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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office Clinical Pharmacology Review

NDA#/eCTD	205,422/0000
NDA Type	Standard
Related INDs	IND101,871; IND103,958
Proposed Brand Name	REXULTI
Generic Name	Brexpiprazole
Dosage Form	Immediate-Release Tablet
Dosage Strength (mg)	0.25, 0.5, 1, 2, 3, 4
Indications	Adjunctive Major Depressive Disorder & Schizophrenia
Sponsor	Otsuka
Submission Type	505(b)(1) NME
Submission Date	July 11, 2014
OCP Review Team	Huixia Zhang, Li Zhang, Praveen Balimane, Kofi Kumi, Jeffrey Kraft, Christian Grimstein, Kevin Krudys, Hao Zhu

Summary

This document, which includes the clinical pharmacology review for individual study reports, is an addendum to the clinical pharmacology QBR review finalized in DARRTS on March 9, 2015.

Reviewer's Role:

Section	Primary Reviewer	Secondary Reviewer
General Clinical pharmacology -Effect of hepatic & renal impairment -Age & gender effect	Huixia Zhang -Praveen Balimane -Kofi Kumi	Hao Zhu
Pharmacometrics	Li Zhang	Kevin Krudys
Pharmacogenomics	Jeffrey Kraft	Christian Grimstein

Analytical Methods: wherever it is mentioned throughout the document that the performance of the analytical method is acceptable, it implies that the method used met the following requirements:

• Quality control sample range is acceptable	☑ Yes ☐ No
• Internal standard was used	☑ Yes ☐ No
• Method was validated prior to use	☑ Yes ☐ No
• Sample chromatograms were provided	☑ Yes ☐ No
• Calibration range samples accuracy and precision are acceptable	☑ Yes ☐ No
• Quality control samples accuracy and precision are acceptable	☑ Yes ☐ No
Method overall performance is acceptable	☑ Yes ☐ No

Acronyms used for brexpiprazole in the review: OPC-3312; OPC-34712

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General Clinical Pharmacology

I. In Vitro Studies

1. Plasma Protein Binding

Report # 019405
Title: In Vitro Protein Binding of ^{14}C-OPC-34712 to Mouse, Rat, Rabbit, Dog, Monkey and Human Sera by Equilibrium Dialysis Method

- **Objective:** To determine the in vitro protein binding of OPC-34712 in mouse, rat, rabbit, dog, monkey and human as part of the pharmacokinetic study.
- **Method:** The equilibrium dialysis was carried out using serum containing ^{14}C-OPC-34712. Sample (0.8 mL) was placed into the receiver half-cell, and 0.8 mL phosphate buffer was placed into the opposing half-cell. The dialysis was conducted at 37°C and the cells were rotated at a setting of 20 rpm for 8 hr. Final serum protein binding was determined at 3 concentrations (0.05, 0.5 and 5 µg/mL) in triplicate.
- **Results:** Protein binding of OPC-34712 (brexpiprazole) in human serum is shown in the table below. Each value represents the mean ± standard deviation (n=3).

Nominal Concentration of ^{14}C-OPC-34712 (µg/mL)	Protein Binding (%)
0.05	Not Calculated
0.5	99.8±0.0
5	99.8±0.0

- **Conclusion:** brexpiprazole is a highly bound to human serum proteins.
- **Reviewer's Comments:** Protein binding at 0.05 µg/mL was not calculated because its concentration was below limit of detection in the dialysate. The tested concentration range of brexpiprazole (0.05-5 µg/mL) is considered clinical relevant (Cmax,ss about 200 ng/mL, 4mg once daily administration for 14 days, Trial 331-08-025). Protein binding for brexpiprazole was also determined in a mass balance study (331-07-201 Arm 2, 2 mg brexpiprazole single dose). The result is found to be consistent with findings from this in vitro study. The assay also determined protein binding of brexpiprazole in nonhuman sera, but the results were not reviewed.

Report # 023150
Title: Protein Binding of DM-3411 in Mouse, Rat, Monkey and Human Serum Proteins by Equilibrium Dialysis Method

- **Objective:** To determine the in vitro protein binding of DM-3411, a main metabolite of OPC-34712, to the mouse, rat, rabbit, dog, monkey and human as part of the pharmacokinetic study.
- **Method:** The equilibrium dialysis was carried out using serum containing DM-3411. Sample (0.8 mL) was placed into the receiver half-cell, and 0.8 mL phosphate buffer was placed into the opposing half-cell. The dialysis was conducted at 37°C and the cells were rotated at a setting of 20 rpm for 8 hr. Final serum protein binding was determined at 3 concentrations (0.05, 0.5 and 5 µg/mL) in triplicate. All concentrations were determined using LC-MS/MS.
- **Results:** Protein binding of DM-3411 in human serum is shown in the table below. Each

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value represents the mean ± standard deviation (n=3).

Nominal Concentration of DM-3411 (µg/mL)	Protein Binding (%)
0.05	96.9±0.2
0.5	97.0±0.2
5	95.5±0.3

- **Conclusion:** DM-3411 is a highly bound to human serum proteins.
- **Reviewer's Comments:** The tested concentration range (0.05-5 µg/mL) embraces the mean steady state maximal plasma concentration of DM-3411(about 65 ng/mL, after 4mg brexpiprazole once daily administration for 14 days, Trial 331-08-025), and therefore is considered clinically relevant concentrations. The assay also determined protein binding of DM-3411 in nonhuman sera, but the results were not reviewed.

Report # 022036
Title: Protein Binding of ^{14}C-OPC-34712 in Human Albumin, α1-Acid Glycoprotein and γ-Globulin by Equilibrium Dialysis Method

- **Objective:** To determine the in vitro protein binding of OPC-34712 to human albumin, α1-acid glycoprotein and γ -Globulin.
- **Method:** The human albumin, human α1-acid glycoprotein and human γ-globulin were dissolved in PBS (pH 7.4) to match physiological concentrations (40 mg/mL, 1 mg/mL and 12 mg/mL, respectively). After preincubation for 5 min, 35 µL of ^{14}C-OPC-34712 solution (5 or 50 µg/mL) was added to 3.5 mL of protein solutions to make the samples in the final concentration of 0.05 or 0.5 µg/mL for an equilibrium dialysis. To the receiver half-cell, 0.8 mL of the samples were applied, and 0.8 mL of PBS were applied to the opposing half-cell (n = 3). The equilibrium dialysis device was placed in a water bath set at 37°C and rotated at a setting of 20 rpm for 8 hours. After the defined time, the radioactivity in 200 µL of the dialysate was measured in triplicate.
- **Results:** Table 1: Protein Binding (mean± standard deviation, n=3) of ^{14}C-OPC-34712 to Human Albumin, Human α1-Acid Glycoprotein and Human γ -Globulin

Protein	Nominal concn.	Protein Binding (%)	Free Fraction (%)	Protein Binding / Free Fraction
Human Albumin	0.5 µg/mL	97.23 ± 0.26	2.77 ± 0.26	35.36 ± 3.40
	0.05 µg/mL	90.32 ± 2.54	9.68 ± 2.54	9.92 ± 3.35
Human α_1-Acid Glycoprotein	0.5 µg/mL	98.03 ± 0.53	1.97 ± 0.53	51.98 ± 12.52
	0.05 µg/mL	95.57 ± 1.64	4.43 ± 1.64	23.99 ± 9.96
Human γ-Globulin	0.5 µg/mL	25.99 ± 4.45	74.01 ± 4.45	0.35 ± 0.08
	0.05 µg/mL	31.86 ± 8.71	68.14 ± 8.71	0.49 ± 0.18

- **Conclusion:** OPC-34712 bound predominantly to albumin and α1-acid glycoprotein in the human serum
- **Reviewer's Comment:** The tested concentration range (0.05-0.5 µg/mL) is considered clinically relevant concentrations (brexpiprazole Cmax,ss was about 200 ng/mL, 4mg once daily administration for 14 days, Trial 331-08-025). In this study, the protein binding to the albumin and α1-acid glycoprotein was high, compared to those to the human γ-globulin. Sponsor's conclusion is acceptable to the reviewer.

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2. In Vitro Metabolism

Report # 019521
Title: In vitro metabolism of Brexpiprazole in Mouse, Rat, Rabbit, Dog, Monkey and Human Liver 9,000xg Supernatant (S9)

- **Objective:** To elucidate the metabolism of brexpiprazole in liver S9 fractions
- **Method:** Incubation of brexpiprazole was performed with pooled human liver S9 fractions (n=50). The standard mixture contained 100 mM potassium phosphate buffer pH 7.4, 2.5mM NADPH, 2.5 mM NADH, Liver S9 fraction (protein concentration: 1mg/mL) and 10 µM of the test article solution in a final volume of 0.5 mL. The standard mixture was preincubated without NADPH and NADH at 37 °C for 3 minutes. After the addition of NADPH/NADH solution, the reactions were carried out at 37 °C for 10, 30 and 120 min. The reaction was terminated by the addition of 0.5 mL of acetonitrile. Metabolite formation was detected using HPLC.
- **Results:** No product derived from OPC-34712 was detected on the chromatogram of HPLC in the reaction without any addition of NADH and NADPH. Detected metabolites were listed in Table 1.

Table 1. Metabolites of OPC-34712 in pooled human liver S9.

Time (min)		Products (pmol eq. of OPC-34712/mg protein)						Reaction activity (pmol eq. of OPC-34712/mg protein/min)					
		M2	M4	M5	M6	M7	M8	M2	M4	M5	M6	M7	M8
10	1	465	ND	58.6	ND	35.4	ND	39.6	2.12	5.19	0.471	3.69	0.690
	2	485	ND	62.0	ND	38.5	ND						
	Mean	475	ND	60.3	ND	36.9	ND						
30	1	1155	61.1	152	ND	80.0	22.0						
	2	1165	66.0	154	ND	76.7	19.3						
	Mean	1160	63.6	153	ND	78.4	20.7						
120	1	1958	111	229	53.7	53.8	62.9						
	2	1949	86.5	226	59.4	57.3	47.5						
	Mean	1954	98.7	227	56.5	55.5	55.2						

- **Conclusion:** Brexpiprazole was metabolized to several metabolites in human liver S9 fractions by NDAH- or NADPH-dependent enzymes.
- **Reviewer's Comments:** Overall, brexpiprazole is metabolically unstable in human liver S9 fractions. Several metabolites were identified. Metabolism of brexpiprazole in liver S9 fractions from animal species were also investigated in this study but was not reviewed. Please refer to Pharm/Tox review for detailed information.

Report # 019635
Title: Structural Estimation and Identification of Metabolites Produced by in Vitro Metabolism of OPC-34712 Using Mouse, Rat, Rabbit, Dog, Monkey and Human Liver 9000g Supernatant (S9) Reaction Samples

- **Objective:** To estimate the structure of in vitro metabolites detected in liver S9 fractions
- **Method:** Incubation of brexpiprazole was performed with pooled human liver S9 fractions (n=50). The standard mixture contained 100 mM potassium phosphate buffer pH 7.4, 2.5mM NADPH, 2.5 mM NADH, Liver S9 fraction (protein concentration: 1mg/mL) and 10 µM of the test article solution in a final volume of 0.5 mL. The standard mixture was preincubated without NADPH and NADH at 37 °C for 3 minutes. After the addition of NADPH/NADH solution, the reactions were carried out at 37 °C for 10, 30 and 120 min. The reaction was stopped by the addition of 0.5 mL of acetonitrile. Structural estimation and identification of the metabolites was analyzed using LC-

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MS/MS.

- **Results:** Eight metabolites (H1-H8) were identified in pooled human liver S9 fractions incubated for 120 min. H1 was the main metabolite produced and was determined to be DM-3411. It was identified that H2, H4, H6 and H7 were SFO-34318, OPC-54050, OPC-3952 and DM-3404, respectively.
- **Reviewer's Comment:** Structure estimation for brexpiprazole metabolites using animal S9 fractions were also performed, please refer to Pharm/Tox review for detailed information. Overall, it seemed no human-specific metabolites were identified.

Report # 019018
Title: In Vitro Metabolism of OPC-34712 by Human Cytochrome P450s Baculovirus Insect Cell Expressed

- **Objective:** To elucidate CYPs that are concerned with the metabolism of OPC-34712
- **Method:** The standard mixture contained 100 mM potassium phosphate/Tris-HCl buffer pH 7.4, 2.5 mM NADPH, 2.5 mmol/L NADH, microsomes (total protein:0.375 mg, P450 content: 25 pmol) and 10 µM of the test article in a final volume of 0.5 mL (n = 2). The standard mixture was preincubated without NADPH and NADH at 37 °C for 3 min. After the addition of NADPH/NADH solution, the reactions were carried out at 37 °C for 30 min. The reaction was stopped by the addition of 0.5 mL of acetonitrile. The reaction mixture was analyzed using HPLC/UV.
- **Results:** No product derived from OPC-34712 was detected on the chromatogram of HPLC in the reaction without any addition of NADH and NADPH.

Table 1. Total reaction activity in the mixture of OPC-34712 with human CYP1A1, CYP2B6, CYP2C19, CYP2D6 or CYP3A4 supersomes.

	Reaction activity (pmol eq. of OPC-34712/pmol P450/min)				
	CYP1A1	CYP2B6	CYP2C19	CYP2D6	CYP3A4
M1	-	-	-	-	0.494
M2	0.367	0.457	0.278	8.169	10.041
M3	-	-	-	0.575	NC[*1]
M4	0.140	-	-	-	0.297
M5	0.064	-	-	0.070	0.748
M6	0.368	-	-	-	0.349
M7	0.326	0.250	0.090	-	-
M8	0.306	-	-	-	-
M9	-	-	-	0.918	-
Total	1.571	0.707	0.368	9.732	11.929

- **Conclusion:** The rank order of the activity to produce OPC-34712 metabolite was CYP3A4 > CYP2D6 >> CYP1A1 > CYP2B6 > CYP2C19. The main metabolite was M2, which was produced by CYP1A1, CYP2B6, CYP2C19, CYP2D6 and CYP3A4. The predominant CYP involved in the metabolism of OPC-34712 seemed to be CYP3A4 and CYP2D6.
- **Reviewer's Comments:** Overall, several CYP enzymes are involved in the metabolism of brexpiprazole. Sponsor's conclusion seems to be acceptable.

Report # 020893
Title: In Vitro Metabolism of 14C-OPC-34712 by Microsomes From Baculovirus Infected Insect Cell Transformed With Human Flavin-containing Monooxygenase cDNAs

- **Objective:** To elucidate the FMO isoform(s) involved in the metabolism of OPC-34712
- **Method:** The reaction mixture (n = 1) contained 30 µM 14C-OPC-34712, 0 or 2.5 mM β-NADPH, 100 mM phosphate buffer (pH 7.4) and 0 or 0.2 mg protein/mL control or FMO

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microsomes. The reaction mixture was preincubated at 37°C for 3 min before microsomes were added to initiate the reaction. Methanol (0.2 mL) was added to terminate the reaction after 10, 20, 30 and 60 min. Samples (20 µL of each supernatant) were analyzed using Liquid Scintillation Counter and HPLC.

- **Results:**OPC-34835 FRE was produced by the FMO3 isoform but other metabolites were not produced. Moreover, DM-3411 was not detected in the chromatograms of the FMO1, 3 and 5 reaction samples. The formation of OPC-34835 FRE produced by the FMO3 isoform was 0.3211 pmol eq/pmol FAD/min.

Table 1: Production of OPC-34835 FRE in Human FMO3 supersomes

Isoform	Time (minutes)	Peak-area	Production (pmol eq/pmol FAD)	Production rate (pmol eq/pmol FAD/minute)
FMO3	10	196	1.45	0.3211
	20	752	5.99	
	30	1150	9.07	
	60	2465	19.98	

- **Conclusion:** FMO3 isoform was partially involved in the metabolism of OPC-34712 in the human liver.
- **Reviewer's Comment:** Sponsor's conclusion seems to be acceptable. Mass balance study did not indicate OPC-34835 was a major metabolite (Trial 331-07-201, Arm 2)

Report # 021400
Title: Identification of Human Cytochrome P450 Isoforms Involved in Metabolism of OPC-`34712 and Kinetic Analysis in Human Liver Microsomes (HLM)

- **Objective:** To identify the CYP isoforms responsible for the metabolism of OPC-34712
- **Method:** OPC34712 (brexpiprazole, 20 µM) was incubated in HLM (pooled/individual, 0.4 mg protein/mL) for 30 min with/without CYP specific chemical inhibitors (table below), or enzyme specific antibodies. Formation of metabolites DM-3411, SFO-34318 and OPC-3952 was detected using HPLC with the Flow Scintillation Analyzer system.

Inhibitor	Target CYP	Final concentration
Furafylline	1A1/2	0, 0.1, 0.3, 1, 3, 10 µmol/L
Orphenadrine	2B6	0, 0.5, 1.5, 5, 15, 50 µmol/L
Sulfaphenazole	2C9	0, 0.1, 0.3, 1, 3, 10 µmol/L
Tranylcypromine	2C19	0, 0.5, 1.5, 5, 15, 50 µmol/L
Quinidine	2D6	0, 0.1, 0.3, 1, 3, 10 µmol/L
Ketoconazole	3A4	0, 0.1, 0.3, 1, 3, 10 µmol/L

- **Results:** Table 1: Formation Kinetic Parameters of DM-3411, SFO-34318 and OPC-3952 Derived From OPC-34712 in Pooled Human Liver Microsomes

		DM-3411	SFO-34318	OPC-3952
Vmax	(nmol/min/mg protein)	0.976	0.532	0.539
Km	(µmol/L)	33.0	69.6	73.4
Vmax/Km	(mL/min/mg protein)	0.0296	0.00764	0.00734
CLint,h	(µL/min/mg protein)	29.6	7.64	7.34
CLint,h*	(mL/min/g liver)	1.55	0.401	0.386
CLint,h*	(mL/min/kg)	37.7	9.75	9.37

Table 2: Effect of Ketoconazole on Formations of DM-3411, SFO-34318 and OPC-3952 Derived From OPC-34712 in Human Liver Microsomes

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			Control	Ketoconazole concentration (μmol/L)				
				0.1	0.3	1	3	10
DM-3411	Peak area	No.1	9392	5933	3856	3014	2871	1892
		No.2	9600	5840	3511	2960	2441	2027
		Mean	9496.0	5886.5	3683.5	2987.0	2656.0	1959.5
	% of control		100.0	62.0	38.8	31.5	28.0	20.6
SFO-34318	Peak area	No.1	1166	247	228	89	121	138
		No.2	1306	434	286	158	112	108
		Mean	1236.0	340.5	257.0	123.5	116.5	123.0
	% of control		100.0	27.5	20.8	10.0	9.4	10.0
OPC-3952	Peak area	No.1	1210	528	290	200	272	210
		No.2	1272	600	426	296	346	238
		Mean	1241.0	564.0	358.0	248.0	309.0	224.0
	% of control		100.0	45.4	28.8	20.0	24.9	18.0

Table 3: Effect of Quinidine on Formations of DM-3411, SFO-34318 and OPC-3952 Derived From OPC-34712 in Human Liver Microsomes

			Control	Quinidine concentration (μmol/L)				
				0.1	0.3	1	3	10
DM-3411	Peak area	No.1	9602	9179	9352	8676	8980	8283
		No.2	9812	9726	9360	8888	8722	8183
		Mean	9707.0	9452.5	9356.0	8782.0	8851.0	8233.0
	% of control		100.0	97.4	96.4	90.5	91.2	84.8
SFO-34318	Peak area	No.1	1313	1368	1312	1234	1367	1105
		No.2	1292	1291	1185	1323	1363	1178
		Mean	1302.5	1329.5	1248.5	1278.5	1365.0	1141.5
	% of control		100.0	102.1	95.9	98.2	104.8	87.6
OPC-3952	Peak area	No.1	1307	1352	1360	1238	1267	1192
		No.2	1305	1372	1316	1280	1385	1346
		Mean	1306.0	1362.0	1338.0	1259.0	1326.0	1269.0
	% of control		100.0	104.3	102.5	96.4	101.5	97.2

Table 4: Effect of Anti-CYP3A4 Antibody on Formations of DM-3411, SFO-34318 and OPC-3952 Derived From OPC-34712 in Human Liver Microsomes

			Control	Anti-CYP3A4 antibody concentration (%)		
				1	2	4
DM-3411	Peak area	No.1	11272	7543	5576	5280
		No.2	11335	8032	5619	5116
		Mean	11303.5	7787.5	5597.5	5198.0
	% of control		100.0	68.9	49.5	46.0
SFO-34318	Peak area	No.1	1424	572	480	353
		No.2	1371	592	285	221
		Mean	1397.5	582.0	382.5	287.0
	% of control		100.0	41.6	27.4	20.5
OPC-3952	Peak area	No.1	1408	1056	747	296
		No.2	1508	562	384	324
		Mean	1458.0	809.0	565.5	310.0
	% of control		100.0	55.5	38.8	21.3

- Ketoconazole (for CYP3A4) inhibited the formations of DM-3411, SFO-34318 and OPC-3952 above 70% at the highest (10 μM) concentration, whereas furafylline (for CYP1A1/2), orphenadrine (for CYP2B6), sulfaphenazole (for CYP2C9), tranylcypromine (for CYP2C19) and quinidine (for CYP2D6) could negligibly do so (data not shown here).
- Anti-CYP3A4 antibody inhibited the formations of DM-3411, SFO-34318 and OPC-3952 above 50% at the highest (4 v/v%) concentration, whereas anti-CYP1A1/2 antibody, anti-CYP2B6 antibody, anti-CYP2C9 antibody, anti-CYP2C19 antibody and anti-CYP2D6 antibody could negligibly do so (data not shown here).

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- The determination coefficient (r2) values between the specific activity of CYP3A4/5 (testosterone 6β-hydroxylation and midazolam 1'-hydroxylation) were shown in Figure 1. The r2 values between the specific activities of the other enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP4A11 and FMO) and the formations of DM-3411, SFO-34318 and OPC-3952 were low, less than 0.5 (data not shown here).

Table 5: Correlation (R^2)Between CYP3A4 Activities and Formations of Metabolites Derived From OPC-34712 in 16 Individual Human Liver Microsomes (Mean, n = 2)

R^2	DM-3411	SFO-34318	OPC-3952
Testosterone 6B-hydroxylation	0.83	0.89	0.86
Midazolam 1'-hydroxylation	0.69	0.73	0.71

- **Conclusion:** CYP3A4 was considered to be mainly involved in the formation of DM-3411, SFO-34318 and OPC-3952 in human liver microsomes.
- **Reviewer's Comments:** Both selective chemical inhibitors and antibodies for CYP enzymes were utilized in identifying enzymes that were involved in the metabolism of brexpiprazole. Results from this two testing systems seemed to be supportive of each other. Sponsor's conclusion is reasonable.

3. CYP Inhibition & Induction

Report # 020858
Title: Inhibitory Potential of OPC-34712 on Cytochrome P450 Enzymes in Vitro Using Human Liver Microsomes

- **Objective:** To evaluate the inhibitory potential of OPC-34712 (brexpiprazole) towards major CYP enzymes
- **Method:** CYP probe substrate was incubated in pooled human liver microsomes with brexpiprazole at varying concentrations and known specific CYP inhibitor (positive control). Enzyme incubations and metabolite analyses were carried out in duplicate. Formation of the major metabolites was detected using LC-ESI-MS/MS system.
- **Results:** Table 1. Effect of brexpiprazole on major CYP activities

P450	Marker Assay	OPC-34712 or Inhibitor	% of Control * Concentration of OPC-34712 (μM) 1	3	10	30	100
CYP1A2	Phenacetin *O*-deethylation	OPC-34712	91.7	88.7	102.1	83.6	79.5
		Furafylline (10 μM)					BLOQ
CYP2A6	Coumarin 7-hydroxylation	OPC-34712	95.6	98.0	81.2	68.3	70.5
		8-Methoxypsoralen (10 μM)					12.9
CYP2B6	Bupropion hydroxylation	OPC-34712	92.1	81.5	39.6	19.6	12.4
		Orphenadrine (100 μM)					45.2
CYP2C8	Paclitaxel 6α-hydroxylation	OPC-34712	117.9	95.5	75.7	75.8	58.6
		Quercetin (50 μM)					5.8
CYP2C9	Diclofenac 4'-hydroxylation	OPC-34712	111.7	83.8	69.1	39.1	34.9
		Sulfaphenazole (10 μM)					4.7
CYP2C19	S-Mephenytoin 4'-hydroxylation	OPC-34712	93.7	83.0	90.2	55.1	19.4
		Tranylcypromine (50 μM)					8.6
CYP2D6	(±)-Bufuralol 1'-hydroxylation	OPC-34712	85.7	81.2	59.4	24.1	22.1
		Quinidine (10 μM)					18.5
CYP2E1	Chlorzoxazone 6-hydroxylation	OPC-34712	101.0	120.9	174.3	169.0	157.6
		Diethyldithiocarbamate (50 μM)					61.3
CYP3A4	Midazolam 1'-hydroxylation	OPC-34712	89.6	93.0	69.3	41.9	36.4
		Ketoconazole (10 μM)					BLOQ
CYP3A4	Testosterone 6β-hydroxylation	OPC-34712	102.3	88.6	62.9	54.9	44.4
		Ketoconazole (10 μM)					BLOQ

Each value represents the mean.* : The relative activities to the control activity (0 μM)

Table 2. Inhibition of major CYP activity by brexpiprazole

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P450	Marker Assay	IC50 (μM)	Ki (μM)
CYP1A2	Phenacetin *O*-deethylation	> 100	-
CYP2A6	Coumarin 7-hydroxylation	> 100	-
CYP2B6	Bupropion hydroxylation	8.19	5.01
CYP2C8	Paclitaxel 6α-hydroxylation	> 100	-
CYP2C9	Diclofenac 4'-hydroxylation	22.23	-
CYP2C19	S-Mephenytoin 4'-hydroxylation	39.82	-
CYP2D6	(±)-Bufuralol 1'-hydroxylation	13.44	-
CYP2E1	Chlorzoxazone 6-hydroxylation	> 100	-
CYP3A4	Midazolam 1'-hydroxylation	29.88	-
CYP3A4	Testosterone 6β-hydroxylation	40.78	-

Each value represents the mean value of duplicate experiments. -: not examined

- **Conclusion:** Brexpiprazole caused little or no inhibition towards major CYP enzymes with calculated IC_{50} values greater than 10 μM, except for CYP2B6. The estimated Ki for CYP2B6 is about 5 μM.
- **Reviewer's Comments:** According to our draft drug interaction guidance, if the maximum inhibitor concentration [I] relative to the inhibition constant (Ki) is ≥0.1, then an in vivo drug interaction is recommended. To evaluate the potential drug interaction potential, [I]/Ki values were calculated for enzymes that were tested in vitro.

Table 3: [I]/Ki Values of Brexpiprazole (OPC-34712) and DM-3411 for CYP Enzyme Inhibitory Potential

CYP isoform	[I]/Ki
	Brexpiprazole
1A2	ND
2A6	ND
2B6	0.092
2C8	ND
2C9	0.041
2C19	0.023
2D6	0.068
2E1	ND
3A4 (Midazolam 1'-hydroxylation)	0.031
3A4 (Testosterone 6β-hydroxylation)	0.023
[I] (Cmax) values at the steady state in human at 4 mg dose were 0.46 μM for brexpiprazole (Trial 331-08-205). Estimated Ki = 0.5xIC50; ND: not determined	

None of the calculated values were > 0.1, indicating no drug interaction potential. Findings from a clinical drug interaction trial (Trial 331-08-207) were in line with the conclusion that brexpiprazole is not an inhibitor of CYP3A4, CYP2B6, or CYP2D6 after multiple daily dosing (11 days) of 2 mg brexpiprazole.

Report # 21328
Title: Inhibitory Potential of OPC-34712 on Cytochrome P450 Enzymes in Vitro Using Human Liver Microsomes (2)

Reference ID: 3779909

- **Objective:** To investigate mechanism-based inhibition (MBI) potential of OPC-34712 (brexpiprazole) towards major CYPs.
- **Method:** CYP probe substrate was incubated in pooled human liver microsomes (HLM) with brexpiprazole at varying concentrations (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2C8, CYP3A4: 100 µM; CYP2B6, CYP2D6: 30 µM) and known specific CYP inhibitor (positive control). Enzyme incubations and metabolite analyses were carried out in duplicate. Formation of the major metabolites was detected using LC-ESI-MS/MS system.
- **Results:** Table 1: Possibility of MBI of OPC-34712 on Metabolic Activities of Major Human Cytochrome P450 Enzymes in HLM.

P450	Marker assay	% decrease in activity	Possibility of MBI
CYP1A2	Phenacetin *O*-deethylation	1.2	Little possible
CYP2A6	Coumarin 7-hydroxylation	4.0	Little possible
CYP2B6	Bupropion hydroxylation	-3.7	Little possible
CYP2C8	Paclitaxel 6α-hydroxylation	-4.5	Little possible
CYP2C9	Diclofenac 4'-hydroxylation	5.1	Little possible
CYP2C19	S-Mephenytoin 4'-hydroxylation	-4.6	Little possible
CYP2D6	(±)-Bufuralol 1'-hydroxylation	0.9	Little possible
CYP3A4	Testosterone 6β-hydroxylation	41.4	Possible
CYP3A4	Midazolam 1'-hydroxylation	30.5	Possible

"Little possible" represents ≤ 20% for % decrease in activity; "Possible" represents ≥20 % for % decrease in activity.

Table 2: MBI Data of OPC-34712 on Metabolic Activities of Human CYP3A4 Enzymes in HLM

P450	Marker assay	k_{obs} (minute^{-1}) OPC-34712 (µmol/L) 0	3	10	30	100	K_I (µmol/L)	k_{inact} (minute^{-1})
CYP3A4	Testosterone 6β-hydroxylation	0.0015	0.0061	0.0180	0.0210	0.0188	4.7	0.0221
	Midazolam 1'-hydroxylation	0.0047	0.0010	0.0059	0.0125	0.0148	32.1	0.0196

- **Conclusion:** Brexpiprazole demonstrated little or no MBI towards major CYP enzymes under current experimental conditions, except for CYP3A4. The lowest estimated Ki for CYP3A4 is about 4.7 µM.
- **Reviewer's Comments:** Overall, brexpiprazole did not show potent inhibition towards major CYP enzymes, except for CYP3A4. According to our draft drug interaction guidance, estimation of the potential of brexpiprazole to inhibit CYP3A based on MBI was shown below.

Reactions	K_I (µM)	k_{inact} (min^{-1})	[I] (µM)	K_{obs} (min^{-1})	K_{deg} (min^{-1})	R_2
Midazolam 1'-hydroxylation	32.1	0.02	0.39	0.00024	0.00008	4.0
					0.0005	1.5
Testosterone 6β-hydroxylation	4.7	0.022	0.39	0.00169	0.00008	22.1
					0.0005	4.4

$R_2 = (K_{obs} + K_{deg})/K_{deg}$, and $K_{obs} = k_{inact} \times [I]/(K_I + [I])$, [I] ($C_{max}$) value at the steady state in human at 4 mg dose was 0.39 µM for brexpiprazole (Trial 331-10-242)

Assessment of MBI of CYP3A4 by brexpiprazole revealed the R2 value ≥1.5, indicating a

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potential CYP3A4 related MBI-based drug interaction. However, clinical interaction study using lovastatin as a CYP3A4 probe showed no clinically important interaction after multiple daily dosing (11 days) of 2 mg brexpiprazole (Trial 331-08-207).

Report # 022587
Title: Inhibitory Potential of OPC-34712 on Cytochrome P450 Enzyme, CYP2B6, in Vitro Using Human Liver Microsomes

- **Objective:** to investigate the inhibition of OPC-34712 (brexpiprazole) towards CYP2B6 in vitro
- **Method:** Brexpiprazole (30 µM) was incubated in pooled human liver microsomes (HLM) with or without NADPH for 30 min before bupropion was added into the reaction. Incubation with bupropion was 10 min before assay termination. Ticlopidine (10 µM) was used as a positive control. Enzyme incubations and metabolite analyses were carried out in duplicate. Formation of 6-hydroxybupropion was detected using LC-MS/MS system.
- **Results:** Table 1: Possibility of MBI of OPC-34712 on CYP2B6

P450	Marker Assay	% Decrease in Activity	Possibility of MBI
CYP2B6	Bupropion Hydroxylation	-2.6	Little Possible

- **Conclusion:** Brexpiprazole demonstrated little or no MBI towards CYP2B6.
- **Reviewer's Comment:** The sponsor's conclusion is acceptable to the reviewer.

Report # 024600
Title: Inhibitory Potential of DM-3411 on Cytochrome P450 Enzymes in Vitro Using Human Liver Microsomes

- **Objective:** To examine the inhibitory potential of DM-3411 on the specific activities of cytochrome P450 (CYP) isoforms using human liver microsomes.
- **Method:** CYP probe substrate was incubated in pooled human liver microsomes (HLM) with DM-3411at varying concentrations (0-100 µM) and known specific CYP inhibitor (positive control) under standard incubation conditions. Enzyme incubations and metabolite analyses were carried out in duplicate. Formation of the major metabolites was detected using LC-ESI-MS/MS system.
- **Results:** Table 1. Inhibitory potential of DM-3411 on CYP enzymes in pooled HLM

Reference ID: 3779909

CYP isoform	Metabolic reaction	Remaining activity (%)					
		DM-3411 (μmol/L)					Positive control [a]
		1	3	10	30	100	
CYP1A2	Phenacetin *O*-deethylation	103.4	109.1	119.3	115.2	100.4	4.9
CYP2A6	Coumarin 7-hydroxylation	100.0	100.8	101.3	102.0	101.5	23.0
CYP2B6	Bupropion hydroxylation	98.0	96.0	93.7	85.7	56.0	14.3
CYP2C8	Paclitaxel 6α-hydroxylation	100.6	98.8	93.4	82.5	57.3	16.9
CYP2C9	Diclofenac 4'-hydroxylation	99.5	98.3	94.0	83.3	61.5	9.6
CYP2C19	(*S*)-Mephenytoin 4'-hydroxylation	96.4	96.4	97.3	81.6	51.0	20.6
CYP2D6	Bufuralol 1'-hydroxylation	93.1	80.8	58.5	34.4	15.6	14.0
CYP2E1	Chlorzoxazone 6-hydroxylation	111.9	120.3	138.1	147.5	133.1	39.2
CYP3A4	Midazolam 1'-hydroxylation	96.7	91.1	73.0	46.4	19.9	4.3
CYP3A4	Testosterone 6β-hydroxylation	99.5	100.0	99.0	92.1	64.4	4.6

Each CYP substrate was incubated with human liver microsomes (0.2 mg protein/mL) for the designated times in the presence of DM-3411 (0, 1, 3, 10, 30, and 100 μmol/L).
Remaining activity was calculated from the mean metabolic activity of duplicate samples.

