maximum concentration, k_{el} = elimination rate constant, $t_{1/2}$ = half-life, NA = not applicable.

Table. Summary of Pharmacokinetic Parameters for Plasma N-acetyl Metabolite of Retigabine Following Administration of a Single 400-mg Retigabine Dose under Fed or Fasted Conditions

	Treatment A Fed	Treatment B Fasted	
Pharmacokinetic Parameters	**Mean ± SD**	**Mean ± SD**	**% MR (90% CI)[a]**
AUC_{0-t} (ng*hr/mL)	8785.9 ± 1697.6	7840.1 ± 1998.3	113.40 (106.18, 121.11)
AUC_{0-inf} (ng*hr/mL)	9085.9 ± 1684.0	8313.5 ± 2031.4	109.76 (103.36, 116.56)
AUC_R	0.966 ± 0.0195	0.946 ± 0.0236	NA
C_{max} (ng/mL)	645.3 ± 104.7	462.3 ± 143.5	144.72 (128.72, 162.72)
t_{max} (hr)	4.00 (2.50, 8.00)[b]	4.00 (3.00, 12.0)[b]	NA
k_{el} (1/hr)	0.101 ± 0.0143	0.0855 ± 0.0181	NA
$t_{1/2}$ (hr)	7.05 ± 1.19	8.51 ± 2.06	NA

[a] 90% CI and % mean ratios (% MR) were calculated based on ln-transformed parameters
[b] t_{max} is presented as median (minimum, maximum)

The extent of retigabine absorption, as measured by AUC(0-inf), was not affected by administration of the Market Image IR tablet formulation with a high fat breakfast. However, the mean Cmax values were ~38% higher when administered with food. Median time to Cmax following administration of Market image IR tablet with food (2.5 h) was delayed slightly relative to administration in the fasted state (Median 1.75 h). The agency considers the applicant's proposal acceptable regarding taking retigabine with or without food based on the following considerations; (1) retigabine has been administered and studied without regard to food in clinical trials, and (2) there is a dosing window for allowing dosage adjustment. Nevertheless, in view of magnitude of increase in Cmax, caution may be taken when patients are given the highest therapeutic doses with food.

2.6 Analytical Section

The bioanalytical reports and assay methods used to support the retigabine pharmacokinetic studies are summarized in Table 34. Unless otherwise stated regressions of the standard curve are assumed to be linear. In this section retigabine is described as D-23129, while N-acteyl retigabine is described AWD21-360. The assay validations for retigabine and its N-acetyl- and N-glucuronide metabolites, including the adequate concentrations of quality controls, are considered acceptable according to the acceptance criteria set by the Agency's Bioanalytical Guidance.

Table 34. Summary of all analytical and and cross-validation reports

Report number (Study #)	**Method**	**Biological Matrix**	**Analyte**	**Calibration Range**	**LLOQ**	**Intra-day Precision (% CV)**	**Intra-day Accuracy (% bias)**
						Inter-day Precision (% CV)	**Inter-day Accuracy (% bias)**

Retigabine and AWD21-360 Methods Validated at (b) (4)							
D-23129/7095850003 (3065A1-100)	HPLC-Fluorescent Detection	Plasma	D-23129	1.5 – 800 ng/mL	3.1 ng/mL	< 1.8 %	-5.6 ~ 12.8 %
						< 6.1 %	5.2 ~ 8.2 %
23129/7096430006 (3065A1-100)	HPLC-Fluorescent Detection	Urine	D-23129	12.5 – 2000 ng/mL	12.5 ng/mL	≤ 2.9%	-8.6 ~ -5.8%
						≤ 5.1%	-7.0 ~ -3.6%
D-23129/7096051007 (3065A1-101)	HPLC-Fluorescent Detection	Plasma	D-23129	6.25 – 2000 ng/mL	6.25 ng/mL	≤ 2.9%	-0.9 ~ 5.0%
						≤ 9.8%	3.3 ~ 1.6%
			AWD21-360	12.5 – 2000 ng/mL	12.5 ng/mL	≤ 3.0%	4.7 ~ 0.7%
						≤ 8.5%	-5.7 ~ -11.5%
D-23129/7097077013 (3065A1-101)	HPLC-APCI-MS/MS	Plasma, urine	D-23129	6.25 – 2000 ng/mL	6.25 ng/mL	≤ 2.9%	-0.9 ~ 5.0%
						≤ 9.8%	4.7 ~ 0.7%
			AWD21-360	12.5 – 2000 ng/mL	12.5 ng/mL	≤ 3.0%	3.3 ~ 1.6%
						≤ 3.0%	-5.7 ~ -11.5%
D-23129/9321020113 (Studies 3065A1-110, 3065A1-113, 3065A1-205)	LC-MS/MS	Plasma	D-23129	1.00 – 1000 ng/mL	1.00 ng/mL	≤ 9.1%	0.16% ~ 6.4%
						≤ 19.7%	5.0% ~ 10.7%
			AWD21-360	2.5 – 1000 ng/mL	2.5 ng/mL	≤ 16.0%	-7.9% ~ 6.0%
						≤ 9.4%	-6.2% ~ 0.3%
D-23129/7099022032 (3065A1-108)	HPLC-UV Detection	Plasma	D-23129	25.0 – 1000 ng/mL	25.0 ng/mL	≤ 5.4%	-4.6% ~ 4.1%
						≤ 5.3%	-2.3% ~ 3.1%
			AWD21-360	25.0 – 1000 ng/mL	25.0 ng/mL	≤ 16.0%	-7.9% ~ 6.0%
						≤ 5.1%	-8.5 ~ -0.62%
D-23129/7079004008 (Stability testing)	HPLC	Plasma	D-23129, AWD21-360, N-glucuronide-retigabine				10.5 ~ 16.2% No loss
Retigabine and NAMR Methods Validated at (b) (4) **in Support of Studies Conducted by Valeant Pharmaceuticals**							
SWA5003	LC-MS/MS	Plasma	D-23129	5.00 – 2000 ng/mL	5.00 ng/mL	≤ 6.6%	-11.8 ~ -0.8%
						≤5.0%	-11.4 ~ -1.2%
			AWD21-360	15.0 – 2000 ng/mL	15.0 ng/mL	≤ 6.5%	-6.6 ~ -1.8%
						≤ 7.1%	-7.8 ~ -3.1%
SWA5015 (VRX-RET-E22-101, VRX-RET-E22-102, VRX-RET-E22-103, VRX-RETE22-104, VRX-RET-E22-105, VRX-RET-E22-106, VRX-RET-E22-	LC-MS/MS	Plasma	D-23129	5.00 – 2000 ng/mL	5.00 ng/mL	≤ 9.3%	-2.8 ~ 7.0%
						≤ 6.3%	-2.3 ~ 12%
			AWD21-360	15.0 – 2000 ng/mL	15.0 ng/mL	≤ 7.0%	-4.3 ~ 3.0%

107, VRX-RET-E22-108, VRX-RET-E22-301, VRX-RET-E22-302, VRXRET-E22-303)						≤ 8.3%	-5.2 ~ 4.0%
SWA5008 (VRX-RET-E22-101, VRX-RET-E22-102)	LC-MS/MS	Plasma	D-23129	5.00 – 2000 ng/mL	5.00 ng/mL	≤ 7.4%	-7.7 ~ -0.6%
						≤ 4.6%	-10.9 ~ -1.9%
			AWD21-360	15.0 – 2000 ng/mL	15.0 ng/mL	≤ 6.3%	-7.1 ~ 1.0%
						≤ 4.3%	-8.3 ~o 3.0%
SWA5012 (VRX-RET-E22-101)	LC-MS/MS	Tris buffered Krebs Ringers solution	D-23129 AWD21-360	5.00 – 2000 ng/mL	5.00 ng/mL	≤ 7.5%	-7.2 ~ 9.0%
						≤12.6%	-9.2 ~ 6.0%
			AWD21-360	15.0 – 2000 ng/mL	15.0 ng/mL	≤ 6.5%	2.0 ~ 8.0%
						≤ 10.2%	0.0 ~ 8.0%

Few issues in analytical reports of individual studies were noted and listed below:

- The results for the 100 mg dose group from study 3065A1-100 should be interpreted with caution because of the precision (≤35.1%) for QC samples of the lowest concentration during the analysis of the samples.

- The assay used for quantitation of retigabine (D-23129) in urine samples from study 3065A1-100 had stability concern

- The results from study 3065A1-101 should be interpreted with caution because of the lack of internal standard and precision (≤32.9%) for QC samples of the lowest concentration for retigabine.

- The regression line seems to be missing the highest points of the standard curves at the time of the validation during the analysis of the samples for retigabine (D-23129) in studies 3065A1-110, 3065A1-113 and 3065A1-205.

- The cross-validation (HPLC-MS/MS vs. HPLC with fluorescence detection) was not successful for the N-acetyl metabolite of retigabine (AWD21-360) at the lowest concentration of 15 ng/ml due to interferences from the plasma matrix.

Reviewer's Comment: The above concerns have been taken into consideration in interpretation for the individual PK study results.

3 Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for Potiga™ immediate release oral tablets for adjunctive treatment of partial onset seizures and found it acceptable provided that the following revisions are made to the labeling language.

Labeling recommendation to be sent to the Sponsor:
The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~strikethrough~~ is recommendation for deletion from the perspective of OCP.

4 Appendices

4.1 Proposed Labeling

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

4.2 Consult Reviews

Office of Clinical Pharmacology:
Pharmacometric review

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there any significant covariate which influences retigabine PK?

The sponsor's population PK analysis for retigabine identified the creatinine clearance (CRCL), body surface area (BSA), dose and the use of lamotrigine on clearance (CL) and age on volume of distribution (V) as the statistically significant covariates. For N-acetyl metabolite, CRCL and SGPT were the significant covariates on CL and dose on V. However, the effects didn't appear to be clinically meaningful.

The PK of retigabine and its N-acetyl metabolite was assessed in healthy subjects, subjects with hepatic and renal impairment, and patients with epilepsy from 23 studies (15 Phase I studies, 5 Phase II studies, 3 Phase III studies).

A two-compartment model was developed for retigabine and N-acetyl metabolite separately. The sponsor's final model for retigabine predicted CL at 35.1 L/h for the subjects with normal renal function (CRCL=120ml/min), which was decreased to 24.2 L/h for the subjects with severe renal impairment (CRCL=25mL/min) at the same condition (assuming a subject with BSA of 1.96m^2, a dose of 150mg without lamotrigine). However, the effect of CRCL on CL is clearly underestimated compared to renal impairment study (VRX-RET-E22-101). The use of lamotrigine caused a 7.5% reduction in retigabine CL.

The final model for N-acetyl metabolite indicated that over the investigated range of CRCL (20-150 mL/min), the CL of the metabolite increased linearly from 3.3 L/hr to 6.3 L/hr; increase in SGPT from 20 U/L (normal) to 140 U/L resulted in an approximately 10% increase in CL. Due to the weak activity of the N-acetyl metabolite of retigabine, physiologically induced changes in its pharmacokinetics alone do not justify any specific dose adjustments.

1.1.2 Is there any co-administered antiepileptic drug (AED) which interacts with Retigabine PK?

As more than 75% patients received 2 or more concomitant AEDs, the evaluation of the potential interaction between AEDs and retigabine PK was considered.

The effect of background antiepileptic drugs (AEDs) treatments (carbamazepine, phenytoin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, topiramate and valproate) on PK of retigabine was investigated in the population pharmacokinetic analysis as a covariate (0=no use/1=use). The use of lamotrigine was identified as a significant covariate on CL of retigabine. However, the effect on CL is not clinically relevant (6.7% reduction).

The impact of co-administration of retigabine on PK of existing AEDs was investigated using a confidence interval approach by examining the trough AED concentrations before and after retigabine administration using data from 2 Phase III studies (301 and 302). Overall, retigabine had little or no effect on the trough concentrations of a wide range of concomitant AEDs. For most AEDs, the 90% confidence intervals of their geometric mean ratios with and without concomitant retigabine fell within the 80% to 125% bioequivalence limits. However, retigabine co-administration was associated with a 20% decrease in lamotrigine concentrations (see Figure 5).

1.1.3 Is there any significant exposure-response relationship?

Yes, there is a significant relationship between the primary endpoint (change in standardized seizure frequency from baseline) and retigabine exposures (AUC, h·μg/mL), which was also confirmed by responder analyses.

The sponsor evaluated the relationship based on two primary endpoints in order to support international registration of retigabine as follows;
1. percent change from baseline to the double-blind period (titration through maintenance), in total partial seizure frequency per 4 weeks : FDA requirement.
2. proportion of responders experiencing a ≥50% reduction from baseline to the maintenance phase, in total partial seizure frequency per 4 weeks : EMEA requirement.

In the efficacy analyses three placebo-controlled studies (study 205, 301 and 302) were included. The results on the percent change in total partial seizure frequency showed that 900 mg/day (300mg TID) and 1200 mg/day (400mg TID) doses were statistically superior to placebo in the studies of 205 and 302 ($p<0.05$) but 600 mg/day (200mg TID) dose was statistically superior to placebo in the study of 302 ($p=0.007$) but not the study of 205 ($p=0.156$). The results from responder analyses showed similar trend (refer to appendix).

For the exposure-response analyses, two phase III studies (301 and 302) were included for both efficacy and safety evaluation related to the retigabine concentration.

The efficacy of retigabine was assessed based on both primary endpoints in the correlation with retigabine predicted area under the concentration-time curve (AUC,

h·µg/mL). Figure 1 shows the relationship between percent change and AUC (h·µg/mL) from the reviewer's analysis which appears to be clearly significant relationship and seems to reach a plateau at 1200mg/day. Based on the reviewer's assessment, the percent reduction during double-blind (DB) phase from baseline in total partial seizure frequency ranged from approximately 17% at placebo to the maximum of 50% reduction.

Figure 1. The relationship between percent change in seizure frequency during DB phase from the baseline and AUC (h·µg/mL) from the studies of 301 and 302. Then orange dots and green triangles indicate the observed percent reduction during DB phase at decile of AUC and at each dose group which were marked at the median exposure. The boxplots represent the distribution of exposure at three dose levels.

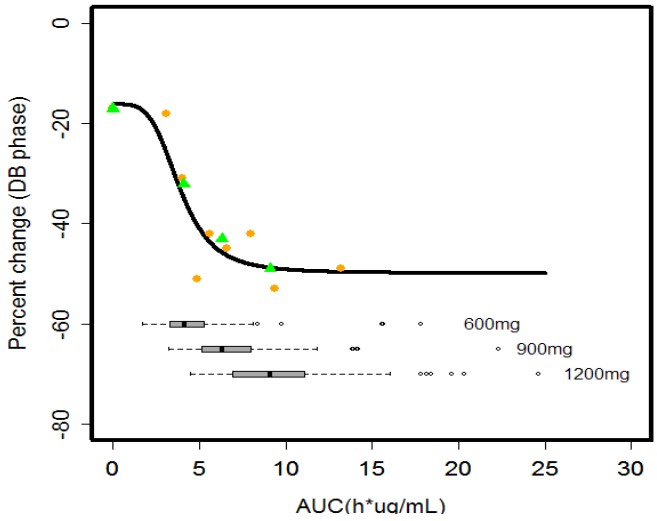
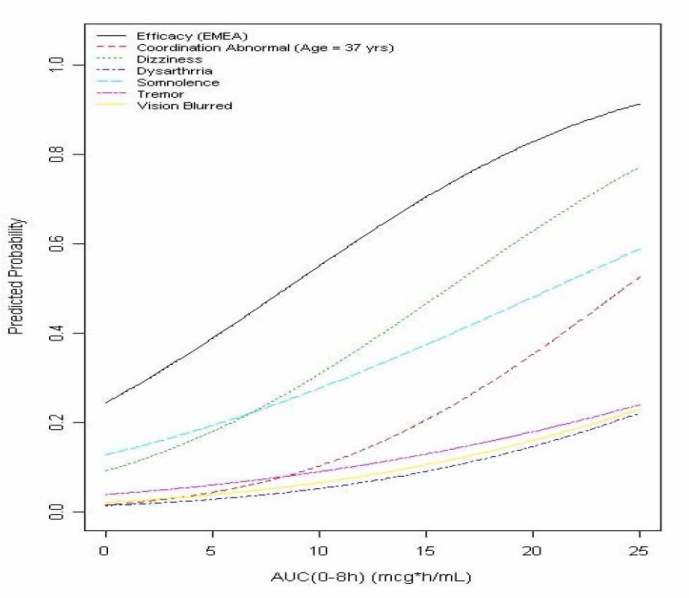


Figure 2 displays the probability of responder along with the probability of six adverse events of interest including coordination abnormal, dizziness, dysarthria, somnolence, tremor, and blurred vision in the correlation with retigabine predicted AUC based on the sponsor's logistic regression. AUC was found to be significant predictors for the probability of responder, meaning that the probability of responder tends to go up as the exposure is increased. In terms of safety endpoints, all six endpoints showed exposure-dependent relationship. The slope of the exposure-response relationship for probability of responder was similar to that for dizziness and coordination abnormal whereas the slope of the exposure response relationship for dysarthria, somnolence, tremor and vision blurred were less steep, indicating that these latter AEs were less sensitive to changes in exposure.

Figure 2. Probability of responder (≥50% reduction in seizure frequency) and adverse events in correlation with retigabine AUC.



1.2 Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 22345) and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

2 PERTINENT REGULATORY BACKGROUND

This is the original submission. The sponsor is seeking the marketing approval for 200 mg TID, 300 mg TID, and 400 mg TID retigabine tablets indicated for the adjunctive therapy in the treatment of partial-onset seizures in adults. Unlike other AEDs, retigabine specifically targets the KCNQ/Kv7 channels that are now widely believed to contribute to abnormal neuronal excitability in epilepsy.

Retigabine clinical program includes 44 clinical studies including 28 Phase I studies (one remains ongoing), 5 completed Phase II studies; 2 completed Phase III studies; and 6 long-term, open-label extension studies (of which, the extensions of the two Phase 3 studies remain ongoing).

The recommended dose schedule is summarized as follows: Retigabine should be administered in 3 divided doses daily with or without food; dosed at 100 mg 3 times a day (300 mg/day) for the first week of treatment; titrated to a maintenance dose by increasing the dose by up to 150 mg/day at weekly intervals; optimized to an effective dose between 600 to 1200 mg/day.

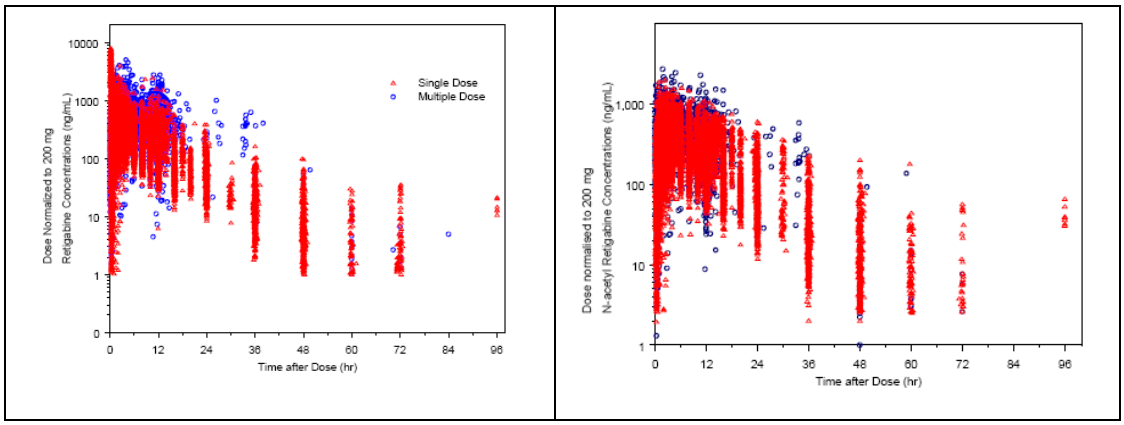
3 RESULTS OF SPONSOR'S ANALYSIS

Population PK analysis

The sponsor conducted the population PK analysis to identify covariates and other AEDs which affects on the PK of retigabine. A total of 23 studies (15 phase I studies, 5 Phase II studies, 3 Phase III studies) were included in the analysis. Given individual study objectives, the schedule of blood sample collection for PK assessments varied, with the majority of sampling schemes considered extensive. In the two Phase III studies, the investigator was encouraged to schedule a patient's visits at different times throughout the day (early/late morning; early/late afternoon), so that PK samples for retigabine were evenly distributed over the 8-hour retigabine dosing interval.