Table 2: IC50 values of DM-3411 for CYP enzymes in human liver microsomes

CYP isoform	Metabolic reaction	IC_{50} (μmol/L)
CYP1A2	Phenacetin *O*-deethylation	>100
CYP2A6	Coumarin 7- hydroxylation	>100
CYP2B6	Bupropion hydroxylation	>100
CYP2C8	Paclitaxel 6α-hydroxylation	>100
CYP2C9	Diclofenac 4'-hydroxylation	>100
CYP2C19	(*S*)-Mephenytoin 4'-hydroxylation	>100
CYP2D6	Bufuralol 1'-hydroxylation	15.3
CYP2E1	Chlorzoxazone 6-hydroxylation	>100
CYP3A4	Midazolam 1'-hydroxylation	25.8
CYP3A4	Testosterone 6β-hydroxylation	>100

- **Conclusion:** DM-3411 caused little or no inhibition towards major CYP enzymes with calculated IC_{50} values greater than 15 μM.
- **Reviewer's Comments:** According to our draft drug interaction guidance, if the maximum inhibitor concentration [I] relative to the inhibition constant (Ki) is ≥0.1, then an in vivo drug interaction is recommended. To evaluate the potential drug interaction potential, [I]/Ki values were calculated for enzymes that were tested in vitro, using CYP2D6 as an example, as it has the highest interaction potential (smallest IC50 value). Estimated Ki = 0.5xIC50. [I] (Cmax) values at the steady state in humans at 4 mg dose were 0.14 μM for DM-3411(Trial 331-08-205). [I]/Ki for CYP2D6 is 0.02, less than 0.1, indicating no drug interaction potential.

Report # 022783
Title: In vitro Evaluation of OPC-331 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

Reference ID: 3779909

- **Objective:** To investigate the induction potential of OPC-331 on the expression of CYPs in human hepatocytes
- **Method:** Cultured human hepatocytes (n=3) were treated daily for three consecutive days with OPC-331 (brexpiprazole, 0.1, 1, or 10 µM), or omeprazole (100 µM), or rifampin (10 µM). Approximately 24 hrs after the last treatment, RNA and microsomes were isolated for measurement of enzyme mRNA expression level (qPCR) and activity, respectively. Formation of specific metabolite was detected using LC-MS/MS.

Table 1: Summary of assay conditions

Enzyme	Substrate	(b) (4) SOP	Substrate concentration (µM)	Quantity of protein (mg/incubation)	Incubation volume (mL)	Incubation time (min)
CYP1A2	Phenacetin *O*-dealkylation	L3260.02	80	0.008	0.2	30
CYP2C9	Diclofenac 4´-hydroxylation	L3260.02	100	0.008	0.2	10
CYP3A4/5	Testosterone 6β-hydroxylation	L3260.02	250	0.008	0.2	10

- **Results:** Table 1: The effects of treating cultured human hepatocytes with OPC-331 or prototypic inducers on enzyme activity: Comparison with positive control

Treatment	Concentration	Percent positive control [a]		
		Phenacetin *O*-dealkylation (CYP1A2)	Diclofenac 4´-hydroxylation (CYP2C9)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	0 ± 0	0 ± 0	0 ± 0
OPC-331	0.1 µM	NA	NA	NA
OPC-331	1 µM	NA	NA	3.09 ± 1.32
OPC-331	10 µM	1.75 ± 2.36	NA	6.03 ± 3.80
Omeprazole	100 µM	100 ± 0	ND	ND
Rifampin	10 µM	ND	100 ± 0	100 ± 0

$$\text{Calculated percent positive control for each individual human preparation} = \frac{(\text{activity in test article group - activity in vehicle control})}{(\text{activity in positive control - activity in vehicle control})} \times 100$$

Table 2: The effects of treating cultured human hepatocytes with OPC-331 or prototypic inducers on enzyme mRNA expression: Comparison with positive control

Treatment	Concentration	Percent positive control [a]		
		Phenacetin *O*-dealkylation (CYP1A2)	Diclofenac 4´-hydroxylation (CYP2C9)	Testosterone 6β-hydroxylation (CYP3A4)
Dimethyl sulfoxide	0.1% (v/v)	0 ± 0	0 ± 0	0 ± 0
OPC-331	0.1 µM	NA	NA	NA
OPC-331	1 µM	0.211 ± 0.306	NA	NA
OPC-331	10 µM	2.36 ±2.32	NA	9.31 ± 6.34
Omeprazole	100 µM	100 ± 0	ND	ND
Rifampin	10 µM	ND	100 ± 0	100 ± 0

$$\text{Percent positive control (\%)} = \frac{[(\text{fold change in treated sample}) - 1]}{[(\text{fold change in positive control}) - 1]} \times 100$$

- **Conclusion:** Brexpiprazole up to 10 µM demonstrated minimal induction potential towards CYP1A2, CYP2C9 or CYP3A4.
- **Reviewer's Comments***:* The highest tested concentration for brexpiprazole was 10 µM (4.3µg/mL), and it is about 20-fold higher than the observed Cmax at steady state after 4 mg brexpiprazole daily dosing (about 200 ng/mL, Trial 331-08-025). Therefore, the possibility of brexpiprazole to induce CYP1A2, CYP2C9 and CYP3A4 is rather small. A clinical interaction study using lovastatin as a CYP3A4 probe showed no clinically important interaction after multiple daily dosing (11 days) of 2 mg brexpiprazole (Trial 331-08-207). No in vivo drug interaction is recommended for CYP1A2 or CYP2C9 based on these findings.

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Report # 029149
Title: Effect of OPC-34712 on CYP2B6 Expression in Cultured Human Hepatocytes

- **Objective:** To evaluate the induction potency of OPC-34712 on the expression of CYP2B6 mRNA in cultured human hepatocytes
- **Method:** Cultured human hepatocytes (n=3) were treated daily for two consecutive days with OPC-34712 (0.05, 0.5, or 5 µM), or phenobarbital (750 µM), before RNA were isolated for measurement of enzyme mRNA expression level by quantitative real-time PCR.
- **Results:** Table 1: Fold Increase in CYP2B6 mRNA Expression in Cultured Human Hepatocytes Treated With Vehicle, OPC-34712, or Phenobarbital

Treatment	Concentration	Fold Increase in CYP2B6 mRNA Expression
Dimethyl Sulfoxide	0.1% (v/v)	1.00 ± 0.00
OPC-34712	0.05 µmol/L	1.02 ± 0.02
OPC-34712	0.5 µmol/L	1.18 ± 0.05
OPC-34712	5 µmol/L	1.14 ± 0.30
Phenobarbital	750 µmol/L	7.20 ± 0.48

Table 2: Percent Positive Control of CYP2B6 mRNA Increase in Cultured Human Hepatocytes Treated With OPC-34712, or Phenobarbital

Treatment	Concentration	Percent Positive Control (%) CYP2B6 mRNA
OPC-34712	0.05 µmol/L	0.3 ± 0.3
OPC-34712	0.5 µmol/L	2.9 ± 0.9
OPC-34712	5 µmol/L	2.2 ± 4.8
Phenobarbital	750 µmol/L	100.0 ± 0.0

- **Conclusion:** Brexpiprazole up to 5 µM demonstrated minimal induction potential towards CYP2B6.
- **Reviewer's Comments:** The highest tested concentration for brexpiprazole was 5 µM (2 µg/mL), and it is about 10-fold higher than the observed Cmax at steady state after 4 mg brexpiprazole daily dosing (200 ng/mL, Trial 331-08-025). Therefore, possibility of brexpiprazole to induce CYP2B6 activity in vivo is rather small. Findings from a clinical interaction study using bupropion as a CYP2B6 probe showed no clinically important interaction after multiple daily dosing (11 days) of 2 mg brexpiprazole (Trial 331-08-207), which was in line with the in vitro study results.

4. Transporter Studies

Report # 022491
Title: Recognition of ^{14}C-OPC-331 by MDR1 and Inhibition of OPC-331 on Digoxin Transport in the MDR1 Expressing LLC-PK1 Cells

- **Objective:** To evaluate the potential inhibitory and substrate activity of brexpiprazole toward P-gp using the LLC-PK MDR1 expressing cells.
- **Method:**

1) P-gp substrate assessment: bidirectional permeability assessment (basolateral to apical, B→A) and apical to basolateral, A→B) of ^{14}C-OPC-331 (brexpiprazole, 1 µM) was

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conducted using LLC-PK1 control cells and cells expressing MDR1 grown on Transwell system and were measured after incubation for 1, 2, 4 hr at 37 ºC. Permeation clearance ratio was calculated as (PappB→A/PappA→B).

2) P-gp inhibitor assessment: bidirectional transport of ^{3}H-digoxin was measured in the absence and presence of brexpiprazole (0-30 μM) or verapamil (positive control, 30 μM) in LLC-PK cells after incubation for 2 hr.

- **Results:** Table 1: Bidirectional transport in LLC-PK cells

	Permeation clearance ratio		Net Efflux Ratio
Treatment (1 μM)	MDR1	Control cells	
^{14}C-Brexpiprazole	1.7	0.9	0.72
^{3}H-Digoxin	22.0	1.1	0.90
^{14}C-mannitol*	0.8	0.6	0.77

*: ^{14}C-mannitol: 10 μM

Table 2: P-glycoprotein Inhibitory Activity of Brexpiprazole

Treatment	Brexpiprazole concentration (μM)	PappB→A/ PappA→B
[3H]-digoxin+Verapamil	-	1.1
[3H]-digoxin + Brexpiprazole	0	15.4
	0.1	14.8
	0.3	16.6
	1	16.7
	3	9.7
	10	3.4
	30	2.2

The estimated IC_{50} of brexpiprazole for P-gp activity was 6.31 μM (2.735 μg/mL)

- **Conclusion**: Brexpiprazoel showed concentration-dependent inhibition on P-gp activity.
- **Reviewer's Comments:** Our Drug Interaction Studies Guidance (Draft) recommends the following ratios as the criteria to establish whether a drug is a P-gp inhibitor:
  - the ratio of [I]1/IC50. Where, [I]1 is the mean steady state Cmax (bound plus unbound) of the highest proposed clinical dose . The Guidance recommends that if [I]1/IC50 > 0.1, then the investigational drug is likely a P-gp inhibitor; if [I]1/IC50 < 0.1, then the drug is likely a weak P-gp inhibitor and further in vivo DDI study is not needed.
  - the ratio of [I]2/IC50. Where, [I]2 is the theoretical maximal gastrointestinal concentration of a NME after oral administration calculated as the highest clinical dose (mg) in a volume of 250 mL. The Guidance recommends that if [I]2/IC50≥ 10, then the evaluation of in vivo P-gp inhibitory activity of an investigational drug is recommended.

Table 3: Evaluation of in vivo drug interaction potential of brexpiprazole as an inhibitor for P-gp

Moiety	[I]1 (ng/mL)	[I]2 (ng/mL)	IC_{50} (ng/mL)	[I]1/IC_{50}	[I]2/IC_{50}
Brexipirpazole	200	16000	2735	0.073	5.85
In vivo drug interaction study	--	-	-	No	No

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recommended?					
[I]1: According to the study result of Trial 331-08-025, the mean Cmax,ss of brexpiprazole after 4 mg daily dose administration for 14 days was about 200 ng/mL. [I]2: The maximal recommended dose per proposed labeling is 4 mg/day. [I]2 =4mg/250ml=16ug/mL					

Based on the above analysis, brexpiprazole showed no drug interaction potential towards P-gp. The conclusion was confirmed by a clinical interaction study using fexofenadine as a P-gp probe, which showed no clinically important interaction was observed after multiple daily dosing (11 days) of 2 mg brexpiprazole (Trial 331-08-207).

Report # 028953
Title: Recognition of ^{14}C-OPC-331 by BCRP Transporter and Inhibitory Effects of OPC-331 and DM-3411 on MDR1 and BCRP Transporters Using Expressing Cells

- **Objective:** To evaluate the potential inhibitory and substrate activity of brexpiprazole toward BCRP and P-gp using the LLC-PK MDR1 expressing cells.
- **Method:**
  1) Substrate assessment: bidirectional permeability assessment (basolateral to apical (B→A) and apical to basolateral (A→B) of ^{14}C-OPC-331 (1 μM), ^{3}H-Prazosin (0.01 μM), and ^{14}C-Mannitol (10 μM), was conducted using LLC-PK1 control cells and cells expressing BCRP grown on Transwell system and were measured after incubation for 0.5, 1 and 2 hr at 37 ºC (^{3}H-Prazosin: 0.25, 0.5 and 1 hr). Permeation clearance ratio was calculated as (PappB→A/PappA→B). Net efflux ratio was calculated as the ratio of permeation clearance ratio in transporter expressing cells over the permeation clearance ratio in control cells.
  2) Inhibitor assessment: the bidirectional transport of ^{3}H-digoxin (1 μM) or ^{3}H-Prazosin (0.01 μM) was measured in the absence and presence of brexpiprazole (0-30 μM), DM-3411 (0-30 μM), verapamil (30 μM for P-gp inhibition) or Ko134 (1 μM for BCRP inhibition) in LLC-PK cells. Incubation for BCRP and P-gp assays was 1 hr and 2 hr long, respectively.
- **Results:** Table 1: Bidirectional transport in LLC-PK cells

	Permeation clearance ratio		Net Efflux Ratio
Treatment	BCRP expressing cells	Control cells	
^{14}C-Brexpiprazole (1 μM)	2.1	1.3	1.6
^{3}H-Prazosin (0.01 μM)	9.0	1.6	5.6
^{14}C-mannitol (10 μM)	0.7	0.9	0.8

Table 2: Inhibitory Effects of OPC-331 and DM-3411 on the ^{3}H-Prazosin (0.01 μM) Transport Across Control and BCRP Expressing Cell Monolayers

Treatment	Inhibitor concentration (μM)	Net Efflux Ratio
[^{3}H]- Prazosin +Ko143	-	0.9
[^{3}H]-Prazosin + Brexpiprazole	0	5.3
	0.1	4.6
	0.3	5.2
	1	3.3
	3	2.1

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	10	1.6
	30	1.1
[^{3}H]-Prazosin + DM3411	0.1	5.9
	0.3	5.5
	1	4.3
	3	3.3
	10	2.5
	30	1.5

Table 3: Inhibitory Effects of OPC-331 and DM-3411 on the ^{3}H-Digoxin (1 μM) Transport Across Control and MDR1 Expressing Cell Monolayers

Treatment	Inhibitor concentration (μM)	Net Efflux Ratio
[3H]- Digoxin+Verapamil	-	2.0
[^{3}H]-Digoxin + DM3411	0	33
	0.1	29.7
	0.3	19.3
	1	25.7
	3	22.2
	10	16.6
	30	11.2

Table 4: Brexpiprazole and DM-3411 Inhibition on BCRP and P-gp activity.

IC_{50}	BCRP	P-gp
Brexpiprazole	1.16 uM (0.5ug/mL)	6.31 (2.73ug/mL)*
DM-3411	3.04 uM (1.37ug/mL)	7.84 (3.53ug/mL)

**results from Report #022491*

- **Conclusions***:*
  1) Brexpiprazole is likely to be a weak substrate of BCRP.
  2) Brexpiprazole and DM-3411 showed concentration-dependent inhibition towards BCRP activity.
- **Reviewer's Comments:** Our Drug Interaction Studies Guidance (Draft) recommends certain criteria to establish whether a drug is an inhibitor for BCRP or P-gp and whether an in vivo study is recommended and whether an in vivo study is recommended (see comments for Report #022491).

Table 5: Evaluation on the drug interaction potential of brexipiprazole and DM-3411 towards BCRP.

Moiety	[I]1 (ng/mL)	[I]2 (ng/mL)	IC_{50} (ng/mL)	$[I]1/IC_{50}$	$[I]2/IC_{50}$
Brexipirpazole	200	16000	500	0.4	32
DM-3411	65	-	1370	0.047	-
In vivo drug interaction study recommended based on guidance criterion?	--	-	-	YES	YES
[I]1: According to the study result of Trial 331-08-025, the mean Cmax,ss of brexpiprazole and DM-3411 after 4 mg daily dose of brexpiprazole for 14 days was about 200 ng/mL and 65 ng/mL, respectively.					

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[I]2: The maximal recommended dose per proposed labeling is 4 mg/day for brexpiprazole. [I]2 =4mg/250ml=16ug/mL

Table 6: Evaluation on the drug interaction potential of DM-3411 towards P-gp.

Moiety	[I]1 (ng/mL)	[I]2 (ng/mL)	IC_{50} (ng/mL)	[I]1/IC_{50}	[I]2/IC_{50}*
DM-3411	65	-	3530	0.018	-
In vivo drug interaction study recommended based on guidance criterion?	--	-	-	NO	-

[I]1: According to the study result of Trial 331-08-025, the mean Cmax,ss of DM-3411 after 4 mg daily dose administration of brexpiprazole for 14 days was about 65 ng/mL.
*[I]2: The maximal recommended dose per proposed labeling is 4 mg/day. Calculation is not applicable to metabolite.

Based on the above analysis, brexpiprazole is likely to be a BCRP inhibitor in vivo. The sponsor has conducted a study to evaluate inhibitory potential of BCRP in vivo (Trial 331-12-207), and no clinically important interactions were observed. For details, please refer to the review of that study.

Report # 028790
Title: Inhibitory Potential of OPC-34712 and its Metabolite, DM-3411, on Human BSEP Expressing Membrane Vesicles

- **Objective:** To evaluate the inhibitory activity of brexpiprazole (OPC-34712) and, and no clinically important interactions were observed DM3411 toward BSEP using membrane vesicles expressing human BSEP.
- **Method:** Reaction mixture except vesicle was prepared in a 1.5 mL tube on ice water bath (Table 1). The reaction tube was incubated for 5 min for 5 minutes at 37 ºC in the temperature controlled bath. After addition of vesicle, the reaction mixture was kept at 37 ºC for 2 minutes before termination.

Table 1: Reaction mixture

Name	Volume	Final Concentration
Buffer A1	12.5 µL	(Not Applicable)
BSEP expression vesicle or control vesicle (5 mg protein/mL)	5 µL	0.5 mg protein/mL
Reagent C1 (10 mmol/L MgATP solution)	20 µL	4 mmol/L
^{3}H-TCA solution (40 µmol/L)	2.5 µL	2 µmol/L
DMSO, Test article solution 1, 2, 3, 4, 5 or Cyclosporin A (positive control) [a]	10 µL	OPC-34712 or DM-3411: 0, 0.3, 1, 3, 10, 30 µmol/L Cyclosporin A: 30 µmol/L

- **Results:**

Table 2: Effects of OPC-34712 and DM-3411 on BSEP-mediated Uptake of ^{3}H-TCA

Treatment	Inhibitor concentration (µM)	% of control
Cyclosporin A	30	0
OPC-34712	0	100
	0.3	99.1±25
	1	134.4±19.8
	3	119.7±12.3

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	10	103.9±32.1
	30	66.4±6.4
Cyclosporin A	30	9.1±4.0
DM-3411	0	100
	0.3	83.7±15.5
	1	108.8±7.4
	3	102.5±4.9
	10	81.8±4.1
	30	54.0±11.1

- **Conclusion**: OPC-34712 and DM-3411 were slightly inhibitory to the BSEP-mediated TCA uptake with IC_{50} value of greater than 30 μM (66.4% and 54.0% of control at 30 μM, respectively).
- **Reviewer's Comment:** BSEP activity somehow was activated at concentrations of 1 μM and 3 μM of brexpiprazole and DM-3411, but the trend of decreasing BSEP activity was observed with increasing concentrations of brexpiprazole and DM-3411 from1 μM concentration onward. Sponsor's conclusion is acceptable.

Report # 028954
Title: Recognition of ^{14}C-OPC-331 by SLC Transporters and Inhibitory Effects of OPC-331 and DM-3411 on SLC Transporters Using Expressing Cells

- **Objectives:** 1) To evaluate whether OPC-331 is a substrate of OATP1B1, OATP1B3 or OCT1. 2) To evaluate the inhibitory effects of OPC-331 and DM-3411 on OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2.
- **Method:**

1) Uptake assay: Uptake of OPC-331 was investigated using 1μM ^{14}C-OPC-331 after incubation for 0.5, 1, 2, 5 and 10 min at 37°C. Typical substrate of OATP1B1/3, OCT1, and OAT1/3 was ^{3}H-E217βG (0.05 μM, incubation time: 2 min), ^{14}C-Metformin (10 μM, incubation time: 5 min), and ^{3}H-PAH (1 μM, incubation time: 2 min).
2) Inhibitor assessment: Typical substrate of OATP1B1/3, OCT1/2, OAT1, and OAT3 used in the assay was ^{3}H-E217βG (0.05 μM), ^{14}C-Metformin (10 μM), 3H-PAH (1 μM), 3H-E3S (0.05 μM). All incubation was 2 min long except for OCT1, incubation was 5 min. Typical inhibitors for OAT1/3, OATP1B1/3, OCT1, and OCT2 were probenecid (100 μM), rifampcin (10 μM), quinidine (100 μM), and quinidine (300 μM), respectively. Tested concentrations for OPC-331 and DM-3411 were 0, 0.1, 0.3, 1, 3, 10 and 30 μM.

- **Results:** Table 1: Substrate activity (uptake ratio) of 14C-OPC-331 (1 μM) in OATP1B1-, OATP1B3-, OCT1-expressing cells

Incubation time (min)	OATP1B1	OATP1B3	OCT1
0.5	1.2	1.0	0.9
1	1.3	1.1	0.9
2	1.2	1.0	0.9
5	1.5	0.9	0.8
10	1.5	1.1	0.8
Typical substrate	242.3	41.4	4.5

Table 2: Inhibitory Effects of OPC-331 and DM-3411 on Uptake of Typical Substrates Mediated

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by SLC Transporters

Test Substances	IC_{50} (µmol/L)					
	OAT1	OAT3	OATP1B1	OATP1B3	OCT1	OCT2
OPC-331	>30	>30	8.39	>30	13.0	4.27
DM-3411	>30	>30	9.13	>30	11.4	6.50

- **Conclusions**:
  1) Brexpiprazole (OPC-331) is not a substrate of OATP1B1, OATP1B3 or OCT1 transporters.
  2) Brexpiprazole and DM-3411 demonstrated some inhibition toward OCT2 and OATP1B1 in vitro, no inhibition or weak inhibition toward OAT1, OAT3 or OATP1B3.
- **Reviewer's Comments:** Among the transporters tested, brexpiprazole and DM-3411 seemed to have most inhibitory potential toward OCT2, with IC_{50}=4.27µM (1850 ng/mL) and 6.50µM (2930 ng/mL) for brexpiprazole and DM-3411, respectively. In evaluating drug interaction potential towards OCT2, OAT1 or OAT3, our Drug Interaction Studies Guidance (Draft) recommends: 1) if unbound Cmax/IC_{50} is ≥0.1, then an in vivo DDI study is recommended; 2) if unbound Cmax/IC_{50} is < 0.1, then an in vivo DDI study is not needed.

Table 3: Evaluation on the drug interaction potential of brexpiprazole and DM-3411 towards OCT2

Moiety	Cmax (ng/mL)	% unbound	Unbound Cmax (ng/mL)	IC_{50} (ng/mL)	unbound Cmax /IC_{50}
Brexpiprazole	200	1	2	1850	0.001
DM-3411	65	4.5	2.925	2930	0.001
In vivo drug interaction study recommended based on guidance criterion?	--		-	NO	NO

[I]1: According to the study result of Trial 331-08-025, the mean Cmax,ss of brexpiprazole after 4 mg daily dose administration for 14 days was about 200 ng/mL. Unbound fraction for brexpirpazole is ~ 1% (report 019405), and for DM=341, is about 4.5% (Report 023150).

Based on the above calculation, neither brexpiprazole nor DM-3411 is likely to be a potent inhibitor of OCT2 in vivo. For OAT1 and OAT3, the likelihood of brexpiprazole and DM-3411 to significantly inhibit their activities is even smaller (greater IC50 values compared to OCT2). No in vivo drug interaction study is recommended based on the analysis.

In evaluating drug interaction potential towards OTTP1B1, or OATP1B3, our Drug Interaction Studies Guidance (Draft) recommends: 1) if Cmax/IC_{50} is ≥0.1, then an in vivo DDI study is recommended; 2) if Cmax/IC_{50} is < 0.1, then an in vivo DDI study may not be needed.

Table 4: Evaluation on the drug interaction potential of brexpiprazole and DM-3411 towards OATP1B1

Moiety	Cmax (ng/mL)	IC_{50} (uM)	IC_{50} (ng/mL)	Cmax /IC_{50}
Brexpiprazole	200	8.39	3640	0.05
DM-3411	65	9.13	4110	0.01
In vivo drug interaction study recommended based	--		NO	NO

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on guidance criterion?				
According to the study result of Trial 331-08-025, the mean Cmax,ss of brexpiprazole and DM-3411 after 4 mg daily dose administration for 14 days was about 200 ng/mL and 64ng/mL, respectively.				

Based on the above calculation, neither brexpiprazole nor DM-3411 is likely to be a potent inhibitor of OATP1B1 in vivo. For OATP1B3 and OCT1, the likelihood of brexpiprazole and DM-3411 to significantly inhibit their activities is even smaller (greater IC50 values compared to OATP1B1). No in vivo drug interaction study is recommended based on the analysis.

Report # 029151
Title: Inhibitory Effects of OPC-331 and DM-3411 on MATE1 and MATE2-K Transporters Using Expressing Cells

- **Objective:** To evaluate the inhibitory activity of brexpiprazole (OPC-34712) and DM-3411 toward MATE1/2 using HEK293 cells expressing human MATE1/2.
- **Method:** Before study initiation, MATE1- and MATE2-K- expressing and control HEK293 cells were preincubated at 37°C for 15 min. Incubation was initiated by adding 300 µL of the typical substrate solution containing 0.2% DMSO, test substance or typical inhibitor (incubation solution) to the cells. After the cells were incubated at 37°C for 5 min, cells were then washed and dissolved in 0.5 mL of 0.1 M NaOH. A 300 uL aliquot if the cell lysate were used to measure radioactivity using an LSC. ^{14}C-Metformin (10 µM) was used as the substrate, cimetidine, 10 µM and 100 µM was used to inhibit MATE1 and MATE2-K activity, respectively. Tested concentrations for OPC-331 and DM-3411 were 0, 0.1, 0.3, 1, 3, 10 and 30 µM.
- **Results:** Table 1: Inhibitory effects of OPC-331 and DM-3411 on MATE1- and MATE2-K mediated transport of ^{3}H-metformin (10 µM)

Treatment	Inhibitor conc. (µM)	Remaining activity (% of control)	
		MATE1	MATE2-K
Cimetidine	10	15.6	10.7
OPC-331	0	100	100
	0.1	99.6	99.6
	0.3	78.4	75.4
	1	71.1	47.4
	3	45.9	39.6
	10	32.3	11.6
	30	13.2	5.1
Cimetidine	10	14.1	10.7
DM-3411	0	100.0	100.0
	0.1	77.9	59.0
	0.3	80.4	39.3
	1	55.0	16.6
	3	35.3	12.4
	10	17.0	4.9
	30	7.3	2.2

Table 2: Inhibitory effects of OPC-331(brexpiprazole) and DM-3411 on transport of ^{14}C-metformin (10 µM) mediated by MATE1 and MATE2-K

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Test Substances	IC_{50} (μM)		IC_{50} (ng/mL)	
	MATE1	MATE2-K	MATE1	MATE2-K
brexpiprazole	2.79	1.57	1210	680
DM-3411	1.83	0.154	820	70

- **Conclusion***:* OPC-331 and DM-3411 were inhibitory to MATE-1 and MATE2-K mediated metformin transport with varying potency, with DM-3411 showed highest potency toward MATE2-K activity.
- **Reviewer's Comments:** Brexpiprazole (OPC-311) and DM-3411 seemed to have inhibitory effects toward MATE-1 and MATE2-K activities. There are no specific recommendations regarding MATE DDIs in our Drug Interaction Studies Guidance (Draft). Considering that MATE transporters are mainly expressed at the apical side of the kidney or liver cells pumping substrate outside of the cell, a similar decision tree to that of OCT or OAT drug interaction was adopted in evaluating whether an in vivo drug interaction is needed. The decision tree for OCT or OAT inhibitor interactions outlines as follows: if unbound $Cmax/IC_{50} \geq 0.1$, a clinical DDI study with a sensitive substrate is recommended; if unbound $Cmax/IC_{50} < 0.1$, DDI study is not needed.

Table 3: Evaluation on the drug interaction potential of brexpiprazole and DM-3411 towards MATE1 and MATE2-K

Moiety	IC_{50} (ng/mL)		Unbound C_{max}/IC_{50}	
	MATE1	MATE2-K	MATE1	MATE2-K
brexpiprazole	1210	680	0.0016	0.0029
DM-3411	820	70	0.045	0.0423
In vivo drug interaction study recommended based on guidance criterion?	-	-	No	No
[I]1: According to the study result of Trial 331-08-025, the mean Cmax,ss of brexpiprazole and DM-3411 after 4 mg daily dose of brexpiprazole for 14 days was about 200 ng/mL and 65 ng/mL, respectively. Unbound fraction for brexpirpazole is ~ 1% (report 019405), and for DM=341, is about 4.5% (Report 023150).				

Hence, based on the above analysis, no in vivo DDI study is recommended at this time. However, an in vivo evaluation might be needed later on.

Reference ID: 3779909

II. Pharmacokinetics

1. Absolute Bioavailability

Report # 331-10-241 **Study Period**: 6/20/2011-8/30/2011
Title: An Open-label, Two-period Trial of Absolute Bioavailability of OPC-34712 Oral Tablets in Healthy Subjects

- **Objective:** To determine the absolute bioavailability of oral OPC-34712 tablets in healthy male and female subjects following single dose administration of a 2-mg oral tablet and a 0.25-mg IV solution of OPC-34712 (brexpiprazole).
- **Study Design:** This was a single-center, open-label, 2-period trial of a 2-mg oral tablet and a 0.25-mg IV solution of brexpiprazole administered to 16 male and female subjects.
  The following treatments were administered in a sequential manner to each subject: a 0.25-mg IV solution of brexpiprazole infused in 1 hour (infusion rate: 0.042 mL/min) on Day 1 followed by a 2-mg oral tablet of brexpiprazole on Day 10. Blood samples for PK analysis were collected on Days 1 through 18.Doses were administered under fasting conditions.
- **Blood Sampling Times (PK):**
  Day 1: Predose (-30 min), 5, 15, 30, 45, and 60 (end of the infusion) min; and then at 1.5, 2, 3, 4, 5, 7, 9, 13, 17, 25, 37, 49, 73, 97, 121, 145, 169, and 193 hours after the start of the infusion or at early termination (ET)
  Day 10: 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours postdose or at ET
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Method	6825-271	6825-271
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Performance	Acceptable	Acceptable

- **Results:**

Study Population

	All subjects
Treated/Completed/ withdrawn by investigator	19/16/3
Age [Mean (range)]	27.9(18-44)
Male/Female	14/5
Race (Caucasian/Black/Asian/other)	12/1/4/2

Pharmacokinetics

Table 1: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 0.25-mg Brexpiprazole IV Infusion and 2-mg Brexpiprazole Oral Tablet to Healthy Subjects

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PK Parameter	0.25-mg IV Infusion (n = 16)	2-mg Oral Tablet (n = 16)
C_{max} (ng/mL)	5.51 (2.22)	23.7 (6.88)
t_{max} (h)[a]	1.00 (0.75-1.50)	5.00 (2.00-6.00)
AUC_t (ng·hr/mL)	158 (89.9)	1320 (645)
AUC_∞ (ng·hr/mL)	222 (118)[b]	1670 (1090)[c]
$t_{1/2,z}$ (h)	64.9 (25.8)[b]	82.1 (30.8)[c]
CL_{tot}, CL/F (mL/h/kg)[d]	19.8 (10.0)[b]	21.8 (11.1)[c]
V_d, V_z/F (L/kg)[e]	1.56 (0.418)[b]	2.20 (0.722)[c]
$AUC_{partial\ oral}$ (ng·hr/mL)[f]	ND	1220 (718)
F[g]	ND	0.959 (0.129)

ND = Not determined. [a]Median (minimum-maximum).[b]n = 13. [c]n = 15. [d]CLtot for the IV treatment and CL/F for the oral treatment. [e]Vd for the IV treatment and Vz/F for the oral treatment. [f]AUCpartial oral was used for F calculation; for each subject, the time to the last quantifiable brexpiprazole plasma concentration in the IV data was used to calculate a corresponding partial AUC in the oral data. [g]$F = (AUC_{partial\ oral}/Dose_{oral})/(AUC_{t,\ IV}/Dose_{,IV})$.

Table 2: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 0.25-mg Brexpiprazole IV Infusion and 2-mg Brexpiprazole Oral Tablet to Healthy Subjects

PK Parameter	0.25-mg IV Infusion (n = 15)	2-mg Oral Tablet (n = 16)
C_{max} (ng/mL)	0.840 (0.472)	7.50 (4.70)
t_{max} (h)[a]	25.00 (9.00-49.00)	12.00 (3.00-24.00)
AUC_t (ng·hr/mL)	51.5 (39.3)	601 (302)
AUC_∞ (ng·hr/mL)	122 (31.3)[b]	726 (357)[c]
$t_{1/2,z}$ (h)	48.7 (7.0)[b]	68.1 (24.9)[c]

[a]Median (minimum-maximum). [b]n = 4. [c]n = 12.

Table 3: Brexpiprazole Absolute Bioavailability and 90% Confidence Intervals Following Administration of 2-mg Brexpiprazole Oral Tablet to Healthy Subjects

PK Parameter	Oral 2-mg Brexpiprazole Tablet	0.25-mg Brexpiprazole IV Infusion
Dose adjusted AUC geometric mean (ng·hr/mL)/mg[a]	520	547
F[b] (90% CI)	0.951 (0.897, 1.009)	

$AUC_{partial\ oral}$ was used for F calculation; for each subject, the time to the last quantifiable brexpiprazole plasma concentration in the IV data was used to calculate a corresponding partial AUC in the oral data. [b]$F = (_{AUCpartial\ oral}/Dose_{oral})/(AUC_{t,\ IV}/Dose_{IV})$.

Figure 1: Plasma Concentrations (ng/mL) of Brexpiprazole (left panel) and DM-3411 (right panel) Following Administration of 0.25-mg Brexpiprazole IV Infusion and 2-mg Brexpiprazole Oral Tablet to Healthy Subjects

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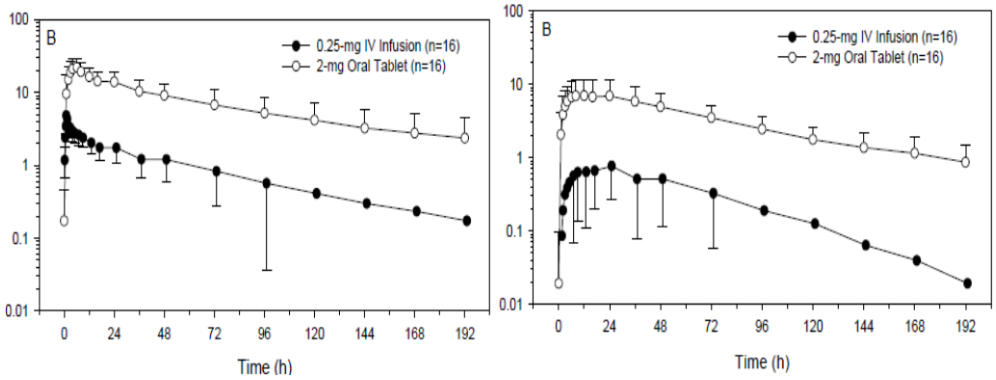

- The pharmacokinetics of brexpiprazole is best described by:
  ☐ Mono-exponential decay, ☑multi-Exponential Decay
- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusion:** Brexpiprazole (oral tablet) is highly bioavailable with a mean absolute bioavailability of 95%.
- **Reviewer's Comments:**
  1) $AUC_{partial\ oral}$ was used for F calculation; for each subject, the time to the last quantifiable brexpiprazole plasma concentration in the IV data was used to calculate a corresponding partial AUC in the oral data, where $F = (AUC_{partial\ oral}/Dose_{oral})/(AUC_{t,\ IV}/Dose_{,IV})$. T is defined as the last observation. $AUC_{partial,\ oral}$ was used for absolute bioavailability calculation because of the BLQ levels (BLQ levels were treated as zero in calculation) at later time points after IV administration. Considering the approximate linear kinetics demonstrated by brexpiprazole in the dose range of 0.25 to 8 mg (Trial 331-07-201) after single dose administration, it is acceptable to use $AUC_{partial}$ to calculate absolute bioavailability.
  2) Brexpiprazole seems to be a low extraction ratio drug. The results from this study indicated that brexpiprazole had a total plasma clearance of 19.8 mL/hr/kg after IV administration. After blood/plasma partition correction, the blood clearance was estimated to be 33 mL/hr/kg. Compared to the typical human hepatic blood flow of about 1.3 L/hr/kg, brexpiprazole is a very low extraction ratio drug. This is consistent with the observed high absolute bioavailability, with minimal first pass metabolism.
  3) Elimination of brexpiprazole can be described by a two-exponential decay model, with the estimated half-life of IV and oral brexpiprazole being 65 hrs and 82 hs, respectively. The sampling time post dose (up to 192 hr, on the borderline of 3 half-lives) may be relative short for an accurate estimation of terminal half-life. . However, estimated values are still similar to those obtained from other clinical trials.
  4) It was found that for 5 out of 16 subjects at time 0 for oral brexpiprazole had quantifiable residual concentration from IV administration. This probably was due to the sequential design feature of the study, and long half -life of brexpiprazole, The mean time 0 concentration was about 0.17 ng/mL. Comparing to the mean 192 hr post dose concentration of about 2.36 ng/mL, it could be considered negligible in calculation of PK parameters. The study could have used a longer washout time between study periods.
  5) Overall the estimated F is considered acceptable.

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2. Single Ascending Dose-in Healthy Subjects

Report # 331-07-201 (Arm 1) **Study Period**: 04/15/2008-3/28/2009
Title: A Phase 1, Randomized, Double Blind, Placebo Controlled Study to Assess the Tolerability, Safety, and Pharmacokinetics of Ascending Single Oral Doses of Brexpiprazole in Healthy Subjects

- **Objective:** To assess the safety, tolerability, and PK characteristics of brexpiprazole after single-dose administration.
- **Study Design:** This was a single-center, randomized, double-blind, placebo-controlled, parallel-arm, single ascending-dose trial of brexpiprazole conducted in seven cohorts of 8 healthy subjects (6 active and 2 placebo) each. Doses studied were 0.2 mg, 0.5 mg, 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg. Doses were given under fasted conditions.
- **Sampling Times:**
  Blood samples were collected before dosing (within 15 min prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose.
  Urine samples were collected on Days 1 through 3 during the following intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 16, 16 to 24, 24 to 48, and 48 to 72 hours postdose. All voids in a collection interval were pooled before urine volume was measured and aliquots taken for bioanalytical analysis.
  Pharmogenomics: A 10-mL blood sample was collected predose on Day 1.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411	Brexpiprazole	DM-3411
Method#	6825-271	6825-271	6825-273	6825-273
Matrix	plasma	plasma	urine	urine
Range (ng/mL)	0.3 to 100	0.3 to 100	0.6 to 200	0.6 to 200
Performance	Acceptable	Acceptable	Acceptable	Acceptable

- **Results:**
  Study Population

	All subjects
Treated/Completed/ withdrawn due to AE	56/54/2
Age [Mean (range)]	27 (18,45)
Male/Female	55/1
CYP2D6 URM/EM/IM/PM/Unknown(placebo)	1/29/10/2/14
Race (Caucasian/Black/Asian/other)	42/11/3/0

Pharmacokinetics
Table 1: Mean (SD) Brexpiprazole Plasma Pharmacokinetic Parameters Following Single-dose Administration of Brexpiprazole (0.2 mg to 8 mg) to Healthy Subjects

Reference ID: 3779909

Parameter	0.2 mg (N = 6)	0.5 mg (N = 6)	1 mg (N = 6)	2 mg (N = 6)	4 mg (N = 6)	6 mg (N = 5)	8 mg (N = 5)
C_{max} (ng/mL)	2.84 (0.713)	6.58 (1.16)	12.1 (3.79)	24.6 (5.58)	47.3 (16.4)	72.7 (17.0)	93.0 (48.9)
t_{max} (h)[a]	2.00 2.00-4.00	2.06 1.50-4.00	6.00 2.10-6.27	4.00 4.00-6.10	6.00 4.00-6.03	4.00 2.12-6.00	6.00 1.50-12.0
AUC_t (ng·h/mL)	111 (42.1)	289 (114)	537 (177)	1550 (648)	2370 (1380)	4040 (1680)	5990 (2290)
AUC_∞(ng·h/mL)	143 (56.5)	387 (239)	612 (222)	1940 (989)	2690 (1710)	5040 (2520)	7950 (3310)
$t_{1/2}$ (h)	50.4 (13.2)	54.9 (20.9)	55.4 (14.0)	66.0 (16.2)	48.3 (15.8)	64.8 (25.1)	80.8 (31.7)
CL/F (mL/h)	1550 (496)	1580 (595)	1860 (796)	1280 (622)	1970 (1020)	1490 (796)	1190 (594)
CL_r (mL/h)	0.00 (ND)	0.162 (0.397)	0.590 (0.434)	2.11 (1.29)	1.23 (0.691)	2.08 (0.643)	2.56 (1.67)

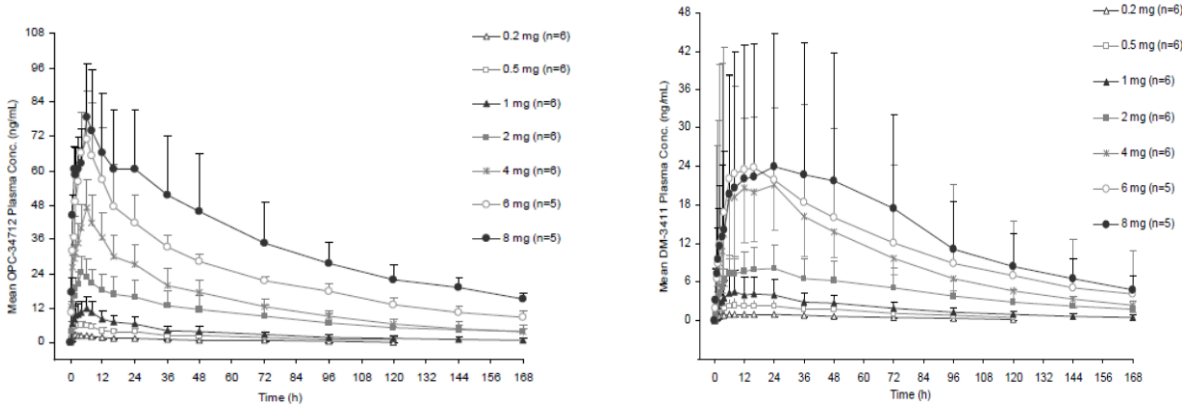
ND: not determined; PK: pharmacokinetic; SD: standard deviation. [a] tmax is median (range). ---source: Table 1.9.2.3.1.2-1 of study report 331-07-201

Table 2: Mean (SD) DM-3411 Plasma Pharmacokinetic Parameters Following Single-dose Administration of Brexpiprazole (0.2 mg to 8 mg) to Healthy Subjects

Parameter	0.2 mg (N = 6)	0.5 mg (N = 6)	1 mg (N = 6)	2 mg (N = 6)	4 mg (N = 6)	6 mg (N = 5)	8 mg (N = 5)
C_{max}(ng/mL)	1.06 (0.484)	2.59 (1.03)	5.87 (3.33)	8.79 (3.40)	22.5 (8.94)	25.6 (17.0)	24.3 (20.6)
t_{max} (h)[a]	16.00 4.00-36.0	10.00 2.00-24.0	12.00 6.00-24.0	24.00 6.00-24.0	24.00 8.00-24.0	16.00 12.0-24.0	24.00 24.0-36.0
AUC_t (ng·h/mL)	72.7 (38.2)	168 (52.9)	324 (143)	773 (385)	1610 (456)	1990 (254)	2390 (1880)
AUC_∞ (ng·h/mL)	110 (44.4)	208 (61.3)	370 (147)	950 (489)	1790 (479)	2420 (167)	2900 (1870)
$t_{1/2}$ (h)	66.5 (15.1)	49.1 (16.3)	55.6 (15.4)	63.8 (15.2)	48.6 (13.6)	63.2 (22.3)	77.5 (33.1)

[a]tmax is presented as median (minimum-maximum). -source: Table 1.9.2.3.1.3-1 of study report

Figure 1**:** Mean (SD) Brexpiprazole (left panel) and DM-3411 (right panel) Plasma Concentration- Time Profiles Following Single-Dose Administration of Brexpiprazole to Healthy Subjects



- **Conclusion:** Brexpiprazole C_{max}, AUC_t, and AUC_∞ increased proportionally to the dose administered.

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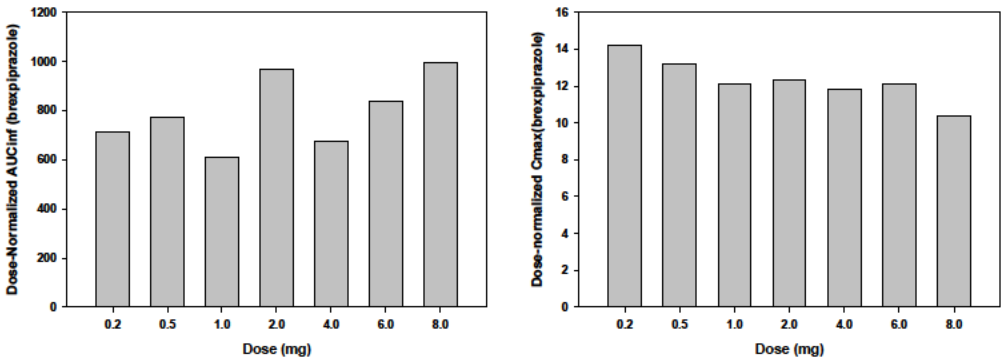
- **Reviewer's Comments:**
  1. Brexpiprazole PK seems to have a large inter-subject variability. The observed % CV from this study varied in the range of 36%-64%. The small sample size and different CYP2D6 genotypes in each dose group could contribute to the observed variability.
  2. % extrapolation in obtaining AUC_{inf} values were mostly less than 25%, except for the 0.5mg dosing group. The accuracy in estimating the PK parameters is acceptable.
  3. Sponsor also collected urine samples. It was found less than 0.22% of the dose administered was excreted as unchanged brexpiprazole, and less than 15% of the dose was excreted as metabolites.
  4. Reviewer agrees that approximate dose proportionality was observed in the dose range of 0.2 mg to 8 mg (Table and Figure below).

Table: PK parameters of brexpiprazole after single dose administration

dose (mg)	0.2	0.5	1	2	4	6	8
C_{max}	2.84	6.58	12.1	24.6	47.3	72.7	83
AUC_{inf}	143	387	612	1940	2690	5040	7950
AUC_t	111	289	537	1550	2370	4040	5990
AUC_{inf} SD	56.5	239	222	989	1710	2520	3310
%CV	39.5	61.8	36.3	51.0	63.6	50.0	41.6
%extrapolation	22.4	25.3	12.3	20.1	11.9	19.8	24.7
dose-normalized AUC_{inf}	715	774	612	970	672.5	840	993.75
dose-normalized C_{max}	14.2	13.2	12.1	12.3	11.8	12.1	10.4

Figure: Dose-normalized AUC (left panel) and Cmax (right panel) for brexpiprazole after single dose administration



3. Mass Balance

Report # 331-07-201 (Arm 2) **Study Period**: 04/15/2008-3/28/2009
Title: A Phase 1, Randomized, Double Blind, Placebo Controlled Study to Assess the Tolerability, Safety, and Pharmacokinetics of Ascending Single Oral Doses of Brexpiprazole in Healthy Subjects

Reference ID: 3779909

- **Objectives:** To obtain information on the mass balance, metabolism, rate and extent of excretion of OPC-34712, and to identify metabolites that had a plasma AUC that was at least 10% of the parent compound AUC and their disposition.
- **Study Design:** The study was a single center, open-label, parallel-arm, single dose trial in healthy subjects. Dosing was conducted in 2 cohorts of 8 subjects each. Subjects were administered a single oral 2-mg dose of ^{14}C-OPC-34712 (< 270 nCi) on Day 1: 8 subjects received the 2-mg dose of ^{14}C-OPC-34712 with the radiolabel inserted in the quinolinone ring and 8 subjects received the 2-mg dose of ^{14}C-OPC-34712 with the radiolabel inserted in the benzothiophene ring. As OPC-34712 is poorly soluble in aqueous solutions, the dose was administered in a pH-adjusted solution. Doses were given under fasting conditions.
- **Sampling Times:**
  Blood samples were collected before dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216/ET hours postdose.
  Urine sample was collected prior to dosing and at every 24 hour intervals through Day 20. Voids collected prior to the end of the collection interval were kept refrigerated. All voids in a collection interval were pooled before urine volume was measured and aliquots taken for bioanalytical analysis.
  Feces sample was collected prior to dosing and at every 24 hour intervals through Day 20. At the end of the collection interval, the number of fecal specimens collected in the interval and the total weight were recorded.
  Pharmacogenomics: A 10-mL blood sample was collected predose on Day 1.
- **Analytical Methods:**
  LC-MS/MS:

Analyte	Brexpiprazole & DM-3411	Brexpiprazole & DM-3411	Brexpiprazole
Matrix	plasma	urine	feces
Range (ng/mL)	0.3 to 100	0.6 to 200	1 to1000
Method	6825-271	6825-273	6825-284
Performance	Acceptable	Acceptable	Acceptable

  Radioactivity: radioactivity in samples was analyzed by acceleration mass spectrometric.
- **Results:**
  Study Population:

	All subjects
Treated/Completed/ withdrawn due to AE	16/15/0
Age [Mean (range)]	32 (19,45)
Male/Female	16/0
CYP2D6 URM/EM/IM/PM	0/14/2/0
Race (Caucasian/Black/Asian/other)	13/2/1/0

  Pharmacokinetics:
  Table 1: Mean (SD) OPC-34712, DM-3411, and DM-3412 Plasma PK Parameters After Single Dose Administration of 2 mg ^{14}C-OPC-3471 to Healthy Subjects

Reference ID: 3779909

Parameters[a]	OPC-34712 (N = 16)	DM-3411 (N = 16)	DM-3412 (N = 16)
C_{max} (ng/mL)	30.9 (5.84)	7.59 (2.31)	0.723 (0.520)
t_{max} (h)[b]	2.02 (1.50-6.00)	8.00 (4.00-24.00)	72.00 (36.00-192.00)
AUC_t (ng·h/mL)	1580 (676)	552 (208)	101 (80.3)
AUC_∞ (ng·h/mL)	1660[c] (856)	547[d] (204)	258[e] (122)
$t_{1/2}$ (h)	69.1[c] (23.8)	35.7[d] (10.1)	130[e] (38.0)
CL/F (mL/h)	1550[c] (937)	ND	ND

ND = not determined. [a]PK parameters for MOP-54522, OPC-34385, and OPC-3952 metabolites not reported as all reported concentrations were BQL (LLQ = 0.300 ng/mL). [b]tmax is presented as median (minimum-maximum). [c]n = 12.[d]n = 9. [e]n = 5.

Total Radioactivity

Table 2: Mean (SD) Total Plasma Radioactivity AUC and Plasma AUC of OPC-34712 and Metabolites After Single Dose Administration of 2 mg ^{14}C-OPC-34712

Parameter[a,b]	Total Plasma Radioactivity (N = 8)	OPC-34712 (N = 8)	DM-3411 (N = 8)	DM-3412 (N = 8)	Total OPC-34712 and Metabolites (N = 8)
Benzothiophene Ring					
AUC_∞ (μMol.h)[c]	8.23 (3.54)	4.24 (1.39)	1.39 (0.358)	0.332 (0.311)	5.96 (1.45)
Percent total radioactivity (%)[b]	ND	54.8 (13.9)	18.3 (5.02)	4.16 (0.311)	77.4 (15.2)
Quinolinone Ring					
AUC_∞ (μMol.h)[c]	6.19 (2.67)	3.81 (2.42)	1.18 (0.527)	0.234 (0.211)	5.22 (2.57)
Percent total radioactivity (%)[b]	ND	58.8 (20.3)	20.2 (6.77)	3.26 (3.06)	82.7 (14.5)

ND = not determined. [a]PK parameters for MOP-54522, OPC-34385 and OPC-3952 metabolites not reported as all reported concentrations were BQL (LLQ = 0.300 ng/mL). [b]Percent total radioactivity calculated as percentage of each analyte versus total plasma radioactivity based on AUC∞ μMol values. [c]OPC-34712 molecular weight (MW) = 433.2; DM-3411 MW = 449.2; and DM-3412 MW = 467.2.

Figure 1: Mean Total Plasma Radioactivity and OPC-34712, DM-3411 and DM-3412 Plasma Concentration-time Profiles Following Single Dose Administration of 2 mg ^{14}C-OPC-34712 (< 270 nCi) to Healthy Subjects

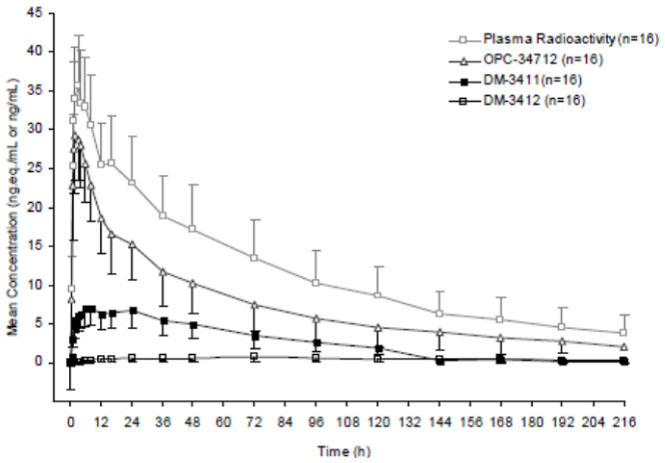


Table 3: Mean (SD) Cumulative Urinary Excretion Parameters of OPC-34712, Metabolites and

Reference ID: 3779909

Radioactivity After Single Dose Administration of 2 mg ^{14}C-OPC-34712 (< 270 nCi) to 480 Hours Postdose in Healthy Subjects

Parameter[a]	Total Radioactivity (N = 16)	OPC-34712 (N = 16)	DM-3411 (N = 16)	DM-3412 (N = 16)	OPC-3952 (N = 16)
A_e (µg, ug-eq)[b]	492 (73.3)	2.85 (2.30)	136 (37.8)	21.7 (16.3)	80.6 (37.4)
f_e (%)[c]	24.6 (3.66)	0.143 (0.115)	6.55 (1.82)	1.00 (0.756)	7.06 (3.27)

[a]Urinary excretion for MOP-54522 and OPC-34385are not reported as all reported concentrations were BQL (LLQ = 0.600 ng/mL). [b]Ae = amount excreted. [c]fe = fraction of dose excreted.

Figure 2: Mean Urinary Radioactivity of OPC-34712 and Metabolites Following Single Dose Administration of 2 mg ^{14}C-OPC-34712 to 480 Hours Postdose to Healthy Subjects

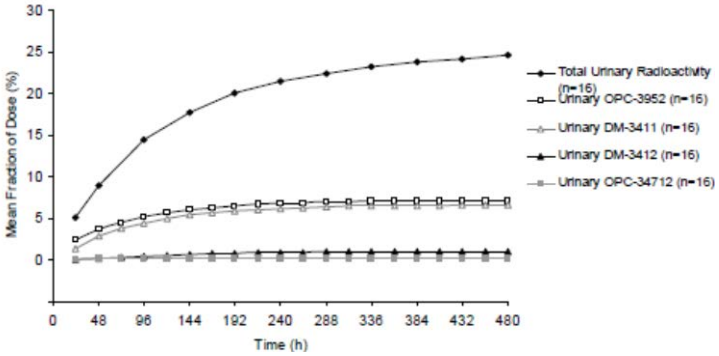


Table 4: Mean (SD) Cumulative Total Fecal Radioactive and OPC-34712 Excretion After Single Dose Administration of 2 mg ^{14}C-OPC-34712 to 480 Hours Postdose in Healthy Subjects

Parameter	Total Radioactivity Feces (N = 12)	OPC-34712 Feces (N = 12)
A_e (ug or µg-eq)[a]	921 (485)	280 (143)
f_e (%)[b]	46.0 (24.2)	14.0 (7.14)

[a]Ae = amount excreted. [b]fe = fraction excreted as a percentage of total dose.

Figure 3: Mean Fecal OPC-34712 Cumulative Fraction of Total Radioactivity Following Single Dose Administration of 2 mg ^{14}C-OPC-34712 to 480 Hours Postdose in Healthy Subjects

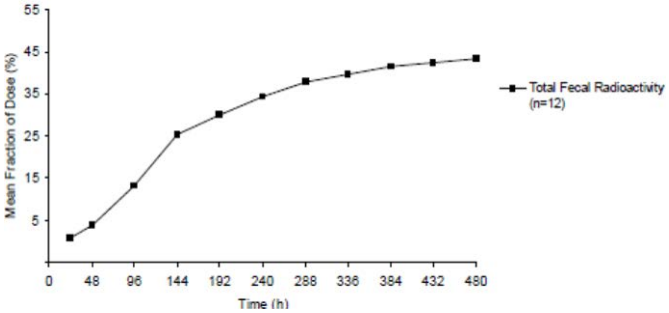


Table 5: Mean (SD) Cumulative Urinary, Fecal and Total Radioactive Excretion of OPC-34712

Parameter	Feces (N = 12)	Urine (N = 16)	Total (N = 12)
Ae (µg-eq)[a]	921 (485)	492 (73.3)	1423 (457)
fe (%)[b]	46.0 (24.2)	24.6 (3.66)	71.1 (24.3)

[a]Ae = amount excreted. [b]fe = fraction excreted as a percentage of total dose.

Table 6: Mean (SD) Protein Binding of OPC-34712 in Healthy Subjects

Reference ID: 3779909

Parameter	Bound (N = 16)	Unbound (N = 16)
Percent (%)	99.8 (0.0365)	0.140 (0.0849)

Table 7: Mean (SD) Whole Blood to Plasma Partition Ratio

Parameter	Hematocrit (%)	Blood/Plasma Ratio[a] (N = 16)	Adjusted Blood/Plasma Ratio[b] (N = 16)
Ratio	43.3 (2.22)	0.617 (0.126)	1.086 (0.224)

- **Conclusions:**
  1) Based on the hematocrit-adjusted ratio of blood to plasma total radioactivity, OPC-34712 does not preferentially bind to red blood cells.
  2) Brexpiprazole was highly protein bound in plasma.
  3) A majority of the total plasma radioactivity was accounted for by OPC-34712, DM-3411, and DM-3412 analytes (77.4% to 82.7%).
  4) Unchanged OPC-34712 recovered in urine and feces constitute less than 1% and 14% of the total radioactivity dose administered, respectively.
  5) Total feces and urine radioactivity was 71.1% of the total dose. Brexpiprazole and metabolites were mainly excreted in feces, followed by urine (46.0% and 24.6%, respectively.
- **Reviewer's Comments:**
  1) Though the recovery of radioactivity is only ~71% of the administered radioactivity (collected up to 480 hr postdose), it is a reasonable recovery. Unreportable fecal samples in some of the subjects partially explained the incomplete recovery.
  2) A total of 16 subjects were included in the study. Comparing to the typical number of 4 to 6 subjects in mass balance studies, the large sample size allowed a better characterization of the excretory and metabolic profiles for brexpiprazole.
  3) The total radioactivity administered to the subjects was <270nCi. Comparing to the typical literature reported 100 µCi for ^{14}C, subjects were exposed to minimal radioactivity.
  4) Protein binding was also evaluated in the study. It was found bexpiprazole is highly protein bound, with >99% bound in plasma. Result from this study is consistent with findings from in vitro study #019405.
  5) It was found that unchanged brexpiprazole was accountable for less than 14% of total radioactivity in the feces. Compared to the high absolute bioavailability (~ 95%), the finding indicated that some brexpiprazole was excreted unchanged into the bile.

4. Multiple Ascending Dose (1)-in Healthy Subjects

Report # 331-08-206 **Study Period**: 10/08/2008-06/11/2009
Title: A Phase 1, Open-label, Multiple-dose, Parallel-group Study to Assess the Pharmacokinetics and Safety of Oral OPC-34712 in Healthy Subjects

- **Objectives:** 1) To determine the steady-state PK of OPC-34712 and its metabolites in plasma following multiple oral doses of OPC-34712 (Arm 1); 2) To determine the safety of OPC-34712 following multiple oral dosing (Arm 2); 3) To determine the effects of dose titration on the safety of OPC-34712 following multiple oral dosing (Arm 3).

ARM 1:

- **Study Design:** Arm 1 of the trial was a single-center, multiple-dose, open-label, parallel-

Reference ID: 3779909

group design. Dosing was conducted at 2 dose levels with 12 subjects at each dose level. The first 12 subjects were assigned to the 0.5-mg dose of OPC-34712 followed by 12 subjects assigned to the 1-mg dose of OPC-34712. The first OPC-34712 dose was administered on Day 1, followed by a 96-hour washout (Days 2 to 5), after which OPC-34712 was administered once daily (QD) for 14 days (Days 5 to 18). A 96-hour washout separated the first dose and the subsequent doses within each dose group. OPC-34712 was administered in the fasted state.

- **Sampling Times:**
  Blood samples for PK analysis were drawn on Day 1 predose (within 10 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hr postdose; at predose were Days 14, 15, 16, and 17; and on Day 18 predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 hours post last dose.
  Urine samples were collected at the following intervals: Day 1 at 0-4, 4-8, 8-12, 12-16, and 16-24 hours postdose; Days 2 through 4 at 0-8, 8-16, and 16-24 hours postdose and Day 18 at 0-4, 4-8, 8-12, 12-16, and 16-24 hours post last dose.
- **Analytical Methods:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Brexpiprazole & DM-3411
Matrix	plasma	urine
Range (ng/mL)	0.3 to 100	0.6 to 200
Method	6825-271	6825-273
Performance	Acceptable	Acceptable

- **Results:**

Study Population:

Brexpiprazole dosing group	0.5 mg	1 mg
Randomized/Completed/ Discontinued Due to AE	12/11/1	12/12/0
Age [Mean ±SD]	30.4±4.4	29.3±7
Male/Female	12/0	12/0
Race (Caucasian/Black/Asian/other)	12/0/0/0	11/1/0/0

Pharmacokinetics

Table 1: Mean (SD) OPC-34712 Plasma PK Parameters Following Single- and Multiple-dose Administration of 0.5 mg or 1 mg of OPC-34712 to Healthy Subjects.

Reference ID: 3779909

Parameter	Single Dose		Multiple Dose	
	0.5 mg (n = 12)	1 mg (n = 12)	0.5 mg (n = 11)	1 mg (n = 11)
C_{max} (ng/mL)	6.85 (1.35)	12.6 (2.59)	27.9 (14.3)	44.7 (18.8)
t_{max} (h)[a]	4.00 (2.00-8.00)	4.00 (2.00-6.05)	4.00 (1.00-16.00)	4.00 (3.00-8.00)
AUC_t (ng•h/mL)	310 (99.6)	545 (186)	ND	ND
AUC_∞ (ng•h/mL)	414[b] (148)	889[b] (412)	ND	ND
AUC_{0-24h} (ng•h/mL)	119 (27.5)	215 (48.5)	506 (299)	827 (351)
$t_{1/2}$ (h)	52.1[b] (11.5)	60.9[b] (21.2)	84.8[c] (39.6)	73.6[c] (20.1)
CL/F[d] (mL/h)	1380[b] (554)	1370[b] (622)	1220 (511)	1500 (666)
CL_r (mL/h)	1.94 (2.91)	6.48 (6.30)	3.56 (1.80)	6.06 (3.23)
$R_{ac}(C_{max})$	ND	ND	4.18 (1.94)	3.44 (1.21)
$R_{ac}(AUC)$[e]	ND	ND	4.33 (2.02)	3.68 (1.13)

ND = not determined; Rac(AUC) = accumulation ratio based on AUC; [b]n = 11. [c]n = 10.
Rac(Cmax) = accumulation ratio based on Cmax. [a]tmax is reported as median (range).
- Source: Table 9.2.3.1-1 in the study report

Table 2: Mean (SD) DM-3411 Plasma PK Parameters Following Single- and Multiple-dose Administration of 0.5 mg or 1 mg of OPC-34712 to Healthy Subjects.

Parameter	Single Dose		Multiple Dose	
	0.5 mg (n = 12)	1 mg (n = 12)	0.5 mg (n = 11)	1 mg (n = 11)
C_{max} (ng/mL)	1.94 (0.893)	4.28 (1.91)	9.75 (3.25)	19.4 (9.34)
t_{max} (h)[a]	16.0 (3.00-24.00)	24.0 (6.00-24.00)	6.00 (3.00-35.2)	4.00 (4.00-8.02)
AUC_t (ng•h/mL)	121 (54.0)	255 (130)	ND	ND
AUC_∞ (ng•h/mL)	201[b] (69.6)	418[c] (239)	ND	ND
AUC_{0-24h} (ng•h/mL)	38.3 (17.3)	80.7 (32.3)	191 (73.2)	395 (207)
$t_{1/2}$ (h)	55.2[b] (13.9)	59.4[c] (21.9)	76.4[d] (32.0)	85.0 (33.2)

ND = not determined. [a]tmax is median (range). [b]n = 10. [c]n = 11. [d]n = 9.
-Source: Table 9.2.3.1-2 in the study report

ARM2:

- **Study Design:** Arm 2 of the trial was a single-center, randomized, single-blind, placebo-controlled, multiple-rising-dose design. At each dose level of OPC-34712 (2 mg, 3 mg, 4 mg, 5 mg, and 6 mg), up to 6 subjects were to be randomized to receive OPC-34712 and 2 subjects were to be randomized to receive placebo (3:1 randomization). Subjects were to receive QD administration of OPC-34712 or placebo for 14 days. OPC-34712 or placebo was administered in the fasted state.
- **Sampling Times:**
  Blood samples for PK analysis were drawn on Day 1 predose (within 10 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hr postdose; at predose (within 10 minutes prior to dosing) on Days 10, 11, 12, and 13; and on/after Day 14 predose and at 0.5, 1, 2 , 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 96, 120, 144, 168, 192, and 216 hr post dose.

Urine samples were collected at the following intervals: Day 1 at 0-4, 4-8, 8-12, 12-16, and 16-24 hr postdose; and Day 14 at 0-4, 4-8, 8-12, 12-16, and 16-24 hr post last dose.