Figure 3 displays the observed concentration-time profile for both retigabine and metabolite. Based on this observation, two compartment models were employed to describe the PK of retigabine and metabolite.

Figure 3. The observed concentration-time profile for retigabine (left) and N-acetyl metabolite (right).



Source : sponsor's report, "Population Pharmacokinetic Analysis of Retigabine and its Nacetyl Metabolite in Refractory Epilepsy Patients with Partial-Onset Seizures and Healthy Subjects" on pages 46 and 48.

In terms of covariate analyses, the use of AED treatments (carbamazepine, phenytoin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, topiramate or alproate), genotype (UGT1, NAT2), formulation (solution/tablet/capsule/IV), food (fasted/fed), disease status (healthy/patient), smoking status (smoker/non-smoker), race (Caucasian/Asian/Black/Hispanic/other), gender, age (yrs), weight (kg), BSA (m^2), BMI (kg/m^2), SGPT (U/L), SGOT (U/L), Bilirubin (g/dL) and CRCL (ml/min) were evaluated, and Table 1 and Table 2 present the summary statistics of each covariate.

Table 1. The summary of continuous covariates included in population PK analysis.

Variable		N	Mean (SD)	Median	Min – Max
Age (years)	AGE	1218	37.1 (12.4)	35.0	16.0 – 82.0
Weight (kg)	WT	1219	76.0 (16.5)	74.4	40.6 – 163
BSA (m^2)	BSA	1214	1.97 (0.24)	1.96	1.36 – 3.03
BMI (kg/m2)	BMI	1214	26.0 (5.34)	24.9	15.9 – 60.3
SGPT (U/L)	SGPT	1218	31.1 (63.32)	18.0	3.00 – 667
SGOT (U/L)	SGOT	1218	20.5 (17.1)	18.0	2.00 – 341
Bilirubin (g/dL)	BILI	1218	10.1 (5.91)	9.0	0.30 – 73.5
CRCL (mL/min)	CRCL	1213	118 (26.3)	119	14.2 – 150

Source : sponsor's report, "Population Pharmacokinetic Analysis of Retigabine and its Nacetyl Metabolite in Refractory Epilepsy Patients with Partial-Onset Seizures and Healthy Subjects" on pages 41.

Table 2. The summary of categorical covariates included in population PK analysis.

Variable		Category	N (%)
Gender	SEX	Male	715 (58.7%)
		Female	504 (41.3%)
		Missing	1
Race	RACE	Caucasian	1003 (83.4%)
		Asian	7 (0.6%)
		African American	93 (7.7%)
		Hispanic	77 (6.4%)
		Other	22 (1.8%)
		Missing	18
Smoking status	SMOK	Smoker	59 (81.9%)
		Non-smoker	13 (18.1%)
		Missing	1148
Disease state	DESI	Healthy	237 (19%)
		Patients	983 (81%)
Carbamazepine	CM01	Off	724 (59%)
		On	496 (41%)
Phenytoin	CM02	Off	1043 (85%)
		On	177 (15%)
Valproate	CM03	Off	968 (79%)
		On	252 (21%)
Topiramate	CM04	Off	996 (82%)
		On	224 (18%)
Phenobarbital	CM05	Off	1111 (91%)
		On	109 (9%)
Lamotrigine	CM06	Off	954 (78%)
		On	266 (22%)
Levetiracetam	CM07	Off	1053 (86%)
		On	167 (14%)
Oxcarbazepine	CM08	Off	1094 (90%)
		On	126 (10%)
Food	FOOD	Fasted	232 (19%)
		Fed	177 (15%)
		Unknown	811 (66%)
Formulation	FRML	Solution	4 (0 %)
		Tablet	637 (52%)
		Capsule	560 (46%)
		IV	19 (2%)
UGT Genotype	UGT1	UGT1A1 6/6	185 (46%)
		UGT1A1 7/7	217 (54%)
		Missing	818
Acetylator Genotype	NAT2	Fast	46 (11%)
		Intermediate	180 (45%)
		Slow	176 (44%)
		Missing	818

Source : sponsor's report, "Population Pharmacokinetic Analysis of Retigabine and its Nacetyl Metabolite in Refractory Epilepsy Patients with Partial-Onset Seizures and Healthy Subjects" on pages 42-43.

The final model for retigabine identified the statistically significant relationships of CL with CRCL (positive nonlinear), of CL with BSA (positive nonlinear), of CL with dose (negative linear), of CL with lamotrigine coadministration (negative proportional), and of V2 with age (positive nonlinear) as follows;

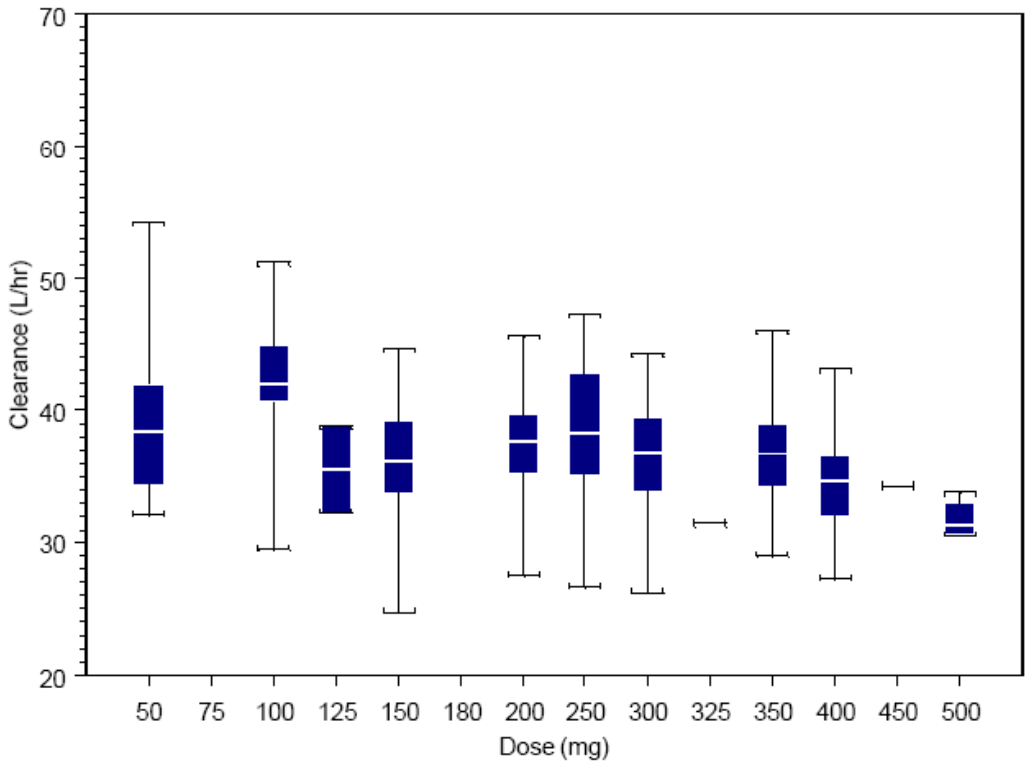
$$CL = [10.4_{,L/hr} * (CRCL_{,mL/min}^{0.209}) * (BSA_{,m^2}^{0.483}) * (1 + CM06*(-0.067))] - (4.03_{,L/hr} * DOSE_{,mg} / 150_{,mg})$$

where, if a patient was on lamotrigine, CM06 = 1; if patient was not on lamotrigine, CM06 = 0

$$V2 = 68.5_{,L} * Age_{,yr}^{0.339}$$

The sponsor's final model for retigabine predicted CL at 35.1 L/h for the subjects with normal renal function (CRCL=120ml/min), which was decreased to 24.2 L/h for the subjects with severe renal impairment (CRCL=25mL/min) at the same condition(assuming a subject with BSA of 1.96m^2., a dose of 150mg without lamotrigine). However, the effect of CRCL on CL is clearly underestimated compared to renal impairment study (VRX-RET-E22-101). The use of lamotrigine caused a 7.5% reduction in retigabine CL.
The sponsor claimed that although dose was shown to be a statistically significant covariate in the population pharmacokinetic analysis, this appears to have been mainly driven by higher clearance values in the 100mg dose group (Figure 4).

Figure 4. Individual predicted CL of retigabine by dose from the population PK analysis.



The population PK analysis for the N-acetyl metabolite of retigabine identified the statistically significant relationships of V2 with retigabine dose proportional increase), of CL with CRCL (proportional increase), and of CL with SGPT (nonlinear increase) as follows;

$$CL = 2.83_{,L} + 2.79 * (CRCL/119_{,mL/min}) + 0.677 * Log\ (SGPT/18_{,U/L})$$

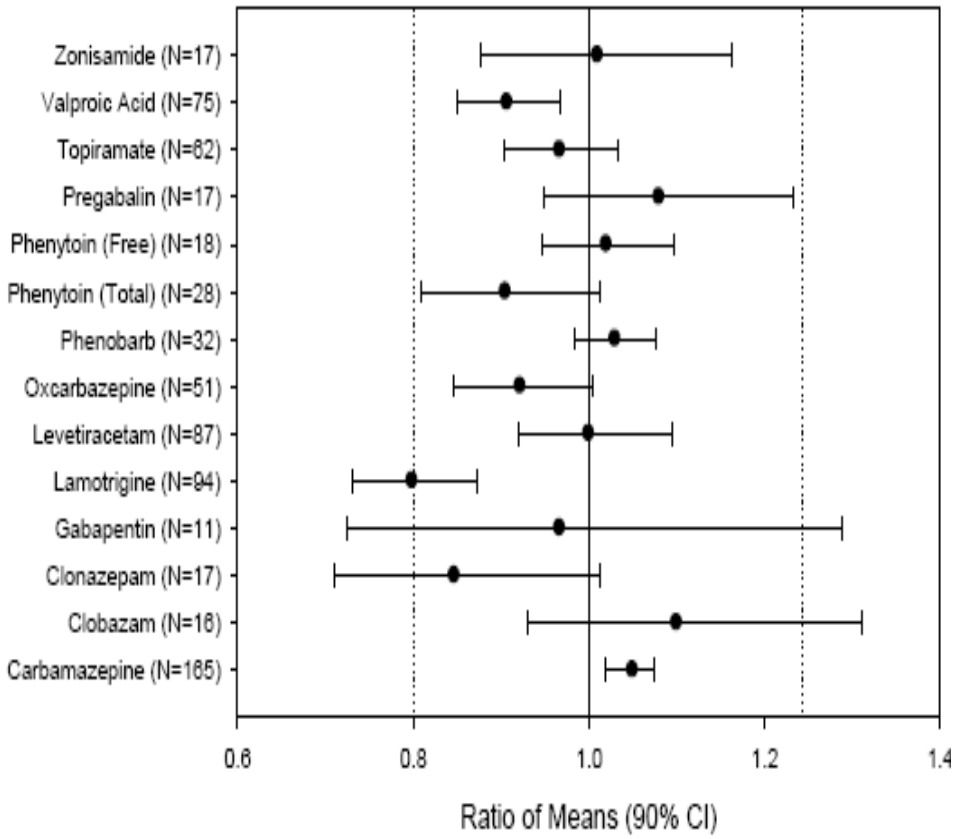
$$V2 = 6.57_{,L} + 10.7 * (DOSE_{,mg} / 150_{,mg})$$

The final model for N-acetyl metabolite indicated that over the investigated range of CRCL (20-150 mL/min), the CL of the metabolite increased linearly from 3.3 L/hr to 6.3 L/hr; increase in SGPT from 20 U/L (normal) to 140 U/L resulted in an approximately 10% increase in CL. Due to the weak activity of the N-acetyl metabolite of retigabine, physiologically induced changes in its pharmacokinetics alone do not justify any specific dose adjustments.

As well as the effects of AEDs on retigabine PK which was evaluated as the covariates in the population PK analysis, the evaluation of the potential influence of co-administration of retigabine on PK of AEDs was also considered by a confidence interval approach using data from two phase III studies (301 and 302); the trough AED concentrations prior to and after retigabine administration were examined. Overall, retigabine had little or no effect on the trough concentrations of a wide range of concomitant AEDs. For most AEDs, the 90% confidence intervals of their geometric mean ratios with and without concomitant retigabine fell entirely within the 80% to 125% bioequivalence limits.

However, retigabine co-administration was associated with a 20% decrease in lamotrigine concentrations. The results from this analysis are summarized in Figure 5.

Figure 5. With to without retigabine ratios of mean AED trough concentrations and corresponding 90% CI.



Source : sponsor's report, "Population Pharmacokinetic Analysis of Retigabine and its Nacetyl Metabolite in Refractory Epilepsy Patients with Partial-Onset Seizures and Healthy Subjects" on page 110.

Exposure-Response analysis

The evidence of effectiveness of retigabine was demonstrated in three placeo-controlled studies in patients with partial-onset epilepsy; a phase IIb study conducted by Wyeth, study 3065A1-205 (study 205) and two phase III studies conducted by Valeant, study VRX-RET-E22-301 (Study 301) and study VRX-RETE22-302 (study 302). Table 3 shows the summary of study design for three controlled studies.

Table 3. Overview of primary study design.

	Study 205	Study 301	Study 302
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland Portugal ,Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK Ukraine, and US

Source : sponsor's report, "Clinical overview" on page 22.

The sponsor evaluated the relationship based on two primary endpoints in order to support international registration of retigabine as follows;
1. percent change from baseline to the double-blind period (titration through maintenance), in total partial seizure frequency per 4 weeks.
2. proportion of responders experiencing a ≥50% reduction from baseline to the maintenance phase, in total partial seizure frequency per 4 weeks

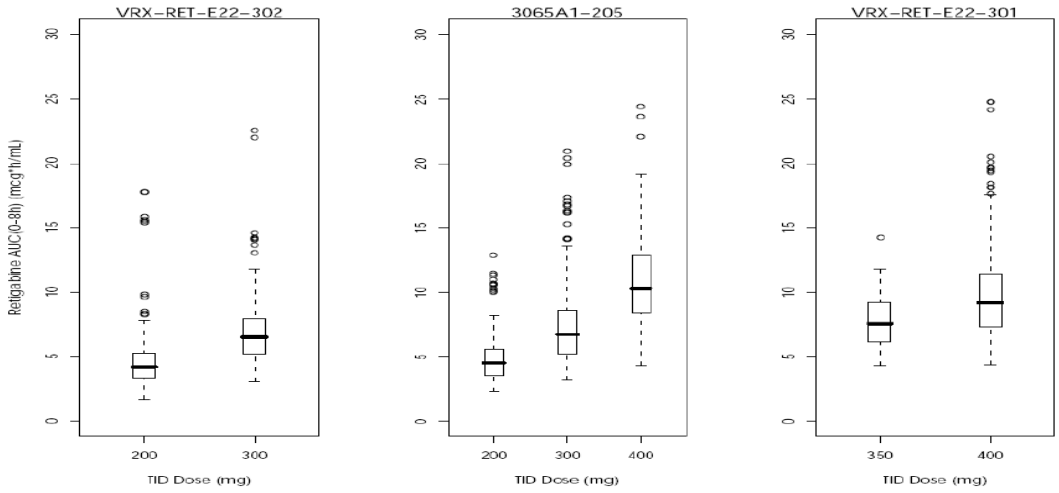
In the efficacy analyses three placebo-controlled studies (study 205, 301 and 302) were included. The results on the percent change in total partial seizure frequency showed that 900 mg/day (300mg TID) and 1200 mg/day (400mg TID) doses were statistically superior to placebo in the studies of 205 and 302 ($p<0.05$) but 600 mg/day (200mg TID) dose was statistically superior to placebo in the study of 302 ($p=0.007$) but not the study of 205 ($p=0.156$). The results from responder analyses showed similar trend (refer to appendix).

For the exposure-response analyses, two phase III studies (301 and 302) were included for both efficacy and safety. The efficacy of retigabine was assessed based on both primary endpoints in the correlation with retigabine predicted area under the concentration-time curve (AUC, h·μg/mL), Cmax (μg/mL) and Cmin (μg/mL). As the analyses across all three exposure parameters ended up with same results, the analyses using AUC are presented in this review.

Although the primary endpoint was the percent change from the baseline during DB phase (titration phase + maintenance phase), the sponsor performed analyses based on maintenance phase only. The reviewer reanalyzed data using DB phase in the reviewer's assessment to be consistent with efficacy analyses and to meet the primary endpoint.

First, Figure 6 shows the distribution of predicted AUC (h·μg/mL) by dose group which shows the moderate overlap over 600mg/day to 1200mg/day.

Figure 6. The distribution of AUC (h·μg/mL) by dose group.



Source : sponsor's report, "Clinical overview" on page 40.

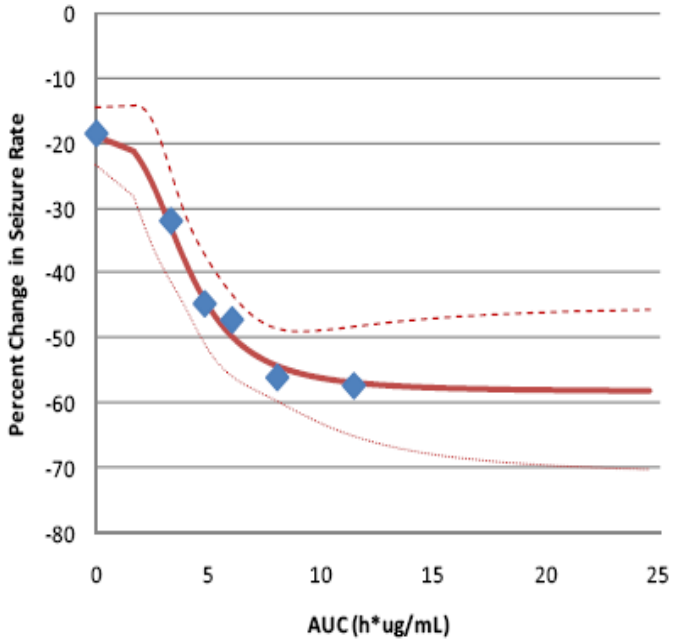
Retigabine exposure-efficacy relationships were evaluated via inhibitory Hill equation modeling of percent change in total partial seizure frequency as follows;

$$Y = E_0 + \frac{E_{\max} x^c}{EC_{50}^c + x^c} + \varepsilon$$

Where Y is the percent change from baseline of the total partial seizure frequency or the median corresponding to the exposure quintile, E0 is the placebo effect, Emax is the maximal effect of retigabine, EC50 is the retigabine systemic exposure level that yields a 50% of the maximal change from baseline, c is the shape parameter, and x is AUC (h·μg/mL), and ε is the residual error.

The sponsor's exposure-response analyses showed that the percent reduction from baseline in total partial seizure frequency ranged from approximately 15 to 20% at placebo to a maximum of 60% reduction from baseline in total partial seizure frequency at an AUC (h·μg/mL) value which approximates to the median AUC (h·μg/mL) associated with the 1200mg/day dose. The AUC (h·μg/mL) associated with 50% of the maximum response corresponds approximately to the median AUC (h·μg/mL) observed for the dose of 600 mg/day.

Figure 7. Median percent changes from baseline in total partial seizure frequency as a function of retigabine median AUC (maintenance phase) in AUC quintiles.