- **Analytical Methods:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Brexpiprazole & DM-3411
Matrix	plasma	urine
Range (ng/mL)	0.3 to 100	0.6 to 200
Method	6825-271	6825-273
Performance	Acceptable	Acceptable

- **Results:**

Study Population:

Brexpiprazole dosing group	2 mg	3 mg	Placebo
Randomized/Completed/ Discontinued Due to AE/Other	6/3/0/3	6/1/2/3	4/2/0/2
Age [Mean ±SD]	28.2±3.5	35.7±6.1	30±5.9
Male/Female	6/0	6/0	4/0
Race (Caucasian/Black/Asian/other)	5/1/0/0	5/1/0/0	3/0/0/1

Pharmacokinetics

Table 1: Mean (SD) OPC-34712 Plasma PK Parameters Following Single- and Multiple-dose Administration of 2 mg and 3 mg of OPC-34712 to Healthy Subjects

Parameter	Day 1		Day 14	
	2 mg (n = 6)	3 mg (n = 6)	2 mg (n = 4)	3 mg (Only one subject completed)
C_{max} (ng/mL)	21.8 (7.70)	31.8 (7.81)	69.3 (15.3)	NR
t_{max} (h)[a]	4.50 (4.00-8.00)	3.50 (1.00-8.00)	4.00 (4.00-24.00)	NR
AUC_{0-24h} (ng•h/mL)	366 (130)	528 (179)	1377 (365)	NR
$t_{1/2}$ (h)	ND	ND	78.5 (13.3)	NR
CL/F[b] (mL/h)	2120 (1230)	2320 (974)	1548 (489)	NR
CL_T (mL/h)	1.88 (0.929)	2.66 (1.58)	2.97 (1.07)	NR
$R_{ac}(C_{max})$	ND	ND	3.83 (0.90)	NR
$R_{ac}(AUC)$[c]	ND	ND	4.43 (1.11)	NR

ND = not determined; NR = no results reported; Rac(AUC) = accumulation ratio based on AUC; Rac(Cmax) = accumulation ratio based on Cmax.
Note: Only one subject completed the 3 mg dose on Day 14.
[a]tmax is reported as median (range). [b]CL/F for single and Multiple dose calculated as Dose/AUC0-24h.
[c]Rac: Accumulation Ratio calculated as the ratio of AUC0-24h after single and multiple dosing
Source: Table 9.2.3.2-1 in the study report

Table 2: Mean (SD) DM-3411 Plasma PK Parameters Following Single- and Multiple-dose Administration of 2 mg and 3 mg of OPC-34712 to Healthy Subjects

Reference ID: 3779909

Parameter	Day 1		Day 14	
	2 mg (n = 6)	3 mg (n = 6)	2 mg (n = 4)	3 mg (Only one subject completed)
C_{max} (ng/mL)	5.50 (2.34)	12.5 (5.07)	29.9 (11.4)	NR
t_{max} (h)[a]	23.9 (12.00-23.9)	12.00 (5.00-24.00)	5.50 (3.00-24.00)	NR
AUC_{0-24h} (ng•h/mL)	106 (49.3)	239 (96.1)	631 (244)	NR
$t_{1/2}$ (h)	ND	ND	76.2 (15.3)	NR

ND = not determined; NR = no results reported. [a]tmax is reported as median (range).
Note: Only one subject completed the 3 mg dose on Day 14.
Source: Table 9.2.3.2-2 in the study report

ARM3:

- **Study Design:** Arm 3 of the trial was a single-center, randomized, single-blind, placebo-controlled, multiple-rising-dose design. In this arm of the trial, the dose of OPC-34712 was titrated up to a fixed dose (3 mg, 4 mg, 5 mg, or 6 mg). Within each cohort, 6 subjects were to receive OPC-34712 and 2 subjects were to receive placebo.
- **Sampling Times:**
  Blood samples for PK analysis were drawn on Day 1 predose (within 10 minutes prior to dosing); Days 10, 11, 12, and 13 of the fixed-dose treatment period: predose (within 10 minutes prior to dosing); Day 14 of the fixed-dose treatment period: predose (within 10 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216/ET hours post last dose.
  Urine samples were collected during the following intervals on Day 14 of the fixed dose treatment period: 0 to 4, 4 to 8, 8 to 12, 12 to 16, and 16 to 24 hours post last dose.
- **Analytical Methods:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Brexpiprazole & DM-3411
Matrix	plasma	urine
Range (ng/mL)	0.3 to 100	0.6 to 200
Method	6825-271	6825-273
Performance	Acceptable	Acceptable

- **Results:**
  Study Population:

Brexpiprazole dosing group	3 mg	Placebo
Randomized/Completed/ Discontinued Due to AE/Sponsor discontinued trial	6/0/2/4	2/0/0/0/2
Age [Mean ±SD]	30.3±5	34.5±6.4
Male/Female	6/0	2/0
Race (Caucasian/Black)	6/0	1/1

  Pharmacokinetics: No PK analysis was performed for this arm of the trial.
- **Sponsor's Conclusions:**
  1) OPC-34712 and DM-3411 metabolite Cmax and AUC PK parameters increased proportionally to the dose administered after single- (0.5 mg to 3 mg) and multiple-dose administration (0.5 mg to 2 mg) of OPC-34712.
  2) Steady state was reached after 12 days of dosing and accumulation ratio of OPC-34712 was 3.4 to 4.4 times after multiple daily administration of OPC-34712.

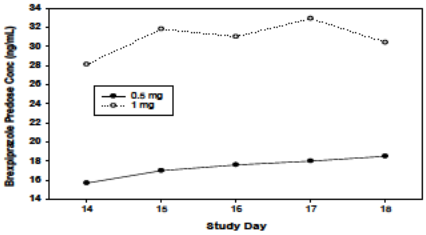
Reference ID: 3779909

3) At steady state, DM-3411 is the most abundant metabolite. Its AUC0-24h represented 46.9% to 52.6% of the AUC0-24h of OPC-34712.

- **Reviewer's Comments:**

1) Metabolites: in addition to DM-3411, sponsor also measured the concentrations of other metabolites. No considerable MOP-54522, OPC-34835, OPC-3952, OPC-54050, or OPC-34318 plasma concentrations were observed in any of the subjects. Brexpiprazole and most of the metabolites except DM-3411 were excreted in the urine at less than 0.4% of the dose. Major excreted urinary analytes were OPC-3952 and DM-3411 with up to approximately 7.8% and 5.5% of the dose administered, respectively. The results indicated that urinary excretion is a minor elimination pathway for brexpiprazole, which is consistent with the results from mass balance study (331-07-201, Arm 2).
2) Steady state evaluation: predose concentration of brexpiprazole was obtained from Day 14 to Day 19 (Figure below, once daily doing started on Day 5), and about ~ 15% of increase was observed from Day 14 to Day 18. Considering the inter-subject PK variability observed (>30%), it is reasonable to conclude that brexpiprazole is approaching steady state after 10-12 days once daily dosing of 0.5 mg or 1 mg brexpiprazole.

Figure: Mean predose concentration of brexpiprazole



3) Because of tolerability and toxicity issues, originally planned doses greater than 2 mg were not tested in healthy volunteers. The MTD for multiple dosing with OPC-34712 in healthy male subjects was determined to be 2 mg.

5. Multiple Ascending Dose (2)-in Schizophrenia Patients

Report # 331-08-205 **Study Period**: 12/15/2008-9/04/2009
Title: A Phase 1, Multi-center, Randomized, Double-blind, Comparator-controlled Study to Assess the Tolerability, Safety, Efficacy, and Pharmacokinetics of Ascending Multiple Oral Doses of OPC-34712 in Adult Subjects with a Diagnosis of Schizophrenia or Schizoaffective Disorder

- **Objectives:** 1) To determine the tolerability and safety of OPC-34712 following multiple ascending oral dosing, 2) to determine the PK profile of OPC-34712 and its metabolite(s) in plasma following multiple ascending oral dosing of OPC-34712, 3) to evaluate, on a preliminary basis, the ability of OPC-34712 to maintain a stable symptom profile in subjects with schizophrenia or schizoaffective disorder.
- **Study Design:** This was a phase 1, multi-center, randomized, double-blind, comparator-controlled multiple dose trial conducted at 2 investigational centers in otherwise healthy male and female subjects with schizophrenia or schizoaffective disorder. The dose

Reference ID: 3779909

escalation for testing was 2, 4, 6, 8, 10, and 12 mg. Dose escalation was conducted in 6 cohorts of 8 subjects (total of 48 subjects). Within each cohort of 8 subjects, 6 subjects were randomized to the test dose of OPC-34712 and 2 subjects were randomized to the control dose (1 mg plus placebo tablets to match the number of tablets in the test dose). Subjects received once daily (QD) oral dosing for 14 days.

- **Blood Sampling Times:**
  Pharmacokinetics**:** A serial of blood samples were taken on Day 1 and Day 14 predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 16 hours postdose. Trough concentrations were measured between Day 2 and Day 13. Blood samples were also taken 24, 36, 48, 72, 96, 120, 144 and 168 hr post dosing on Day 14.
  Pharmacogenomics: A blood sample was collected predose on Day 1.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Method	6825-271	6825-271
Performance	Acceptable	Acceptable

- **Results:**

1. Study Population:

Brexpiprazole dosing group	2mg	4mg	6mg	8mg	10mg	12mg	Pooled 1mg
Randomized/Completed/ Discontinued Due to AE	6/6/0	6/6/0	6/6/0	6/5/1	6/6/0	6/4/1	12/12/0
Age [Mean(SD)]	41.5 (8.4)	38 (11)	45 (7.7)	37.8 (8.8)	40.5 (10.9)	39.7 (9.1)	46.5 (4.6)
Male/Female	6/0	5/1	6/0	6/0	4/2	4/2	8/4
Race (Caucasian/Black/ American Indian)	0/6/0	6/0/0	1/5/0	0/6/0	0/6/0	1/5/0	2/9/1

2. Pharmacokinetics

Table 1: Mean (SD) OPC-34712 Plasma PK Parameters Following Daily Administration of 1 mg to 12 mg of OPC-34712 to Subjects with Schizophrenia or Schizoaffective Disorder.

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Day 1							
Parameter	1 mg (N = 12)	2 mg (N = 6)	4 mg (N = 6)	6 mg (N = 6)	8 mg (N = 6)	10 mg (N = 6)	12 mg (N = 6)
C_{max} (ng/mL)	11.9 (3.9)	23.1 (5.28)	55.1 (12.4)	64.0 (14.1)	86.3 (15.3)	98.5 (43.0)	115 (23.2)
t_{max} (h)[a]	4.64 2.25-8.25	4.50 2.25-8.00	4.12 3.00-5.00	6.00 2.25-8.00	5.12 2.00-12.27	7.00 3.00-16.00	7.00 4.00-12.00
AUC_{0-24h} (ng·h/mL)	191 (58.4)	416 (97.9)	943 (281)	1070 (217)	1450 (226)	1830 (876)	2050 (397)
Day 14							
	1 mg (N = 12)	2 mg (N = 6)	4 mg (N = 5)	6 mg (N = 6)	8 mg (N = 5)	10 mg (N = 6)	12 mg (N = 4)
$C_{ss,max}$ (ng/mL)	39.2 (26.0)	81.2 (28.3)	199 (134)	228 (93.9)	276 (80.7)	200 (185)	382 (30.3)
$C_{ss,min}$ (ng/mL)	21.2 (10.9)	56.8 (23.0)	112 (75.3)	143 (52.3)	171 (59.7)	112 (93.1)	205 (51.7)
$t_{ss,max}$ (h)[a]	3.00 0.50-8.00	2.00 2.00-3.00	8.00 3.00-23.95	14.48 3.00-23.95	4.30 0.50-12.00	7.50 0.00-23.95	3.00 2.00-6.00
AUC_{0-24h} (ng·h/mL)	728 (493)	1620 (594)	3950 (2860)	4530 (1910)	5280 (1790)	4040 (3890)	6950 (797)
$t_{1/2,z}$ (h)	81.14 (32.56)	104.72 (25.49)	86.93[b] (14.50)	95.97 (37.08)	106.83[c] (10.96)	104.78 (44.20)	100.22 (32.02)
CL/F_{ss}[d] (mL/h)	2110 (1650)	1390 (517)	1390 (730)	1620 (876)	1800 (1050)	10700 (17700)	1740 (215)
$R_{ac}(C_{max})$	3.56 (2.73)	3.45 (0.55)	3.34 (1.28)	3.56 (1.36)	3.23 (1.20)	1.88 (1.41)	3.53 (0.43)
$R_{ac}(AUC)$[e]	4.07 (3.39)	3.68 (0.82)	3.45 (1.59)	4.12 (1.27)	3.72 (1.58)	1.55 (1.17)	3.66 (0.58)

[a]tmax is median (range). [b]n=3 [c]n=4 dCL/Fss for Day 14 calculated as dose/AUC0-24h.
[e]Rac: Accumulation ratio calculated as the ratio of AUC0-24h on Day 1 and Day 14
-source: Table 9.2.3.1-1

Table 2: Mean (SD) DM-3411 Plasma PK Parameters Following Daily Administration of 1 mg to 12 mg of OPC-34712 to Subjects with Schizophrenia or Schizoaffective Disorder

Day 1							
Parameter	1 mg (N =12)	2 mg (N =6)	4 mg (N =6)	6 mg (N =6)	8 mg (N =6)	10 mg (N =6)	12 mg (N =6)
C_{max} (ng/mL)	3.32 (1.75)	3.96 (1.47)	13.4 (5.06)	13.8 (4.35)	23.3 (14.5)	26.7 (13.7)	34.8 (23.1)
t_{max} (h)[a]	18.10 4.27-23.95	23.92 5.00-23.95	10.26 4.00-23.95	23.92 4.00-23.95	14.14 5.00-23.95	16.00 12.00-23.95	23.95 23.92-23.95
AUC_{0-24h} (ng·h/mL)	61.5 (31.5)	71.9 (27.3)	261 (104)	259 (85.4)	424 (260)	465 (223)	607 (375)
Day 14							
	1 mg (N = 12)	2 mg (N = 6)	4 mg (N = 5)	6 mg (N = 6)	8 mg (N = 5)	10 mg (N = 6)	12 mg (N = 4)
$C_{ss,max}$ (ng/mL)	15.2 (8.76)	17.3 (2.92)	64.3 (28.4)	57.6 (16.3)	103 (25.9)	71.1 (68.2)	209 (89.9)
$t_{ss,max}$ (h)[a]	6.00 0.00-24.00	3.00 0.50-24.00	8.00 3.00-23.95	23.95 8.00-24.00	8.00 0.50-24.00	8.00 2.00-23.95	4.00 2.00-16.00
AUC_{0-24h} (ng·h/mL)	299 (170)	374 (65.7)	1280 (508)	1190 (381)	1900 (463)	1390 (1390)	4240 (1730)
$t_{1/2,z}$ (h)	72.00 (22.85)	127.05 24.70	55.03[b] (ND)	85.24[c] (34.51)	87.37[d] (13.92)	99.02 (39.70)	88.91 (49.93)

[a]tmax is median (range) [b]n=2 [c]n=5 [d]n=3 (-source: Table 9.2.3.2-1)

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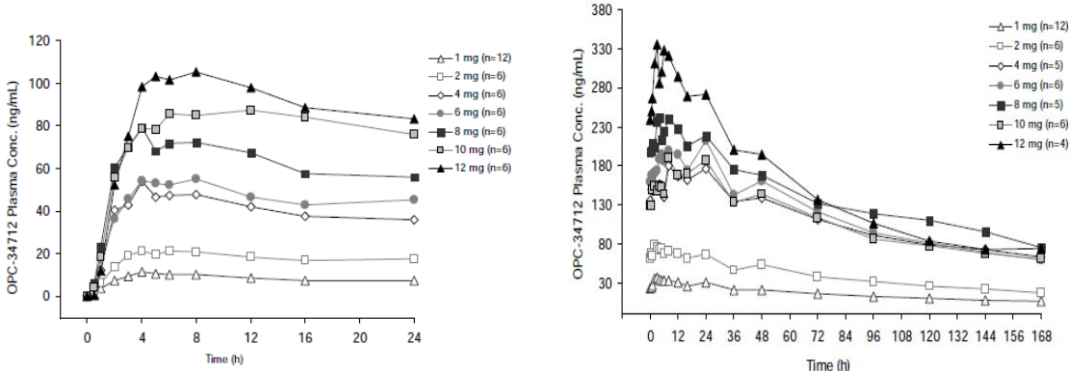
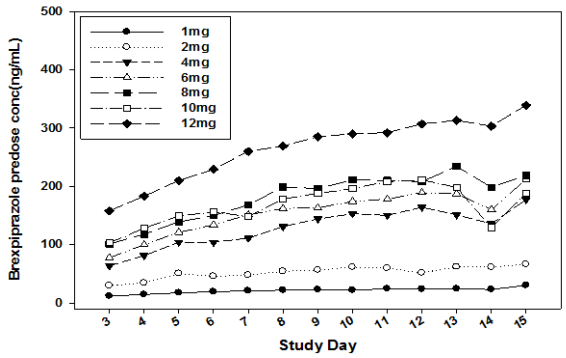
Figure 1: Mean OPC-34712 Plasma Concentration-Time Profiles on Day 1(left) and Day 14(right) Following Administration of 1 to 12 mg of OPC-34712 to Subjects with Schizophrenia or Schizoaffective Disorder



-Sources: Figure 9.2.3.1-1 and Figure 9.2.3.1-2 of the study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusions:**
  1. For OPC-34712 and its DM-3411 metabolite, the C_{max} and AUC PK parameter increased proportionally to the dose administered after multiple daily doses of 1 mg to 12 mg OPC-34712.
  2. At steady state, OPC-34712 and DM-3411 mean terminal elimination half-lif was 95.4 and 89.3 hours, respectively; median T_{max} was 3.00 and 8.00 hours, respectively.
  3. Steady state was reached after 10 days of dosing and the Rac of OPC-34712 was 3.5 to 4.1 times after multiple daily doses of OPC-34712, excluding the 10 mg cohort.
  4. At steady state, DM-3411 was the most abundant metabolite, with its $AUC_{0\text{-}24h}$ representing 42.2% of the $AUC_{0\text{-}24h}$ of OPC-34712.
- **Reviewer's Comments:**
  1) Steady state evaluation: predose concentration time profile indicates brexpiprazole seemed to reach a plateau at about 10 days after multiple daily dosing. Sponsor's conclusion is acceptable.

     Figure: Mean predose concentrations of brexpiprazole after multiple dosing in schizophrenia or Schizoaffective Disorder patients



  2) Dose Proportionality evaluation: Using the mean values obtained on Day 14, it seems to the reviewer that over the range of tested doses (i.e., 1-8 mg), brexpiprazole showed an approximate dose-proportional increase in exposure. From 8 mg above, a less than dose proportional increase was observed. The sponsor explained that one subject in the

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10mg cohort consistently exhibited low concentration of brexpiprazole and DM-3411 on Days 3 to 14, but no deviation of the protocol was identified. The subject was not excluded from analysis.

Table: Ratio of brexpiprazole PK parameters

Dose (mg)	1	2	4	6	8	10	12
Dose Ratio	**1**	**2**	**4**	**6**	**8**	**10**	**12**
AUC Ratio	1	2.2	5.4	6.2	7.3	5.5	9.5
Cmax Ratio	1	2.1	5.1	5.8	7.0	5.1	9.7
Cmin Ratio	1	2.7	5.3	6.7	8.1	5.3	9.7

3) Terminal half- life of brexpiprazole was estimated to be 81 to 106 hr in the study. However, due to relatively short sampling time post dose, only up to 168 hr post the last dose, the estimation was considered marginally reliable.
4) Out of the studied 48 subjects, 4 and 2 of them were found to be ultra-rapid metabolizer and poor metabolizer of CYP2D6, respectively. All others were either extensive (n=33) or intermediate (n=9) metabolizer. The variability in CYP2D6 genotype contributed to the observed variability in the estimated PK parameters.
5) Patients with schizophrenia seemed to have similar PK parameters of brexpiprazole and DM-3411 to healthy volunteers (Trial 331-08-206).

6. Multiple Ascending Dose (3)- in MDD Patients

Report # 331-09-221 **Study Period**: 9/23/2010-01/04/2010
Title: A Phase 1, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ascending High Doses of OPC-34712 as Adjunctive Therapy in the Treatment of Subjects with Major Depressive Disorder

- **Objectives:** 1) To evaluate the safety and tolerability of OPC-34712 (3 and 4 mg/day) as adjunctive therapy to antidepressant therapy (ADT) in the proposed patient population with major depressive disorder. 2) To determine the steady-state pharmacokinetics of OPC-34712 (3 and 4 mg/day) and its metabolites following multiple oral doses.
- **Study Design:** This was a phase 1, multi-center, randomized, double-blind, placebo-controlled, multiple ascending high dose study to assess the safety, tolerability, and PK of OPC-34712 as an adjunctive agent in subjects with MDD between the ages of 18 and 45 years. The safety and tolerability of higher doses (3 and 4 mg/day) were explored within the targeted subject population with MDD. Patients receiving either fluoxetine or paroxetine were grouped in Group 2 of each Cohort and patients receiving other ADT were grouped in Group 1 of each cohort.

Table 1: Study Design Scheme for Patients on Brexpiprazole

Day(s)	**Cohort 1**		**Cohort 2**	
	Group 1	Group 2*	Group 1	Group 2*
1	1mg	0.5mg	2mg	1mg
2	1mg	0.5mg	2mg	1mg
3	2mg	1mg	3mg	1.5mg
4	2mg	1mg	3mg	1.5mg
5-18	3mg	1.5mg	4mg	2mg

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* [a]Subjects receiving either fluoxetine or paroxetine

- **Blood Sampling Times:** On Days 1, 16, and 17 predose (within 10 minutes prior to dosing); on Day 18 predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16; on Days 19 to 26 at 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours post-last-dose.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Method	6825-271	6825-271
Performance	Acceptable	Acceptable

- **Results:**

Study Population:

Brexpiprazole dosing group	1.5mg	2mg	3mg	4mg	placebo
Randomized/Completed/ Discontinued Due to AE	6/2/0	6/4/0	6/5/0	6/4/2	8/7/0
Age [Mean(SD)]	35.3 (6.4)		31.4(7.3)		32.3 (7.9)
Male/Female	8/4		5/7		4/4
Race (Caucasian/Black/ American Indian)	7/4/1		5/7/0		5/3/0

Pharmacokinetics:

Table 2: Mean (SD) OPC-34712 Pharmacokinetic Parameters Following Daily Administration of OPC-34712 with Antidepressants to Subjects with MDD

PK Parameter	Cohort 1		Cohort 2	
	Group 1	Group 2[a]	Group 1	Group 2[a]
	3 mg/day OPC-34712 (n = 6)	1.5 mg/day OPC-34712 (n = 3)	4 mg/day OPC-34712 (n = 4)	2 mg/day OPC-34712 (n = 4)
C_{max} (ng/mL)	146 (44.2)	108 (75.2)	188 (66.3)	125 (28.2)
t_{max} (h)[b]	3.00 (1.00-3.00)	1.00 (1.00-1.00)	2.53 (1.00-3.00)	4.50 (1.00-24.0)
$t_{1/2,z}$ (h)	131 (66.2)	63.7 (ND)	83.6 (22.2)	120 (61.6)
AUC_{τ} (ng·h/mL)	2668 (993)	1899 (1378)	3499 (1495)	2406 (629)
CL_{ss}/F (L/h)	1.29 (0.560)	1.55 (0.869)	1.33 (0.580)	0.874 (0.220)

ND: Not determined [a]Subjects receiving either fluoxetine or paroxetine .[b]Median (minimum-maximum).
Source: Table 9.2.3.2.1-1 of the study report

Table 3: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Daily Administration of OPC-34712 with Antidepressants to Subjects with MDD

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PK Parameter	Cohort 1		Cohort 2	
	Group 1	Group 2[a]	Group 1	Group 2[a]
	3 mg/day OPC-34712 (n = 6)	1.5 mg/day OPC-34712 (n = 3)	4 mg/day OPC-34712 (n = 4)	2 mg/day OPC-34712 (n = 4)
C_{max} (ng/mL)	56.4 (36.1)	38.3 (16.5)	94.2 (40.9)	23.7 (6.12)
t_{max} (h)[b]	3.00 (2.00-3.00)	3.50 (3.00-4.00)	2.03 (2.00-3.00)	4.50 (1.00-8.00)
$t_{1/2,z}$ (h)	84.1 (45.1)	58.6 (ND)	74.2 (13.5)	107 (17.3)
AUC_{τ} (ng·h/mL)	1139 (793)	779 (426)	1889 (827)	470 (134)

ND: Not determined [a]Subjects receiving either fluoxetine or paroxetine [b]Median (minimum-maximum). –-Source: Table 9.2.3.2.2-1 of the study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusion:** OPC-34712 and DM-3411 plasma and PK parameters increased with increasing doses of brexpiprazole following daily administration of brexpiprazole in the dose ranges of 1.5 to 2 mg daily, and 3 to 4 mg daily in patients with MDD receiving ADT concomitantly.
- **Reviewer's Comments:**

1) In addition to evaluate the PK of brexpiprazole after multiple dosing in MDD patients, the sponsor also investigated whether coadministration of CYP2D6 strong inhibitors would increase the exposure of brexpiprazole by inhibiting its metabolism. However, subjects receiving concomitant paroxetine or fluoxetine did not seem to achieve the expected exposure level of brexpiprazole compared to their reference group. Small sample size (n=3/4) and large intersubject variability might contributed to the observation. The results were considered as exploratory. A definitive study (Trial 331-08-208) was conducted to evaluate the effect of strong CYP2D6 inhibitors on the PK of brexpiprazole.
2) The reviewer agrees with the sponsor that linear PK was observed at 1.5mg to 2mg, and 3mg to 4mg for brexpiprazole. However, such conclusion cannot be drawn in the wider dose range from 1.5 mg to 4 mg because of the design of the study (i.e., some patients were on strong CYP2D6 inhibitors while others were not).
3) On face, the PK of brexipiprazole looks different in MDD patients as compared to healthy subjects. It is to note that MDD patients received fluoxetine or paroxetine as concomitant medication. It is anticipated that brexipiprazole exposure should be approximately doubled with decreased clearance due to drug-drug interaction. After adjusting the drug-drug interaction effect, the PK in MDD patients is not expected to be different from healthy volunteers. Overall speaking, brexpiprazole demonstrated similar PK properties in MDD patients, schizophrenic patients, or healthy volunteers.

Table: Mean (SD) Pharmacokinetic Parameters for Brexpiprazole and DM-3411 on Day 14 after Daily Administration of 2 mg Brexpiprazole in Patients with Schizophrenia, MDD, or Healthy Volunteers

Parameters	**MDD* (n=4)**	**Schizophrenia (n=11)**	**Healthy Volunteers (n=4)**
Trial #	331-09-221	331-08-205	331-08-206
Brexpiprazole			
C_{max} (ng/mL)	125 (28.2)	81.2 (28.3)	69.3 (15.3)
T_{max} (hr)	4.5 (1-24)	2 (2-3)	4 (4-24)

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AUC_{0-24} (hr.ng/mL)	2406 (629)	1620 (594)	1377 (365)
Cl/F (L/hr)	874 (220)	1390 (517)	1548 (489)
$T_{1/2}$ (hr)	120 (61.6)	104.7 (25.5)	78.5 (13.3)
DM-3411			
C_{max} (ng/mL)	23.7 (6.12)	17.3(2.9)	29.9 (11.4)
T_{max} (hr)	4.5 (1-8)	3(0.5-24)	5.5 (3-24)
AUC_{0-24} (hr.ng/mL)	470 (134)	374 (65.7)	631 (244)
$T_{1/2}$ (hr)	107 (17.3)	127 (24.7)	76.2 (15.3)

*patients were on fluoxetine or paroxetine; exposure was expected to be doubled for brexpiprazole

7. Multiple Ascending Dose (4)-in Elderly MDD Patients

Report # 331-12-291 **Study Period**: 08/09/2012-05/03/2013
Title: A Phase 1, Multicenter, Randomized, Double-blind, Sequential Cohort, Placebo-controlled Trial to Assess the Safety and Tolerability of Ascending Multiple Oral Doses of Brexpiprazole as Adjunctive Therapy in the Treatment of Elderly Subjects With Major Depressive Disorder

- **Objective:** To assess the safety and tolerability of ascending multiple oral doses of brexpiprazole as adjunctive therapy in the treatment of elderly subjects with major depressive disorder.
- **Study Design:** This was a phase 1, multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose trial planned in 3 sequential cohorts of elderly subjects (age 70 to 85 years old, inclusive) with MDD. Brexpiprazole was administered as an adjunct treatment to the subject's current antidepressant therapy. In each cohort, 6 subjects received brexpiprazole and 2 subjects received placebo as following:

	7 days	7 days	7 days	7 days	7 days	7 days
Cohort 1	*0.5 mg brexpiprazole or placebo QD*	*1 mg brexpiprazole or placebo QD*	**2 mg brexpiprazole or placebo QD**		**3 mg brexpiprazole or placebo QD**	
Cohort 2	*0.5 mg brexpiprazole or placebo QD*	*1 mg brexpiprazole or placebo QD*	**3 mg brexpiprazole or placebo QD**			
Cohort 3[1]	*0.5 mg brexpiprazole or placebo QD*	*1 mg brexpiprazole or placebo QD*	*2 mg brexpiprazole or placebo QD*	**3 mg brexpiprazole or placebo QD**		

[1]Cohort 3 was not conducted. *Italics denotes titration phase*; **bold type denotes fixed dose phase**.

- **Blood Sampling Times:**
  Pharmacokinetics: Blood samples were collected on Day 1 (titration phase) predose and Day 28 (fixed dose phase, Cohort 1) or Day 14 (fixed dose phase, cohort 2) at predose and 2, 6, 12, and 24 hours postdose or at early termination.
  Pharmacogenomics: A blood sample was collected on Day 1.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Method	6825-271	6825-271
Performance	Acceptable	Acceptable

Reference ID: 3779909

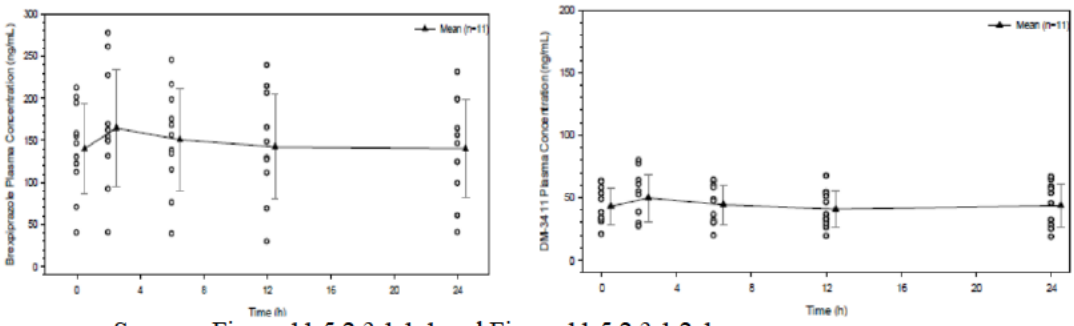
- **Results:**

Study Population:

Brexpiprazole dosing group	Cohort 1	Cohort 2	Placebo pooled
Randomized/Completed/ Discontinued Due to AE	6/6/0	7/5/ unknown	5/4/ unknown
Age [Mean(SD)]	73.2 (4.0)	76 (5.3)	72.6 (1.5)
Male/Female	2/4	2/5	1/4
Race (Caucasian/Black/ American Indian)	4/2/0	6/1/0	5/5/0

Pharmacokinetics

Figure 1: Mean (SD) Brexpiprazole (left) and DM-3411 (right) Plasma Concentrations Following Daily Administration (14 days) of 3-mg Brexpiprazole to Elderly Subjects with Major Depressive Disorder.



-Sources: Figure 11.5.2.3.1.1-1 and Figure 11.5.2.3.1.2-1

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusions:** Brexpiprazole and DM-3411 plasma concentrations in elderly subjects with MDD were comparable to plasma concentrations in adult subjects with MDD in previous clinical trials.
- **Reviewer's Comments:**
  1) PK parameters were not estimated in this study.
  2) A third cohort with an alternative titration scheme was originally planned but not enrolled. Sponsor stated that it was because of the favorable safety and tolerability results from Cohorts 1 and 2.
  3) To evaluate whether the sponsor's conclusion about similarity in exposure to brexpiprazole between the elderly and adult MDD patients, results from Trial 331-09-221 were compared (Table below). Based on the similarity between mean Cmax values. the sponsor's conclusion appears to be reasonable.

	Trial 331-09-221	Trial 331-09-291
MDD Patients age range (years)	18-41	70-84
Brexpiprazole dose (mg)	3	3
Mean $C_{max,ss}$ (ng/mL)	146	165

8. Dose Strength Equivalence

Reference ID: 3779909

Report # 331-10-245 **Study Period**: 03/05/2012-05/29/2012
Title: An Open-label, Randomized, Two-way, Crossover Trial of Dose Strength Equivalency of Oral Doses of Brexpiprazole Long Term Stability Tablets in Healthy Subjects

- **Objective:** To assess the dose strength equivalency of four 1-mg LTSS tablets of brexpiprazole with one 4-mg LTSS tablet of brexpiprazole
- **Study Design:** This was a single center, open-label, randomized, 2-way, crossover trial conducted in 30 healthy male and female subjects. Subjects received a single oral dose of four 1-mg LTSS tablets or one 4-mg LTSS tablet of brexpiprazole on Days 1 and 18 according to the randomization schedule after an overnight fast of at least 10 hours.
- **Blood Sampling Times:**
  Pharmacokinetics**:** Blood samples were collected on Days 1 and 18: predose (within 15 minutes prior to dosing) and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 216, 264, and 312 hours postdose.
  Pharmacogenomics: A blood sample was collected predose on Day 1.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Method	6825-271	6825-271
Performance	Acceptable	Acceptable

- **Results:**

Study Population:

Randomized/Completed/ Discontinued Due to AE/Withdrawal of Consent	30/28/1/1
Age [Mean(SD)]	33 (6.9)
Male/Female	19/11
CYP2D6 URM/EM/IM/PM	1/20/8/1
Race (Caucasian/Black/Asian/Other)	16/12/1/1

Pharmacokinetics

Table 2: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of Four 1-mg LTSS and One 4-mg LTSS Brexpiprazole Tablets to Healthy Subjects

PK Parameter	Four 1-mg LTSS (n = 25)	One 4-mg LTSS (n = 26)
C_{max} (ng/mL)	61.3 (17.0)	57.7 (18.4)
t_{max} (h)[a]	5.00 (2.00-6.00)	5.00 (2.00-6.02)
AUC_t (ng·h/mL)	3840 (1520)	3720 (1810)
AUC_∞ (ng·h/mL)	4230 (1800)[b]	3710 (1730)[b]
$t_{1/2,z}$ (h)	89.4 (31.2)[b]	90.7 (26.3)[b]
CL/F (mL/h/kg)	15.4 (9.30)[b]	17.4 (10.4)[b]

-Source: Table 9.2.3.2.1-1 of study report

Table 3: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of Four 1-mg LTSS and One 4-mg LTSS Brexpiprazole Tablets to Healthy Subjects

Reference ID: 3779909

Comparison	PK Parameter	GMR	90% CI
Four 1-mg LTSS (T) Versus One 4-mg LTSS (R)	C_{max}	1.0514	0.9736-1.1355
	AUC_t	1.0441	0.9918-1.0990
	AUC_∞	1.0595	1.0016-1.1208

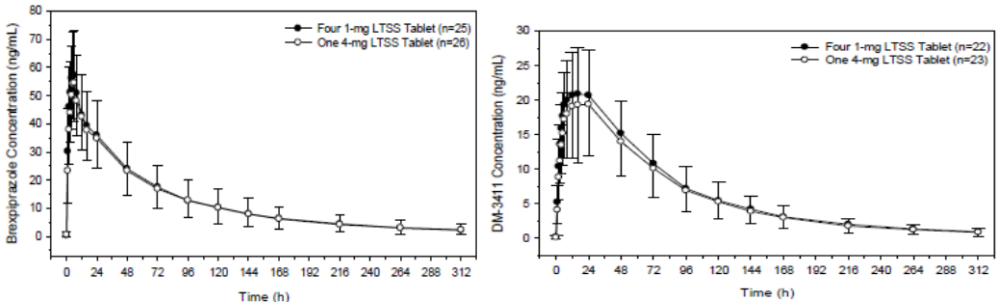
-Source: Table 9.2.3.3.1-1of study report

Table 4: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of Four 1-mg LTSS and One 4-mg LTSS Brexpiprazole Tablets to Healthy Subjects

PK Parameter	Four 1-mg LTSS (n = 22)	One 4-mg LTSS (n = 23)
C_{max} (ng/mL)	22.5 (9.40)	21.1 (8.39)
t_{max} (h)[a]	16.00 (2.00-24.00)	16.00 (5.00-24.00)
AUC_t (ng·h/mL)	2010 (858)	1870 (788)
AUC_∞ (ng·h/mL)	2170 (946)[b]	2010 (864)[c]
$t_{1/2,z}$ (h)	86.6 (32.0)[b]	89.7 (30.8)[c]

-Source: Table 9.2.3.2.2-1of study report

Figure 1: Mean (SD) Brexpiprazole (left panel) and DM-3411 (right panel) Plasma Concentrations Following Administration of Four 1-mg LTSS and One 4-mg LTSS Brexpiprazole Tablets to Healthy Subjects.



-Sources: Figure 11.5.2.3.1.1-1 and Figure 11.5.2.3.1.2-1 of study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusion:** Four 1-mg LTSS tablets and one 4-mg LTSS tablet of brexpiprazole are bioequivalent.
- **Reviewer's Comments:** There were 22 out of 30 subjects that had measurable brexpiprazole predose concentration at Period 2, and 3 of them who predose concentrations greater than 5% of C_{max}. Sponsor performed statistical analysis both without and with those subjects using corrected C_{max} and AUC, and under both scenarios, the 90% CI fell within the BE range of 0.80 to 1.25. Sponsor's conclusion is acceptable.

Reference ID: 3779909

III. Intrinsic Factors

1. Hepatic Impairment

Report # 331-09-225 **Study Period**: 12/20/2010-6/10/2011
Title: A Single-dose, Open-label, Parallel Group, Matched Study Evaluating the Pharmacokinetics of Oral OPC-34712 Tablet in Subjects with Normal Hepatic Function and Hepatically Impaired Subjects
EDR Link
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Objective:
To evaluate the pharmacokinetics (PK) of OPC-34712 in subjects with normal hepatic function and subjects with varying degrees of hepatic impairment.

Test drug/investigational product: Brexpiprazole (OPC-34712). A single oral 2-mg dose of brexpiprazole was administered as two 1-mg tablets (lot 08L70A001B). Brexpiprazole was manufactured by Otsuka Pharmaceutical Co., Ltd. (Japan).

Study design:
This was a multicenter, open-label, parallel-arm trial in 1 group of subjects with normal hepatic function and 3 groups of subjects with varying degrees of hepatic impairment (mild, moderate, and severe). Brexpiprazole (2 mg) was administered as a single oral dose to assess the effect of varying levels of hepatic impairment on brexpiprazole metabolism and elimination. Subjects were encouraged to remain either seated or in a semirecumbent position for the first 6 hours following dosing except during brief periods when protocol-related procedures were performed. After 6 hours postdose, subjects were allowed to ambulate but were to avoid strenuous exercise. On the day of dosing, brexpiprazole was administered in the fasted state (at least 8 hours of fasting) and subjects received lunch approximately 4 hours postdose. Except as part of the dosing procedure, water was allowed up to 1 hour prior to dosing and was restricted until 2 hours postdose. Subjects were confined to the clinic from Days -1 to 8. The trial duration was approximately 6 months. The duration for trial participation for each individual subject, including Screening, In-clinic Period, and Follow-up was 52 days.

Subjects were divided into 4 groups as noted in the table below. Hepatic impairment was assessed using the Child-Pugh Classification scheme. Group 1 (normal hepatic function) consisted of subjects with normal hepatic function as defined in the eligibility criteria.

Number of Subjects Enrolled by Child-Pugh Classification			
Group	Subjects Planned	Subjects Enrolled	Child-Pugh Classification
1	22	23	Normal hepatic function
2	8	8	A (Mild)
3	8	8	B (Moderate)
4	6	6	C (Severe)

Subjects: 45 male or female (non- childbearing potential) subjects with normal hepatic function and hepatic impairment ≥ 18 years of age were enrolled. All 45 completed the study.

Reference ID: 3779909

Diagnosis and Main Criteria for Inclusion: Subjects were male or female; ≥ 18 years of age; within ± 30% of ideal body weight with a minimum body weight of 50 kg; and had a Child-Pugh Classification of normal hepatic function or Grades A (mild), B (moderate), or C (severe). Each subject with normal hepatic function was matched to a hepatically impaired subject for age (within the decile or ± 5 years, whichever was less), sex, and weight (± 15%).

Single-Dose	Non-Randomized	Open-Label	Parallel	Multi-Center	
No. of Groups	☑Normal	☑Mild	☑Moderate	☑Severe	
No. of Subject /Completed	23/23	8/8	8/8	6/6	
Males/Females	18/5	5/3	6/2	6/0	
Age, Mean(range)	56.2 (27-71)	59.5 (50-75)	57.8 (50-63)	51.2 (44-56)	
Dose	2 mg- SD	2 mg- SD	2 mg-SD	2 mg- SD	

- Screening: Screening performed from day -21 to -2 to ensure all subjects met the inclusion criteria and did not meet any exclusion criteria.

- Sampling Times:

PK, plasma:
Blood samples were collected within 15 minutes prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose or at ET. Every effort was made to draw the sample at the appropriate time. If a sample could not have been drawn at the designated time, a window of ± 3 minutes for each blood draw was acceptable, provided the exact time of the draw was recorded.

Urine:
Urine was collected predose (single void) and as 24-hour urine collections through Day 8.

Protein Binding: ☑All ☐Limited (in all subjects):
A blood sample for the determination of plasma protein binding was collected ≤ 30 minutes prior to dosing on Day 1 for all subjects.
Method: Equilibrium dialysis

- Classification of hepatic function is consistent with the FDA Guidance Recommendations: ☑ Yes ☐ No
- Hepatic function was determined via Child-Pugh classification ☑ Yes ☐ No
- Hepatic function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☐ Smoking Status ☐ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

Reference ID: 3779909

Bioanalytical: Plasma and urine concentrations of brexpiprazole and its major metabolite, DM-3411, were quantified by a validated assay using high performance liquid chromatography with tandem mass spectrometry detection. The determination of brexpiprazole protein binding was performed using a rapid equilibrium dialysis device. Aliquots of the plasma and the dialysate were analyzed by liquid scintillation counting and the percent free fraction was calculated.

- Study samples were analyzed within the established stability period: Yes
- Quality control samples range is acceptable: Yes
- Internal standard was used : Yes
- Method was validated prior to use : Yes
- Chromatograms were provided : Yes
- Overall performance is acceptable : Yes

Analyte		Brexpiprazole	DM-3411
Method		LC-MS/MS	LC-MS/MS
Matrix		Plasma	Plasma
Calibration	Range	0.3- 100 ng/mL	0.3- 100 ng/mL
	N	11	12
	R^2 (mean co-efficient)	0.9987	0.9985
Quality Control	% relative std dev.	4.3	4.0

Selection of dose(s)
Single oral doses of brexpiprazole up to 6 mg have been shown to be safe and well tolerated in healthy subjects. However, in order to provide a reasonable margin of safety, a dose of 2 mg was selected for this trial, which provided at least a 3-fold margin of safety in case hepatic impairment resulted in higher exposure to brexpiprazole and its metabolites.

Pharmacokinetics
A summary of “unbound” brexpiprazole plasma PK parameters following administration of 2 mg brexpiprazole to subjects with hepatic impairment (mild, moderate, and severe) and matched subjects with normal hepatic function is presented in the table below:

Table 1: Mean (sd) Unbound Brexpiprazole Plasma Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Subjects With Hepatic Impairment (Mild, Moderate, and Severe) and Matched Subjects With Normal Hepatic Function

Reference ID: 3779909

PK Parameter	Mild[a]		Moderate[a]		Severe[a]	
	Hepatic Impaired (n = 8)	Matched Normal Hepatic Function (n = 8)	Hepatic Impaired (n = 8)	Matched Normal Hepatic Function (n = 8)	Hepatic Impaired (n = 6)	Matched Normal Hepatic Function (n = 6)
$C_{max,u}$ (ng/mL)	0.104 (0.0259)	0.114 (0.0270)	0.0648 (0.0143)	0.0779 (0.0224)	0.0392 (0.0105)	0.0760 (0.0258)
t_{max} (h)[b]	3.50 (1.00-5.00)	3.50 (2.00-5.00)	4.50 (3.00-24.0)	4.50 (1.00-6.00)	5.00 (4.00-24.0)	5.00 (2.00-6.00)
$AUC_{t,u}$ (ng·h/mL)	5.95 (2.58)	4.87 (1.78)	5.41 (1.37)	4.28 (1.95)	3.27 (0.933)	3.63 (1.54)
$AUC_{\infty,u}$ (ng·h/mL)	8.59 (5.29)[c]	5.85 (3.11)[d]	8.50 (2.17)[c]	5.62 (3.13)[c]	3.49 (0.848)[e]	3.36 (0.871)[f]
$t_{1/2,z}$ (h)	103 (51.1)[c]	64.7 (24.6)[d]	116 (25.8)[c]	64.2 (26.2)[c]	81.8 (17.1)[e]	51.4 (8.21)[f]
CL_u/F (mL/h/kg)	5674 (7165)[c]	5730 (2944)[d]	3115 (494)[c]	6768 (5833)[c]	6598 (1182)[e]	7697 (2635)[f]

SD = standard deviation.
[a]Mild: Child-Pugh Classification A; Moderate: Child-Pugh Classification B; Severe: Child-Pugh Classification C.
[b]Median (minimum - maximum).
[c]n = 7.
[d]n = 6.
[e]n = 3.
[f]n = 5.

A summary of "total" brexpiprazole plasma PK parameters following administration of 2 mg brexpiprazole to subjects with hepatic impairment (mild, moderate, and severe) and matched subjects with normal hepatic function is presented in the table below:

Table 2: Mean (sd) of "total" Brexpiprazole Plasma Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Subjects With Hepatic Impairment (Mild, Moderate, and Severe) and Matched Subjects With Normal Hepatic Function

Reference ID: 3779909

PK Parameter	Mild[a]		Moderate[a]		Severe[a]	
	Hepatic Impaired (n = 8)	Matched Normal Hepatic Function (n = 8)	Hepatic Impaired (n = 8)	Matched Normal Hepatic Function (n = 8)	Hepatic Impaired (n = 6)	Matched Normal Hepatic Function (n = 6)
C_{max} (ng/mL)	22.9 (7.60)	26.7 (9.09)	14.6 (4.63)	19.3 (4.98)	7.65 (2.69)	17.7 (7.38)
t_{max} (h)[b]	3.50 (1.00-5.00)	3.50 (2.00-5.00)	4.50 (3.00-24.0)	4.50 (1.00-6.00)	5.00 (4.00-24.0)	5.00 (2.00-6.00)
AUC_t (ng·h/mL)	1271 (569)	1145 (539)	1213 (405)	1048 (422)	622 (163)	817 (306)
AUC_∞ (ng·h/mL)	1827 (1103)[c]	1393 (881)[d]	1960 (579)[c]	1345 (697)[c]	831 (234)[e]	788 (230)[f]
$t_{1/2,z}$ (h)	103 (51.1)[d]	64.7 (24.6)[c]	116 (25.8)[d]	64.2 (26.2)[c]	81.8 (17.1)[e]	51.4 (8.21)[f]
CL/F (mL/h/kg)	24.5 (28.2)[c]	25.4 (12.3)[d]	13.8 (2.72)[c]	26.0 (19.2)[c]	28.2 (6.70)[e]	34.2 (16.3)[f]
CL_r (mL/h/kg)	0.0468 (0.0353)	0.0263 (0.0244)	0.0360 (0.0286)	0.0422 (0.0383)	0.0402 (0.0872)	0.0193 (0.0203)

SD = standard deviation.
[a]Mild: Child-Pugh Classification A; Moderate: Child-Pugh Classification B; Severe: Child-Pugh Classification C.
[b]Median (minimum - maximum).
[c]n = 7.
[d]n = 6.
[e]n = 3.
[f]n = 5.

Table 3: Mean (sd) of "total" DM-3411 plasma PK parameters following administration of 2 mg brexpiprazole to subjects with hepatic impairment (mild, moderate, and severe) and matched subjects with normal hepatic function is presented in the table below:

PK Parameter	Mild[a]		Moderate[a]		Severe[a]	
	Hepatic Impaired (n = 8)	Matched Normal Hepatic Function (n = 8)	Hepatic Impaired (n = 8)	Matched Normal Hepatic Function (n = 8)	Hepatic Impaired (n = 6)	Matched Normal Hepatic Function (n = 6)
C_{max} (ng/mL)	6.49 (5.13)	10.5 (4.26)	3.19 (1.56)	7.25 (4.83)	2.15 (0.880)	7.13 (3.73)
t_{max} (h)[b]	5.00 (2.00-24.0)	6.00 (5.00-24.0)	5.00 (2.00-24.0)	7.00 (2.00-24.0)	4.50 (3.00-24.0)	6.00 (5.00-16.0)
AUC_t (ng·h/mL)	380 (195)	683 (246)	284 (164)	486 (263)	151 (51.4)	479 (226)
AUC_∞ (ng·h/mL)	489 (210)[c]	692 (259)[d]	382 (262)[c]	530 (211)[d]	187 (67.2)[e]	329 (167)[f]
$t_{1/2,z}$ (h)	78.8 (37.6)[c]	59.7 (15.7)[d]	87.2 (45.7)[d]	62.0 (26.4)[d]	84.6 (12.0)[e]	56.1 (8.25)[f]
CL_r (mL/h/kg)	2.67 (1.31)	1.83 (0.828)	3.96 (2.32)	1.90 (0.568)	4.08 (1.68)	2.33 (1.01)

SD = standard deviation.
[a]Mild: Child-Pugh Classification A; Moderate: Child-Pugh Classification B; Severe: Child-Pugh Classification C.
[b]Median (minimum - maximum).
[c]n = 5.
[d]n = 6.
[e]n = 4.
[f]n = 3.

Table 4: The Geometric Mean Ratios and 90% Confidence Intervals for Unbound Brexpiprazole Following Administration of 2 mg Brexpiprazole to Subjects With Hepatic Impairment (Mild,

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Moderate, and Severe) and Matched Subjects With Normal Hepatic Function

Comparison	PK Parameter	GMR	90% CI
Hepatic (Mild) versus Matched Normal Hepatic Function	$C_{max,u}$	0.904	0.707-1.156
	$AUC_{t,u}$	1.166	0.776-1.751
	$AUC_{\infty,u}$	1.255	0.702-2.244
Hepatic (Moderate) versus Matched Normal Hepatic Function	$C_{max,u}$	0.850	0.665-1.087
	$AUC_{t,u}$	1.375	0.915-2.066
	$AUC_{\infty,u}$	1.727	0.977-3.052
Hepatic (Severe) versus Matched Normal Hepatic Function	$C_{max,u}$	0.531	0.399-0.705
	$AUC_{t,u}$	0.929	0.581-1.488
	$AUC_{\infty,u}$	1.041	0.506-2.142
Hepatic versus Normal Hepatic Function	$C_{max,u}$	0.764	0.649-0.901
	$AUC_{t,u}$	1.164	0.916-1.479
	$AUC_{\infty,u}$	1.371	0.976-1.927

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Treatment with 2 mg brexpiprazole was generally safe and well tolerated when administered as a single dose. A total of 13 out of 45 subjects (28.9%) experienced at least 1 treatment-emergent adverse event (TEAE) following brexpiprazole treatment. The mild hepatically impaired group experienced 3 TEAEs reported by 3 out of 8 subjects (37.5%). The moderate hepatically impaired group experienced 5 TEAEs reported by 3 out of 8 subjects (37.5%). The severe hepatically impaired group experienced 1 TEAE reported by 1 out of 6 subjects (16.7%). In comparison, the subjects with normal hepatic function group experienced 6 TEAEs reported by 6 out of 23 subjects (26.1%). All TEAEs were mild or moderate in intensity. The most common TEAEs (incidence ≥ 2 subjects overall) included headache, fatigue, and somnolence. No serious TEAEs were reported during the trial and no subject discontinued trial medication due to a TEAE. Overall, there was no meaningful difference in the types or frequencies of the TEAEs reported by the hepatically impaired subjects and the subjects with normal hepatic function. No clinically meaningful changes from baseline over time or trends were noted in clinical laboratory tests, vital sign assessments, or ECGs. No incidences of suicidal ideation or suicidal behavior were observed or reported during the trial.

Conclusions

- No dose adjustment for brexpiprazole appears to be needed in subjects with mild, moderate, or severe hepatic impairment. However, with some increase in exposure with hepatic impairment doses greater than 2 mg might need to be used with caution.
- Administration of 2 mg brexpiprazole was generally safe and well tolerated in both subjects with normal hepatic function and hepatically impaired subjects.
- No clinically meaningful changes from baseline over time or trends in clinical laboratory test results, vital sign assessments, or ECGs were noted.

Comments

The Office of Clinical Pharmacology has reviewed the study report and agrees with the

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sponsor's analysis.

2. Renal Impairment

Report # 331-09-226 **Study Period**: 01/14/2011-01/05/2012
Title: A Single-dose, Open-label, Parallel-group, Matched Trial Evaluating the Pharmacokinetics of Oral OPC-34712 Tablets in Subjects with Normal Renal Function and Renally Impaired Subjects
EDR Link
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Objective:
Primary: The primary objective was to determine the effect of renal impairment on the pharmacokinetics (PK) of OPC-34712 following a single 3-mg oral dose.

Secondary: The secondary objective was to assess the safety of OPC-34712 in subjects with renal impairment following administration of a single 3-mg oral dose.

Test drug/investigational product:
A single oral 3-mg dose of brexpiprazole was administered as three 1-mg tablets (lot 08L70A001B) on Day 1. Brexpiprazole was manufactured by Otsuka Pharmaceutical Co., Ltd. (Japan).

Study design:
This was an open-label, multicenter, parallel-arm, single-dose trial in 2 groups: 1 group of subjects with normal renal function and 1 group of severely renally impaired subjects. Subjects were confined to the clinical research facility from Day −2 until Discharge on Day 8 after completion of all scheduled assessments. The trial duration was approximately 12 months. The duration for trial participation for each individual subject, including Screening, In-clinic Period, and Follow-up, was 54 days.

Subjects were divided into 2 groups based on their creatinine clearance (CL_{cr}) levels as noted below.

Group	Subjects Planned	Subjects Enrolled	Renal Function Classification
1	10	9	Normal renal function (Estimated CL_{cr} > 80 mL/min)
2	10	10	Renally impaired (Estimated CL_{cr} < 30 mL/min and not requiring dialysis)

Subjects within ± 35% of their ideal body weight (minimum body weight of 50 kg) were enrolled. Healthy subjects with normal renal function were matched to a renally impaired subject for age (within the decile or ± 5 years, whichever was less), gender, and weight (± 15%).

Subjects:

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19 subjects (9 subjects with normal renal function and 10 subjects with severe renal impairment) were enrolled. Nineteen subjects were included in the safety analysis and completed the trial.

Diagnosis and Main Criteria for Inclusion:
Male or female (nonchildbearing potential) subjects were ≥ 18 years of age; within ± 35% of ideal body weight with a minimum body weight of 50 kg; and had a renal function classification of normal (estimated CL_{cr} > 80 mL/min) or renally impaired (estimated CL_{cr} < 30 mL/min and not requiring dialysis).

Single-Dose	Non-Randomized	Open-Label	Parallel	Multi-Center	
No. of Groups	☑Normal	☐Mild	☐Moderate	☑Severe	
No. of Subject /Completed	9/9			10/10	
Males/Females	6/3			7/3	
Age, Mean(range)	58.8 (36-69)			62.9 (39-81)	
Dose	3 mg- SD			3 mg- SD	

Screening:
Subjects were screened between Days −23 and −3, and if the subjects met the inclusion criteria and none of the exclusion criteria they were admitted to the trial center on Day −2 for 24-hour urine collection for creatinine clearance (CLcr) calculation. Subjects were assigned a unique identification number and administered trial medication on Day 1. Blood samples for PK analysis were collected on Days 1 through 8

- Sampling Times:

PK, plasma:
Blood samples were to be collected on Day 1 at predose (within 15 minutes of dosing) and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose or at early termination. Every effort was made to draw the sample at the appropriate time. If a sample could not have been drawn at the designated time, a window of ☐☐ 3 minutes for each blood draw was acceptable, provided the exact time of the draw was recorded.

Urine:
Brexpiprazole and its metabolite, DM-3411, concentrations in urine and urine volume were measured. Urine was collected predose (single void; subjects emptied bladder prior to dosing) and at intervals of 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours postdose.

Protein Binding: ☑All ☐Limited (in all subjects):
A blood sample for the determination of plasma protein binding was collected
☐☐ 30 minutes prior to dosing on Day 1 for all subjects.
Method: Equilibrium dialysis

- Classification of renal function is consistent with the FDA Guidance Recommendations:

☐ Yes ☑ No
Renal impairment guidance document suggests normal subjects should have renal function

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with CLcr ≥ 90 mL/min. However, the sponsors used a lower cut-off of ≥ 80 mL/min of CLcr for normal renal function.

- Renal function was determined via estimated creatinine clearance (CLcr) ☑ Yes ☐ No
- Renal function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☐ Smoking Status ☐ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

Bioanalytical: Plasma and urine concentrations of brexpiprazole and its major metabolite, DM-3411, were quantified by a validated assay using high performance liquid chromatography with tandem mass spectrometry detection. The determination of brexpiprazole protein binding was performed using a rapid equilibrium dialysis device. Aliquots of the plasma and the dialysate were analyzed by liquid scintillation counting and the percent free fraction was calculated.

- Study samples were analyzed within the established stability period: Yes
- Quality control samples range is acceptable: Yes
- Internal standard was used : Yes
- Method was validated prior to use : Yes
- Chromatograms were provided : Yes
- Overall performance is acceptable : Yes
-

Criteria for Evaluation:

Pharmacokinetics: For brexpiprazole and its major metabolite, DM-3411, the following PK parameters were estimated: unbound maximum (peak) plasma concentration ($C_{max,u}$; brexpiprazole only), unbound area under the plasma concentration-time curve to the last observable concentration ($AUC_{t,u}$; brexpiprazole only), unbound area under the plasma concentration-time curve to infinity ($AUC_{\infty,u}$; brexpiprazole only), maximum (peak) plasma concentration (C_{max}), area under the plasma concentration-time curve to the last observable concentration (AUC_t), area under the plasma concentration-time curve to infinity (AUC_∞), time to maximum (peak) plasma concentration (t_{max}), terminal-phase elimination half-life ($t_{1/2,z}$), apparent clearance of drug from plasma after extravascular administration (CL/F; brexpiprazole only), apparent unbound clearance of drug from plasma after extravascular administration (CL_u/F; brexpiprazole only), cumulative amount of drug excreted into urine ($A_{e,u}$), fraction of the systemically available drug excreted into the urine ($f_{e,u}$), and renal clearance (CL_r).

Safety: Reported adverse events, vital signs, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), neurological examinations, and clinical laboratory tests were assessed for safety.

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Analyte		Brexpiprazole	DM-3411	
Method		LC-MS/MS	LC-MS/MS	
Matrix		Plasma	Plasma	
Calibration	Range	0.3- 100 ng/mL	0.3- 100 ng/mL	
	N	11	12	
	R^2 (mean co-efficient)	0.9987	0.9985	
Quality Control	% relative std dev.	4.3	4.0	
	% accuracy	111.1	91.5	

Selection of dose(s)

Single oral doses of brexpiprazole up to 6 mg have been shown to be safe and well tolerated in healthy subjects. Based on available data, brexpiprazole plasma concentrations in subjects with severe renal impairment were not expected to be significantly different than in subjects with normal renal function. However, in order to provide a reasonable margin of safety, a dose of 3 mg was selected for this trial, which provided at least a 2-fold margin of safety in case renal impairment resulted in higher exposure to brexpiprazole and its metabolites.

Pharmacokinetics

A summary of brexpiprazole plasma PK parameters following administration of 3 mg brexpiprazole to subjects with normal renal function and severe renal impairment are presented in the table below:

Table 1: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 3 mg Brexpiprazole to Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

PK Parameter	Renally Impaired (N = 10)	Normal (N = 9)
$C_{max,u}$ (ng/mL)	0.198 (0.0702)	0.195 (0.0662)
$AUC_{t,u}$ (ng·h/mL)	13.3 (6.26)	8.17 (1.37)
$AUC_{\infty,u}$ (ng·h/mL)	18.0 (8.72)[a]	9.58 (2.26)[a]
CL_u/F (mL/h/kg)	0.0686 (0.0336)[a]	0.110 (0.0493)[a]
f_u (%)	0.492 (0.0346)	0.476 (0.0525)
C_{max} (ng/mL)	41.1 (16.5)	41.0 (13.2)

Reference ID: 3779909

PK Parameter	Renally Impaired (N = 10)	Normal (N = 9)
t_{max} (h)[b]	4.00 (2.00-8.00)	4.00 (1.00-8.00)
AUC_t (ng·h/mL)	2750 (1370)	1720 (269)
AUC_∞ (ng·h/mL)	3800 (1970)[a]	2050 (510)[a]
CL/F (mL/h/kg)	14.2 (6.46)[a]	23.0 (8.05)[a]
$t_{1/2,z}$ (h)	87.4 (28.9)[a]	71.7 (23.8)[a]
CL_r (mL/h/kg)	0.118 (0.0766)[c]	0.0439 (0.0359)
$f_{e,u}$ (%)	0.690 (0.516)[c]	0.189 (0.179)

SD = standard deviation.
[a]n = 7.
[b]Median (minimum-maximum).
[c]n = 9.

A summary of DM-3411 plasma PK parameters following administration of 3 mg brexpiprazole to subjects with normal renal function and severe renal impairment are presented in the table below.

Table 2: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 3 mg Brexpiprazole to Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

PK Parameter	Renally Impaired (N = 10)	Normal (N = 9)
C_{max} (ng/mL)	19.8 (12.3)	18.2 (6.24)
t_{max} (h)[a]	30.0 (3.00-144)	12.0 (8.00-24.0)
AUC_t (ng·h/mL)	2080 (1230)	1410 (423)
AUC_∞ (ng·h/mL)	ND	1730 (566)[b]
$t_{1/2,z}$ (h)	ND	74.9 (38.5)[b]
CL_r (mL/h/kg)	0.683 (0.471)[c]	1.38 (0.883)
$f_{e,u}$ (%)	2.55 (1.19)[c]	3.91 (1.66)

ND = Not determined; SD = standard deviation.
[a]Median (minimum-maximum).
[b]n = 7.
[c]n = 9.

The geometric mean ratios (GMR) and 90% CI for unbound brexpiprazole Cmax,u, AUCt,u, and AUC□,u following administration of 3 mg brexpiprazole to subjects with normal renal function and severe renal impairment are presented in the table below.

Table 3: Geometric Mean Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters of Unbound Brexpiprazole Following Administration of 3 mg Brexpiprazole to Subjects With Severe Renal Impairments and Subjects With Normal Renal Function

Comparison	PK Parameter	GMR	90% CI
Severe renal impairment (Test) versus normal renal function (Reference)	$C_{max,u}$	1.011	0.765, 1.335
	$AUC_{t,u}$	1.477	1.123, 1.942
	$AUC_{\infty,u}$	1.723	1.261, 2.354

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Reference ID: 3779909

Treatment with 3 mg brexpiprazole was generally safe and well tolerated when administered as a single dose to subjects with normal renal function and subjects with renal impairment. A total of 8 out of 19 subjects (42.1%) experienced at least 1 treatment-emergent adverse event (TEAE) following brexpiprazole treatment. Five out of 10 subjects (50.0%) experienced 9 TEAEs in the renally impaired group. Three out of 9 subjects (33.3%) experienced 3 TEAEs in the normal renal function group. Eleven of the 12 total TEAEs were mild in intensity. One severe TEAE of orthostatic hypotension that was potentially drug-related was reported by 1 subject in the renally impaired group. The most common TEAEs (incidence ≥ subjects) reported in the renally impaired group were somnolence (3/10 subjects, 30.0%) and orthostatic hypotension (2/10 subjects, 20.0%). No TEAE was reported by more than 1 subject each in the normal renal function group. One subject in the normal renal function group experienced a vital sign-related TEAE of hypotension. No serious TEAEs were reported during the trial, and no subject discontinued trial medication due to a TEAE. No clinically meaningful changes from baseline over time in clinical laboratory test results, vital sign assessments, or ECGs were noted.
No incidences of suicidal ideation or suicidal behavior as measured by the C-SSRS were observed or reported during the trial, and no abnormal neurological examination findings were reported.

Conclusions

- For AUCα,u, the GMRs and the 90% CI in subjects with severe renal impairment versus subjects with normal renal function were 1.7 and [1.3-2.4], respectively.
- Additionally, the ratio of AUCt for the major metabolite DM-3411 was increased by around 50% in severe renal impaired subjects compared to normal
- Administration of 3 mg brexpiprazole was generally safe and well tolerated in subjects with normal renal function and subjects with renal impairment. There were no apparent differences in the safety profile between the subjects with normal renal function and subjects with renal impairment.
- No clinically meaningful changes from baseline over time in clinical laboratory test results, vital sign assessments, or ECGs were noted.

Comments

The Office of Clinical Pharmacology has reviewed the study report and agrees with the sponsor's analysis.
With the increase in drug concentration (around 72% increase in exposure of brexpiprazole) in the severe renal impaired subjects compared to normal subjects, it is recommended that "dose reduction" might be required for renally impaired patients.

3. Age & Gender

Report # 331-10-224 **Study Period**: 5/18/11 – 10/11/11
Title: A Open-Label, Single-dose Trial of the Tolerability, Safety, and Pharmacokinetics of Orally Administered OPC-34712 Tablets in Healthy Adult and Elderly Male and Female Subjects

Reference ID: 3779909

- **Objectives:** To determine the tolerability, safety, and pharmacokinetics (PK) of OPC-34712 in healthy adult and elderly subjects (male and female) following single dose administration of OPC-34712

- Study design: Open-label, single-dose trial conducted in 48 healthy non-smoking adult and elderly male and female subjects. Twenty-four (24) subjects were between 18 and 45 years of age, inclusive [12 male and 12 female subjects] and 24 subjects ≥ 65 years of age 12 male subjects and 12 female subjects were enrolled. Subjects received a single oral 2-mg brexpiprazole dose on Day 1 with 240 mL water. Subjects were administered the brexpiprazole dose in the fasted state (at least 8 hours of fasting) and no food was allowed for 4 hours postdose. Except as part of the dosing procedure, water was restricted from 1 hour prior to dosing until 2 hours postdose. Subjects were housed in the clinic from Day −1 until discharge on Day 9 after completion of all scheduled assessments. Blood samples for PK analysis were collected through Day 9.

To establish bioequivalence for the primary PK parameters between the 2 age groups within each gender group and the 2 gender groups within each age group, 90% CI for the difference in the means of the log-transformed data was calculated using an analysis of variance with main effect terms for age (2 levels) and gender (2 levels) and age by gender interaction term. The antilog of the CI derived from the previous step provided a 90% CI for the ratio of the geometric means for each comparison. Bioequivalence was claimed for a PK parameter if the 90% CI for the ratio of the geometric means of the PK parameter was contained within the interval (0.5, 2.0).

- **Sampling Times (PK, plasma):** Blood samples for determination of brexpiprazole and DM-3411 were collected before dosing and at 1, 2, 3, 4, 6, 8, 12 , 16, 24, 48, 72, 96, 120, 144, 168 and 192 hours after dosing.
- **Analytical Method:** plasma samples were analyzed using LC-MS/MS .
  The performance of the analytical method is acceptable Yes ☑ No ☐
  Calibration curve range: 0.3 to 100 ng/mL
  Lower limit of quantification: 0.3 ng/mL

Table 1: Regression Parameters obtained for OPC-34712 and Metabolite in Human Plasma During Method Validation

Analyte	Linear Range (ng/mL)	Mean Slope ±SD (10^{-2})	Mean Intercept (10^{-3})	Mean Correlation Coefficient
OPC−34712	0.300−100	7.91±1.23	-1.63	0.9987
DM−3411	0.300−100	3.01±0.157	-0.900	0.9985

Table 2: Precision and Accuracy Data Obtained for OPC-34712 and Metabolite QC Samples in Human Plasma During Method Validation

Analyte	QC Sample Concentration (ng/mL)					
	0.900		10.0		75.0	
	%RSD	%Accuracy	%RSD	%Accuracy	%RSD	%Accuracy
OPC−34712	3.5	111.1	4.3	105.0	2.4	110.0
DM−3411	4.0	97.1	1.8	91.5	3.3	97.3

%RSD: percent relative standard deviation
%Accuracy: calculated results divided by theoretical (nominal) concentration x 100

Reference ID: 3779909

- **Results:**

1. Study Population :

Overall, subjects were mostly White (35/48 subjects; 72.9%); the remaining subjects were Black or African American (13/48 subjects; 27.1%). More elderly subjects were White (elderly male: 12/12 subjects [100.0%]; elderly female: 10/12 subjects [83.3%]) compared to adult subjects (adult male: 6/12 subjects [50.0%]; adult female: 7/12 subjects [58.3%]). The overall mean age was 51.7 years (range, 20 to 80 years). The overall mean weight was 75.34 kg (range 51.0 to 99.6 kg). The mean weight of adult male subjects was higher than the mean of elderly male subjects (adult male: 86.00 kg, range 66.4 to 99.4 kg; elderly male: 81.18 kg, range 58.8 to 99.6 kg); the mean weight of adult female subjects was lower than elderly female subjects (adult female: 63.81 kg, range 51.0 to 87.9 kg; elderly female: 70.36 kg, range 51.8 to 90.9 kg).