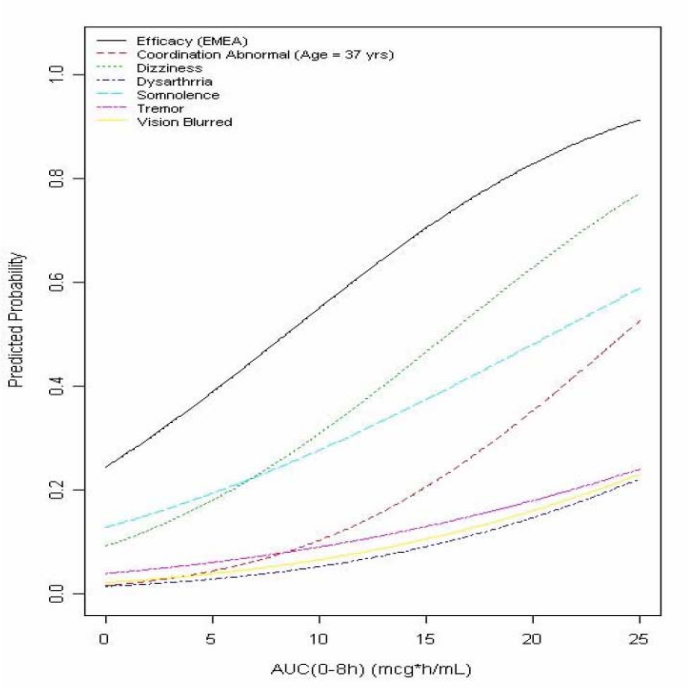


Source : sponsor's report, "Population Pharmacokinetic/Pharmacodynamic Analysis of Retigabine in Refractory Epilepsy Patients with Partial-Onset Seizures and Healthy Subjects" on page 84.

For the sponsor's responder analyses, the logistic regression with probit link was employed. The probability of responder P(response) = Φ(b0 + b1 log x), where x is the exposure parameter, b0 and b1 are parameters to be estimated, and Φ(z) is the cumulative normal distribution function. In terms of safety-exposure relationship, six adverse events (AEs) of interest including coordination abnormal, dizziness, dysarthria, somnolence, tremor, and blurred vision were included in the correlation with retigabine predicted exposure at steady state. The probability of an AE of interest occurred at any time during the maintenance phase was modeled using logistic regression with a probit link function.

Figure 8 displays the probability of responder along with the probability of six adverse events of interest including coordination abnormal, dizziness, dysarthria, somnolence, tremor, and blurred vision in the correlation with retigabine predicted AUC based on the sponsor's logistic regression. AUC was found to be significant predictors for the probability of responder, meaning that the probability of responder tends to go up as the exposure is increased. In terms of safety endpoints, all six endpoints showed exposure-dependent relationship. Also the analysis showed that over the observed AUC range in the studies of 301 and 302, the probability of responder (>50% decrease from baseline in seizure frequency) was higher than the probability of any of the AE occurring. The slope of the exposure-response relationship for probability of responder was similar to that for dizziness and coordination abnormal whereas the slope of the exposure response relationship for dysarthria, somnolence, tremor and vision blurred were less steep, indicating that these latter AEs were less sensitive to changes in exposure.

Figure 8. Probability of responder (≥50% reduction in seizure frequency) and adverse events in correlation with retigabine AUC.



Source : sponsor's report, "Clinical overview" on page 39.

Table 4 summarizes the overall results from the sponsor analyses. The sponsor's prediction on the percent reduction (%) in seizure frequency was higher than efficacy analysis results due to the use of maintenance phase rather than DB phase. However, the sponsor's exposure-response analyses support the effectiveness of retigabine.

Table 4. The prediction of median percent reduction, probability of responder and six adverse events at each dose (the median exposure at each dose group) from the sponsor's analyses.

Dose	Placebo	600 mg/day	900 mg/day	1200 mg/day
Median AUC(0-τ) (ug.h/mL)	0	4.35	6.78	9.67
Predicted % change in seizure frequency	-18.9	-40.9	-51.8	-55.9
Probability of >50% reduction in seizure frequency	0.24	0.37	0.44	0.54
Probability of Dizziness	0.09	0.17	0.22	0.30
Probability of Somnolence	0.13	0.18	0.22	0.27
Probability of Coordination Abnormal	0.02	0.04	0.06	0.10
Probability of Dysarthria	0.01	0.03	0.04	0.05
Probability of Tremor	0.04	0.06	0.07	0.09
Probability of Vision Blurred	0.02	0.04	0.05	0.06

Source : sponsor's report, "Clinical overview" on page 38.

Reviewer's comment:

- *For the sponsor's population PK model,*
  - *The effect of CrCL on CL was underestimated compared to dedicated study,* VRX-RET-E22-101 *(30% reduction vs. 100% reduction between normal and severe renal impaired patients)*
  - *PK of retigabine is linear but population PK analysis showed that CL linearly depends on dose*
  - *Shrinkage estimate for CL is 0.45 (1-(0.1176/sqrt(0.046)))*
- *The sponsor's exposure-response analysis based on the percent change in seizure frequency during maintenance phase from the baseline is not the primary endpoint based on US FDA's requirement.*
- *The sponsor's exposure-response analysis for the probability of responder was based on the linearity assumption. However, it was observed that the relationship reached a plateau at the certain level of exposure so the linearity assumption would not be justified.*

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor's analyses performed exposure-response analyses based on percent change in seizure frequency from the baseline to maintenance period. However, the primary endpoint is the percent change in seizure frequency from the baseline to double blind phase which included both titration and maintenance periods based on US FDA requirement. Hence, the reviewer aims to reanalyze the relationship between exposure and responses based on double blind phase. Also the sponsor's exposure-response analysis for the probability of responder (EMEA endpoint) was performed based on linearity assumption. However, the reviewer observed that the observed proportion of responder seemed to reach a plateau at the certain level of exposure so the linearity assumption didn't seem to fit quite well. Hence, the E-R relationship for the probability of responder was refitted using Emax model which is more consistent with the relationship between exposure and the percent change in seizure frequency (US FDA's endpoint).

4.2 Objectives

- To reanalyze the exposure-response (percent reduction in seizure frequency during DB phase from the baseline) relationship
- To reanalyze the exposure-response for the probability of responder using Emax model.

4.3 Method

To reanalyze the E-R relationship based on the percent change in seizure frequency, the data during double blind phase was extracted and merged with PK dataset. The same inhibitory Emax model which was used for the sponsor's analysis was employed, and AUC (h·μg/mL) was evaluated as an exposure.

For the responder analysis, the following model was fitted

$$\log \frac{p(responder)}{1-p(responder)} = \beta_0 + \frac{E\max \times AUC^h}{EC50^h + AUC^h}$$

where β_0 is the place effect, Emax is the maximum effect and EC50 is the retigabine exposure which yields a 50% of the maximum effect, finally *h* represents the hill-coefficient which governs the shape of relationship.

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
VRX-RET-E22-301 VRX-RET-E22-302	drate301.sas7bdat Drate302.sas7bdat Pk_eff_placebo.sas7bdat	

4.3.2 Software

SAS 9.2 was used for the analysis.

4.4 Results

Reanalysis of percent change in seizure frequency

First, the reviewer compared the observed median percent change in seizure frequency during DB phase (titration phase + maintenance phase) to during maintenance phase only, and Table 6 shows the difference. Both show clear dose-dependent increase and maximum effect size appears to be bigger when analyzed using maintenance phase only.

Table 6. The median percent change in seizure frequency during maintenance and DB phase by dose group.

	DB phase	Maintenance phase
Placebo	-17.11	-18.4
600mg /day	-32.26	-35.28
900mg/day	-42.74	-44.26
1200mg/day	-48.81	-54.55

The Table 7 shows the comparison of parameter estimates between the sponsor and the reviewer's analyses. It shows the subtle difference, especially in Emax parameter estimate which is consistent with the observation in Table 6.

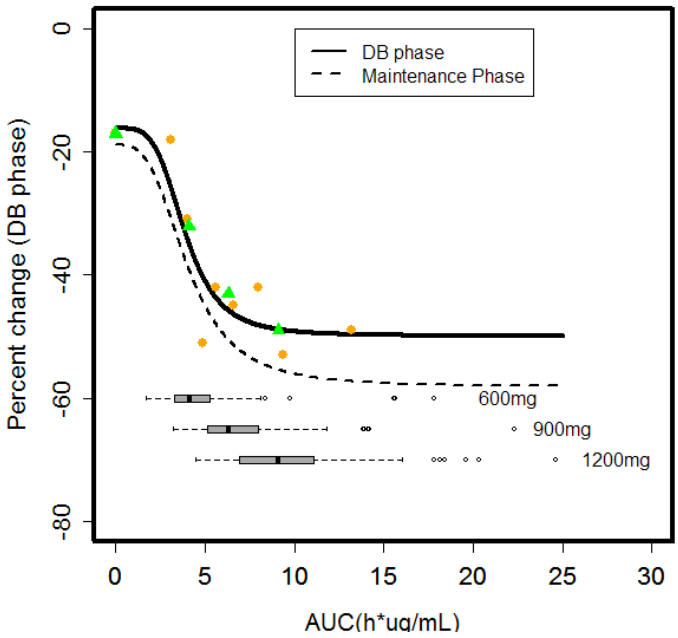
Table 7. The parameter estimates with standard error from the inhibitory Emax model from the sponsor's analysis and the reviewer's analysis.

	Parameter estimates (SE)	
	The sponsor's analysis (N=728)	The reviewer's analysis (N=831)
E0	-18.90 (2.25)	-16.22 (2.15)
Emax	-39.27 (7.01)	-33.69 (6.57)
EC50	4.03 (0.72)	3.88 (0.66)
Hill coefficient	1.15 (0.53)	1.39 (0.76)
Degree of freedom for t distribution	2.62 (0.29)	3.00 (0.36)
sigma	31.86 (1.56)	30.95 (1.46)

Figure 9 shows the corrected relationship between the percent change in seizure frequency from the baseline using the data during double blind phase. The relationship appears to be shallower; maximum percent change in seizure frequency was approximately 50%, which was compared to 60% in the sponsor's analysis. However, overall conclusion of clear exposure-dependent decrease in seizure frequency and reaching a plateau at the highest dose remained same.

Figure 9. The percent change in seizure frequency during DB phase (the reviewer's analyses) in relation to the AUC, compared to same endpoint during maintenance phase (the sponsor's analysis). Then orange dots and green triangles indicate the observed percent reduction during DB phase at decile of AUC and at each dose group which were

marked at the median exposure. The boxplots represent the distribution of exposure at three dose levels.



Responder analysis

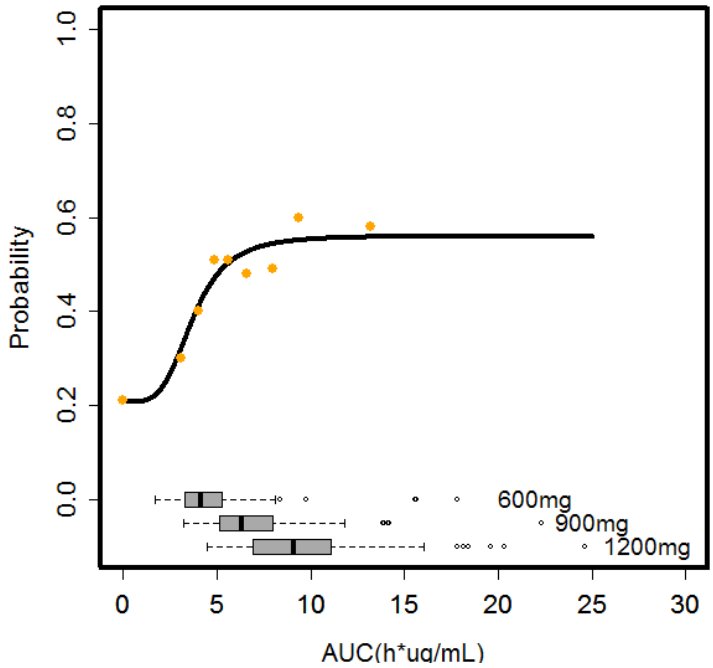
The reviewer fit the Emax model to the same dataset and Table 8 shows the parameter estimates. **Figure 10** presents the model predicted relationship with the observed proportion of responder at the octile of AUC. The model fit seems to improve, which is confirmed by AIC (linear model : 796.5 vs. Emax model: 785.0). As consistent with the exposure-response relationship for the percent change in seizure frequency from the baseline to double blind phase, the relationship between the probability of responder and AUC appears to reach a plateau at 1200mg/day.

Table 8. The parameter estimates from the reviewer's Emax model for the probability of responder

	Parameter estimates (SE)
E0	-1.34 (0.14)
Emax	1.58 (0.30)
EC50	3.51 (0.62)

Hill coefficient	1.34 (0.85)

Figure 10. The probability of responder during maintenance phase in relation to the AUC. Then orange dots indicate the observed proportion of responder at octile of AUC. The boxplots represent the distribution of exposure at three dose levels.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Reviewer_ER_DB.sas	The percent change during DB phase analysis	
Reviewer_ER_emax_responder.sas	The probability of responder analysis	

APPENDIX

1. The parameter estimates from the sponsor's final Population PK model :

Retigabine

Model Parameters	Parameter	Estimate	Standard Error	RSE	-95% CI	95% CI
Objective Function Value	OFV	156273.497				
Clearance, CL	Θ(1)	10.4	1.01	9.71%	8.42	12.4
Central Volume of Distribution, V2	Θ(2)	68.5	32.9	48%	4.02	133
Intercompartmental clearance, Q	Θ(3)	52.2	2.8	5.36%	46.7	57.7
Peripheral Volume of Distribution, V3	Θ(4)	189	7.55	3.99%	174	204
Absorption rate constant, KA	Θ(5)	1.10	0.076	6.91%	0.951	1.25
Bioavailability, F1	Θ(6)	0.685	0.0226	3.30%	0.641	0.729
Linear Effect of (Dose/150) on CL	Θ(7)	-4.03	0.153	-3.80%	-4.33	-3.73
Power Effect of CRCL on CL	Θ(8)	0.209	0.0214	10.2%	0.167	0.251
Power Effect of BSA on CL	Θ(9)	0.483	0.0626	13%	0.36	0.606
Power Effect of Age on V2	Θ(10)	0.339	0.133	39.2%	0.0783	0.600
Fractional Effect of CM06 on CL	Θ(11)	-0.067	0.0161	-24%	-0.0986	-0.0354
Interindividual variability CL	h(1)	0.046 CV = 21.7%	0.00674	14.7%	0.0328	0.0592
Interindividual variability V2	h(2)	0.802 CV = 111%	0.0636	7.93%	0.677	0.927
Interindividual variability Q	h(3)	0.273 CV = 56%	0.049	17.9%	0.177	0.369
Interindividual variability V3	h(4)	0.125 CV = 36.5%	0.0219	17.5%	0.0821	0.168
Interindividual variability KA	h(5)	0.808 CV = 112%	0.0963	11.9%	0.619	0.997
Interindividual variability F1	h(6)	0.121 CV = 35.9%	0.00929	7.68%	0.103	0.139
Residual variability (P)	ε(1)	0.138 CV = 37.1%	0.00112	0.81%	0.136	0.140
Residual variability (A)	ε(2)	0.504 SD = 0.71	0.0644	12.8%	0.378	0.630

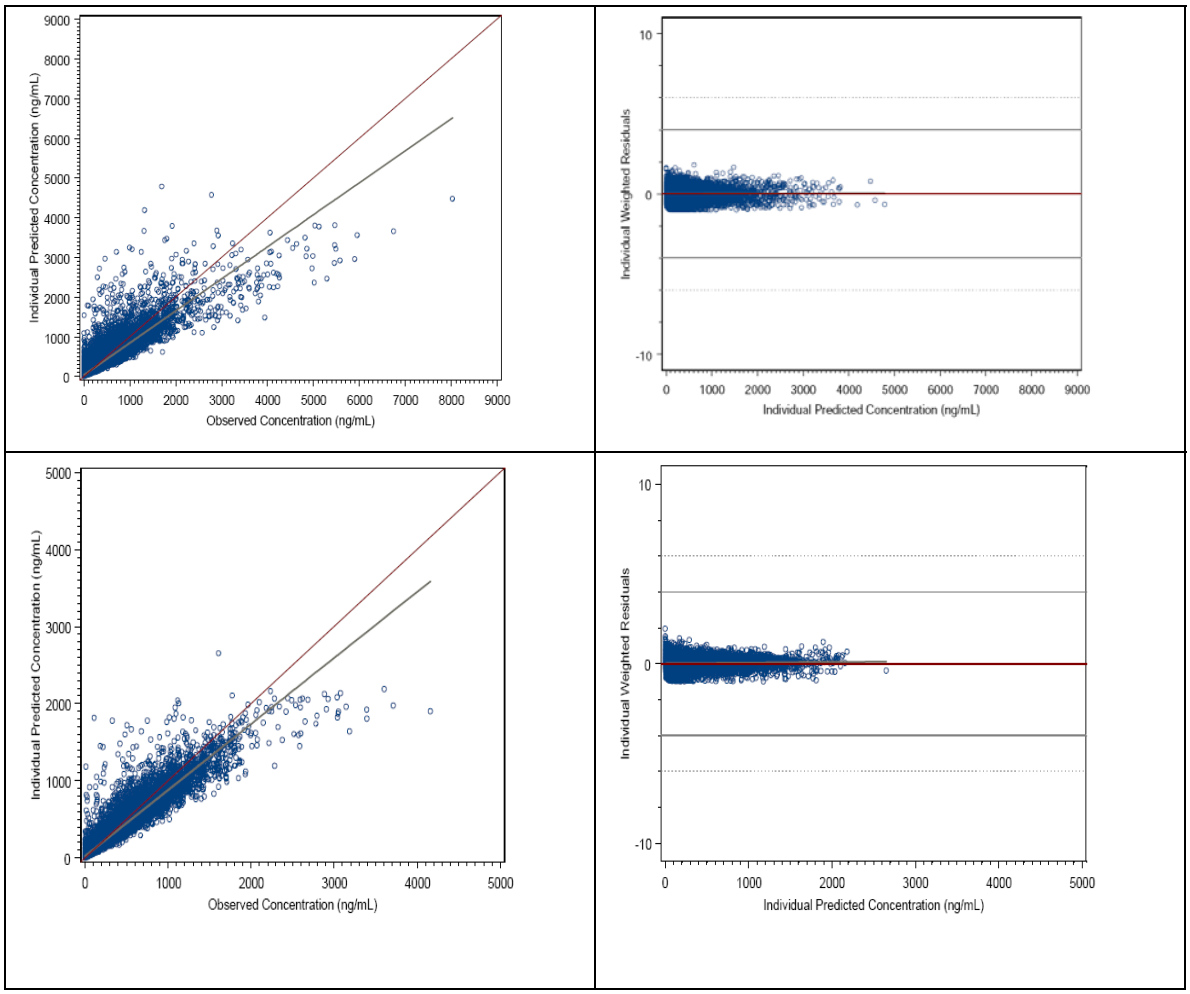
[1]Model 5209 is also the final model
RSE = relative standard error of estimates, SD = Standard deviation, P= proportional, A=additive
CRCL=Creatinine Clearance, BSA= Body Surface Area
Coefficient of variation, %CV, was calculated as: (exp(Variance)-1)½ * 100 for random error, and (Variance)½ * 100 for proportional residual error; SD = (Variance) ½ for additive residual error; RSE = SE/Estimate*100%;
95% Confidence Interval (CI) = Estimate ± (1.96* SE)