Table 3: Demographics and Baseline Characteristics

Parameter	Adult Male (n = 12)	Adult Female (n = 12)	Elderly Male (n = 12)	Elderly Female (n = 12)	Overall (n = 48)
Sex (n [%])					
Female	0 (0.0)	12 (100.0)	0 (0.0)	12 (100.0)	24 (50.0)
Male	12 (100.0)	0 (0.0)	12 (100.0)	0 (0.0)	24 (50.0)
Race (n [%])					
White	6 (50.0)	7 (58.3)	12 (100.0)	10 (83.3)	35 (72.9)
Black or African American	6 (50.0)	5 (41.7)	0 (0.0)	2 (16.7)	13 (27.1)
Ethnicity (n [%])					
Hispanic or Latino	3 (25.0)	6 (50.0)	1 (8.3)	2 (16.7)	12 (25.0)
Not Hispanic or Latino	9 (75.0)	6 (50.0)	11 (91.7)	10 (83.3)	36 (75.0)
Age (years)					
Mean (SD)	30.3 (8.3)	36.5 (6.8)	70.1 (4.2)	69.8 (4.3)	51.7 (19.5)
Range	20 - 44	25 - 44	66 - 77	65 - 80	20 - 80
Weight (kg)					
Mean (SD)	86.00 (10.29)	63.81 (12.18)	81.18 (12.58)	70.36 (11.08)	75.34 (14.26)
Range	66.4 - 99.4	51.0 - 87.9	58.8 - 99.6	51.8 - 90.9	51.0 - 99.6
Height (cm)					
Mean (SD)	180.6 (8.4)	157.6 (8.0)	176.2 (6.4)	162.4 (6.8)	169.2 (12.0)
Range	172 - 198	142 - 167	163 - 186	150 - 172	142 - 198
BMI (kg/m^2)					
Mean (SD)	26.38 (2.62)	25.58 (3.63)	26.08 (3.09)	26.68 (3.85)	26.18 (3.25)
Range	22.2 - 30.6	19.9 - 31.5	22.1 - 30.9	20.0 - 31.2	19.9 - 31.5

SD = standard deviation.

2. Pharmacokinetics:

Figure 1: Mean (SD) Brexpiprazole Plasma Concentrations Following Administration of 2 mg Brexpiprazole to Healthy Adult and Elderly Subjects Stratified by Gender (Male or Female)

Reference ID: 3779909

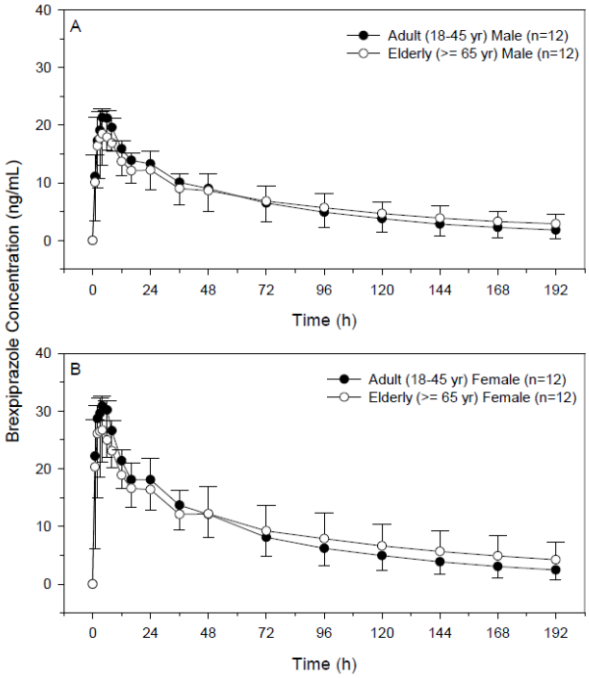
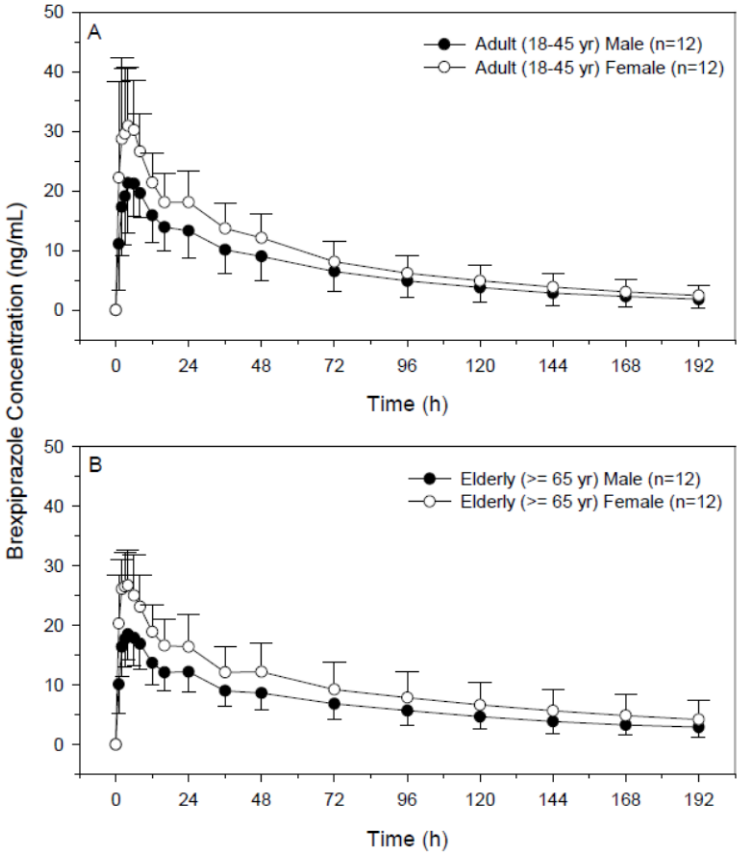
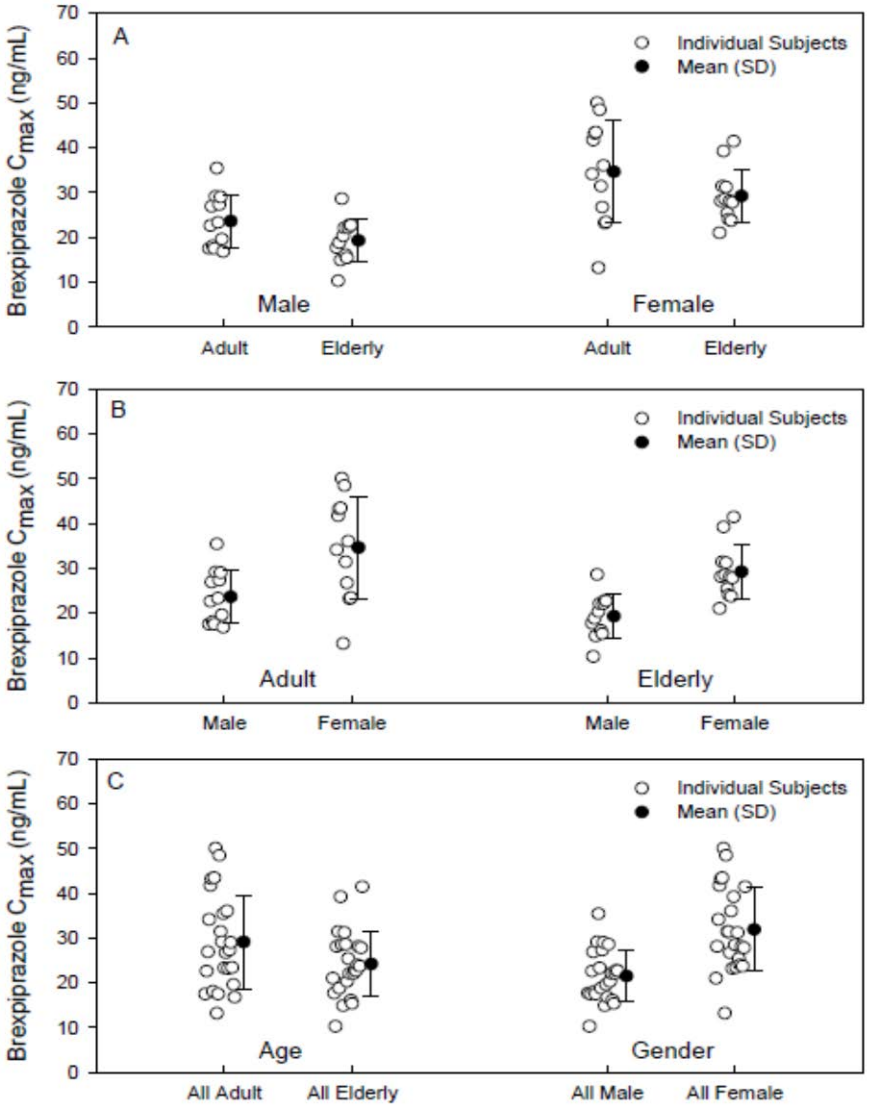


Figure 2: Mean (SD) Brexpiprazole Plasma Concentrations Following Administration of 2 mg Brexpiprazole to Healthy Male and Female Subjects Stratified by Age (Adult or Elderly)



Reference ID: 3779909

Figure 3: Scatter Plots of Individual and Mean (SD) Brexpiprazole Cmax Following Administration of 2-mg Brexpiprazole to Healthy Adult (18 to 45 years) and Elderly (greater than 65 years) Male and Female Subjects



Reference ID: 3779909

Figure 4: Scatter Plots of Individual and Mean (SD) Brexpiprazole AUC∞ Following Administration of 2-mg Brexpiprazole to Healthy Adult (18 to 45 years) and Elderly (greater than 65 years) Male and Female Subjects

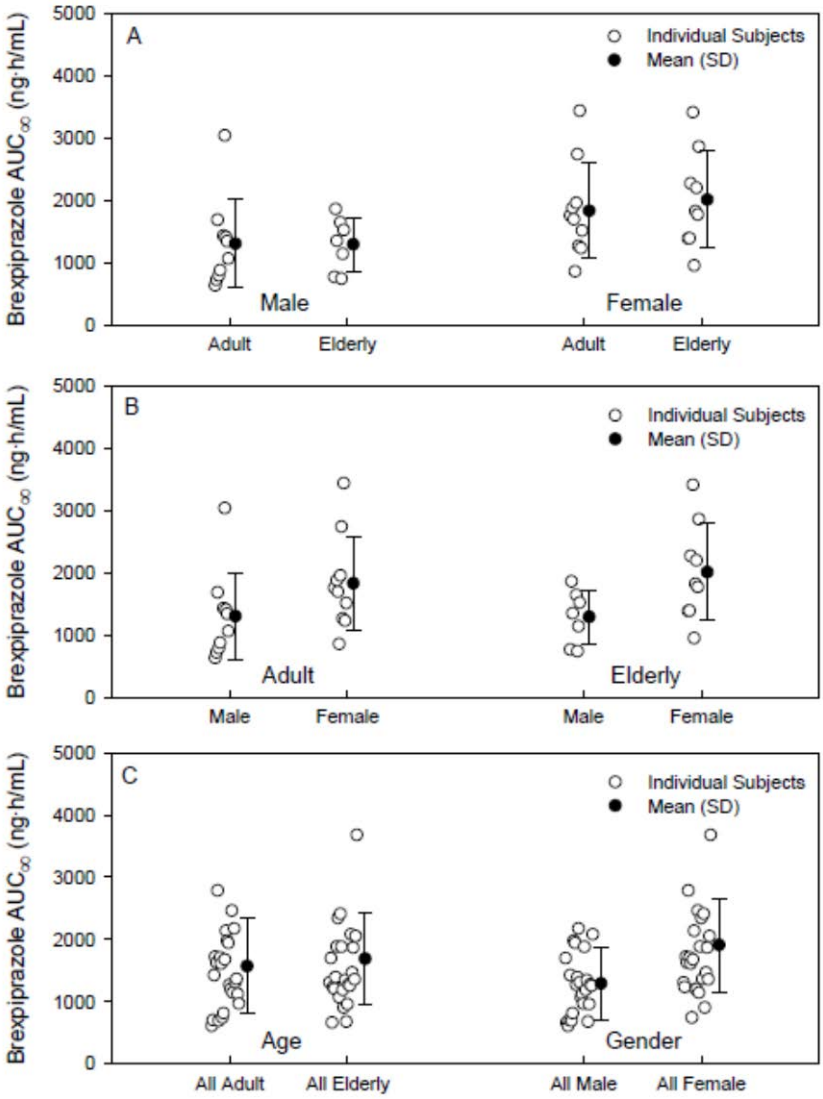
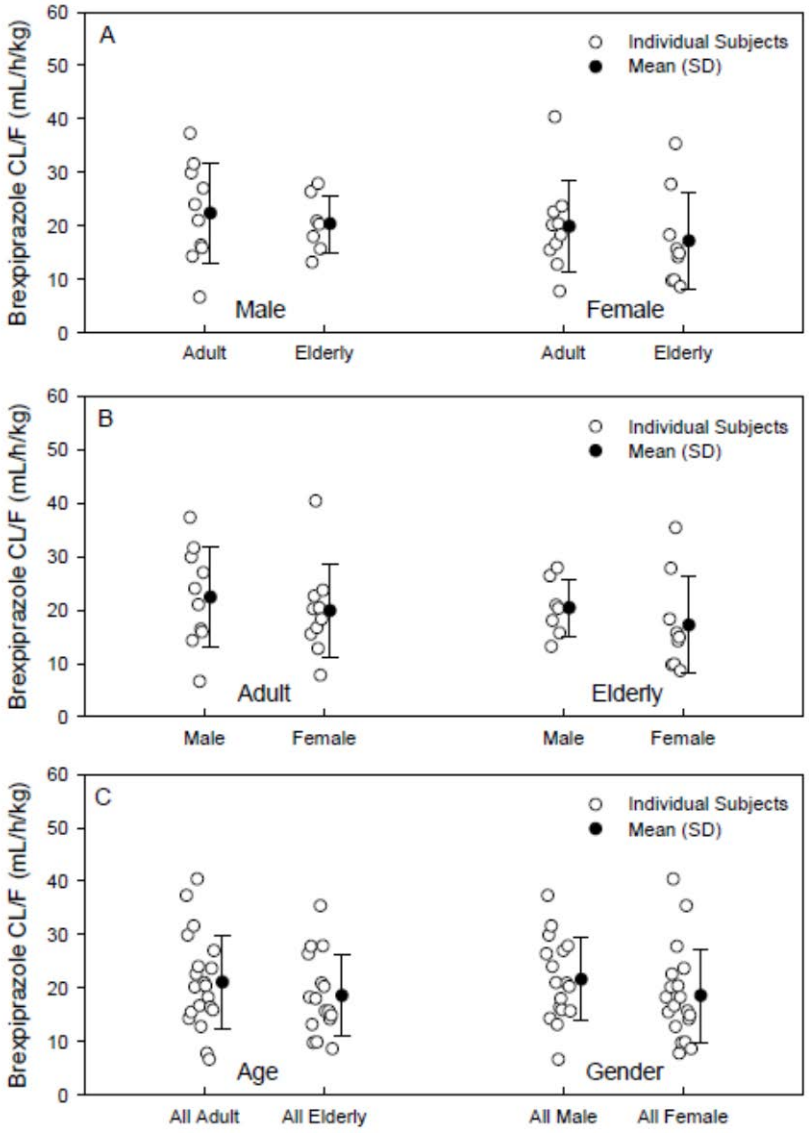


Figure 5: Scatter Plots of Individual and Mean (SD) Brexpiprazole CL/F Following Administration of 2-mg Brexpiprazole to Healthy Adult (18 to 45 years) and Elderly (greater than 65 years) Male and Female Subjects



Reference ID: 3779909

Table 4: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Healthy Adult Male, Adult Female, Elderly Male and Elderly Female Subjects

PK Parameter	Adult (18-45 y) Male (n=12)	Adult (18-45 y) Female (n=12)	Elderly (≥ 65 y) Male (n=12)	Elderly (≥ 65 y) Female (n=12)
C_{max} (ng/mL)	23.6 (5.96)	34.6 (11.4)	19.3 (4.82)	29.2 (6.04)
t_{max} (h)[a]	4.00 (2.27-8.05)	4.00 (1.07-6.03)	3.54 (2.00-8.00)	3.00 (1.02-6.00)
AUC_t (ng·h/mL)	1250 (540)	1680 (568)	1290 (436)	1810 (756)
AUC_∞ (ng·h/mL)	1300 (706)[b]	1830 (759)[b]	1290 (430)[c]	2010 (774)[d]
$t_{1/2,z}$ (h)	65.9 (23.6)[b]	69.0 (21.7)[b]	80.4 (13.1)[c]	82.3 (19.6)[d]
CL/F (mL/h/kg)	22.4 (9.32)[b]	19.9 (8.64)[b]	20.4 (5.36)[c]	17.2 (8.96)[d]

y = years.
[a]Median (minimum-maximum).
[b]n = 10.
[c]n = 7.
[d]n = 9

Figure 6: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Healthy Adult Male, Adult Female, Elderly Male and Elderly Female Subjects

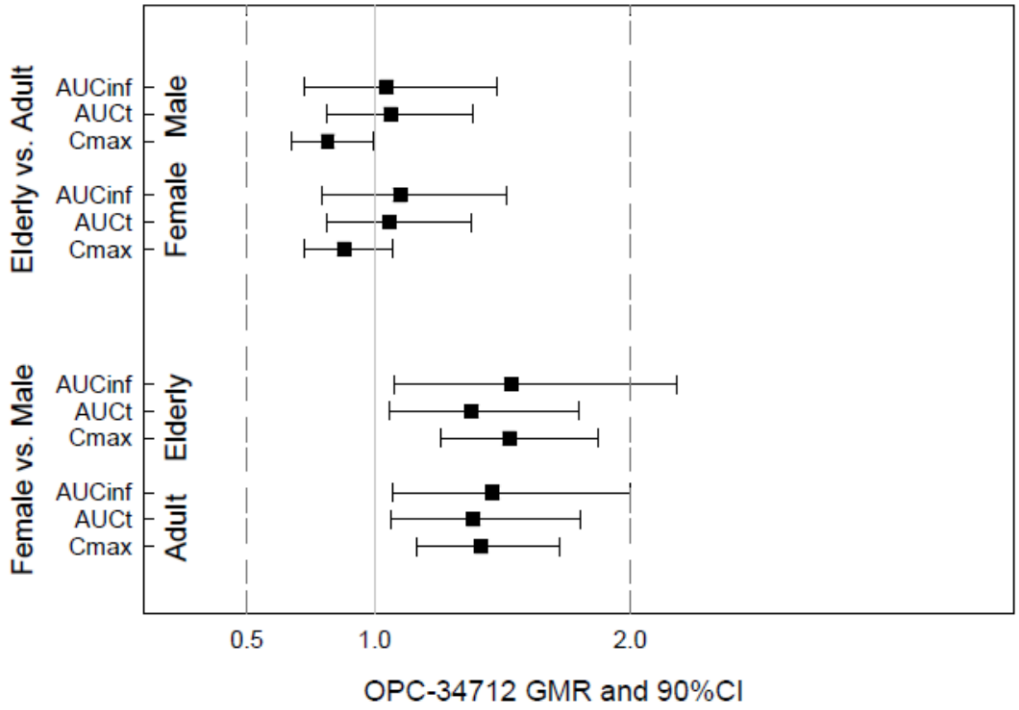


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Table 5: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Healthy Adult Male, Adult Female, Elderly Male, and Elderly Female Subjects

Comparison		PK Parameter	GMR	90% CI
Female (T) versus Male (R)	Adult (18-45 y)	C_{max}	1.418	1.167-1.724
		AUC_t	1.387	1.064-1.806
		AUC_∞	1.463	1.069-2.001
	Elderly (≥ 65 y)	C_{max}	1.528	1.258-1.857
		AUC_t	1.381	1.060-1.799
		AUC_∞	1.535	1.078-2.186
Elderly (≥ 65 y) (T) versus Adult (18-45 y) (R)	Male	C_{max}	0.817	0.672-0.993
		AUC_t	1.063	0.816-1.385
		AUC_∞	1.048	0.742-1.480
	Female	C_{max}	0.880	0.724-1.070
		AUC_t	1.059	0.813-1.380
		AUC_∞	1.100	0.797-1.518

y = years.

Brexpiprazole pharmacokinetics were similar between adult (18 to 45 years) and elderly (≥ 65 years old) subjects. Weight adjusted mean apparent clearance (CL/F) values were similar in elderly and adult subjects.

Comparison of brexpirazole pharmacokinetics for female and male subjects within adult and elderly subjects showed a trend towards higher exposures within female compared to male subjects. About a 50% higher exposure (AUC and Cmax) to brexpiprazole was observed among females compared to males. However, male and female subjects exhibited similar weight adjusted mean apparent clearance (CL/F). Therefore, the higher AUC and Cmax could be deemed to be weight related as the females had a lower overall weight compare to male subjects.

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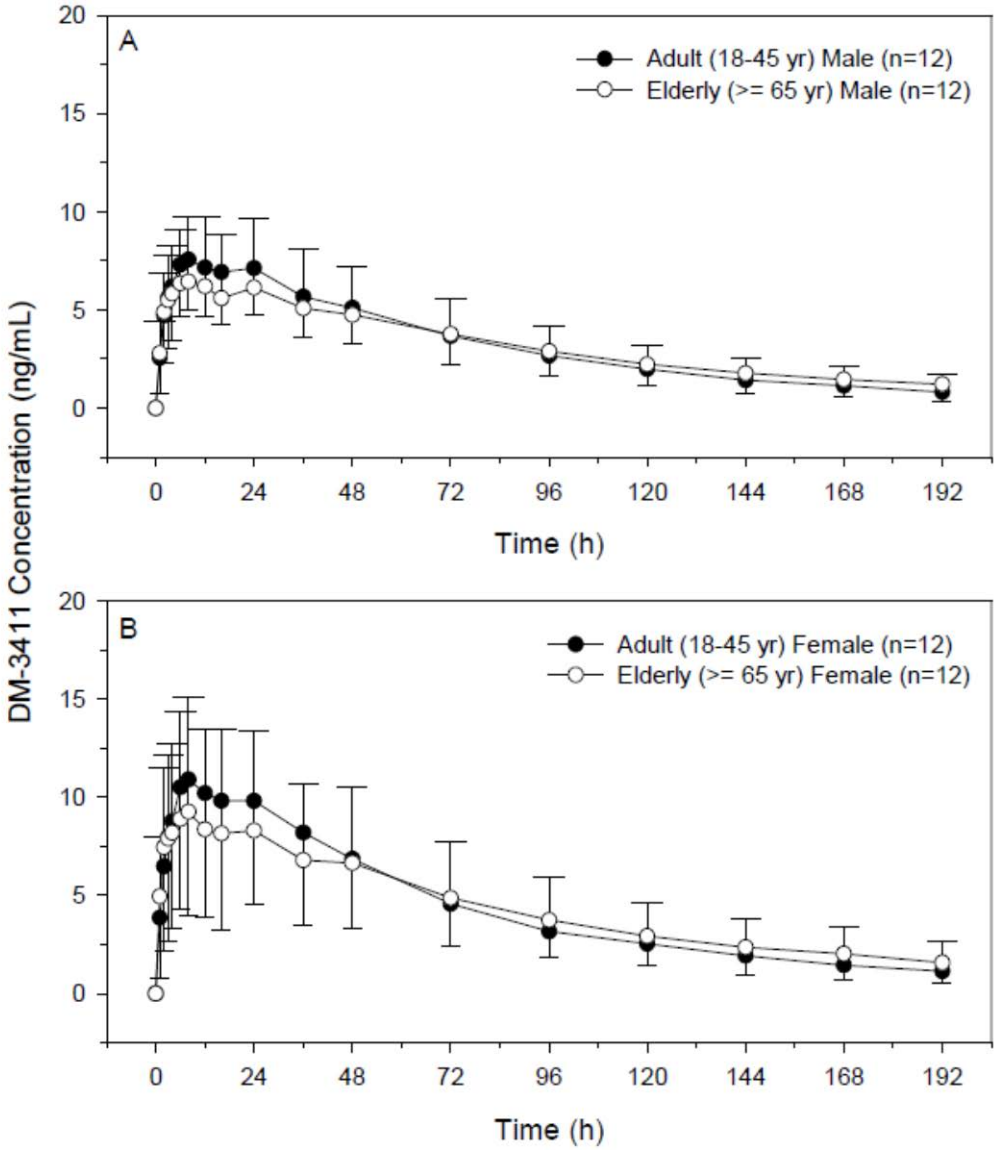
Metabolite (DM-3411) Pharmacokinetics

Figure 7: Mean (SD) DM-3411 Plasma Concentrations Following Administration of 2 mg Brexpiprazole to Healthy Adult and Elderly Subjects Stratified by Gender (Male or Female)



Reference ID: 3779909

Figure 8: Mean (SD) DM-3411 Plasma Concentrations Following Administration of 2 mg Brexpiprazole to Healthy Male and Female Subjects Stratified by Age

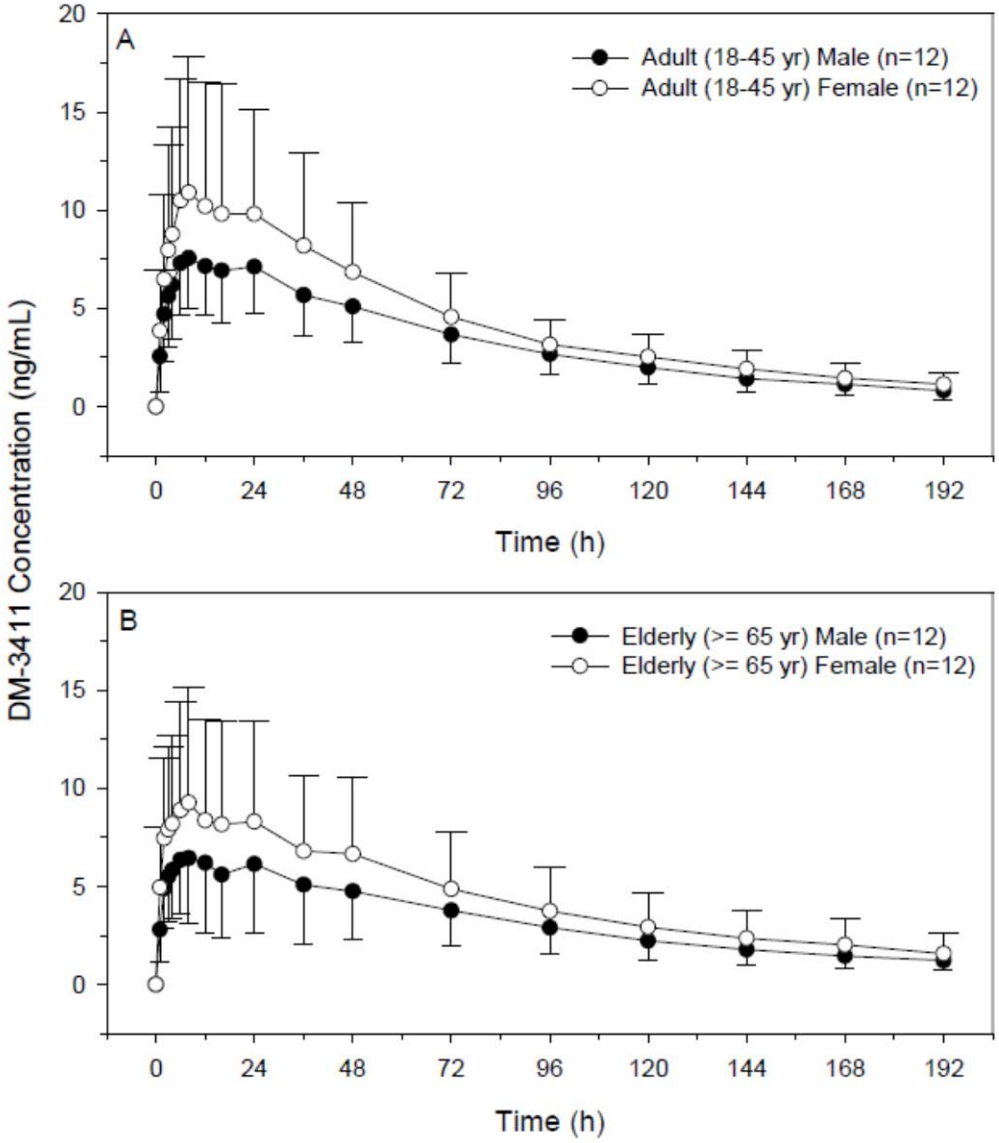


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Figure 9: Scatter Plots of Individual and Mean (SD) DM-3411 Cmax Following Administration of 2-mg Brexpiprazole to Healthy Adult (18 to 45 years) and Elderly (greater than 65 years) Male and Female Subjects

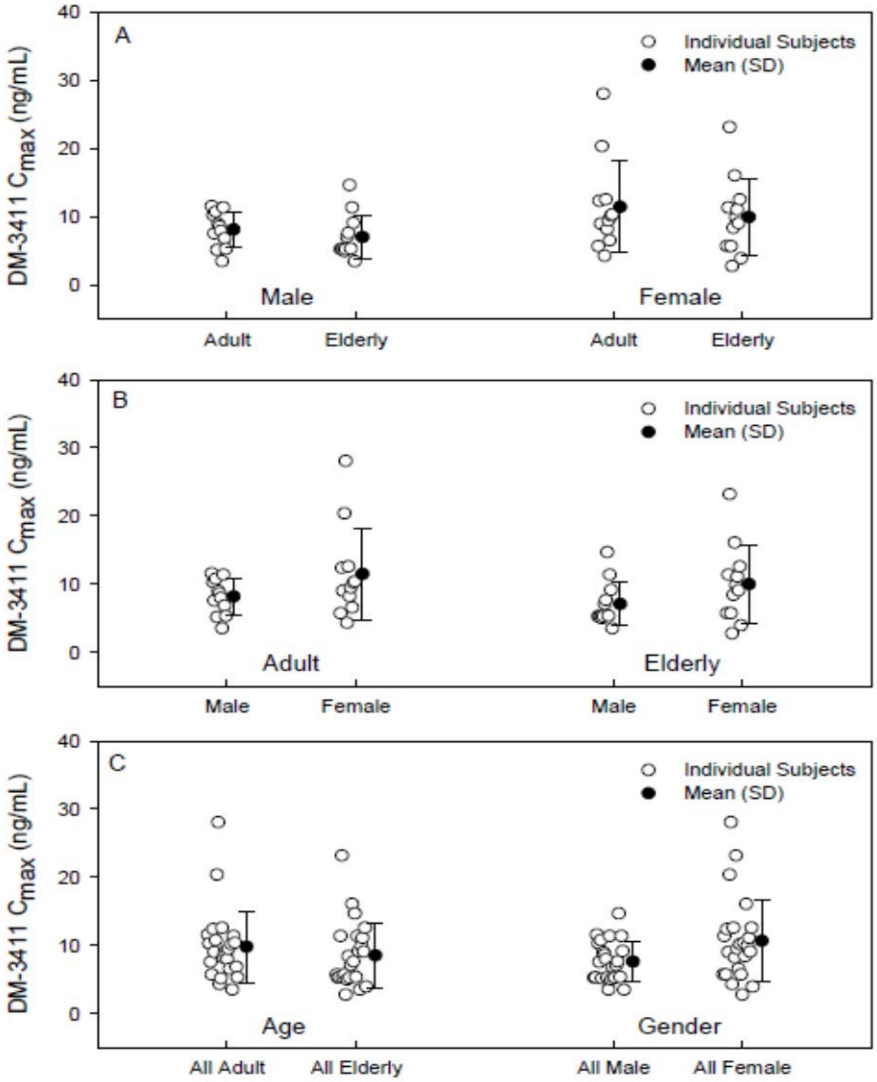

Figure 10: Scatter Plots of Individual and Mean (SD) DM-3411 AUC∞ Following Administration of 2-mg Brexpiprazole to Healthy Adult (18 to 45 years) and Elderly (greater than 65 years) Male and Female Subjects

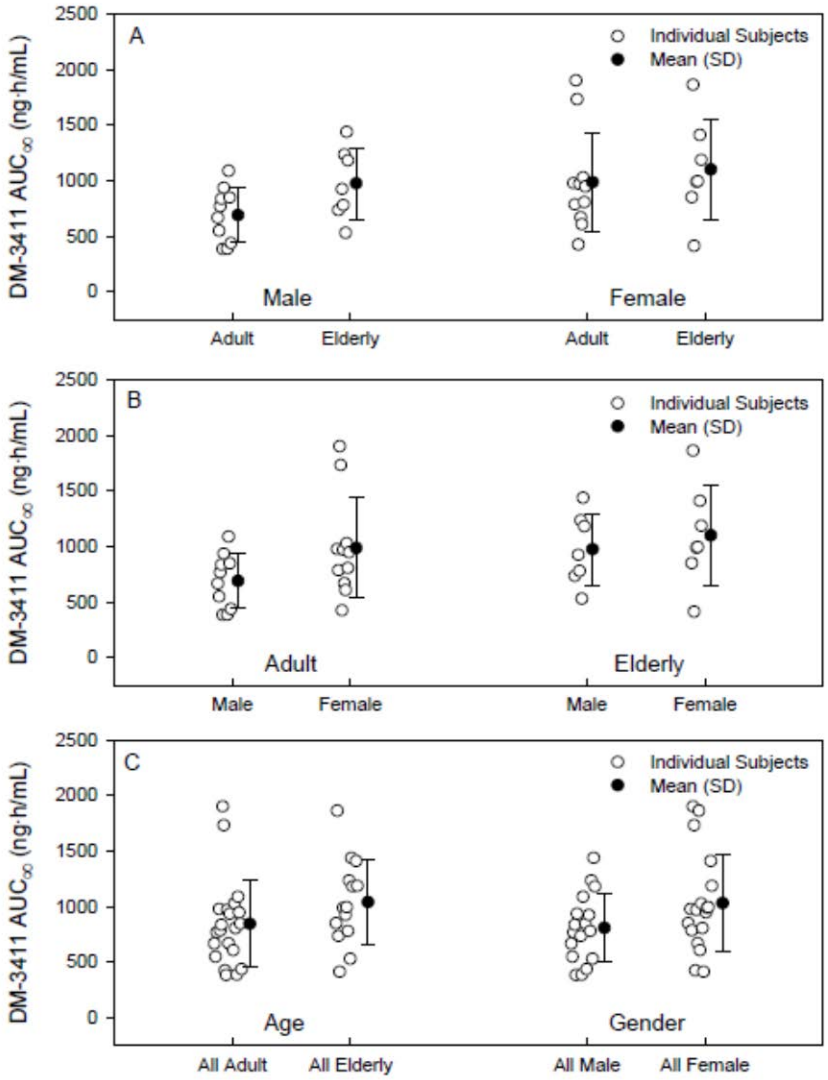

Table 6: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Healthy Adult Male, Adult Female, Elderly Male, and Elderly Female Subjects

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Table 9.2.3.2.2-1 Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole to Healthy Adult Male, Adult Female, Elderly Male, and Elderly Female Subjects				
PK Parameter	Adult (18-45 y) Male (n=12)	Adult (18-45 y) Female (n=12)	Elderly (≥ 65 y) Male (n=12)	Elderly (≥ 65 y) Female (n=12)
C_{max} (ng/mL)	8.19 (2.62)	11.5 (6.67)	7.09 (3.22)	10.0 (5.63)
t_{max} (h)[a]	8.02 (6.00-24.00)	8.00 (6.00-24.00)	7.00 (2.00-24.00)	6.14 (2.00-24.00)
AUC_t (ng·h/mL)	631 (214)	846 (416)	627 (297)	846 (464)
AUC_∞ (ng·h/mL)	689 (245)[b]	985 (450)[c]	974 (322)[d]	1100 (455)[d]
$t_{1/2,z}$ (h)	67.3 (27.2)[b]	57.0 (12.6)[c]	82.9 (22.1)[d]	67.4 (20.2)[d]

y = years.
[a]Median (minimum-maximum).
[b]n = 10.
[c]n = 11.
[d]n = 7

DM-3411 PK parameters were comparable between adult (18 to 45 years) and elderly (≥ 65 years) subjects within male and female subjects. DM-3411 exposure among female subjects were higher in comparison to the male subjects based on C_{max} and AUC PK parameters which is expected due to the observed higher exposure to brexpiprazole in females in comparison to the male subjects.