N-acetyl Retigabine

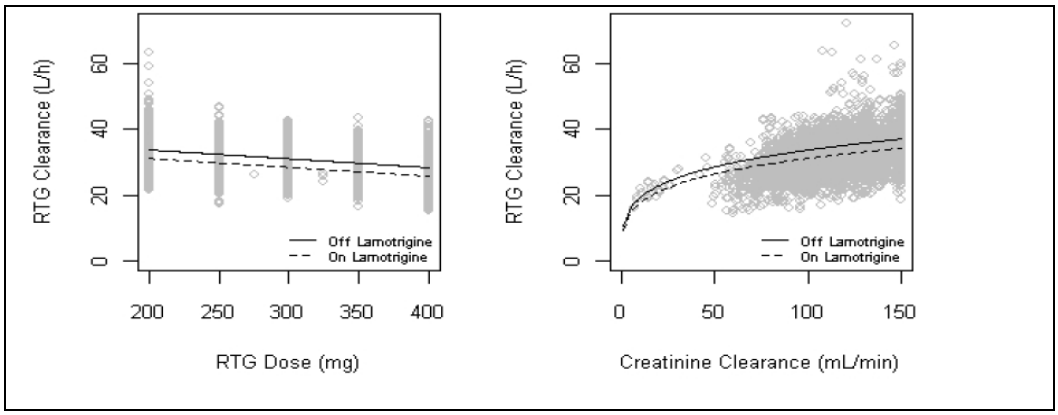
Model Parameters	Parameter	Estimate	Standard Error	RSE	-95% CI	95% CI
Objective Function Value	OFV	137451.273				
Clearance, CL	Θ(1)	2.83	0.704	24.9%	1.45	4.21
Central Volume of Distribution, V2	Θ(2)	6.57	1.72	26.2%	3.20	9.94
Intercompartmental clearance, Q	Θ(3)	5.82	0.843	14.5%	4.17	7.47
Peripheral Volume of Distribution, V3	Θ(4)	32.9	4.75	14.4%	23.6	42.2
Absorption rate constant, KA	Θ(5)	0.220	0.0218	9.91%	0.177	0.263
Bioavailability, F1	Θ(6)	0.111	0.0189	17.0%	0.0740	0.148
Effect of DOSE on V2	Θ(7)	10.7	1.96	18.3%	6.86	14.5
Effect of CRCL on CL	Θ(8)	2.79	0.446	16.0%	1.92	3.66
Effect of SGPT on CL	Θ(9)	0.677	0.278	41.1%	0.132	1.22
Interindividual variability CL	η(1)	1.32 CV=166 %	0.195	14.8%	0.938	1.70
Off-diagonal correlation CL-V2	η(1,2)	1.26 corr=0.887	0.222	17.6%	0.825	1.70
Interindividual variability V2	η(2)	0.153 CV=190 %	0.263	17.2%	1.01	2.05
Off-diagonal correlation CL-V3	η(1,3)	0.297 corr=0.749	0.0754	25.4%	0.149	0.445
Off-diagonal correlation V2-V3	η(2,3)	0.259 corr=0.607	0.0768	29.7%	0.108	0.410
Interindividual variability V3	η(3)	0.119 CV=35.5 %	0.0364	30.6%	0.0477	0.190
Off-diagonal correlation CL-F1	η(1,4)	1.25 corr=0.951	0.191	15.3%	0.876	1.62
Off-diagonal correlation V2-F1	η(2,4)	1.30 corr=0.918	0.221	17.0%	0.867	1.73
Off-diagonal correlation V3-F1	η(3,4)	0.271 corr=0.686	0.0710	26.2%	0.132	0.410
Interindividual variability F1	η(4)	1.31 CV=165 %	0.192	14.7%	0.934	1.69
Residual variability	ε(1)	0.0876 CV=29.6%	0.00275	3.14%	0.0822	0.0930
Residual variability	ε(2)	1.60 SD=1.26	1.78	111%	-1.89	5.09

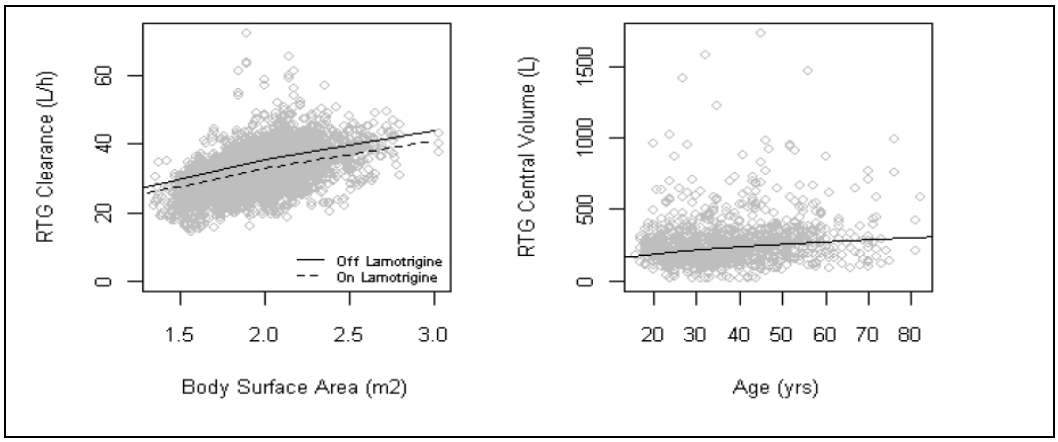
Coefficient of variation, %CV, was calculated as: (exp(Variance)-1)½ * 100 for random error, and (Variance)½ * 100 for proportional residual error; SD = (Variance) ½ for additive residual error; RSE = SE/Estimate*100%;
95% Confidence Interval (CI) = Estimate ± (1.96* SE) ; corr=$\eta(i,j)^{*}\ \eta(i)^{-0.5}\ ^{*}\ \eta(j)^{-0.5}$; SD = standard deviation

2. Model diagnostics for population PK analyses. Top panel : retigabine, bottom panel : N-acetyl metabolite.



2. The covariates which showed the significant effects on retigabine CL.



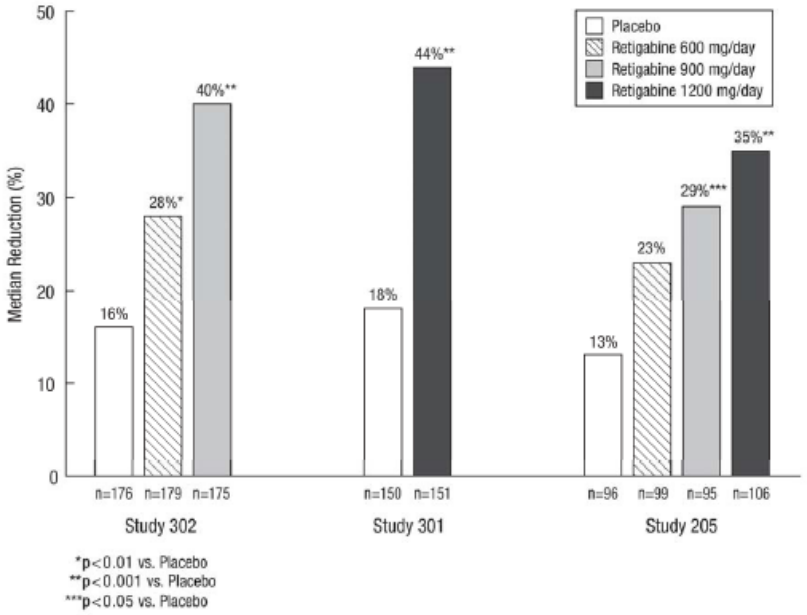


3. The parameter estimates of logistic regression for the sponsor's responder analyses.

Independent Variable	Effect	Parameter Estimate	Standard Error	P-value
AUC	Intercept	-0.6942	0.07043	<0.0001
	AUC	0.08194	0.01222	<0.0001
Cmin	Intercept	-0.6447	0.06778	<0.0001
	Cmin	0.7962	0.1307	<0.0001
Cmax	Intercept	-0.7086	0.07166	<0.0001
	Cmax	0.5573	0.08122	<0.0001

4. The results from efficacy analyses.

- Percent Change from Baseline in Total Partial Seizure Frequency (Double-Blind Phase) – ITT Population for Study 205 and ITT Double-Blind Population for Studies 301 and 302



- Responder Rates (Maintenance Phase) – ITT Maintenance Population: Studies 205, 301 and 302

	Number (%) of Patients			
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
N	78	83	74	68
Responders	20 (25.6)	23 (27.7)	30 (40.5)	28 (41.2)
Non-responders	58 (74.4)	60 (72.3)	44 (59.5)	40 (58.8)
P-value[a]	-	0.845	0.057	0.010
P-value[b]	-	0.859	0.059	0.053
P-value[c]	-	-	-	0.031
Study 301				
N	137	n/a	n/a	119
Responders	31 (22.6)	n/a	n/a	66 (55.5)
Non-responders	106 (77.4)	n/a	n/a	53 (44.5)
P-value[d]	-	n/a	n/a	<0.001
Study 302				
N	164	158	149	n/a
Responders	31 (18.9)	61 (38.6)	70 (47.0)	n/a
Non-responders	133 (81.1)	97 (61.4)	79 (53.0)	n/a
P-value[d]	-	<0.001	<0.001	n/a

n/a=not applicable (dose not included in this study)
Responders were defined as patients with ≥50% reduction in 28-day total partial seizure frequency

a. The p-values presented are from the original closed test using logistic regression under the assumption of monotonicity
b. The p-values presented are from the *post-hoc* harmonized analysis using Fisher's Exact test
c. The p-value is from the direct comparison vs. placebo using pre-specified statistical method logistic regression but without assumption of monotonicity
d. P-value from Fisher's Exact test

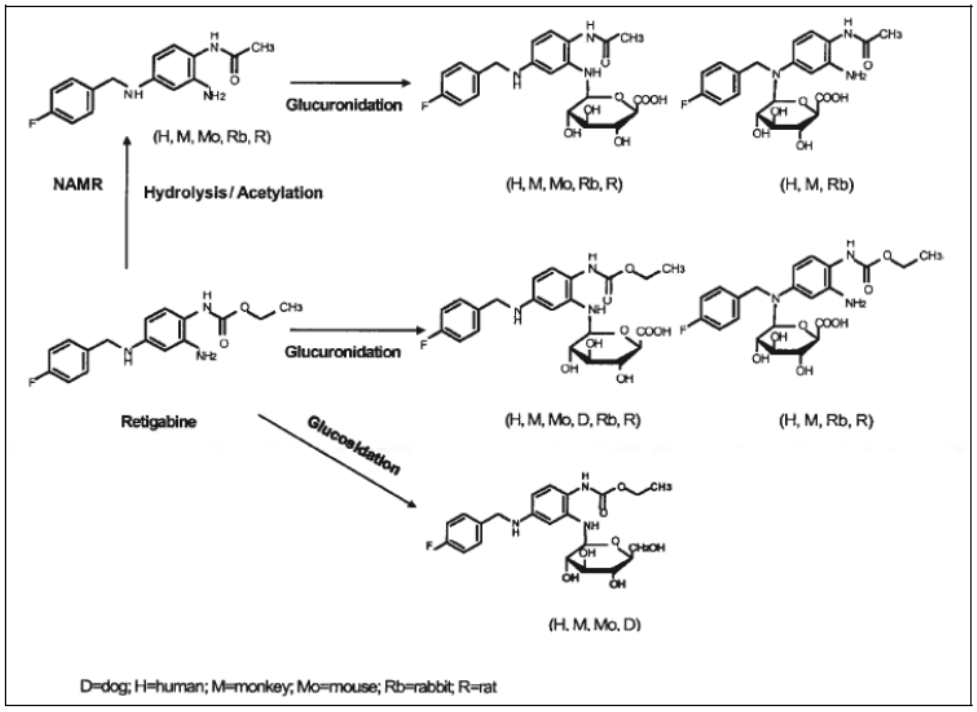
CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

NDA/BLA Number	022345
Submission Type; Code	NME
Applicant Name	Valeant Pharmaceuticals North American
Submission Date	Nov 6, 2009
Brand Name	Potiga
Generic Name	Retigabine
Proposed Indication	Adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization
Genomics Reviewer	Li Zhang, PhD
Team Leader	Issam Zineh, Pharm. D, MPH

TABLE OF CONTENTS

1. BACKGROUND

Retigabine is a novel antiepileptic compound. It opens specific potassium channels, namely, M channels linked to KCNQ2/3 and KCNQ3/5, which are involved in the control of the excitability of neuronal cells. Retigabine also has a concentration-dependent ancillary mode of action by increasing γ-aminobutyric acid-evoked currents. These effects, however, were seen at concentrations of 10 μmol/L, whereas the potassium channel-opening effects occur at concentrations as low as 0.1 μmol/L. The metabolism of this drug is through formation of the N-acetyl metabolite of retigabine (NAMR) and through N-glucuronidation of both retigabine and NAMR. In human plasma, the N2-glucuronide of retigabine is the predominant metabolite (urinary metabolic profile 16% dose). NAMR, which had substantially less activity than retigabine in in-vitro and in-vivo pharmacology models, is also a circulating metabolite of retigabine. The following figure shows the major metabolite in vitro pathways of Retigabine in different species.



In vitro studies have shown that the glucuronidation of retigabine is performed by several uridine diphosphate glucuronyl transferase (UGT) isozymes, including UGT1A1, UGT1A4, UGT1A3 and UGT1A9. A further major metabolite is AWD21-360, which is formed by acetylation of an intermediary metabolite (hydrolyzed and decarboxylated retigabine).

2. NDA CONTENT RELATED TO GENOMICS

The main goal of the pharmacogenomic study is to investigate the impact of the frequently occurring genetic polymorphism of UGT1A1 (Gilbert's Syndrome) and NAT2 (slow acetylators) on the PK of retigabine and its main metabolites (i.e. glucuronidation products and mono-acetylated metabolite AWD 21-360). UGT1A1 is one of 9 isozymes encoded by the UGT1A locus, a superfamily of Phase II drug metabolizing enzymes that catalyze the glucuronidation reaction to render xenobiotic and endogenous compounds to water soluble molecules that can be

excreted. Located on chromosome 2q37 [PMID: 8467709]. The promoter region and exon 1 of UGT1A1 contain the most common polymorphisms: an insertion/deletion of (TA)6/(TA)7 (UGT1A1*28). The UGT1A1*28 allele is common in Caucasian populations and populations of African origin (0.26-0.56) [PMID: 10591539] and defines the genetic basis of Gilbert syndrome (the most common hereditary cause of increased bilirubin and is found in up to 5% of the population). The UGT1A1*28 is known to reduce enzymatic activity of UGT1A1, and has been associated with increased risk of adverse outcome and severe toxicity during irinotecan treatment [PMID: 11990381, 12485959]. As to NAT2, the S1, S2 and S3 alleles are clearly associated with the slow phenotype when present without the F1 allele. The F1 allele in heterozygotes and homozygotes produces predominantly the fast phenotype..There appears to be no difference in the S1, S2 or S3 polymorphic alleles in relation to acetylator phenotype [PMID: 1872889].

An open, single-center, single dose (SD) and multiple dose (MD), non-randomized trial was conducted in four parallel groups of healthy subjects with different genotypes. 37 healthy Caucasians (86% Caucasian in clinical efficacy trials and >95% Caucasian in clinical safety trials) are included with predetermined information on their UGT1A1 and NAT2 genotype (female 16.2% and no female in Group 4):

Group (number)	UGT1A1 Genotypes	NAT2 Genotypes
Group 1 (N=11)	6/6 genotype (normal wildtype)	either F1/S2 or F1/S1 kd (fast acetylators)
Group 2 (N=8)	7/7 genotype (Gilbert's Syndrome)	either F1/S2 or F1/S1 kd (fast acetylators)
Group 3 (N=11)	6/6 genotype (normal wildtype)	either S1kd/S2, S1kd/S1kd, S2/S2, S1kd/S1d, or S1k/S3 (slow acetylators)
Group 4 (N=7)	7/7 genotype (Gilbert's Syndrome)	either S1kd/S2, S1kd/S1kd, S2/S2, S1kd/S1d, or S1k/S3 (slow acetylators)

UGT1A1: UDP-Glucuronyl Transferase 1A1, NAT2: N-Acetyl Transferase 2

Before inclusion of a subject, results of genotyping were confirmed by phenotyping of each subject by two screening tests: screening test 1 (caffeine test to estimate NAT2 activity through urine sample) and screening test 2 (fasting test for UGT1A1 status phenotypically from serum bilirubin). If phenotype and genotype were concordant, subjects were included into the study and preceded with the treatment. There was only one discrepancy between UGT genotyping and phenotyping (Subject 36). In this case, phenotyping (wild type) determined the group allocation. In three subjects (Subject 11, 17, 35), NAT2 phenotyping was missing. In these cases NAT2 genotyping was used for group allocation. Bilirubin profiles were performed at the fasting screening test, after the first dose (single dose, day D1, morning), and after the 9th dose (multiple dose, day D6, evening).

3. KEY QUESTIONS AND SUMMARY OF GENOMICS FINDINGS

3.1. Do UGT1A1 or NAT2 variants influence retigabine PK parameters?

The sponsor used the 2-factor ANOVAs (including interaction) method to calculate AUC and C_{max} in a multiplicative model after single dose and multiple doses (steady state) of retigabine. $t_{1/2}$ was evaluated by a linear model in the steady state only. Accumulation from single dose to multiple dose (Day 9, same kinetic profiling over 12 hours) was analyzed by a 3- factor ANOVA with an additional intraindividual period factor. For the AUC and C_{max}, weight normalized values were taken.

The sponsor's results of the pharmacokinetic analysis of the different metabolizer groups for retigabine and AWD21-360 after single and multiple (twice daily) doses are summarized in the following tables. C_{max}, AUC, and CL/F data are geometric mean (range); norm: 70kg body weight normalized; t_{max} and $t_{1/2}$ data are median (range).

Pharmacokinetic parameters of retigabine after a single oral dose of 200 mg retigabine

Subject Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	$AUC_{(0-\infty)}$ [ng·h/ml]	$AUC_{(0-\infty),\,norm}$ [ng·h/ml]	CL/F [ml/(min·kg)]
1: UGT1A1 ext. + NAT2 fast, n=11	380 (254-567)	0.7 (0.3-3.0)	8.5 (6.3-13.8)	3013 (2488-3650)	3182 (2653-3816)	15.0 (27.6-12.5)
2: UGT1A1 poor + NAT2 fast, n=8	411 (318-531)	0.8 (0.3-4.0)	10.5 (6.0-19.3)	2695 (2255-3221)	3066 (2487-3779)	15.5 (12.6-19.1)
3: UGT1A1 ext. + NAT2 slow, n=11	376 (265-535)	0.7 (0.3-3.0)	9.7 (7.5-16.3)	2622 (2340-2937)	3034 (2763-3331)	15.5 (14.1-17.2)
4: UGT1A1 poor + NAT2 slow, n=7	418 (205-851)	0.7 (0.3-4.0)	10.4 (8.3-15.7)	2974 (2150-4113)	3333 (2529-4393)	14.3 (10.8-18.8)

Pharmacokinetic parameters of the acetylated metabolite (AWD21-360) after a single oral dose of 200 mg retigabine

Subject Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	$AUC_{(0-\infty)}$ [ng·h/ml]	$AUC_{(0-\infty),norm}$ [ng·h/ml]
1: UGT1A1 ext. + NAT2 fast, n=11	225 (180-281)	4.0 (0.3-16.0)	10.4 (7.4-21.1)	4051 (3291-4988)	4278 (3557-5144)
2: UGT1A1 poor + NAT2 fast, n=8	265 (199-354)	2.5 (1.0-4.0)	13.3 (7.1-20.3)	4334 (3392-5538)	4930 (3916-6206)
3: UGT1A1 ext. + NAT2 slow, n=11	191 (152-240)	3.0 (0.7-6.0)	10.0 (7.1-16.1)	2982 (2642-3367)	3487 (3046-3992)
4: UGT1A1 poor + NAT2 slow, n=7	198 (118-330)	2.5 (1.7-6.0)	12.9 (8.9-19.9)	3517 (2450-5049)	3942 (2948-5272)

Pharmacokinetic parameters of retigabine after muliple oral dose of 200 mg retigabine BID

Subject Group	$C_{max,ss}$ [ng/ml]	$t_{max,ss}$ [h]	$t_{1/2,ss}$ [h]	$AUC_{\tau,ss}$ [ng·h/ml]	$AUC_{\tau,ss\ norm}$ [ng·h/ml]	CL_{ss}/F [ml/(min·kg)]
1: UGT1A1 ext. + NAT2 fast, n=11	694 (528-911)	0.7 (0.3-2.5)	7.4 (6.0-13.0)	2805 (2378-3308)	2962 (2546-3445)	16.1 (13.8-18.7)
2: UGT1A1 poor + NAT2 fast, n=8	563 (381-831)	0.5 (0.3-3.0)	9.2 (5.4-11.5)	2667 (2233-3186)	3034 (2630-3500)	15.7 (13.6-18.1)
3: UGT1A1 ext. + NAT2 slow, n=10	470 (335-660)	1.2 (0.3-6.0)	7.1 (6.4-13.9)	2400 (2077-2774)	2838 (2475-3256)	16.8 (14.6-19.2)
4: UGT1A1 poor + NAT2 slow, n=7	618 (377-1013)	0.7 (0.3-1.3)	7.4 (5.9-13.2)	2647 (2109-3321)	2967 (2399-3670)	16.1 (13.0-19.9)

Pharmacokinetic parameters of the acetylated metabolite (AWD21-360) after multiple oral dose of 200 mg retigabine BID					
Subject Group	$C_{max,ss}$ [ng/ml]	$t_{max,ss}$ [h]	$t_{1/2,ss}$ [h]	$AUC_{\tau,ss}$ [ng·h/ml]	$AUC_{\tau,ss\ norm}$ [ng·h/ml]
1: UGT1A1 ext. + NAT2 fast, n=11	471 (396-561)	2.0 (0.3-4.0)	7.4 (5.7-21.4)	4009 (3311-4854)	4232 (3584-4997)
2: UGT1A1 poor + NAT2 fast, n=8	494 (388-628)	2.8 (0.7-4.0)	9.4 (5.0-14.4)	4303 (3368-5497)	4894 (3963-6044)
3: UGT1A1 ext. + NAT2 slow, n=10	360 (290-447)	2.1 (0.7-6.0)	7.7 (6.3-15.0)	3244 (2751-3825)	3623 (3062-4287)
4: UGT1A1 poor + NAT2 slow, n=7	449 (380-530)	1.7 (0.7-2.5)	7.8 (6.7-9.4)	3534 (2682-4657)	3961 (3241-4842)

The sponsor concluded that after oral single and multiple dose retigabine treatments, the AUC of the acetylated metabolite was slightly lower in slow acetylators versus fast acetylators and slightly higher in subjects with Gilbert's syndrome versus subjects with UGT1A1 wildtype. Based upon the data from this study, no dose adjustment would be required in slow acetylators or in subjects with Gilbert's syndrome.

FDA Analysis:
The genomics group reviewer analyzed the data separately for each gene, since it is unclear whether joint consideration of UGT1A1 and NAT2 genotypes is more informative than consideration of either gene alone. This allocates more individuals in each genotype group and allows for more power to detect differences of retigabine PK parameters (with geometric mean & 95% confidence interval).

PK parameters of Retigabine after a single dose of 200mg retigabine					
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]	CL/F [ml/(min.kg)]
UGT1A1 ext (N=22)	378.1 (341.8, 515.1)	0.824 (0.680, 1.442)	9.455 (8.621, 10.842)	2811 (2560, 3225)	15.25 (14.18, 16.96)
UGT1A1 poor (N=15)	414.2 (335.8, 609.8)	0.942 (0.663, 2.092)	10.971 (9.347, 14.028)	2822 (2485, 3363)	14.94 (13.19, 17.68)
NAT2 fast (N=19)	392.6 (343.8, 525.5)	0.896 (0.741, 1.854)	9.491 (8.218,12.003)	2875 (2579, 3361)	15.20 (13.85, 17.47)
NAT2 slow (N=18)	392.0 (336.4, 581.3)	0.843 (0.604, 1.545)	10.659 (9.577,12.344)	2753 (2483, 3190)	15.04 (13.73, 17.00)

PK parameters of AWD21-360 after a single dose of 200mg retigabine				
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]
UGT1A1 ext (N=22)	207.4 (187.9,248.8)	2.74 (2.28, 5.21)	10.75 (9.61, 12.84)	3476 (3092, 4178)
UGT1A1 poor (N=15)	231.2 (194.8, 311.6)	2.47 (1.94, 3.61)	12.79 (11.17, 15.48)	3932 (3435, 4837)
NAT2 fast	241.1	2.61	12.28	4168

(N=19)	(213.9, 294.2)	(1.94, 5.33)	(10.88, 14.92)	(3709, 4987)
NAT2 slow (N=18)	193.7 (167.5, 251.9)	2.65 (2.26, 3.86)	10.80 (9.55, 12.87)	3300 (2842,3757)

PK parameters of Retigabine after multiple dose of 200mg retigabine BID					
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]	CL/F [ml/(min.kg)]
UGT1A1 ext (N=21)	576.3 (503.7,773.8)	0.94 (0.73, 1.94)	7.80 (7.04, 8.98)	2604 (2386, 2961)	16.41 (15.23, 18.23)
UGT1A1 poor (N=15)	588.2 (486.7,817.7)	0.65 (4.26, 1.26)	8.44 (7.46, 9.97)	2658 (2380, 3059)	15.86 (14.43, 17.84)
NAT2 fast (N=19)	635.3 (553.4,828.8)	0.74 (0.60, 1.38)	8.16 (7.42, 9.34)	2746 (2502, 3128)	15.92 (14.72, 17.70)
NAT2 slow (N=17)	526.2 (437.0,747.2)	0.88 (0.55, 2.02)	7.95 (6.97, 9.48)	2499 (2266, 2846)	16.47 (15.07, 18.51)

PK parameters of AWD21-360 after multiple dose of 200mg retigabine BID				
Biomarker Group	C_{max} [ng/ml]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng.h/ml]
UGT1A1 ext (N=21)	414.5 (375.8,489.4)	1.91 (1.68, 2.92)	8.42 (7.26, 10.53)	3527 (3183, 4177)
UGT1A1 poor (N=15)	472.1 (418.5,552.1)	1.85 (1.51, 2.82)	8.61 (7.65, 10.07)	3925 (3417, 4770)
NAT2 fast (N=19)	480.6 (435.0,557.9)	1.99 (1.78, 2.88)	8.96 (7.73, 11.23)	4130 (3717, 4854)
NAT2 slow (N=17)	394.1 (353.8,461.8)	1.77 (1.41, 2.89)	8.00 (7.11, 9.31)	3249 (2893, 3844)

After single and multiple dose treatment, the AUCs of the acetylated metabolite (AWD21-360) were around 30% higher in the NAT2 fast groups relative to the NAT2 slow acetylator groups, whereas AUCs of Retigabine were around 10% higher in the NAT2 fast groups relative to the NAT2 slow acetylator groups. After single and multiple dose treatment, AUCs of the acetylated metabolite (AWD21-360) were around 13% higher in the poor UGT1A1 glucuronidator groups relative to the extensive UGT1A1 metabolizer groups, whereas systemic exposure to retigabine was about similar.

ANOVA analyses were performed for the pharmacokinetic parameters in plasma: AUC, Cmax, and $t_{1/2}$. Subject 22 (female, 35 years) was excluded from all analyses because she dropped out after the single dose part. There were no interactions UGT1A1*NAT2. No statistically significant differences between the metabolizer groups were detected for parent drug retigabine for both ANOVA (Sponsor) and General Linear Model (FDA) analyses. However, there are statistically significant differences between the phenotypes UGT1A1 and NAT2 for the metabolite AWD21-360, which seem to become more pronounced in the multiple dose part of the study (steady state).

Retigabine (D-23129) Parameter	Comparison	p (UGT)	p (NAT)	p (UGT*NAT)
AUC (log)	SD	0.4681	0.6919	0.7141
	MD1 (dose 9)	0.6271	0.6455	0.8863
	MD2 (dose 10)	0.8241	0.5494	0.0716
	MD1 versus SD accumulation	0.2563	0.8609	0.6065
C_{max} (log)	SD	0.5020	0.8841	0.8887
	MD1 (dose 9)	0.7846	0.5344	0.2656
	MD2 (dose 10)	0.2666	0.0996	0.6586
	MD1 versus SD accumulation	0.4170	0.7245	0.4709
$t_{1/2}$ (lin)	MD2	0.3768	0.8037	0.7222

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AWD21-360 Parameter	Comparison	p (UGT)	p (NAT)	p (UGT*NAT)
AUC (log)	SD	0.2168	0.1866	0.5541
	MD1 (dose 9)	0.1582	**0.0308**	0.7324
	MD2 (dose 10)	0.1009	0.0975	0.5105
	MD1 versus SD accumulation	**0.0071**	**0.0008**	0.3037
C_{max} (log)	SD	0.2813	0.1034	0.3682
	MD1 (dose 9)	0.0769	0.0996	0.7711
	MD2 (dose 10)	0.0734	**0.0166**	0.9810
	MD1 versus SD accumulation	**0.0174**	**0.0047**	0.4407
$t_{1/2}$ (lin)	MD2	0.9589	0.2268	0.8621

Since there were no relevant differences in systemic exposure to parent retigabine, the sponsor concluded that glucuronidation compensates for impaired acetylation, and acetylation and other UGTs for impaired UGT1A1 glucuronidation.

3.2. Does Retigabine affect 24h serum bilirubin concentration differentially by genetic subgroups?

UGT1A1 defines the genetic basis of Gilbert syndrome, which is the most common hereditary cause of increased bilirubin and is found in up to 5% of the population. The following table shows the AUC_{0-24} for total bilirubin. Subjects received a normal diet during the pharmacokinetic profiling days. The sponsors' data are reported as mean ± standard deviation and range.

24-h Serum Bilirubin

Subject Group	N	AUC_{0-24} [µmol/l·h] Screen (400 kcal/d-diet)	SD (normal diet)	MD (normal diet)
1: UGT1A1 ext. + NAT2 fast	11	377 ± 87 (228 – 540)	315 ± 79 (161 – 439)	339 ± 71 (207 – 443)
2: UGT1A1 poor + NAT2 fast	8	746 ± 276 (516 – 1391)	541 ± 102 (402 – 710)	546 ± 185 (395 – 942)
3: UGT1A1 ext. + NAT2 slow	10-11	394 ± 121 (173 – 678)	342 ± 125 (113 – 586)	356 ± 116 (188 – 589)
4: UGT1A1 poor + NAT2 slow	7	750 ± 232 (523 – 1151)	516 ± 259 (192 – 1020)	476 ± 189 (189 – 816)

FDA Analysis:
Similar to the strategy in question 1, FDA looked into UGT1A1 and NAT2 subgroups respectively, holding more power to detect whether Retigabine affect 24h serum bilirubin concentration differentially by genetic subgroups (with mean and 95% confidence interval).

	AUC [umol/l.h]		
Biomarker group	Screen	SD	MD
UGT1A1 ext (N=22)	385.5 (341.5, 429.5)	328.5 (284.8, 372.2)	347.5 (307.3, 387.7)
UGT1A1 poor (N=15)	747.9 (618.0, 877.7)	529.3 (432.6, 626.1)	513.3 (418.8, 607.9)
NAT2 fast (N=19)	532.4 (447.3, 617.5)	410.2 (370.1, 450.2)	426.2 (367.4, 484.9)
NAT2 slow (N=18)	532.4 (453.3, 611.6)	409.7 (323.3, 496.0)	402.7 (334.4, 470.9)

As expected, baseline AUCs of the 24h serum bilirubin concentration were 94% higher in UGT1A1 poor metabolizers vs. wildtype group There were no obvious differences in mean concentration-time courses after single and multiple dose treatment among the groups. In general, retigabine treatment did not cause elevations in bilirubin AUC in any subgroup.

FDA additionally looked into each biomarker group for 24h bilirubin levels (total). Data are demonstrated as geometric mean and 95% confidence interval. No important differences were noted with the exception that (consistent with expected) baseline 24h bilirubin level in UGT1A1 poor group was 97% higher relative to wildtype group.

Biomarker Group	Screen [mg.dl]	Treated Period [mg.dl]
UGT1A1 ext (N=22)	18.6 (17.1, 21.2)	15.6 (14.3, 18.3)
UGT1A1 poor (N=15)	36.7 (30.8, 49.5)	23.8 (21.0, 28.6)
NAT2 fast (N=19)	24.9 (20.4, 35.5)	19.0 (17.1, 22.9)
NAT2 slow (N=18)	24.0 (19.7 34.9)	18.0 (15.6, 23.5)

3.3. Does retigabine have QT prolonging effects in genetic subgroups?

KCNQ2 and KCNQ3 subunits form heteromeric potassium channels that underlie slow, subthreshold M-type potassium currents in autonomic (and possibly central) neurones. They are related to KCNQ1 and KCNQ4 subunits, mutations of which produce one form of the cardiac long QT syndrome. For safety evaluation, sponsor screen QT variable. The heart rate corrected QTc interval was calculated by the system according to Bazett's formula.

FDA looked into each biomarker group for QT remarkable changes from baseline. Data are demonstrated as geometric mean and 95% confidence interval. P-value was evaluated for the QT difference between genotypes within each biomarker.

Biomarker Group	Screen [ms]	Treated Period [ms]	QT Changes [ms]	P-Value
UGT1A1 ext (N=22)	413.43 (399.81, 429.64)	416.71 (405.47, 429.61)	2.82 (-7.33, 12.97)	0.484
UGT1A1 poor (N=15)	402.99 (392.32, 414.61)	400.99 (387.79,415.67)	-1.73 (-10.73, 7.26)	
NAT2 fast (N=19)	408.54 (398.98, 419.12)	411.63 (401.48, 422.94)	3.16 (-6.52, 12.84)	0.510
NAT2 slow (N=18)	409.83 (393.18, 429.49)	408.83 (393.95,426.05)	-1.33 (-11.74, 9.07)	

There was no QT extreme case (eg. individual change in QTc ≥60 ms). The small mean QT changes are considered to be clinically not relevant. There were no statistically relevant changes in QT between genetic groups within each biomarker.

Overall FDA Conclusions:

- After oral single (200 mg retigabine immediate release) and multiple dose retigabine treatment (200 mg retigabine immediate release BID), the AUC of the acetylated metabolite

was higher in NAT2 fast acetylators versus slow acetylators, and higher in subjects with Gilbert's syndrome versus subjects with UGT1A1 wildtype.

- There was no indication that serum bilirubin concentrations increase with multiple dose of retigabine in subjects with Gilbert's syndrome or according to NAT2 genotypes.
- The small mean QT changes are considered to be clinically not relevant. There were no statistically relevant changes in QT between genetic groups within each biomarker.

4. COMMENTS

1. Since it is unclear whether joint consideration of UGT1A1 and NAT2 genotypes is more informative than consideration of either gene alone. Analyzing the data separately for each gene allocates more individuals in each genotype group and allows for more power to detect differences of retigabine PK parameters.

2. UGT1A4 polymorphisms (except *2 and *3) are observed frequently in the Japanese population. *2 and *3 [PMID: 15057901, 14871856] have allele frequencies for 8%-9% in Caucasian population respectively. Polymorphisms of the hepatic UGT1A4 protein have shown a differential metabolic activity toward mutagenic amines and endogenous steroids, altering hepatic metabolism and detoxification. However, the sponsor did not study UGT1A4, which is a major glucuronyltransferase in humans for Retigabine. In addition, UGT1A9 and UGT1A3 are also known to contribute to Retigabine metabolism, and sponsor also did not demonstrate results of those metabolism genes in the genomic study. Therefore, it is hard to interpret when there were no relevant differences in systemic exposure to parent retigabine but there was genetic influence on acetylated metabolite. Sponsor's conclusion of glucuronidation compensation needs more data to support.

5. RECOMMENDATIONS

The Office of Clinical Pharmacology/Genomics Group has reviewed the information contained in NDA 22-532. The sponsor's report will not impact approvability or labeling of the product submitted under this NDA.

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4.3 Cover Sheet And OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-345**	**Brand Name**	**Potiga™**
OCP Division (I, II, III, IV, V)	**DCP-1**	**Generic Name**	**Retigabine**
Medical Division	**HFD-120**	**Drug Class**	**Anticonvulsant**
OCP Reviewer	**Ta-Chen Wu, Ph.D.**	**Indication(s)**	**Adjunctive treatment of partial onset seizures (in patients 18 years of age and older) with or without secondary generalization**
OCP Team Leader	**Angela Yuxin Men, M.D., Ph.D.**	**Dosage Form**	**Immediate release film-coated tablet (50, (b) (4) 200, 300, and 400 mg strengths)**
Pharmacometrics Reviewer **Pharmacogenomics Reviewer**	**Joo-Yeon Lee, Ph.D.** **Li Zhang, Ph.D.**	**Dosing Regimen**	• **600~1200 mg/day, TID** • **Starting dose is 100 mg tid (300 mg/day) and increased at weekly intervals by a maximum of 150 mg/day (in 3 divided doses) up to recommended doses based on individual patient response and tolerability**
Date of Submission	**10/30/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**06/30/2010**	**Sponsor**	**Valeant Pharmaceuticals & GlaxoSmithKline**
Medical Division Due Date	**07/15/2010**	**Priority Classification**	**S**
PDUFA Due Date	**08/30/2010**		

Clin. Pharm. and Biopharm. Information

Summary:

The sponsor seeks approval of Potiga™ (retigabine) as adjunctive treatment of partial onset seizures (POS) with or without secondary generalization in patients 18 years of age and older with epilepsy with this original NDA 22-345, submitted on October 30, 2009. The proposed commercial dosage form is immediate release film-coated tablet, with proposed 5 strengths being 50, (b) (4), 200, 300, and 400 mg. The recommended dosing regimen for Potiga™ is 600~1200 mg/day, tid, with starting dose being 100 mg tid (300 mg/day) and increased at weekly intervals by a maximum of 150 mg/day (3 divided doses or 50 mg tid) up to recommended doses based on individual patient response and tolerability.

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As stated by the sponsor, retigabine is a first in class neuronal potassium channel opener for the treatment of partial-onset seizures. Mechanism of action contributing to its anti-epileptic activity is mediated through its ability to enhance the neuronal K+ current mediated by the Kv7 subfamily of voltage-gated potassium (KCNQ) channels, predominantly KCNQ2 and KCNQ3. Retigabine can enhance the native M-current and therefore provide a stabilizing effect on excitable, particularly hyperexcitable, neurons. In addition to its primary activity at KCNQ channels, retigabine's augmentation of GABA-mediated inhibitory currents may also contribute a stabilizing effect on neuronal excitability.

According to the sponsor, retigabine is extensively metabolized in humans and is converted to inactive N-glucuronides. Retigabine is also metabolized to an N-acetyl metabolite that is also subsequently glucuronidated. The N-acetyl metabolite of retigabine (NAMR) has antiepileptic activity, but is less potent than retigabine in animal seizure models. There is no evidence for hepatic oxidative metabolism of retigabine or NAMR by cytochrome P450 enzymes.