Safety: Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

In the adult subject group, the most common drug-related TEAEs (incidence ≥ 2 subjects) reported after brexpiprazole treatment were dizziness postural (5/24 subjects), abdominal pain and somnolence (2/24 subjects each), dizziness and headache (2/24 subjects each; male subjects only), and pruritus generalized (2/24 subjects; female subjects only). In the elderly subject group, the most common drug-related TEAEs (incidence ≥ 2 subjects) reported after brexpiprazole treatment were nausea, vomiting, fatigue, and dizziness (2/24 subjects each; female subjects only).
In the male subject group, the most common drug-related TEAEs (incidence ≥ 2 subjects) reported after brexpiprazole treatment were dizziness, dizziness postural, and headache (2/24 subjects each). All of these events were reported in the adult male group. In the female subject group, the most common drug-related TEAEs (incidence ≥ 2 subjects) reported after brexpiprazole treatment were dizziness postural (3/24 subjects; adult females only); nausea, vomiting, fatigue, and dizziness (2/24 subjects each; elderly females only), and pruritus generalized (2/24 subjects; adult females only).

Conclusion:

Based on the results of the primary statistical analysis, the GMR and 90% CI for brexpiprazole Cmax and AUC were unlikely to be clinically meaningufl for elderly (≥ 65 years) subjects in

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comparison to the adult (18 to 45 years) subjects within male and female subject groups. Brexpiprazole weight adjusted mean CL/F values were also comparable in elderly subjects in comparison to the adult subjects within male and female subject groups and, thus, it can be concluded that no differences in brexpiprazole PK were observed based on the age of the subject. Administration of 2 mg brexpiprazole was generally safe and well tolerated in normal adult and elderly male and female subjects. There were no clinically meaningful differences based on age or gender of subjects.

- **Reviewer's comments:**

The reviewer agrees with the sponsor's conclusions that the observed exposure difference is unlikely to be clinically meaningful However, it must be noted there was a trend towards higher exposure (Cmax, AUC) in female subjects compared to male subjects, which appeared to be related to difference in weight between male and female subjects. No significant difference was also observed between the elderly and adult subjects.

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IV. Extrinsic Factors

1. Food Effect

Report # 331-10-246 **Study Period**: 12/15/2011-2/20/2012
Title: An Open-label, Randomized, Two-way Crossover Trial of the Effect of a High-fat Meal on the Pharmacokinetics of OPC-34712 in Healthy Subjects.

- **Objective:** To assess the effect of a high-fat meal on the PK of 4-mg long term stability supply (LTSS) brexpiprazole (OPC-34712) tablets in healthy subjects.
- **Study Design:** This was a single center, open-label, 2-arm, 2-way, crossover trial conducted in 16 healthy subjects. A single 4-mg brexpiprazole LTSS tablet was administered to each subject on Days 1 and 16 in the fed state or in the fasted state according to the randomization schedule after an overnight fast of at least 10 hours. In the fed state, following a fast of at least 10 hours, subjects consumed a high-fat meal within 30 min or less and were administered a single oral dose of 4-mg brexpiprazole LTSS 30 minutes after the start of the meal.
  Meal used meets the FDA Guidance Recommendations: Yes ☑ No ☐
- **Blood Sampling Times:**
  Pharmacokinetics: Days 1 and 16: predose (within 15 min prior to dosing) and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 216, 264, and 312 hr postdose.
  Pharmogenomics: A 10-mL blood sample was collected predose on Day 1.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Method	6825-271	6825-271
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Performance	Acceptable	Acceptable

- **Results:**

Study Population

Randomized/Completed/ Discontinued Due to AE	16/16/0
Age [Median (range)]	31(22-50)
Male/Female	14/2
CYP2D6 EM/IM	11/5
Race (Caucasian/Black/other)	7/7/2

Pharmacokinetics

Table 1: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole to Healthy Subjects in a Fed or Fasted State

Reference ID: 3779909

PK Parameter	Fed (N = 14)[a]	Fasted (N = 14)[a]
C_{max} (ng/mL)	47.3 (14.8)	49.3 (19.3)
t_{max} (h)[b]	5.50 (2.00 - 16.00)	5.00 (2.00 - 6.00)
AUC_t (ng·hr/mL)	3160 (1360)	3010 (1190)
AUC_∞ (ng·hr/mL)	3440 (1730)[c]	3400 (1390)[c]
$t_{1/2,z}$ (h)	93.1 (30.1)[c]	97.3 (36.3)[c]
CL/F (mL/h/kg)	19.6 (7.59)[c]	18.7 (7.33)[c]

[a]Subjects (Subjects 0103 and 0104) with predose concentrations > 5% of Cmax during Period 2 were excluded from descriptive statistics. [b]Median (minimum - maximum). [c]n = 13.
-source: Table 9.2.3.2.1-1 of the study report

Table 2: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole to Healthy Subjects in a Fed or Fasted State

Comparison	PK Parameter	GMR	90% CI
Fed (T) versus fasted (R)	C_{max}	0.9854	0.8553 - 1.1353
	AUC_t	1.0314	0.9080 - 1.1716
	AUC_∞	1.0139	0.8689 - 1.1832

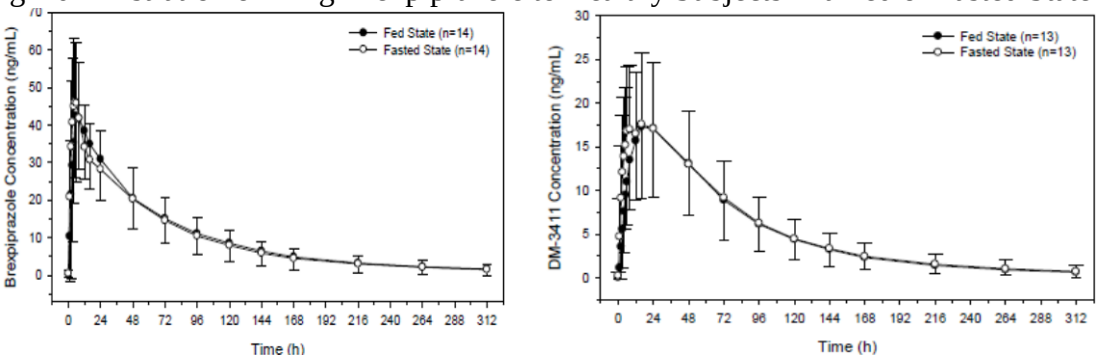
Note: Subjects with predose concentrations > 5% of Cmax during Period 2 were excluded from statistical analysis
-source: Table 9.2.3.3.1-1 of the study report

Table 3: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole to Subjects in a Fed or Fasted State

PK Parameter	Fed (N = 13)[a]	Fasted (N = 13)[a]
C_{max} (ng/mL)	18.3 (8.55)	19.1 (8.04)
t_{max} (h)[b]	24.00 (12.00 - 24.00)	16.00 (2.00 - 24.00)
AUC_t (ng·hr/mL)	1600 (722)	1680 (723)
AUC_∞ (ng·hr/mL)	1710 (844)[c]	1820 (930)[c]
$t_{1/2,z}$ (h)	89.1 (13.9)[c]	90.6 (31.8)[c]

[a]Subjects (Subjects 0103, 0104, and 0113) with predose concentrations > 5% of Cmax during Period 2 were excluded from descriptive statistics. [b]Median (minimum - maximum). [c]n = 11.
-source: Table 9.2.3.2.2-1 of the study report

Figure 1: Mean (SD) Brexpiprazole (Left) and DM-3411 (Right) Plasma Concentrations Following Administration of 4 mg Brexpiprazole to Healthy Subjects in a Fed or Fasted State



-source: Figure 9.2.3.1.1-1 and Figure 9.2.3.1.2-1 of the study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusion:** Food did not significantly affect the PK of brexpiprazole.

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- **Reviewer's Comments:**
  1) The highest to-be-marketed strength for brexpiprazole is 4 mg, which met FDA's requirements about food effect study to be tested at the highest dose strength.
  2) The formulation tested in the study was the long term stability supply (LTSS) tablets, which were commercial tables as well.
  3) There were 12 out of 14 subjects that had measureable predose concentrations of brexpiprazole at Period 2, and 2 of them had greater than 5% Cmax of Period 2. Those subjects were excluded in the statistical analysis.
  4) No food effect was observed in the pilot food-effect trial using 1 mg tablet (2x1-mg table, Trial 331-07-201, study report not reviewed). Results seemed to be consistent between the two trials.
  5) Reviewer agrees with the sponsor that food did not significantly affect the PK of brexpiprazole. Brexpiprazole can be administered without regard to food.

2. DDI- Induction (Rifampin)

Protocol #: 331-09-224 **Study Period**:06/27/2011-09/06/2011
Title: A Drug Interaction Trial to Assess the Effect of Rifampin on OPC-34712 Metabolism in Healthy Subjects

- **Objective:** To assess the potential for clinically meaningful CYP-mediated drug induction of OPC-34712 metabolism via CYP3A4 by rifampin
- **Study Design:** This was a single-center, open-label, sequential design trial conducted in 1 group of 18 subjects. A single 4-mg dose of brexpiprazole (4x 1-mg tablets) was administered on Day 1 followed by rifampin daily dosing of 600 mg (2x300 mg) on Days 11 through 23. A 4-mg single dose of brexpiprazole was administered on Day 18. All doses were administered with 240 ml water. On Days 1 and 18, subjects were administered doses in the fasted state (at least 8 hours of fasting) and no food was allowed for 4 hours postdose.
- **Blood Sampling Time:**
  Pharmacokinetics: Days 1 and 18: predose and at 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, and 216 hr (Day 1 only) postdose.
  For rifampin: Days 15, 16 and17: 2 hours postdose
  Pharmacogenomics: Day 1: predose
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411	Rifampin
Method	6825-271	6825-271	LC-MS/MS
Matrix	plasma	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100	50 to 35,000
Performance	Acceptable	Acceptable	Acceptable

- **Results:**
  Study Population

Randomized/Completed/ Discontinued Due to AE	18/16/0
Age [Mean±SD]	31.7±6.9
Male/Female	13/5
Race (Caucasian/Black/Asian/Other)	14/3/0/1

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Ethnicity (Hispanic/Not Hispanic)	15/3
CYP2D6 (UM/EM/IM/PM)	2/8/7/1

Pharmacokinetics

Table 1: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole Alone or With 600 mg Rifampin to Healthy Subjects

PK Parameter	Brexpiprazole Alone (n=16)	Brexpiprazole With Rifampin (n=16)
C_{max} (ng/mL)	53.9 (12.6)	37.4 (9.97)
t_{max} (h)[a]	5.00 (2.00-6.00)	5.00 (2.00-6.00)
AUC_t (ng·h/mL)	3410 (1490)	1010 (336)
AUC_∞ (ng·h/mL)	4190 (2380)	999 (289)[b]
$t_{1/2,z}$ (h)	82.5 (31.5)	43.7 (21.2)[b]
CL/F (mL/h/kg)	16.4 (9.66)	56.4 (22.5)[b]

[a]Median (minimum - maximum). [b]n = 12. Source: Table 9.2.3.2.1-1 of the study report

Table 2: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole Alone and With 600 mg Rifampin

Comparison	PK Parameter	GMR	90% CI
Brexpiprazole with Rifampin (T) versus Brexpiprazole Alone (R)	C_{max}	0.690	0.610-0.781
	AUC_t	0.307	0.270-0.348
	AUC_∞	0.274	0.225-0.332

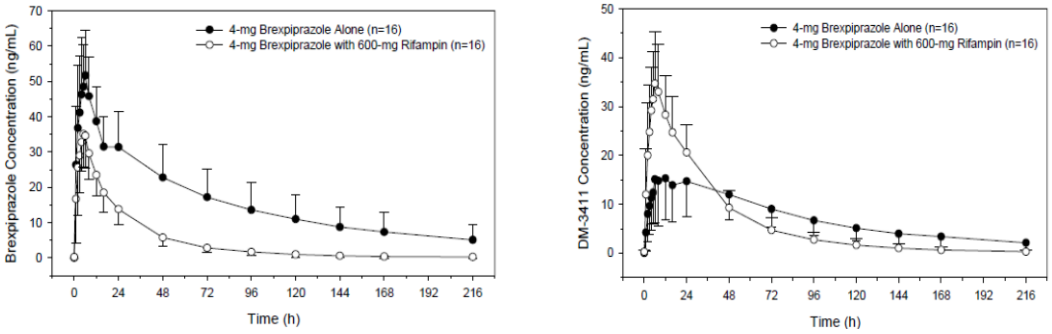
Source: Table 9.2.3.3.1-1 of the study report

Table 3: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole Alone or With 600 mg Rifampin to Healthy Subjects

PK Parameter	Brexpiprazole Alone (n=16)	Brexpiprazole With Rifampin (n=16)
C_{max} (ng/mL)	16.5 (9.67)	35.3 (10.8)
t_{max} (h)[a]	10.00 (6.00-24.00)	6.00 (3.00-12.00)
AUC_t (ng·h/mL)	1550 (652)	1350 (437)
AUC_∞ (ng·h/mL)	1880 (798)[b]	1360 (490)[c]
$t_{1/2,z}$ (h)	73.8 (24.3)[b]	37.0 (8.4)[c]

[a]Median (minimum - maximum). [b]n = 15. [c]n = 13. Source: Table 9.2.3.2.2-1 of the study report

Figure 1: Mean (SD) Brexpiprazole (Left) and DM-3411 (Right) Plasma Concentrations Following Administration of 4 mg Brexpiprazole Alone or With 600 mg Rifampin to Healthy Subjects



-Source: Figure 9.2.3.1.1-1 and Figure 9.2.3.1.2-1 of the study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusions:** Coadministration with rifampin significantly:

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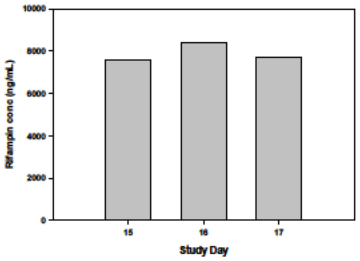
1) decreased exposure (C_{max} and $AUC_{0-\infty}$) of brexpiprazole by 31% and 73%;
2) increased C_{max} of DM-3411 by approximate 100%, but decreased its $AUC_{0-\infty}$ by 28%.
3) Should brexpiprazole dose be adjusted in patients when coadministered with strong CYP3A4 inducers? ☑ Yes ☐No

- **Reviewer's Comments:**

1) In this drug interaction study, rifampin was dosed daily for 13 days, with 7 days before brexpiprazole was given. Steady state seemed to be reached by Day 15 for rifampin. This design allowed to capture the maximal effect of rifampin on brexpiprazole PK.

Figure : Mean postdose 2-hr plasma concentration of rifampin on Day 15 to Day 17



2) The estimated terminal half-life for brexpiprazole was about 83 hrs in the absence of rifampin, which seemed to be consistent with results from other trials.
3) Both the formation and elimination of DM-3411 was mediated by enzyme(s) induced by rifampin, most likely CYP3A4.
4) There were 7 out of 16 subjects that had measureable predose concentrations of brexpiprazole at Period 2, and none of them had greater than 5% Cmax of Period 2. According to our BA/BE guidance, all subjects were included in the statistical analysis.

3. DDI-Inhibition(1) - Effect of Brexpiprazole on Other Drugs

Report # 331-08-207 **Study Period**: 01/19/2009-6/23/2009
Title: A Pilot Study to Assess the Potential for Cytochrome P450-mediated and P-glycoprotein-mediated Drug Interactions with OPC-34712 in Healthy Subjects.

- **Objectives:**

1) To assess the potential for clinically meaningful cytochrome P-450 (CYP)-mediated drug inhibition of OPC-34712 metabolism:
   - Inhibition of OPC-34712 metabolism via CYP3A4 by ketoconazole;
   - Inhibition of OPC-34712 metabolism via CYP2B6 by ticlopidine;
   - Inhibition of OPC-34712 metabolism via CYP2D6 by quinidine.
2) To assess the potential of OPC-34712 for clinically meaningful CYP-mediated drug inhibition of the metabolism of other drugs:
   - Inhibition of CYP3A4 by OPC-34712 using lovastatin as a substrate;
   - Inhibition of CYP2B6 by OPC-34712 using bupropion as a substrate;
   - Inhibition of CYP2D6 by OPC-34712 using dextromethorphan as a substrate.
3) To assess the potential of OPC-34712 for clinically meaningful P-glycoprotein-mediated drug inhibition of the metabolism of other drugs:
   - P-glycoprotein inhibition using fexofenadine as a substrate.

- **Study Design:** This was a single center, open-label, parallel, 8-arm, pilot trial in healthy

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subjects. Dosing was conducted in 8 treatment arms of 5 subjects each, with the exception of dextromethorphan group (n=13, by protocol amendment). Within each group, OPC-34712 (either alone or when coadministered with a probe drug) was administered in the fasted state.
Effect of inhibitors on brexpiprazole: the PK parameters of a single 2-mg dose of brexpiprazole without inhibitors (control group) were compared to its PK parameters when a single 2-mg dose of brexpiprazole was co-administered with one of CYP450 inhibitors in three parallel test groups (CYP inhibitors were administered for 7 days). The following strong inhibitors were used: CYP3A4 (ketoconazole, 400 mg, once daily), CYP2B6 (ticlopidine, 250 mg, twice daily), and CYP2D6 (quinidine gluconate, 324 mg, once daily).
Effect of brexpiprazole on substrates of CYP isozymes or P-gp: the PK parameters of each of four CYP450/P-gp substrates after single-dose administration with and without brexpiprazole were evaluated in a sequential crossover design. Brexpiprazole was administered for at least 8 days prior to and 4 days with the substrates. The following substrates were used: CYP3A4 (lovastatin, 80 mg), CYP2B6 (bupropion sustained release, 150 mg), CYP2D6 (dextromethorphan hydrobromide, 30 mg), and P-gp (fexofenadine, 60 mg).
Administration of OPC-34712 began on Day 3, following the scheme below:
• On Days 3 and 4 (Days 4 and 5 for bupropion group), subjects received a 0.5-mg dose of OPC-34712 QD.
• On Days 5 and 6 (Days 6 and 7 for bupropion group), subjects received a 1.0-mg dose of OPC-34712 QD.
• From Day 7 (Day 8 for bupropion group) to Day 11 (Day 12 for bupropion group), subjects received a 2-mg dose of OPC-34712 QD.
• On Day 11 (Day 12 for bupropion group), subjects received a single dose of the probe drug assigned to each group concomitant with the 2-mg OPC-34712 dose.

- **Sampling Times:**
  Pharmacokinetics: *Lovastatin and fexofenadine* PK blood samples for Groups 5 and 8 were collected on Day 1 and Day 11 at predose (within 15 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours postdose. OPC-34712 PK blood samples for Groups 5, 7, and 8 were collected at predose on Day 3 and Day 11 at predose, 2, 4, 6, 8, 12, 24, and 48 hours. *Bupropion* PK samples were collected on Day 1 and Day 12 at predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose. PK samples for OPC-34712 were collected at predose on Day 4, and Day 12 at predose, 2, 4, 6, 8, 12, 24, and 48 hours postdose.
  Pharmogenomics: A blood sample was collected predose on Day 1.
  Urine samples for dextromethorphan and dextrorphan concentrations were collected during the following intervals at 0 to 12, 12 to 24, 24 to 36, and 36 to 48 hours postdose On Day 1 and Day 11.
- **Analytical Methods:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Lovastatin & lovastatin hydroxyl acid	Bupropion & hydroxy-bupropion	Fexofenadine	Dextrometh -orphan & dextrorphan
Matrix	Plasma (method 6825-271)	plasma	plasma	plasma	urine

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Range (ng/mL)	0.3 to 100	0.1 to 50	1.0 to 1000	5-1000	0.1 to 500
Performance	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

- **Results:**

Study Population

Randomized/Completed/ Discontinued Due to AE	16/16/0
Age [Median (range)]	31 (22-50)
Male/Female	14/2
CYP2D6 EM/IM	11/5
Race (Caucasian/Black/other)	7/7/2

Pharmacokinetics

Table 1: Mean (SD) Lovastatin and Lovastatin Hydroxy Acid Pharmacokinetic Parameters Following 80 mg Lovastatin Alone or With Multiple Oral Doses of OPC-34712 to Healthy Male Subjects

	Lovastatin (n = 5)		Lovastatin Hydroxy Acid (n = 5)	
Parameter	80 mg Lovastatin	80 mg Lovastatin + OPC-34712	80 mg Lovastatin	80 mg Lovastatin + OPC-34712
C_{max} (ng/mL)	8.90 (7.86)	8.50 (6.09)	6.36 (3.14)	4.97 (2.38)
t_{max} (h)[a]	3.00 (1.00-16.00)	0.50 (0.50-6.00)	4.00 (3.00-24.00)	3.00 (2.00-24.00)
AUC_t (ng·h/mL)	97.6 (47.3)	107 (74.1)	91.9 (58.8)	79.0 (50.8)
Ratio of C_{max} Values[b]	--	1.04 (0.28)	--	0.79 (0.15)
Ratio of AUC_t Values[b]	--	1.05 (0.24)	--	0.90 (0.42)

[a]Median (minimum-maximum). [b]Ratio of OPC + drug to drug alone.

-Source: Table 9.2.3.5-1

Table 2: Mean (SD) Bupropion and Hydroxybupropion Pharmacokinetic Parameters Following 150 mg Bupropion Alone or With Multiple Oral Doses of OPC-34712 to Healthy Male Subjects

	Bupropion (n = 5)		Hydroxybupropion (n = 5)	
Parameter	150 mg Bupropion	150 mg Bupropion + OPC-34712	150 mg Bupropion	150 mg Bupropion + OPC-34712
C_{max} (ng/mL)	120 (42.5)	115 (31.9)	273 (41.9)	232 (35.4)
t_{max} (h)[a]	2.00 (2.00-5.00)	4.00 (2.00-5.00)	8.00 (4.00-8.00)	6.00 (4.00-8.00)
AUC_t (ng·h/mL)	1020 (401)	1040 (378)	8920 (1540)	8110 (1350)
$t_{1/2,z}$ (h)	20.8 (7.5)	17.9 (5.0)	23.7 (6.7)	26.4 (7.2)
AUC_∞ (ng·h/mL)	1070 (418)	1090 (407)	10400 (2220)	9740 (2180)
Ratio of C_{max} Values[b]	--	0.98 (0.09)	--	0.86 (0.16)
Ratio of AUC_∞ Values[b]	--	1.03 (0.06)	--	0.94 (0.09)

[a]Median (minimum-maximum). [b]Ratio of OPC + drug to drug alone.

-Source: Table 9.2.3.6-1 of the study report

Table 3: Mean (SD) Fexofenadine Pharmacokinetic Parameters Following 60 mg Fexofenadine Alone or With Multiple Oral Doses of OPC-34712 to Healthy Male Subjects

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Parameter	60 mg Fexofenadine (n = 5)	60 mg Fexofenadine + OPC-34712 (n = 5)
C_{max} (ng/mL)	196 (61.8)	181 (49.2)
t_{max} (h)[a]	2.00 (1.00-2.02)	2.00 (1.00-4.00)
AUC_t (ng ·h/mL)	1070 (211)	1110 (273)
$t_{1/2,z}$ (h)	6.9 (0.6)	8.2 (3.9)
AUC_∞ (ng ·h/mL)	1130 (211)	1180 (283)
Ratio of C_{max} values[b]	--	1.03 (0.53)
Ratio of AUC_∞ values[b]	--	1.06 (0.27)

[a]Median (minimum-maximum). [b]Ratio of OPC + drug to drug alone.

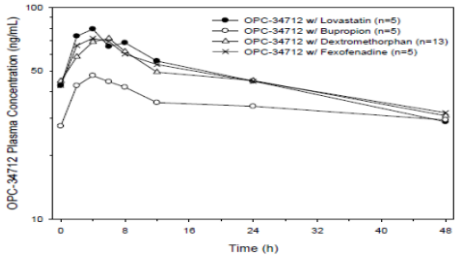
-Source: Table 9.2.3.8-1 of the study report

Table 4: Mean (SD) Amount Excreted in Urine for Dextromethorphan and Dextrorphan and the Dextromethorphan/Dextrorphan Ratios Following 30 mg Dextromethorphan HBr Alone or With Multiple Oral Doses of OPC-34712 to Healthy Male Subjects

Treatment	A_{e48h} (mg)		Dextromethorphan/ Dextrorphan Ratio (n = 12)
	Dextromethrophan (n = 12)	Dextrorphan (n = 12)	
30 mg dextromethorphan alone	0.200 (0.456)	8.57 (2.60)	0.026 (0.064)
30 mg dextromethorphan + OPC-34712	0.201 (0.376)	9.89 (4.91)	0.025 (0.052)

-Source: Table 9.2.3.7-1of the study report

Figure 1: Median OPC-34712 Plasma Concentrations Following Multiple Doses of OPC-34712 With Either Lovastatin, Bupropion, Dextromethorphan, or Fexofenadine to Healthy Male Subjects



-Source: Figure 9.2.3.1.2-1 of the study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusion:** OPC-34712 is not an inhibitor of CYP3A4, CYP2B6, CYP2D6, or P-glycoprotein.
- **Reviewer's Comments:**
  1) Effect of other drugs on brexpiprazole part of this study was not reviewed, as there was a designated trial to evaluate the DDIs (Trial 331-08-208).
  2) Because of tolerability issues in healthy volunteers, 2 mg brexpiprazole (MTD in healthy subjects) was administered 8 days including titration phase before the substrate drug was given. Given the estimated half- life of brexpiprazole of about 91 hr, by the time substrate drug was coadministered, brexpiprazole reached about more than 75% of steady state level.
  3) There were five subjects studied in each drug interaction arm, and it was considered a relative small number. However, the study seemed to be well conducted. Additionally, there is no specific recommendation in Drug Interaction Guidance in terms of sample size. Sponsor's conclusion is acceptable to the reviewer.

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4. DDI-Inhibition (2) -Effect of Other Drugs on Brexpiprazole

Report # 331-08-208 **Study Period**: 7/27/2009-10/21/2009
Title: A Drug Interaction Study to Assess Cytochrome P450-Mediated Inhibition of OPC-34712 Metabolism in Healthy Subjects.

- **Objectives:** To assess the potential for clinically meaningful CYP-mediated drug inhibition of OPC-34712 metabolism: 1) Inhibition of OPC-34712 metabolism via CYP3A4 by ketoconazole; 2) Inhibition of OPC-34712 metabolism via CYP2B6 by ticlopidine; 3) Inhibition of OPC-34712 metabolism via CYP2D6 by quinidine; 4) Inhibition of OPC-34712 metabolism via CYP2B6 and CYP3A4 by ticlopidine and ketoconazole in poor metabolizers of CYP2D6 isozyme.
- **Study Design:** This was a single center, open-label, cross-over trial in healthy subjects. Forty-eight subjects were to be enrolled in 4 groups of 12 subjects per group. Subjects were assigned to Groups 1 to 3 or Group 4 based on the results of the dextromethorphan (a CYP2D6 substrate) metabolism test conducted at screening (poor metabolizer: urine dextromethorphan/dextophan ratios > 0.300; extensive metabolizers: dextromethorphan/dextrophan ratios < 0.300); Subjects who were extensive or intermediate metabolizers of CYP2D6 were enrolled in Groups 1 to 3. Subjects who were poor metabolizers of CYP2D6 isozyme were enrolled in Group 4. OPC-34712 was administered as a single dose alone or with the probe drug(s). Subjects received a single 2-mg oral dose of OPC-34712 on Day 1. After a 13-day washout period, subjects in Groups 1 through 3 received a single 2-mg oral dose of OPC-34712 with a probe drug and subjects in Group 4 were to receive a single 0.2-mg oral dose of OPC-34712 with the probe drugs on Day 15. Administration of the probe drug continued for 7 days (Days 16 to 21). The probe drugs and dosing regimen administered concomitantly with OPC-34712 for Groups 1 to 3 were 200 mg ketoconozole BID, 250 mg ticlopidine·HCl BID, and 324 mg quinidine gluconate QD, respectively. Group 4 was to receive 200 mg ketoconazole BID and 250 mg ticlopidine·HCl BID concomitantly with OPC-34712.
- **Blood Sampling Time:**
  Pharmacokinetics: PK samples for OPC-34712 were collected on Day 1 and Day 15 at predose (within 15 minutes prior to dosing), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168/ET hours postdose. PK samples for ticlopidine, quinidine, and ketoconazole were collected on Day 15 at predose (within 15 minutes prior to dosing), and at 4, 8, 28, and 32 hours postdose.
  Pharmogenomics: All urine collected up to 8 hr post a single dose administration of 30 mg detromethorphan administration.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Ketocona-zole	Ticlodi-pine	Quini-dine	Dextromethor-phan & dextrorphan
Matrix	plasma	plasma	plasma	plasma	urine
Range (ng/mL)	0.3 to 100	5.0 to 1000	1.0 to 1002.4	40.14 to 4014.40	0.1 to 500
Performance	Yes	Yes	Yes	Yes	Yes

Reference ID: 3779909

Acceptable?					

- **Results:**

Study Population

	Keto group	Ticl group	Qui group	OPC only group
Randomized/Completed/ Discontinued Due to AE	12/12/0	12/11/0	11/11/0	6/5/0
Age [Median (range)]	30.2 (18-43)	33.7 (21-45)	32.3 (19-42)	31.3 (26-44)
Male/Female	12/0	12/0	11/0	6/0
CYP2D6 Genotype	EM/IM	EM/IM	EM/IM	PM
Race (Caucasian/Black/other)	10/1/1	6/5/1	9/3/0	6/0/0

Note:Keto: ketoconazole; Ticl:ticlodipine; Qui: quinidine; OPC: brexpiprazole

Pharmacokinetics

Table 1: Mean (SD) OPC-34712 Pharmacokinetic Parameters Following A Single Oral 2-mg Dose of OPC-34712 Alone or with CYP 450 Isozyme Inhibitors to Healthy Subjects

Treatment/ PK Parameter	Group 1		Group 2		Group 3	
	OPC-34712 Alone (n = 12)	OPC-34712 with CYP3A4 Inhibitor (n = 12)	OPC-34712 Alone (n = 12)	OPC-34712 with CYP2B6 Inhibitor (n = 11)	OPC-34712 Alone (n = 12)	OPC-34712 with CYP2D6 Inhibitor (n = 11)
C_{max} (ng/mL)	25.3 (7.24)	29.9 (8.11)	24.8 (11.0)	22.7 (7.48)	22.9 (5.13)	25.7 (6.66)
t_{max} (h)[a]	4.00 (2.00-6.05)	4.51 (1.00-6.00)	5.02 (1.00-8.00)	5.00 (3.00-8.02)	6.00 (2.05-8.00)	6.00 (4.00-8.00)
$t_{1/2,z}$ (h)	61.6 (15.6)	101 (54.7)	62.3 (27.3)	66.7 (19.3)	62.1 (17.6)	103 (36.1)
AUC_t (ng·h/mL)	1322 (578)	2174 (1053)	1406 (780)	1348 (659)	1253 (440)	1988 (595)
AUC_∞ (ng·h/mL)	1624 (735)	3520 (2777)	1769 (1158)	1652 (921)	1479 (630)	2995 (1305)
CL/F (L/h)	1.45 (0.562)	0.880 (0.516)	1.74 (1.38)	1.58 (0.896)	1.63 (0.790)	0.777 (0.303)
Geometric Mean Ratio of C_{max}[b]	1.19 (1.10-1.27)		0.97 (0.80-1.17)		1.11 (1.01-1.22)	
Geometric Mean Ratio of AUC_t[b]	1.59 (1.44-1.75)		1.01 (0.86-1.19)		1.63 (1.34-1.97)	
Geometric Mean Ratio of AUC_∞[b]	1.97 (1.63-2.37)		1.00 (0.85-1.19)		1.94 (1.49-2.53)	

For Groups 1 through 3, 200 mg ketoconazole BID (Group 1), 250 mg ticlopidine·HCl BID (Group 2), or 324 mg quinidine gluconate QD (Group 3) were used as CYP3A4, CYP2B6, and CYP2D6 isozyme inhibitors, respectively. aMedian (minimum-maximum). bGeometric Mean Ratio of OPC + CYP Inhibitor to OPC alone (90% CI).