The current NDA submission consists of 44 studies, including 28 Phase 1 studies, 5 completed Phase 2 studies, 2 completed Phase 3 studies, and 6 long-term, open-label extension studies (of which, extensions to two Phase 3 studies remain ongoing). Two additional Phase 2 studies in bipolar disorder and in post-herpetic neuralgia (PHN) were conducted and will be included in the 120-day safety update. To support the efficacy and safety of retigabine as adjunctive therapy for treating POS, this NDA contains results from three adequate and well-controlled studies in patients with partial-onset epilepsy: a Phase 2b study (Study 3065A1-205 or Study 205) and two Phase 3 studies (Study VRX-RET-E22-301 or Study 301; Study VRXRET-E22-302 or Study 302) conducted in >17 countries. Dosing regimens of these studies are:

- Study 205: Placebo or retigabine 600 mg/day, 900 mg/day, or 1200 mg/day
- Study 301: Placebo or retigabine 1200 mg/day
- Study 302: Placebo or retigabine 600 mg/day or 900 mg/day

The clinical pharmacology development program of retigabine that supports the proposed indication includes:

1. In-vitro studies using human biomaterial: (14 studies)
    - Distribution: (5 reports)
        - Plasma protein binding (2 studies)
        - Permeability in Caco-2 cells (2 studies)
        - Inhibition on P-gp in Caco-2 cells (1 study)
    - Metabolic profiling/DDI potential: (10 reports)
        - Metabolism: (4 studies - 1 in Coao-2)
        - DDI potential: (5 studies)
2. Bioavailability (BA) studies: (4 studies)
3. Comparative BA and bioequivalence (BE) studies: (5 studies)
4. Healthy subject PK and initial tolerability studies: (7 studies)
5. Patient PK and initial tolerability studies: (1 study)
6. Intrinsic factor PK studies: (4 studies + 1 analysis report for race comparison)
7. Extrinsic factor PK studies: (6 studies)
8. Healthy subject PD and PK/PD study: (1 QT/QTc study)
9. Patient PD and PK/PD study: (1 report - Pop PK/PD analysis)
10. Bioanalytical and analytical studies: (1 study)
11. Bioanalytical validation and cross-validation reports: (11 validation reports for retigabine and metabolites in plasma or urine + 1 in buffer + 24 other validation reports (DDI, co-medications))

The main study design features include:

Phase 1 Studies:

- Absolute BA from solution and IR capsule vs. IV
- Relative BA of IR formulations (200mg IR capsules) vs. modified release (SR) formulations
- Dose proportionality (single-dose 25~600mg IR capsules; Pop PK)
- PK and dose-linearity of RTG and N-acetyl metabolites after IV dosing
- Relative BA and BE (dosage strength equivalence => market image 400mg IR tablet vs. 2x50mg +300mg

clinical formulations used in Phase 3; 50mg IR capsules vs. 200mg IR capsules; 200mg IR tablet vs. 200mg IR capsule)
- Food effects (400mg market image IR tablet; 200mg IR tablet & capsule; (b) (4) SR tablets)
- Safety, tolerability, and PK (SD and MD) in healthy subjects and patients
- Safety, tolerability, and PK of titration regimens (b) (4)
- Mass-balance (^{14}C-labeled, 200mg capsule)
- Effects of age and gender (b) (4) in 1 study)
- Impacts of race (a post-hoc meta-analysis across 6 clinical pharmacology studies to compare RTG clearance parameters between healthy Black and Caucasian male subjects)
- Impact of genetic polymorphism (b) (4)) (b) (4) in 1 study)
- Special populations: renal impairment, hepatic impairment
- Inhibitors or Inducers of P450 Enzymes and of Glucuronidation
- Commonly Used AEDs and OCs: steady-state PK drug-drug interactions between RTG and phenobarbital (30 mg), OCs, and lamotrigine (steady-state RTG on single-dose LTG; multiple low-dose LTG on single-dose RTG)
- Alcohol interaction (PD interaction)
- The impact of retigabine on QT/corrected QT (QTc) intervals of electrocardiograms

Phase 2/3 Studies:
- Efficacy, safety, tolerability, PK, and MTD (bid dosing) in patients with partial onset seizures
- Highest tolerated dose, safety, tolerability, preliminary efficacy and PK as add-on or monotherapy (b) (4))
- Phase 2/ 3 dose-ranging, safety and efficacy as add-on therapy (50-, (b) (4) and 200mg capsules) in partial epilepsy patients with AEDs
- Safety and tolerability of titration rates in patients
- Long-term safety, tolerability and efficacy

Exposure-Response:
The relationship between systemic exposure to retigabine and efficacy/safety endpoints from the Phase 3 studies, 301 and 302. For efficacy, two PD endpoints were evaluated - (i) the percent change from baseline in seizure frequency, and (ii) a binary outcome analysis (responder / non responder), where a responder was defined as a subject having a ≥50% reduction from baseline in total partial seizure. For safety, 6 most frequently observed adverse events were evaluated.

Population PK analysis uses sparse PK data from the Phase 3 program in refractory epilepsy patients with POS and healthy subjects for retigabine and its N-acetyl metabolite. Analysis includes UDPGT and NAT genotype, and PD modeling of exposure-response. PK and demographic data from ongoing and Phase 1 &2 studies were incorporated in base model.

Bioanalytical methods:
- Different HPLC-UV, HPLC-fluorescence, and LC-MS/MS bioanalytical methods used for (1) unchanged drug in plasma, (2) N-acetyl and glucuronide metabolites of retigabine in plasma, and (3) urinary retigabine and major metabolites.
- Additional bioanalytical methods used for other drugs
- Method validation, in-study validation, QC performance are provided.

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Formulations: (b) (4)

	Capsule	Initial IR Tablet	Clinical Trial IR Tablet	Market Image IR Tablet
Use	(b) (4)			
Comparison with Preceding Formulation				
Strengths (mg)				
Shape				

	"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**			• Sponsor provided annotated PDF file, but not annotated Word file for labeling • Sponsor provided clean Word file and PDF file for labeling
Reference Bioanalytical and Analytical Methods	**X**			• Method validation: 9 validation reports for retigabine and metabolites + 26 other validation reports (for other drugs) • In-study validation and QC performance are provided.
I. Clinical Pharmacology				
Mass balance:	**X**			Studies 108 and Fb20799: [^{14}C]retigabine 200 mg SD, capsule
Isozyme characterization:	**X**			4 In-vitro study in human liver microsomes and hepatocytes, and Caco-2 cells
Blood/plasma ratio:	**-**			
Plasma protein binding:	**X**			2 in-vitro studies (in Phase 1 studies?)
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

single dose:	**X**			IV: Study 117 PO: Study 100, 101
multiple dose:	**X**			PO: Study 101, 102
Patients-				
single dose:	**X**			Studies 201, 303
multiple dose:	**X**			Studies 201, 303
Dose proportionality -				
fasting / non-fasting single dose:	**X**			IV single-dose PO single-dose
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**			• By common AEDs (CBZ, PB, VA, TPM, LTG) • Pop PK • Effects of alcohol on PK, PD
In-vivo effects of primary drug:	**X**			• On common AEDs (CBZ, PB, VA, TPM, LTG) • On OCs
In-vitro:	**X**			Inhibition and inhibition (enzyme, P-gp, or protein-binding)
Subpopulation studies -				
ethnicity:	**X**			Meta-analysis; no specific study; Caucasian vs. Black
gender:	**X**			Single-dose, study for effects of age and gender
pediatrics:	-			
geriatrics:	**X**			Single-dose, study for effects of age and gender
renal impairment:	**X**			Single-dose, full study design
hepatic impairment:	**X**			Single-dose, full study design
PD -				
Phase 2:	**X**			Study 205 (Phase 2b)
Phase 3:	**X**			Studies 301 and 302 (pivotal Phase 3)
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**			• Study 205 (Phase 2b) • QT/QTc
Phase 3 clinical trial:	**X**			Studies 301 and 302 (pivotal Phase 3)
Population Analyses -				1 report for PopPK 1 report for Pop PK/PD
Data rich:	**X**			Rich data from Phase 1 studies

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Data sparse:	**X**			Sparse data from Phase 2 and Phase 3 studies
II. Biopharmaceutics				
Absolute bioavailability	**X**			Absolute BA from solution and IR capsule vs. IV
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**			• Commercial formulation vs. clinical formulations • Comparison between early formulation (including SR) and clinical formulations
Bioequivalence studies -				
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies	**X**			Food effects on 400mg market image IR tablet, 200mg IR tablet & capsule, (b) (4) , and SR tablets
Bio-waiver request based on BCS	-			
BCS class	**X**			Class 2 (high P, low S)
Dissolution study to evaluate alcohol induced dose-dumping	-			
III. Other CPB Studies				
Genotype/phenotype studies	**X**			• Impact of UGT1A1 and NAT2 in Study 115 • Population analysis on Phase 3 data
Chronopharmacokinetics	-			
Pediatric development plan	-			No pediatric PK study
Literature References	**X**	**47**		
Total Number of Studies		**47 (57 study and validation reports submitted)**	**47 (57 reports reviewed)**	28 PK + 6 in -vitro (categories)(14 in-vitro study reports) + 1 Pop PK + 1 Pop PK/PD (patients) + 1 meta-analysis (race) + 10 validation reports (+24 additional validation reports)

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?	Yes			
2	Has the applicant provided metabolism and drug-	Yes			A review issue regarding

	drug interaction information?				adequacy of characterization for metabolic pathways, respective enzymes, and DDI potential
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	Yes			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	Yes			
5	Has a rationale for dose selection been submitted?	Yes			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Yes			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Yes			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	Yes			
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)?	Yes			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	Yes			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	Yes			A review issue
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)?	Yes			A review issue
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	Yes			A review issue
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?	Yes			A review issue
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes			A review issue
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes			A review issue
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		No		

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.

1. Annotated Word file for labeling was not provided.

2. The following study reports are not text-recognizable, and some contains incorrect hyperlinks in TOC:
   - BA/BE studies -- Studies 123, 104, 110 (incorrect hyperlink from TOC), 120, 103
   - Human PK studies -- Studies 117, 107, 100, 102, 101, 108 (incorrect links for TOC), 108 (plasma concentration monitoring), Fb20799
   - Intrinsic factor -- Study 105
   - Extrinsic factor -- Report 030001, Studies 113, 112

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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/s/

TA-CHEN WU
11/19/2010

HRISTINA DIMOVA
11/19/2010

JOO YEON LEE
11/19/2010

YANING WANG
11/19/2010

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11/22/2010

YUXIN MEN
11/22/2010

MEHUL U MEHTA
11/22/2010

ONDQA BIOPHARMACEUTICS REVIEW ADDENDUM

NDA#:	**22-345**
Submission Date:	10/18/2010
Brand Name:	Potiga
Generic Name:	Ezogabine
Formulation:	Tablets
Strength:	50, (b) (4) 200, 300, and 400 mg
Sponsor:	Valeant Pharmaceuticals North America
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

INTRODUCTION

This is an addendum to the review signed off on August 13, 2010, in which the biowaiver for the lower strengths (50 (b) (4)) were not granted and a bioequivalence study was recommended for the 50 mg strength between the to-be-marketed and the clinical formulations. After the recommendation was conveyed, the applicant requested teleconferences and submitted new data. This addendum reviews these data.

RECOMMENDATION

Based on the discussion between the Agency and the applicant and the new data submitted, we modify our recommendation as follows.

1. The biowaiver for the 50 mg, 200 mg and the 300 mg strengths can be granted.
2. (b) (4)
3. Based on the further discussion between the Agency and the applicant, the modification of the acceptance criterion using the proposed dissolution method as shown below is accepted.

Apparatus:	USP apparatus II (paddle)
Media:	0.01N HCl at 37^{o}C
Volume:	1000 mL
Rotation:	(b) (4)
Acceptance criterion:	Q = (b) (4) at 15 min

Please convey recommendation 1 and 2 to the clinical division and the review team. Recommendation 3 should be conveyed to the applicant.

REVIEWER'S COMMENTS

1. For the 50 mg strength, the currently available results can be summarized in the following table, in which the blue colored rows are the basic criteria for determining similarity and the highlighted cells have f2 values less than 50.

Reference	Media	Surfactant	f2 Value
BE 400 mg	pH1.2	No	NA (48.63)
BE 400 mg	pH4.6	No	35.38
BE 400 mg	pH6.8	No	41.12
BE 400 mg	pH4.6	Yes	66.8
BE 400 mg	pH6.8	Yes	58.1
Clinical 50 mg	pH1.2	No	NA (45)
Clinical 50 mg	pH4.6	No	51
Clinical 50 mg	pH6.8	No	56
Clinical 50 mg	pH4.6	Yes	59
Clinical 50 mg	pH6.8	Yes	62

The results indicate the difference between the to-be-marketed 50 mg strength and the highest strength 400 mg, but the similarity between the 50 mg strength and clinical 50 mg strength. Although a flag is shown at pH 1.2, the dissolution is fast for both the clinical and market image tablets (b) (4) dissolved in 15 minutes). Thus, calculation of an f2 comparison with only two data points is not considered meaningful. This is based on the fact that all drug is essentially dissolved from both formulations of the 50 mg tablet by the time gastric emptying would occur. Data for the 50 mg tablets at pH 4.6 and 6.8 without surfactant resulted in f2 values of greater than 50. Based on these results, the release characteristics of the 50 mg clinical and market image tablets can be considered similar. The dissimilarity between 50 mg strength and the highest strength 400 mg may be explained by solubility differences. The dissolution behavior, combined with the fact that all tablet strengths are made from a common granule and are proportional, support a biowaiver for the 50 mg tablets.

(b) (4)

(b) (4)

3. Therefore, the biowaiver for the to-be-marketed 50 mg strength can be granted. (b) (4)

(b) (4)

Whether these arguments are acceptable is a clinical call.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 22-345, Patrick Marroum, Angelica Dorantes, John Duan

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/s/

JOHN Z DUAN
11/04/2010

PATRICK J MARROUM
11/08/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**22-345**
Submission Date:	10/30/2009, 6/4/2010, 7/20/2010
Brand Name:	Potiga
Generic Name:	Retigabine
Formulation:	Tablets
Strength:	50, (b) (4) 200, 300, 400 mg
Sponsor:	Valeant Pharmaceuticals North America
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

Retigabine is a first in class neuronal potassium channel opener for the treatment of partial-onset seizures. The drug products are immediate-release, film-coated tablets as 50, (b) (4) 200, 300 and 400 mg strengths for three times daily oral administration. The recommended total daily dose of retigabine is 600 to 1200 mg/day.

RECOMMENDATION

The Biopharmaceutics group has reviewed the dissolution information included in NDA 22-345 and has the following comments that should be conveyed to the sponsor:

1. The biowaiver for the 200 mg and the 300 mg strengths can be granted if the bioequivalence study of the 400 mg strength between clinical formulation and to-be-marketed formulation is acceptable.

2. (b) (4)

3. Based on the provided data, the following dissolution method and specification are recommended.

Apparatus:	USP apparatus II (paddle)
Media:	0.1N HCl at 37^{o}C
Volume:	1000 mL
Rotation:	50 rpm
Specification:	Q = (b) (4) at 30 min

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____ _____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 22-345, Patrick Marroum, Angelica Dorantes, John Duan

APPENDIX.

1. Solubility/Permeability of retigabine

Retigabine is poorly soluble in water at pH values above 2.8. Solubility improves in water in the acidic pH range due to protonation of the basic amine. The aqueous solubility of Retigabine at 37º C as a function of pH is shown in the table below.

pH	Solubility (mg/mL)
1.58	(b) (4)
1.82	
2.87	
3.94	
5.00	
6.04	
7.07	
8.20	

The permeability of retigabine was tested by CaCo-2 cell monolayers assay, and was a fast, passive diffusion mechanism. The intestinal absorption should not be the limiting factor of the retigabine uptake. The low solubility and high permeability of retigabine characterize it as a BCS class II drug.

2. Particle size of the drug substance

Particle size data is provided in Table 1 for representative batches of retigabine used in either pivotal clinical studies, primary stability studies or as commercial process drug substance. These data were generated using a laser diffraction method.

Table 1 Particle Size of Retigabine

Drug Substance Batch Number	Use	d50 (μm)	d90 (μm)
0005005	Clinical Study 301, 302, 303, 304	(b) (4)	
0206001	Clinical Study 302		
0206003	Clinical Studies 301, 302, 303, 304 BE Clinical Study 105		
0206004	Clinical Study 303, 304		
02070066	Primary NDA Stability		
02070067	Primary NDA Stability		
02070068	Primary NDA Stability		
02070069	Primary NDA Stability and BE Clinical Study 105		
04090053	Clinical (Commercial Process)		
04090054	Clinical (Commercial Process)		
04090055	Clinical (Commercial Process)		
04090056	Clinical (Commercial Process)		

Pivotal clinical studies were 301 and 302 (highlighted).

3. Dissolution method development and issues identified

The proposed dissolution method and acceptance criterion are as follows.

Apparatus: USP apparatus II (paddle)
Media: 0.01N HCl
Volume: 1000 mL
Rotation: (b) (4)
Specification: Meets USP Criterion, Q = (b) (4) at 30 min

(b) (4)

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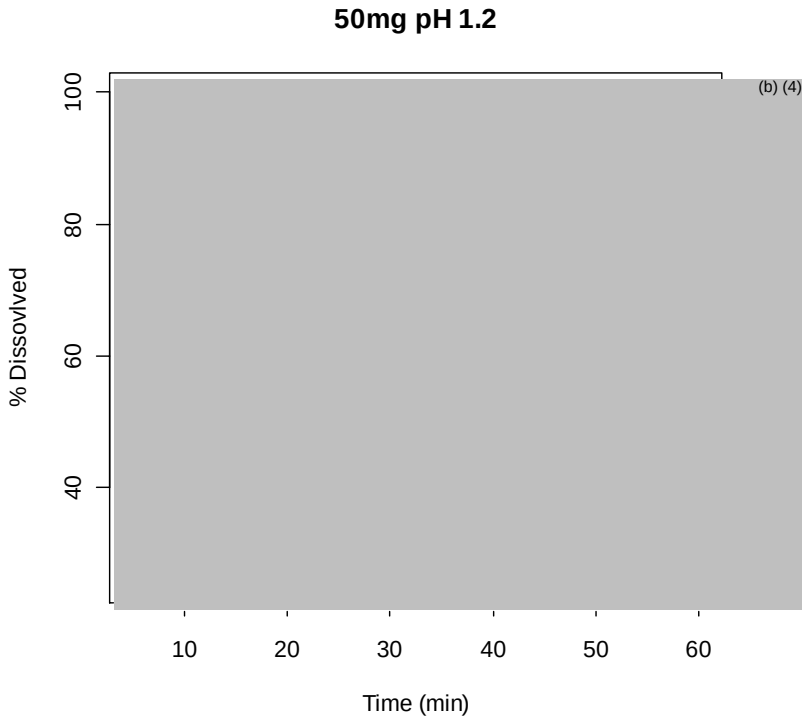
(b) (4)

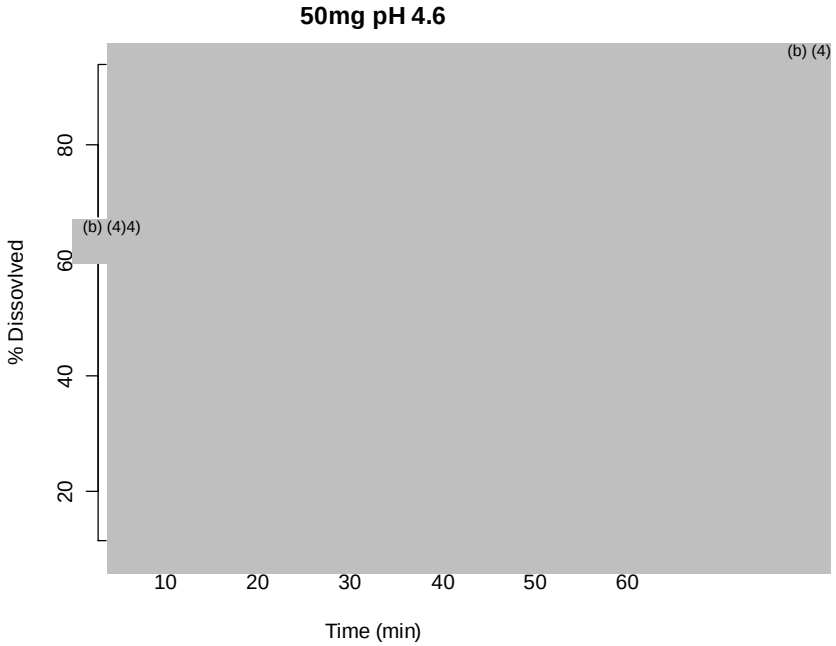
4. The comparisons between the clinical formulation and the to-be-marketed formulations.

The sponsor provided the comparisons between Phase III clinical tablets and market image tablets for the 50, (b) (4) and 300 mg tablet strengths in three media. The dissolution conditions used were USP apparatus II with rotation speed 50rpm in different media as listed below

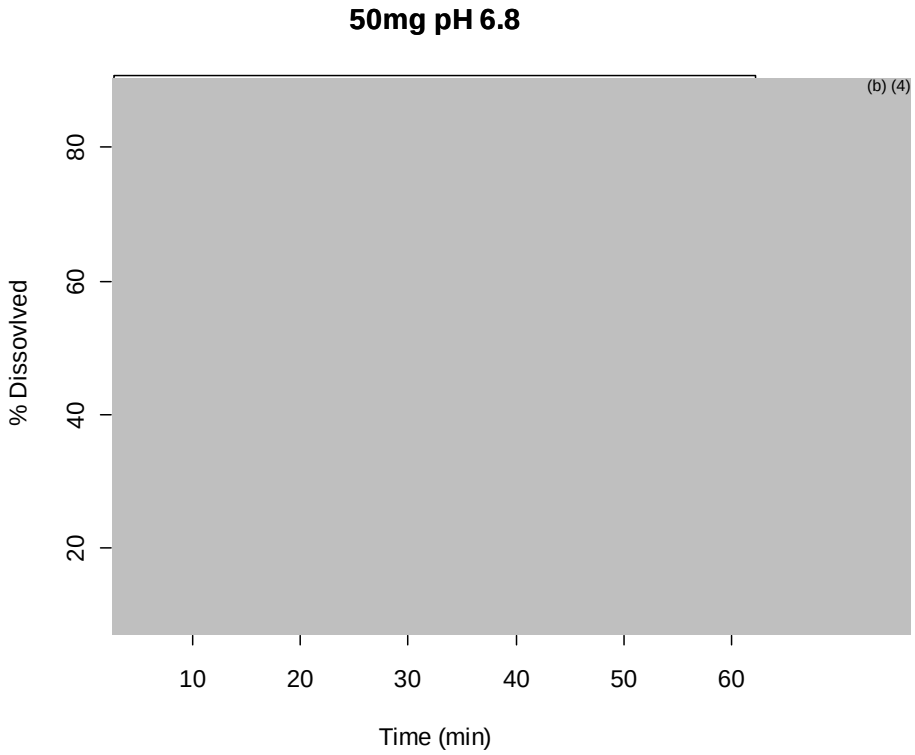
The following figure shows the comparison between clinical and market formulations for the 50mg strength at pH 1.2 (USP simulated gastric fluid without pepsin).



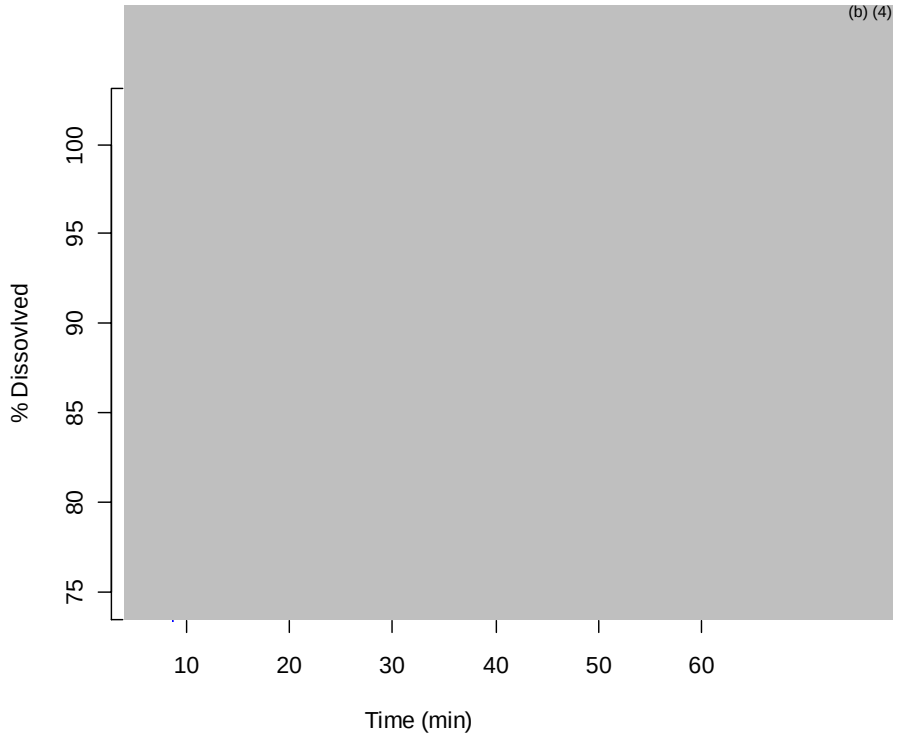
The following figure shows the comparison between clinical and to-be-marketed formulations for the 50mg strength at pH 4.6 (buffer solution using sodium acetate and acetic acid with 0.3% SDS, which should not be used)

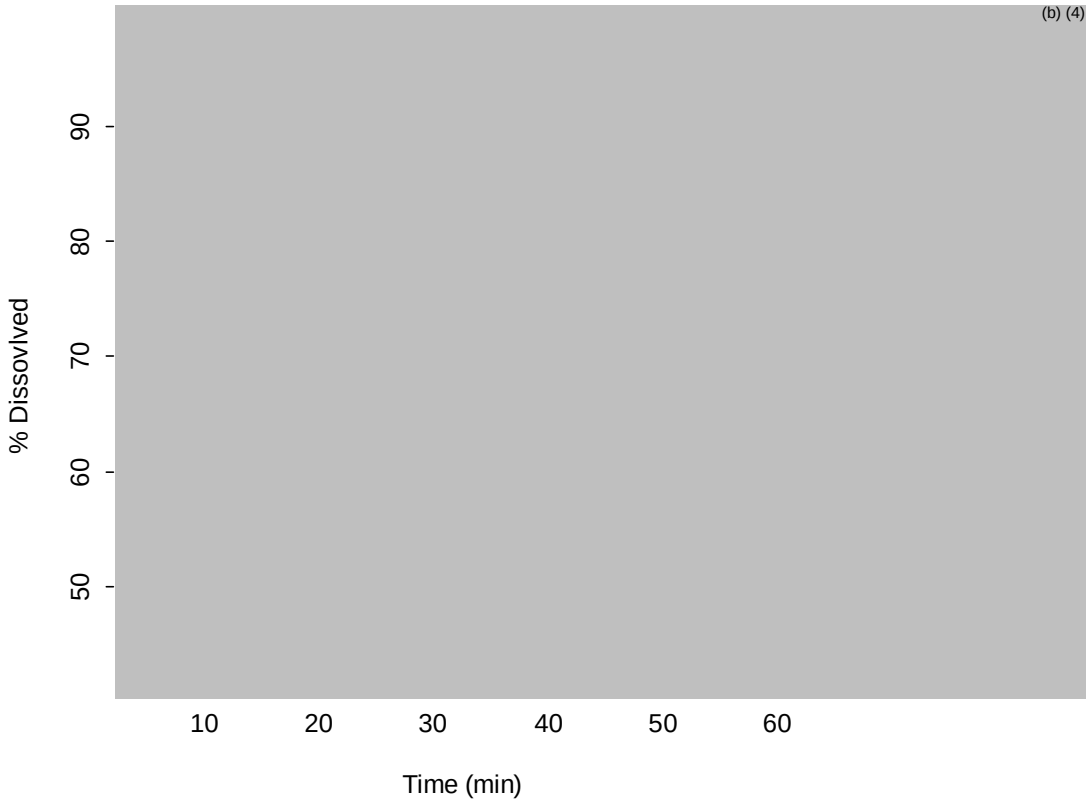


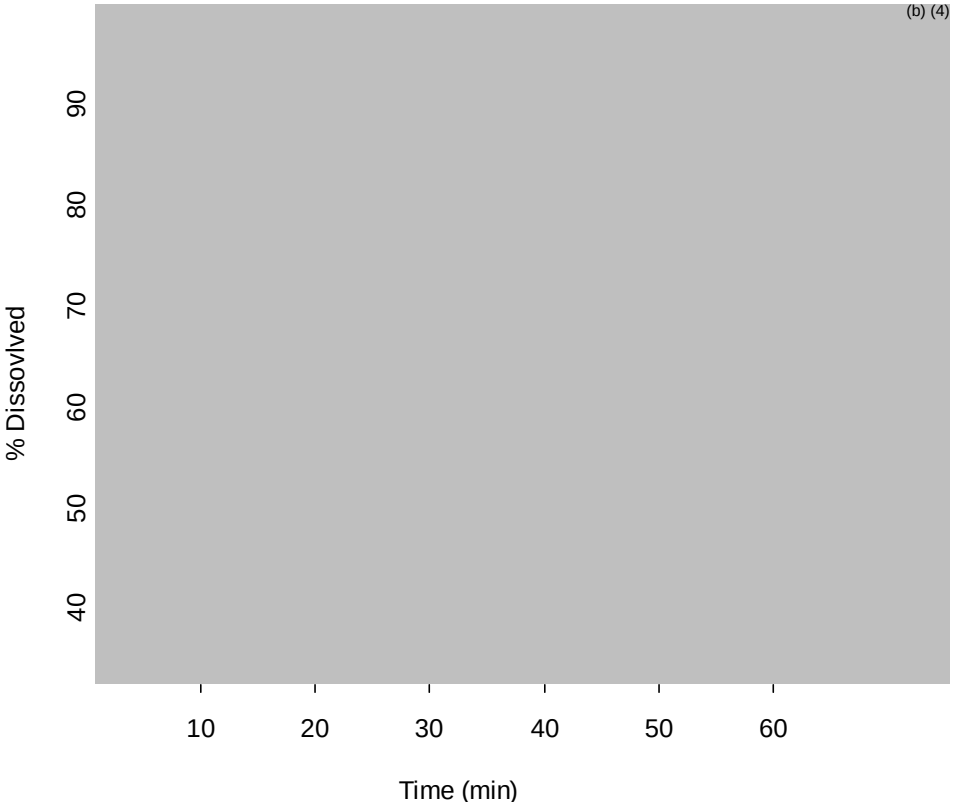
The following figure shows the comparison between clinical and market formulations for 50mg strength at pH 6.8 (buffer using monobasic sodium phosphate with 1.0% SDS).



The following figures are comparisons for (b) (4) strength in the three media, respectively.

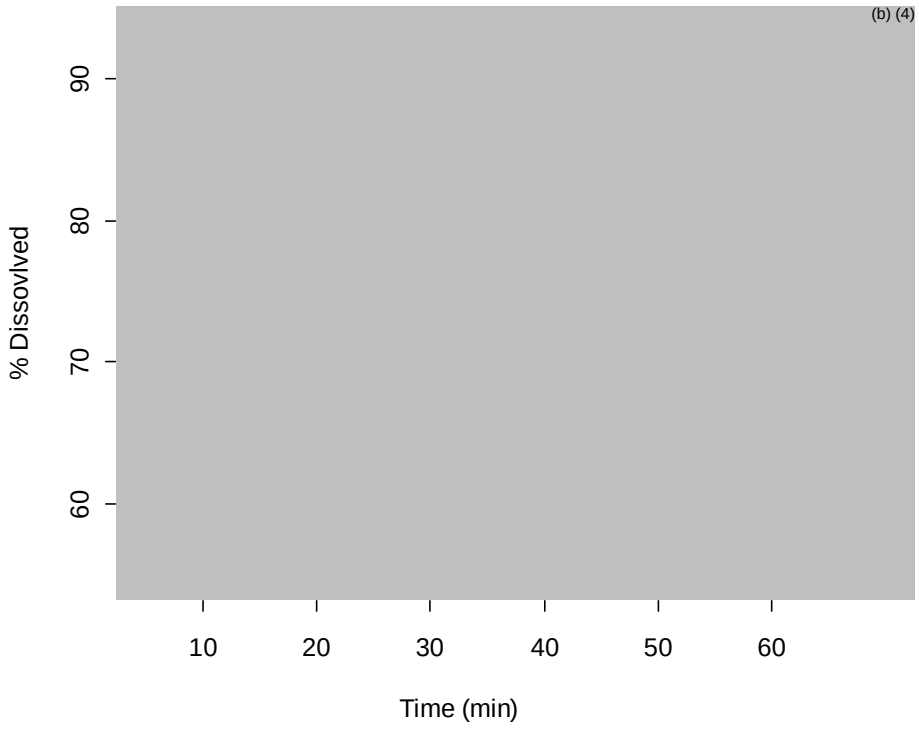

(b) (4)
% Dissovlved
75
80
85
90
95
100
10
20
30
40
50
60
Time (min)

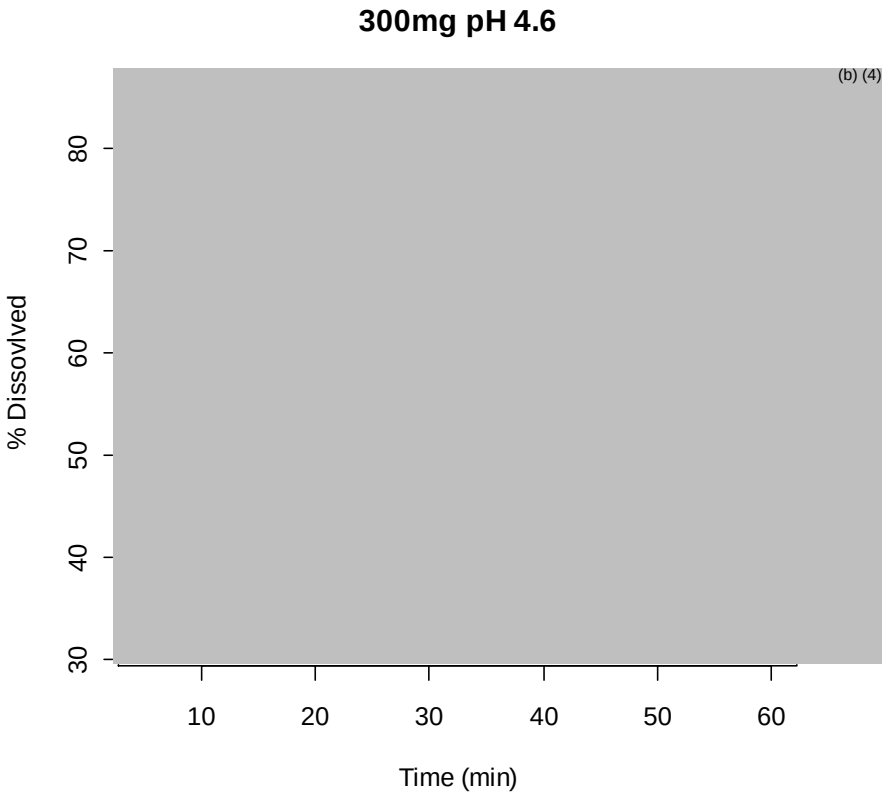

(b) (4)
% Dissovlved
50
60
70
80
90
10
20
30
40
50
60
Time (min)

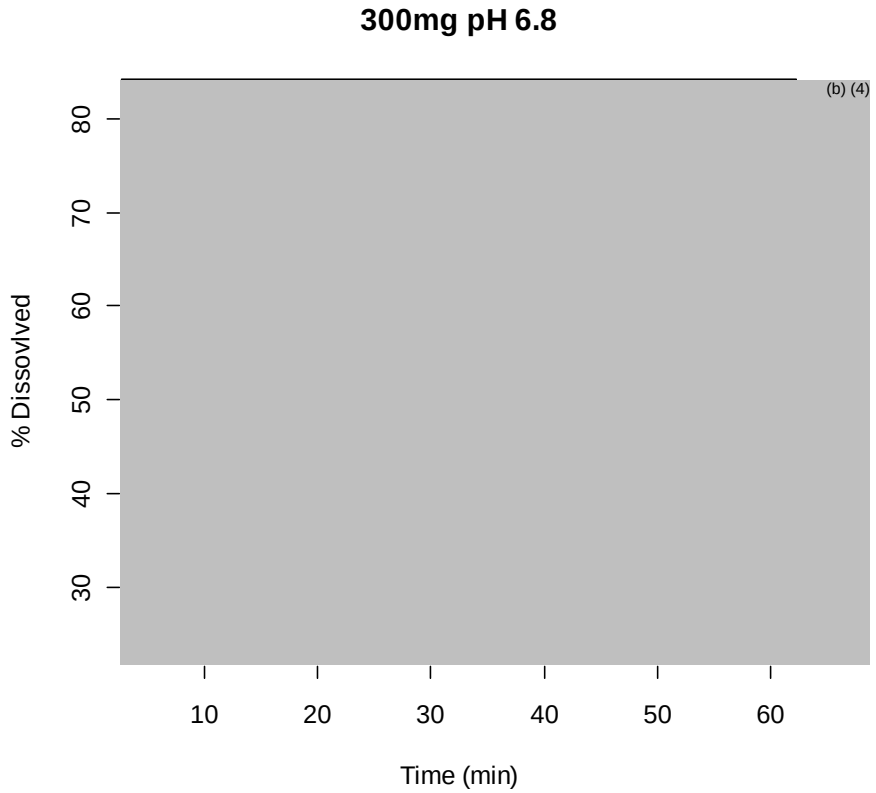


The following figures are the dissolution profile comparisons for 300mg strength in the three media, respectively.

300mg pH 1.2



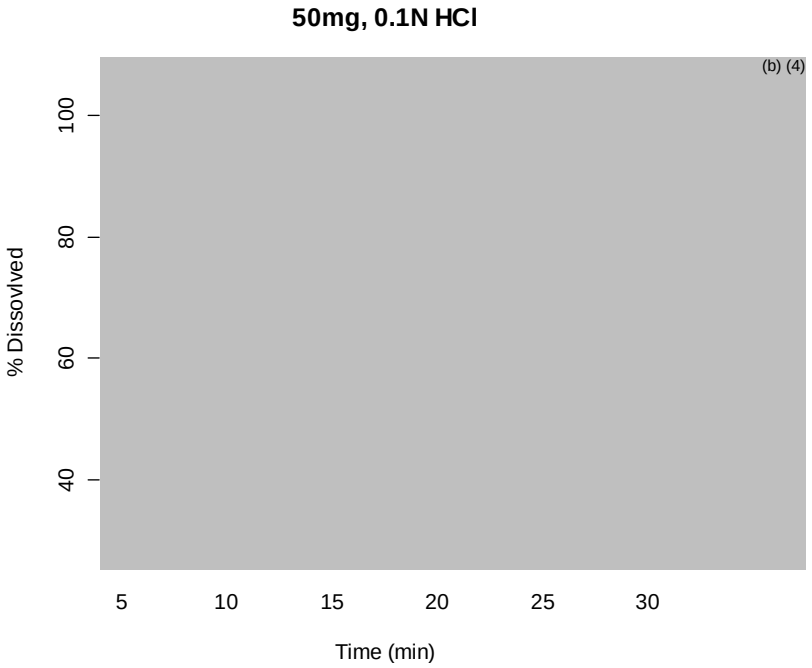




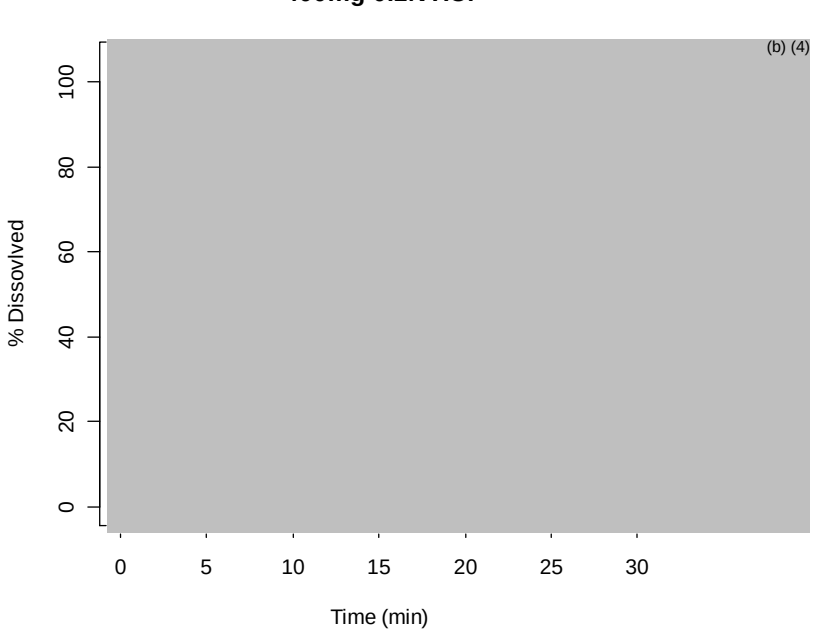
Although the comparisons were conducted in media with surfactants added, which made the comparison not reliable, a bioequivalence study was conducted between the highest strength of to-be-marketed formulation and the clinical formulation, which was reviewed by Office of Clinical Pharmacology (OCP).

5. Dissolution methodology and specifications.

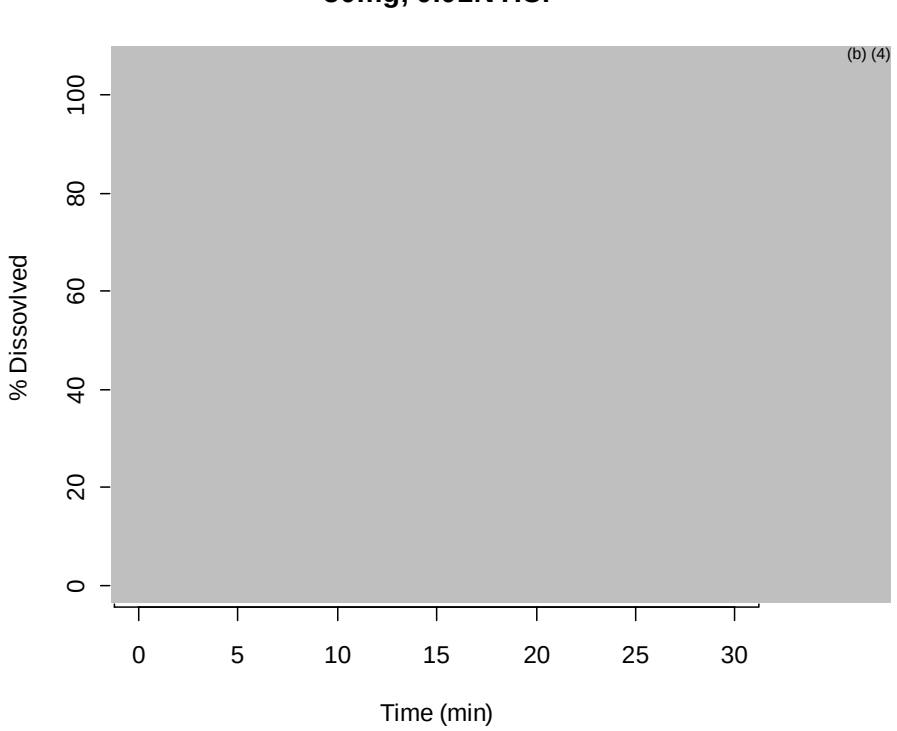
Since the proposed dissolution method using apparatus II in 0.01N HCl at (b) (4) was deemed not optimal, a request was sent to the sponsor to compare dissolution profiles between rotation speeds of 50rpm and (b) (4) for the 50 and 400mg strengths using 0.1N HCl. The following figure shows the dissolution profile for 50mg strength using apparatus 2 (paddle), in 1000 mL 0.1N HCl at 37°C with paddle speed of 50 or (b) (4)



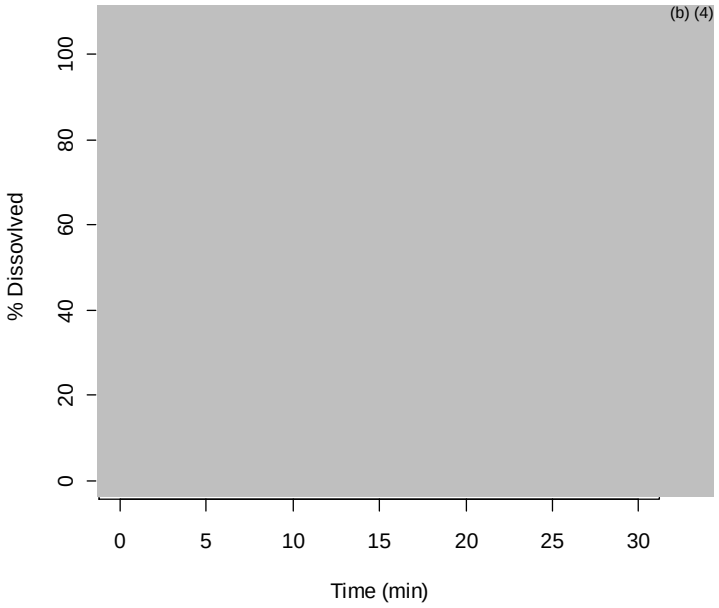
The following figure shows the dissolution profile for 400mg strength using apparatus 2 (paddle), in 1000 mL 0.1N HCl at 37°C with paddle speed of 50 or (b) (4)



In addition, the dissolution profiles at rotation speed of 50rpm and (b) (4) for the 50 and 400mg strengths using 0.01N HCl are also provided. The following figure shows the dissolution profile for 50mg strength using apparatus 2 (paddle), in 1000 mL 0.01N HCl at 37°C with paddle speed of 50 or (b) (4).



The following figure shows the dissolution profile for 400mg strength using apparatus 2 (paddle), in 1000 mL 0.01N HCl at 37°C with paddle speed of 50 or (b) (4)



The above figures show 0.1N HCl at 50rpm may be a better choice for dissolution method.

6. The qualification of the lower strengths

Although the linkage between the highest strength (400 mg) of the market image and the clinical batches could be established by a bioequivalence study (the bioequivalence was reviewed by OCP), the lower strengths (50, (b) (4) 200, and 300 mg) of the market image tablets had not been linked to the clinical batches in the initial submission. Dissolution profile comparison in three media between the lower strengths and the highest strength (400 mg) was requested. The sponsor submitted relevant information and dissolution comparisons between 400 mg strength and the lower strengths. The compositions of the proposed commercial market image tablets are provided in the table below.

Component	Reference to Standards	Function	Composition in mg per Tablet (% w/w)			
			50 mg	(b) (4)	200 mg	300 mg	400 mg
(b) (4)							
Retigabine	Internal	Drug Substance	50.0 (62.5%)		200.0 (62.5%)	300.0 (62.5%)	400.0 (62.5%)
Microcrystalline cellulose	USNF/ Ph. Eur.	(b) (4)					
Hypromellose, 2910	USP/ Ph. Eur.						
Croscarmellose sodium	USNF/ Ph. Eur.						
Magnesium stearate	USNF/ Ph. Eur.						
(b) (4)	USP/ Ph. Eur.						
(b) (4)							
(b) (4)	Internal	(b) (4)					
	Internal						
	Internal						
	USP/ Ph. Eur.						
Theoretical Coated Tablet Weight			83.2	(b) (4)	332.8	499.2	665.6

Notes:

a Removed during processing

b Amounts in table reflect a (b) (4) weight gain. A range of (b) (4) weight gain is acceptable.

q.s. Add sufficient amount

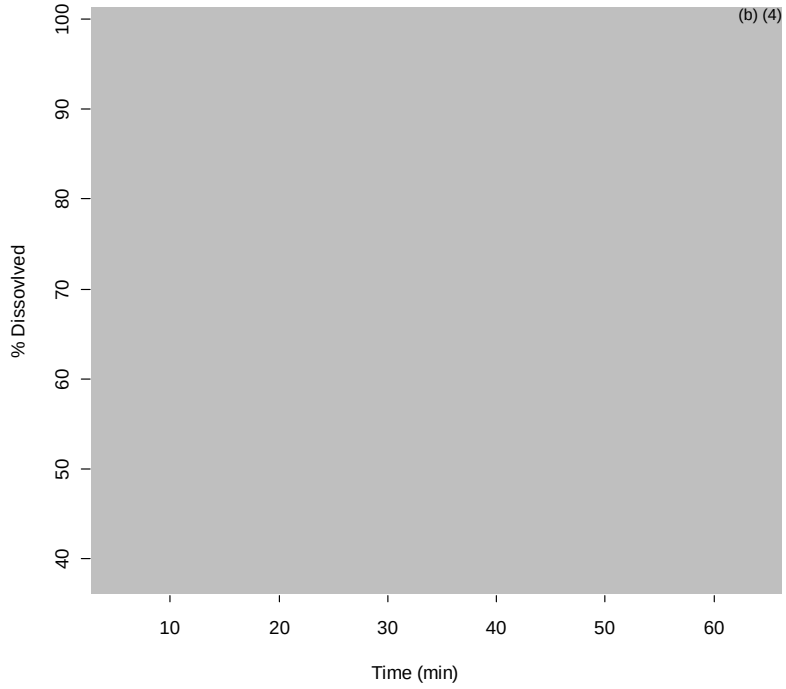
(b) (4). All strengths of Retigabine Tablets are manufactured in an identical manner utilizing the same unit operations and equipment. (b) (4)

Dissolution testing was carried out on one batch each of Retigabine Tablets 50, (b) (4) 200, 300 and 400 mg using USP Apparatus 2 (12 tablet of each strength) at 50 rpm in 1000 mL of each of three different media:

- pH 1.2 - USP Simulated Gastric Fluid without Pepsin
- pH 4.6 - USP Buffer Solution using Sodium Acetate and Acetic Acid pH
- 6.8 - Buffer Solution using Monobasic Sodium Phosphate

Individual data and corresponding dissolution profiles are provided. The following table and figure shows the dissolution of the lower strengths compared with 400 mg strength at pH=1.2.

Time	400mg	300mg	200mg	(b) (4)	50mg
5	(b) (4)				
10					
15					
20					
25					
30					
45					
60					

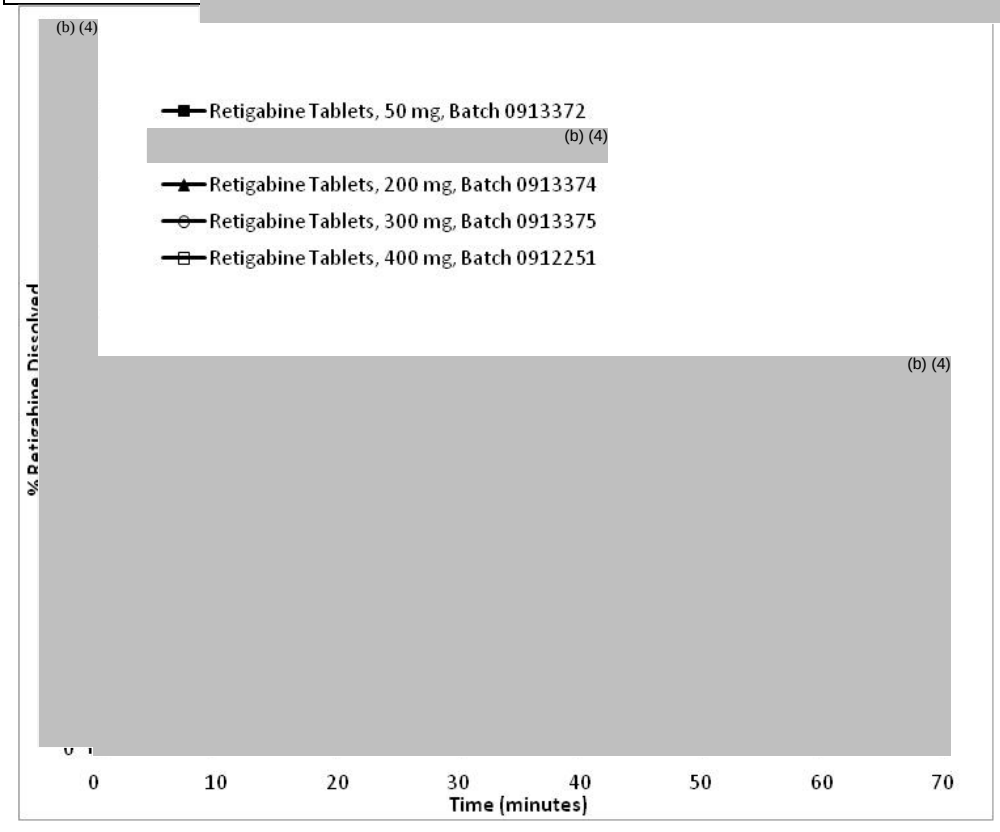


The results of the f2 factor calculations are shown in the following table. In the table, the first row contains the f2 results of the test lots compared to the 400mg lot. The second row provides the results of other test lots compared to the 300mg lot. The third row provides the results of other test lots compared to the 200mg lot. The fourth row provides the results of other test lots compared to the (b) (4) lot.

	% Dissolved (all data)				% Dissolved (standard approach)			
	300mg	200mg	(b) (4)	50mg	300mg	200mg	(b) (4)	50mg
400mg	68.92	60.79	(b) (4)	48.63	62.46	NA	(b) (4)	NA
300mg		67.89	(b) (4)	45.29		NA	(b) (4)	NA
200mg			(b) (4)	51.14			NA	NA
(b) (4)				66.32				NA

The following table and figure show the dissolution of the lower strengths compared with 400 mg strength in pH 4.6 Medium and Apparatus 2 at 50 rpm.

Time	400mg	300mg	200mg	(b) (4)	50mg
5	(b) (4)				
10					
15					
20					
25					
30					
45					
60					

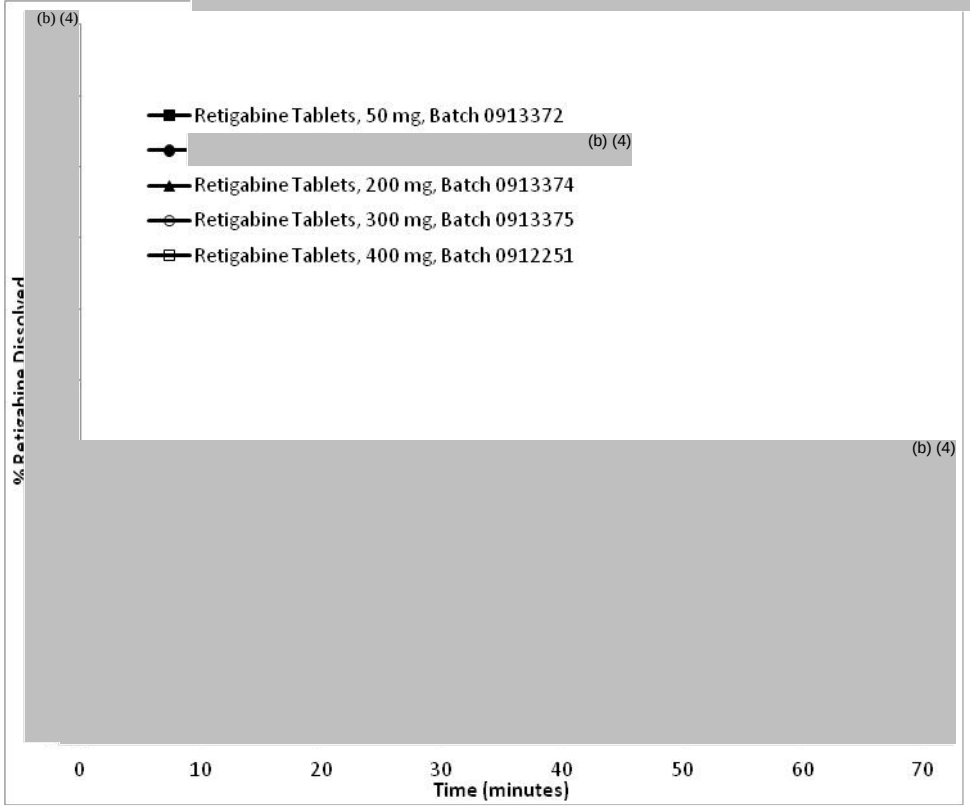


	% Dissolved (all data)				
	300mg	200mg	(b) (4)		50mg
400mg					
300mg					
200mg					
(b) (4)					

The following tables and figure show the dissolution of the lower strengths compared with 400 mg strength in pH 6.8 Medium and Apparatus 2 at 50 rpm.

The dissolution data are shown in the following table and figure.

Time (min)	400mg	300mg	200mg	(b) (4)	50mg
5					
10					
15					
20					
25					
30					
45					
60					



The results of the f2 factor calculations are shown in the following table. In the table, the first row contains the f2 results of the test lots compared to the 400mg lot. The second

row provides the results of other test lots compared to the 300mg lot. The third row provides the results of other test lots compared to the 200mg lot. The other rows contain the similar values.

	% Dissolved (all data)			
	300mg	200mg	(b) (4)	50mg
400mg				
300mg				
200mg				
100mg				

As shown, the comparisons did not show similarity between the lower strengths (50mg (b) (4) and the 400mg strength at all three pH's. The sponsor explained the difference by the coning effects. However, the data did not show a high variability usually resulted from coning.

A biowaiver request was not supported by dissolution profile comparisons. The f2 factors are summarized in the following table.

	Values of f2 factor			
Media	300mg	200mg	(b) (4)	50mg
pH1.2	62.46	NA (60.79)	(b) (4)	NA* (48.63)
pH4.6	67.75	49.69	(b) (4)	35.38
pH6.8	73.84	57.66	(b) (4)	41.12

*NA: not applicable because less than two time points were included in the calculation of f2 factor. When f2 factor is calculated, not more than one point with more than (b) (4) should be included for both test and reference products. Also, more than three time points should be used. The number in parenthesis is calculated using all the time points available.

Therefore, the biowaiver for 50mg and (b) (4) strengths can not be granted (b) (4). A bioequivalence study for 50mg strength between to-be-marketed and clinical formulation is recommended.

Appendix 2. Communications with the applicant

A. The following information requests were sent to the sponsor on 1/12/10.

For the lower strengths of the market image tablets (i.e., 50 mg, (b) (4) 200 mg, and 300 mg), you will need to submit either a formal biowaiver request, with appropriate supporting data, or provide bioequivalence data for these strengths.

You have submitted comparative dissolution profiles for the highest strength tablet (400 mg) of drug product manufactured using drug substance obtained from the (b) (4) process versus the drug product manufactured using drug substance obtained from the (b) (4) process (Refer to Section 3.2.P.2.1, Figure 1). Provide the dissolution conditions that were used and the individual tablet data for review. Additionally, provide comparative dissolution profile data for the other tablet strengths.

Provide the raw data for the dissolution method development, including the individual tablet dissolution value at different time points, drug product batch numbers, drug substance batch numbers and the dissolution conditions used (media, apparatus, rotation speed, etc).

Provide the raw data for the dissolution comparison of the formulations used in the bioequivalence study (individual tablet dissolution data).

Provide the dissolution data from the formulation development, including the individual tablet (b) (4) dissolution data along with the manufacturing parameters used for the formulations resulting in dissolution, such as (b) (4) . Dissolution conditions should be specified.

B. The following information requests were sent to the sponsor on 5/3/2010.

(b) (4)

2. To compare the performance of the drug product manufactured using the (b) (4) drug substance vs. the drug product manufactured using the (b) (4) drug substance; provide comparative dissolution profile data (using 50 rpm paddle rotation speed) in three dissolution media (i.e., pH 1.2, 4.6, and 6.8) and similarity f2 values.

2. You may request that FDA waives the CFR requirement for the submission of in vivo BA/BE data for lower 50, (b) (4) 200, and 300 mg strengths of your product. The waiver request should be supported by the following information; 1) Acceptable bioequivalence data for the highest 400 mg strength, 2) data showing that the formulation for all the

strengths are compositional proportional, and 3) dissolution profile and f2 data in three dissolution media using 50 rpm paddle rotation speed.

C. The following information requests were sent to the sponsor on 6/25/2010.

Provide data regarding the dissolution profile comparisons between the lower strengths (50, (b) (4) 200 and 300 mg) and the highest strength (400 mg) at higher pH's (4.6 and 6.8) performed in the media without any surfactant.

Provide an explanation for the observed dissolution profile differences between the lower strengths (50 mg (b) (4)) and 400 mg strength at pH 1.2.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICALS NORTH AMERICA	RETIGABINE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN Z DUAN
08/13/2010

PATRICK J MARROUM
08/13/2010