-source: Table 9.2.3.2.1-1 of study report

Table 2: Mean (SD) DM-3411 Pharmacokinetic Parameters Following A Single Oral 2-mg Dose of OPC-34712 Alone or with CYP 450 Isozyme Inhibitors to Healthy Subjects

Reference ID: 3779909

Treatment/ PK Parameter	Group 1		Group 2		Group 3	
	OPC-34712 Alone (n = 12)	OPC-34712 with CYP3A4 Inhibitor (n = 12)	OPC-34712 Alone (n = 11)	OPC-34712 with CYP2B6 Inhibitor (n = 11)	OPC-34712 Alone (n = 11)	OPC-34712 with CYP2D6 Inhibitor (n = 11)
C_{max} (ng/mL)	9.17 (3.98)	9.74 (5.74)	8.21 (4.68)	8.82 (4.81)	8.55 (4.48)	5.04 (1.56)
t_{max} (h)[a]	10.01 (6.00-24.00)	24.00 (24.00-72.00)	8.00 (2.00-48.00)	6.00 (2.17-8.00)	8.00 (6.00-24.05)	8.00 (6.00-48.00)
$t_{1/2,z}$ (h)	58.1 (16.4)	78.1 (19.6)	65.3 (24.9)	66.7 (26.5)	55.7 (19.5)	92.8 (27.6)
AUC_t (ng·h/mL)	753 (371)	965 (598)	620 (266)	526 (208)	708 (351)	545 (223)
AUC_∞ (ng·h/mL)	888 (508)	1500 (887)	690 (264)	627 (231)	822 (391)	815 (429)
Geometric Mean Ratio of C_{max}[b]	0.98 (0.85-1.12)		1.12 (0.92-1.37)		0.63 (0.50-0.81)	
Geometric Mean Ratio of AUC_t[b]	1.20 (1.06-1.35)		0.86 (0.75-0.97)		0.79 (0.67-0.92)	
Geometric Mean Ratio of AUC_∞[b]	1.46 (1.34-1.60)		0.84 (0.70-1.00)		0.97 (0.83-1.13)	

-source: Table 9.2.3.2.2-1 of study report

Table 3: Mean (SD) OPC-34712 and DM-3411 Metabolite Pharmacokinetic Parameters Following Administration of 2 mg OPC-34712 to Healthy Subjects (Poor Metabolizers of CYP2D6 isozyme)

Analyte/ PK Parameter	Group 4	
	OPC-34712 (n = 6)	DM-3411 (n = 6)
C_{max} (ng/mL)	29.2 (6.63)	3.73 (1.17)
t_{max} (h)[a]	5.52 (1.00-8.00)	24.00 (2.00-36.03)
$t_{1/2,z}$ (h)	79.9 (11.7)	76.5 (21.0)
AUC_t (ng·h/mL)	2324 (958)	351 (143)
AUC_∞ (ng·h/mL)	3439 (1477)	420 (168)
CL/F (L/h)	0.693 (0.354)	NA
Geometric Mean Ratio of C_{max}[b]	1.23 (0.97-1.58)	0.47 (0.32-0.68)
Geometric Mean Ratio of AUC_t[b]	1.79 (1.27-2.54)	0.52 (0.38-0.72)
Geometric Mean Ratio of AUC_∞[b]	2.21 (1.44-3.39)	0.54 (0.38-0.76)

-source: Table 9.2.3.3.1-1 of study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusions:** Coadministration of potent CYP3A4 or CYP2D6 inhibitors with OPC-34712 resulted in about 2-fold higher exposure and about a 1.5-fold increase in the terminal elimination half- life of OPC-34712. Coadministration of a potent CYP2B6 inhibitor did not result in significant changes in extent and rate of absorption of OPC-34712.
- **Reviewer's Comments:**

1) All subjects enrolled in Group 4 were discontinued prior to administration of the Day 15 dose (OPC + CYP inhibitors). This was likely due to safety consideration. The expected AUC of brexpiprazole in CYP2D6 PMs when ketoconazole was present (ticlopidine was not expected to have clinically meaningful effect on the PK of brexpiprazole), was four times of that when brexpiprazole was given alone; so the expected exposure for a single 2 mg dose would be like as 8 mg when given with ketoconazole in CYP2D6 PMs, and it exceeded the established MTD of 6 mg in healthy volunteers.
2) There were significant amount of subjects had predose concentrations at period 2.

	Keto group	Ticlo group	Quinidine group
# total subjects	12	11	11
#subjects with measureable predose conc at period 2	8	9	8
#subjects with predose con.>5%Cmax at period 2	0	3	1

According to BA/BE guidance, if the predose concentration is ≤ 5% of Cmax value in that subject, the subject's data without any adjustments can be included in all PK measurements and calculations. However, sponsor's analysis included all the subjects. Reviewer performed independent analysis excluding those subjects with predose conc >5% of Cmax for ticlopidin and quinidine groups (Table below). The reanalysis did not change conclusions about the degree of effect of enzyme inhibitors on brexpiprazole exposure.

Geometric mean ratio, T/R (90% CI),	Ticlopidine group N=8	Quinidine group N=10
Cmax	1.06 (0.840, 1.388)	1.13 (1.036, 1.244)
AUC	1.15 (1.017, 1.330)	1.94 (1.602, 2.641)

3) Brexpiprazole AUC was almost doubled, and C_{max} was increased 10-20% when administered with CYP3A4 and CYP2D6 isozyme inhibitors, compared to its administration alone. The limited increase in C_{max} when strong inhibitors were present indicated that minimal first pass metabolism during the absorption of brexpiprazole. This is in alignment with the observed high absolute bioavailability (about 95%).
4) Confounding effect from CYP2D6 genotype was precluded by the study design. Only CYP2D6 EM/IMs were included when evaluating a strong CYP inhibitor's effect.
5) Sponsor's conclusion is acceptable.

5. DDI-Activated Charcoal With Sorbitol

Report # 331-10-239 **Study Period**: 07/22/2011-09/08/2011
Title: A Single-dose, Historic-controlled, Pharmacokinetic Trial to Evaluate the Effect of Orally Administered Activated Charcoal on the Pharmacokinetics of OPC-34712 in Healthy Subjects

- **Objective:** To determine the effect of a single oral dose of activated charcoal and sorbitol on brexpiprazole (OPC-34712) pharmacokinetics (PK) when administered 1 hour after oral administration of OPC-34712.
- **Study Design:** This trial was an open-label, single-dose, single-period trial of 2-mg oral brexpiprazole administered to 12 male and female subjects. Brexpiprazole was administered in the morning of Day 1 after 8 hours of fasting with 240 mL of room temperature, still water. Each subject was administered a single 50-g/240-mL dose of activated charcoal/sorbitol 1 hour after administration of brexpiprazole. No food was consumed for 4 hours after brexpiprazole administration, and subjects were maintained in a sitting position for 4 hours following administration of brexpiprazole.
- **Blood Sampling Times:**

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Pharmacokinetics: Blood samples were collected on Day 1 at predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours postdose or at ET.
Pharmogenomics: A blood sample was collected predose on Day 1.

- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole	DM-3411
Method	6825-271	6825-271
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.3 to 100
Performance	Acceptable	Acceptable

- **Results:**

Study Population

Randomized/Completed/ Discontinued Due to AE	12/11/0
Age [Mean (range)]	28.5(23-44)
Male/Female	6/6
CYP2D6 URM/EM/IM/PM	0/8/2/1
Race (Caucasian/Black/other)	7/5/0

Pharmacokinetics

Table 1: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole Followed by 50 g/240 mL Oral Activated Charcoal/Sorbitol or 2 mg Brexpiprazole Alone (Historical Trials) to Healthy Subjects

PK Parameter	Brexpiprazole (2 mg) With Activated Charcoal/Sorbitol	Brexpiprazole Alone (Historical Trials, 2-mg Single Oral Dose)			
	331-10-239 (N = 10)	331-08-208 (N = 12)	331-10-241 (N = 16)	331-10-243 (N = 40)	331-10-244 (N = 24)
C_{max} (ng/mL)	22.5 (7.57)	25.3 (7.24)	23.7 (6.88)	25.2 (5.59)	29.1 (10.5)
t_{max} (h)[a]	2.00 (2.00-2.00)	4.00 (2.00-6.05)	5.00 (2.00-6.00)	4.02 (1.00-12.00)	4.00 (1.07-8.05)
AUC_t (ng·h/mL)	892 (473)	1322 (578)	1320 (645)	1640 (697)	1470 (585)
AUC_∞ (ng·h/mL)	1090 (678)	1624 (735)[b]	1670 (1090)[c]	1800 (838)[d]	1570 (764)[e]
$t_{1/2,z}$ (h)	75.6 (36.9)	61.6 (15.6)[b]	82.1 (30.8)[c]	93.9 (34.5)[d]	67.5 (22.1)[e]
CL/F (mL/h/kg)	36.9 (31.1)	NR[f]	21.8 (11.1)[c]	17.3 (7.19)[d]	21.1 (8.84)[e]

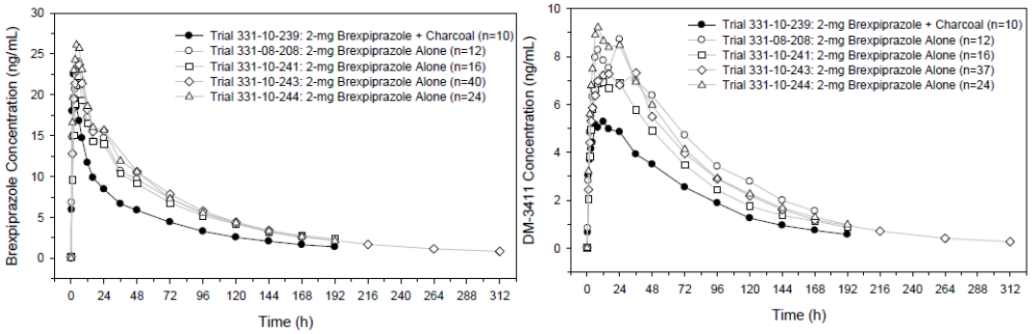
Table 2: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole Followed by 50 g/240 mL Oral Activated Charcoal/Sorbitol or 2 mg Brexpiprazole Alone (Historical Trials) to Healthy Subjects

Reference ID: 3779909

PK Parameter	Brexpiprazole (2 mg) With Activated Charcoal/Sorbitol	Brexpiprazole Alone (Historical Trials, 2-mg Single Oral Dose)			
	331-10-239 (N = 10)	331-08-208 (N = 12)	331-10-241 (N = 16)	331-10-243 (N = 37)	331-10-244 (N = 24)
C_{max} (ng/mL)	5.50 (2.16)	9.17 (3.98)	7.50 (4.70)	7.91 (3.28)	9.82 (5.23)
t_{max} (h)[a]	7.00 (6.00-24.00)	10.01 (6.00-24.00)	12.00 (3.00-24.00)	8.02 (2.00-48.00)	8.00 (6.00-24.00)
AUC_t (ng·h/mL)	434 (199)	753 (371)	601 (302)	728 (318)	738 (341)
AUC_∞ (ng·h/mL)	475 (237)[b]	888 (508)[c]	726 (357)[d]	783 (334)[e]	844 (389)[f]
$t_{1/2,z}$ (h)	68.6 (24.9)[b]	58.1 (16.4)[c]	68.1 (24.9)[d]	81.0 (34.1)[e]	61.9 (21.0)[f]

-source: Table 9.2.3.2.1-1 of study report

Figure 1: Mean Brexpiprazole (left) and DM-3411 (right) Plasma Concentrations Following Administration of 2 mg Brexpiprazole Followed by 50 g/240 mL Oral Activated charcoal/Sorbitol or 2 mg Brexpiprazole Alone to Healthy Subjects



- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusion:** Activated charcoal/sorbitol combination can be used to reduce brexpiprazole absorption in overdose situations. As compared with historical trial data, the mean Cmax and AUCinf of brexpiprazole were reduced by approximately 5% to 23% and 31% to 39%, respectively, when 50 g/240 mL oral activated charcoal/sorbitol was administered 1 hour after dosing with brexpiprazole.
- **Reviewer's Comments:**
  1) The majority of subjects experienced diarrhea, vomiting and nausea in this study, which was an expected outcome due to the administration of oral activated charcoal/sorbitol solution. Because of the objective was to evaluate the effect of activated charcoal/sorbitol on the exposure to brexpiprazole, no subjects were excluded from the PK analysis.
  2) Administration of activated charcoal/sorbitol combination in this trial did not completely eliminate the exposure to brexpiprazole after its administration, which may be due to the 1 hour delay in administration of activated charcoal/sorbitol combination. It is possible that an earlier administration of charcoal/sorbitol may result in even further reduction in brexpiprazole exposure.
  3) Sponsor's conclusion is acceptable.

brexpiprazole	charcoal	DDI	absolute BA	BE	age&gender
study #	331-10-239	331-08-208	331-10-241	331-10-243	331-10-244

Reference ID: 3779909

Cmax	22.5	25.3	23.7	25.2	29.1
AUCinf	1090	1624	1670	1800	1570
% decrease					
Cmax	-	11	5	11	23
AUCinf	-	33	35	39	31

6. DDI-Omeprazole

Report # 331-10-240 **Study Period**: 7/21/2011-10/18/2011
Title: An Open-label, Two-period Trial to Determine the Effect of Increased Gastric pH on the Pharmacokinetics of OPC-34712.

- **Objective:** To assess the effect of increasing gastric pH using omeprazole on the PK of OPC-34712.
- **Study Design:** This was a single center, open-label, sequential design trial in one group of 16 healthy subjects. A single 4-mg dose of brexpiprazole was administered on Day 1 followed by 40 mg omeprazole dosing in the morning on Days 13 through 17. A 4-mg single dose of brexpiprazole was also administered on Day 17, 2 hours after the omeprazole dose. All doses of brexpiprazole were administered after 8 hours of fasting, and lunch was served 4 hours after dose administration.
- **Blood Sampling Times:**
  Pharmacokinetics: Day 1 and Day 17 (brexpiprazole): predose and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, and 216 (Day 1 only) hours postdose
  Days 16 and 17 (omeprazole): 2 hours post-omeprazole dose
  Pharmacogenomics: A 10-mL blood sample was collected predose on Day.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Omeprazole & 5- OH omeprazole
Method	6825-271	
Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.5 to 1000
Performance	Acceptable	Acceptable

- **Results:**

Study Population

Randomized/Completed/ Discontinued Due to AE	16/15/0
Age [Mean (range)]	34.1(25-44)
Male/Female	13/3
CYP2D6 URM/ EM/IM/PM	1/9/6/0
Race (Caucasian/Black/other)	7/7/2

Pharmacokinetics

Table 1: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 4

Reference ID: 3779909

mg Brexpiprazole Alone or With 40 mg Omeprazole to Healthy Subjects

PK Parameter	Brexpiprazole Alone (n = 15)	Brexpiprazole With Omeprazole (n = 15)
C_{max} (ng/mL)	53.1 (20.0)	50.8 (17.9)
t_{max} (h)[a]	6.00 (2.00-8.00)	5.00 (3.00-8.00)
AUC_t (ng·h/mL)	3380 (1760)	4030 (1990)
AUC_∞ (ng·h/mL)	3710 (3150)[b]	4970 (2970)[b]
$t_{1/2,z}$ (h)	78.1 (22.0)[b]	76.3 (25.8)[b]
CL/F (mL/h/kg)	18.3 (9.98)[b]	14.2 (7.64)[b]

[a]Median (minimum-maximum). [b]n = 14. -Source: Table 9.2.3.2.1-1 in Study report

Table 2: Mean (SD) DM-3411 Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole Alone or With 40 mg Omeprazole to Healthy Subjects

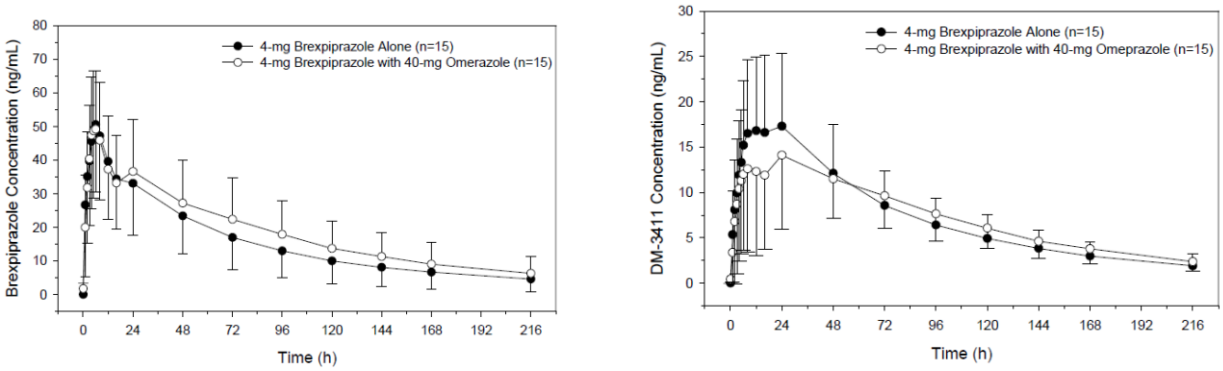
PK Parameter	Brexpiprazole Alone (n = 15)	Brexpiprazole With Omeprazole (n = 15)
C_{max} (ng/mL)	18.4 (8.53)	15.2 (8.76)
t_{max} (h)[a]	16.00 (6.00-24.00)	24.00 (4.00-72.00)
AUC_t (ng·h/mL)	1580 (636)	1580 (550)
AUC_∞ (ng·h/mL)	1740 (751)[b]	1950 (557)[c]
$t_{1/2,z}$ (h)	71.7 (20.9)[b]	69.8 (14.5)[c]

[a]Median (minimum-maximum).[b]n = 14.[c]n = 13. -Source: Table 9.2.3.2.2-1 in Study report

Table 3: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of 4 mg Brexpiprazole Alone and With 40 mg Omeprazole

Comparison	PK Parameter	GMR	90% CI
Brexpiprazole with omeprazole (T) versus brexpiprazole alone (R)	C_{max}	0.980	0.827-1.160
	AUC_t	1.223	1.102-1.357
	AUC_∞	1.180	1.058-1.315

Figure 1: Mean (SD) Brexpiprazole (Left) and DM-3411 (Right) Plasma Concentrations Following Administration of 4 mg Brexpiprazole Alone or With 40 mg Omeprazole to Healthy Subjects



- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusion:** Administration of brexpiprazole with omeprazole did not significantly affect its rate or extent of absorption of brexpiprazole.
- **Reviewer's Comments:**
  1) Prilosec (i.e., omeprazole) label states that "The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days." Therefore, the design of the study (i.e., 5 repeated daily dose and staggered dosing on the

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day with delayed administration of brexpiprazole) was expected to capture the maximal effect of increased pH on brexpiprazole PK.

2) Reviewer agrees that administration of omeprazole did not significantly affect the PK of brexpiprazole. Dosage adjustment of brexpiprazole is not likely to be necessary when coadministered with gastric pH modifiers.
3) There are significant number of subjects that have measureable predose concentrations of brexpiprazole in Period 2

# total subjects	15
#subjects with measureable predose conc at period 2	13
#subjects with predose con.>5%Cmax at period 2	3

According to BA/BE guidance, if the predose concentration is ≤ 5% of Cmax value in that subject, the subject's data without any adjustments can be included in all PK measurements and calculations. However, sponsor's analysis included all the subjects. Reviewer performed independent analysis excluding those three subjects with predose conc >5% of Cmax (Table below). The reanalysis did not change the original conclusion.

Geometric mean ratio, T/R (90% CI)	N=10
C_{max}	0.981 (0.862, 1.232)
AUC	1.180 (1.073, 1.340)

7.DDI-Rosuvastatin

Report # 331-12-207 **Study Period**: 06/25/2013-08/15/2013
Title: A Single-Dose, Open-Label, Cross-Over Trial of Potential for Inhibition of Breast Cancer Resistance Protein (BCRP) Efflux Transporter by Brexpiprazole in Healthy Subjects.

- **Objective:** To assess the inhibitory potential of brexpiprazole on Breast Cancer Resistance Protein (BCRP) efflux transporter using rosuvastatin as a substrate.
- **Study Design:** This was a single center, single-dose, open-label, fixed-sequence and cross-over study of approximately 25 healthy subjects. One 10-mg tablet of rosuvastatin was administered in the morning on Days 1 and 7 after at least an 8 hour fast. On Day 7, two 3 mg brexpiprazole tablets were administered in the morning, 2 hours before the administration of rosuvastatin.
- **Blood Sampling Time:**
  Pharmacokinetics: Blood samples for brexpiprazole and DM-3411 metabolite were collected on Day 1 and Day 7 predose and at 6 and 12 hours postdose on Day 7. Blood samples for rosuvastatin were collected on Days 1 and 7 predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 120, and 144 hours postdose. A blood sample for rosuvastatin was also collected at 144 hours following the Day 7 dose.
  Pharmogenomics: A blood sample was collected predose on Day 1.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411	Rosuvastatin
Method	6825-271	6825-271

Reference ID: 3779909

Matrix	plasma	plasma
Range (ng/mL)	0.3 to 100	0.02 to 20
Performance	Acceptable	Acceptable

- **Results:**

Study Population

Randomized/Completed/ Discontinued Due to AE	25/25/0
Age [Mean (sd)]	31.1(8.18)
Male/Female	11/14
CYP2D6 EM/IM/PM/Inconclusive	11/11/2/1
Race (Caucasian/Black/other)	17/5/3

Pharmacokinetics

Table 1: Mean (SD) Rosuvastatin Pharmacokinetic Parameters Following a Single Dose of 10-mg Rosuvastatin Alone or With 6-mg Brexpiprazole in Healthy Subjects

PK Parameter	Rosuvastatin Alone (n=24)	Rosuvastatin With Brexpiprazole (n=25)
C_{max} (ng/mL)	3.29 (1.58)	2.40 (1.14)
t_{max} (h)[a]	3.00 (1.50-5.00)	3.00 (1.50-5.00)
AUC_t (ng·h/mL)	26.8 (13.0)	26.8 (11.6)
AUC_∞ (ng·h/mL)	25.2 (12.5)[b]	28.1 (12.4)[c]
$t_{1/2,z}$ (h)	18.5 (9.9)[b]	22.0 (6.9)[c]
CL/F (mL/h/kg)	7149 (4045)[b]	5968 (3197)[c]

[a]Median (minimum-maximum). [b]n = 18.[c]n = 15

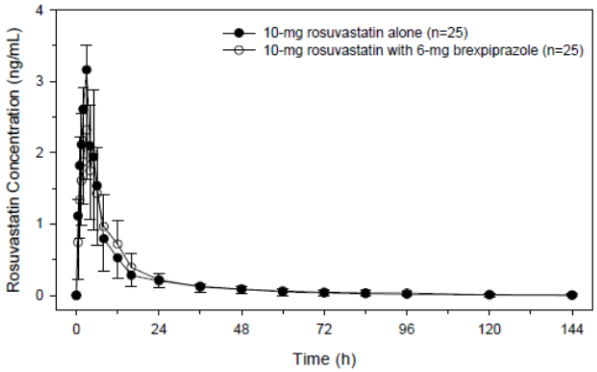
-Source: Table 11.5.2.3.2.1-1 of study report

Table 2: Geometric Mean Ratios (GMR) and 90% Confidence Intervals (CI) for Rosuvastatin Pharmacokinetic Parameters Following Administration of 10-mg Rosuvastatin Alone and With 6-mg Brexpiprazole in Healthy Subjects

Comparison	PK Parameter	GMR	90% CI
Rosuvastatin with Brexpiprazole (T) versus Rosuvastatin Alone (R)	C_{max}	0.76	0.69-0.84
	AUC_t	1.05	0.96-1.15
	AUC_∞	1.10	0.95-1.28

-Source: Table 11.5.2.3.3.1-1 of study report

Figure 1: Mean (SD) Rosuvastatin Plasma Concentrations Following a Single Oral Dose of 10-mg Rosuvastatin Alone or With 6-mg Brexpiprazole Healthy Subjects



-Source: Figure 11.5.2.3.1.1-1 of study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

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- **Sponsor's Conclusion:** Administration of rosuvastatin with brexpiprazole did not affect Cmax, AUCt, and AUC∞ of rosuvastatin.
- **Reviewer's Comments:** A single 6-mg dose, which was the maximally tolerated dose in healthy volunteers, was chose to test the inhibitory effect of brexpiprazole on the PK of rosuvastatin, one of the recommended substrates for BCRP in Drug Interaction guidance. The reviewer agrees that a single 6-mg dose of brexpiprazole did not cause clinically important interaction on rosuvastatin exposure. No dosage adjustment is necessary for rosuvastatin under that scenario.

Reference ID: 3779909

V. Pharmacodynamics

1. Receptor Occupancy (1) in Healthy Volunteers

Report # 331-07-202 **Study Period**:11/25/2008-07/19/2009
Title: A Phase 1, Open-Label, Positron Emission Tomography (PET) Study in Healthy Subjects Following a Single Oral Dose of OPC-34712

- **Objectives:** 1) To determine the degree of striatal D2/D3 receptor occupancy induced by OPC-34712 at different dose levels. 2) To determine the pharmacokinetics (PK) of OPC-34712 and its metabolites following a single oral dose of OPC-34712. 3) To determine the tolerability and safety of OPC-34712 following single oral dosing.
- **Study Design:** This was an open-label, single-dose trial in healthy male and female subjects aged 18 to 45 years, inclusive, to determine the degree of striatal D2/D3 receptor occupancy induced by OPC-34712 at different dose levels. Overall, 15 subjects were enrolled in the trial: 2 subjects each received 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, 4.0 mg, and 6.0 mg OPC-34712; 3 subjects received 5.0 mg OPC-34712. ^{11}C-raclopride was used as a radioligand for the D2/D3 receptor.
- **PET Scan Times:** Three positron emission tomography (PET) scans were performed per subject: baseline, 4 hours postdose, and 23.5 hours postdose to reflect baseline, maximum plasma concentration (Cmax), and post-Cmax time points, respectively.
- **PK Sampling Times:** Blood samples were drawn predose and at 0.5, 1, 2, 2.5, 3, 4, 4.5, 5, 5.5, 6, 8, 12, 16, 23.5, 24, 24.5, 25,36, 48, 72, 96, 120, and 144 hours postdose.
- **Analytical Method:** LC-MS/MS

Analyte	Brexpiprazole & DM-3411
Method	6825-271
Matrix	plasma
Range (ng/mL)	0.3 to 100
Performance	Acceptable

- **Results:**

1. Study population:

Enrolled/Completed/ Discontinued Due to AE	15/14/0
Age [Mean (range)]	33.9 (25-45)
Male/Female	14/1
Race (Caucasian/Black/Asian)	0/13/2

2. Pharmacokinetics

Table 1: Mean OPC-34712 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of OPC-34712 to Healthy Subjects

Reference ID: 3779909

Parameters	0.25 mg (n = 2)	0.5 mg (n = 2)	1.0 mg (n = 2)	2.0 mg (n = 2)	4.0 mg (n = 2)	5.0 mg (n = 2)[a]	6.0 mg (n = 2)
C_{max} (ng/mL)	2.60	7.68	13.1	20.9	50.5	68.7	64.1
t_{max} (h)[b]	2.24	4.34	7.48	4.96	5.71	6.54	9.34
AUC_t (ng·h/mL)	106	332	838	1280	3100	3870	4220
AUC_∞ (ng·h/mL)	134	381	924	2300	4170	5030	7040
$t_{1/2,z}$ (h)	47.86	55.62	124.29	132.44	73.43	74.56	95.06
CL/F (mL/h/kg)	25.7	21.6	14.2	12.2	11.3	15.6	14.2

- Source: Table 9.2.3.3.1-1 of study report

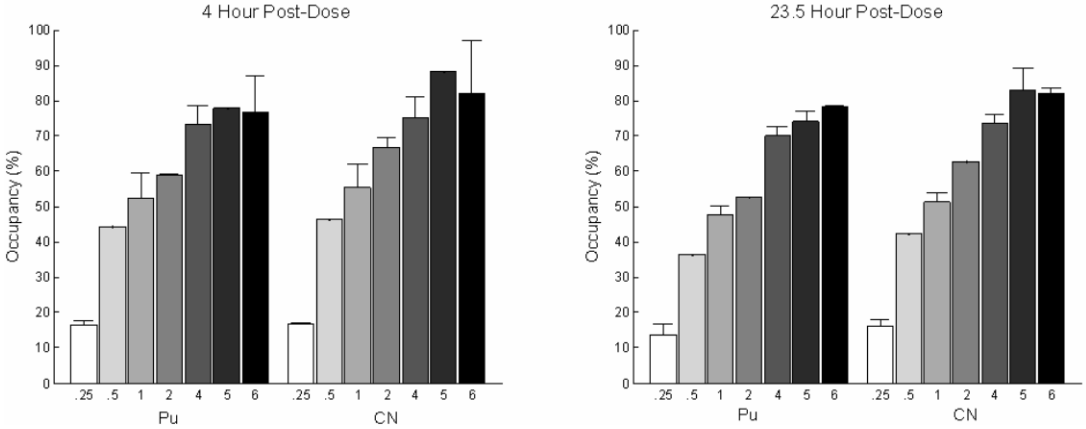
Table 2: Mean DM-3411 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of OPC-34712 to Healthy Subjects

Parameters	0.25 mg (n = 2)	0.5 mg (n = 2)	1.0 mg (n = 2)	2.0 mg (n = 2)	4.0 mg (n = 2)	5.0 mg (n = 2)[a]	6.0 mg (n = 2)
C_{max} (ng/mL)	1.13	2.06	2.84	5.66	6.78	12.2	17.4
t_{max} (h)[b]	12.00	20.2	20.5	25.7	11.2	24.0	11.4
AUC_t (ng·h/mL)	61.0	144	230	430	479	955	1290
AUC_∞ (ng·h/mL)	84.8	170	326	724	724	1470	ND
$t_{1/2,z}$ (h)	42.68	47.63	77.83	50.90	119.71	68.43	ND

Source: Table 9.2.3.3.2-2 of study report

3. Pharmacodynamics: Receptor Occupancy

Figure 1: Mean (SD) D2/D3 Receptor Regional Occupancy After Single Dose Administration of OPC-34712 to Healthy Subjects at 4 Hours and 23.5 Hours Post-Dose



Source: Figure 9.3.1-1 of the study report

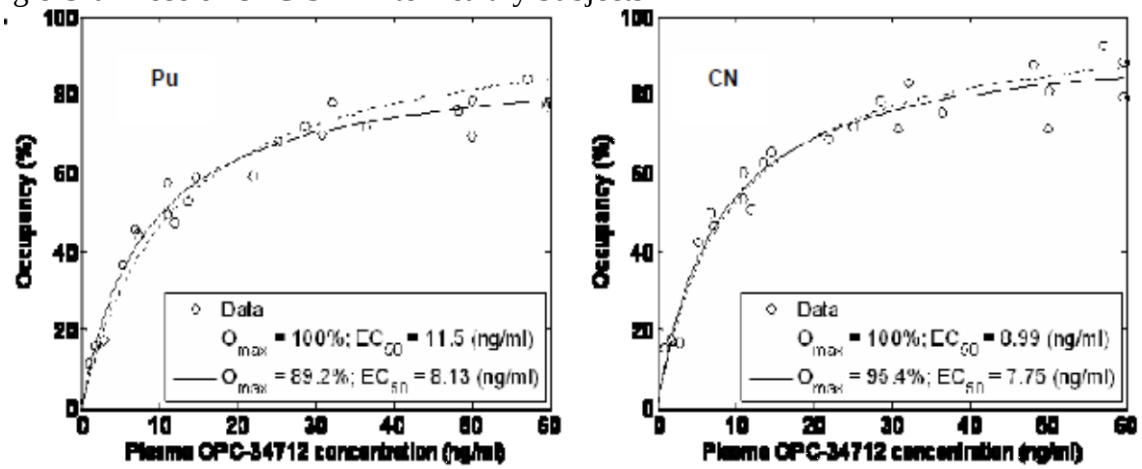
Table 3: Regional estimates of receptor occupancy (%) of 4 and 23.5 hour post-dose scans

Reference ID: 3779909

Dose (mg)	Subjects	Putamen			Caudate Nucleus		
		baseline	4 hours	23.5 hours	baseline	4 hours	23.5 hours
0.25	009	3.41	2.87	3.02	3.01	2.49	2.55
	015	4.01	3.32	3.38	3.41	2.84	2.82
0.5	001	4.28	2.39	2.71	3.67	1.97	2.11
	002	NA	2.67	3.06	NA	2.04	2.4
1	007	2.94	1.55	1.49	2.67	1.32	1.25
	008	4.55	1.94	2.48	3.99	1.59	2.01
2	003	4	1.64	1.89	3.39	1.06	1.27
	014	3.42	1.41	NA	2.72	0.945	NA
4	004	3.98	1.21	1.28	3.29	0.946	0.926
	013	4.37	1.01	1.23	3.57	0.731	0.88
5	011	4.06	NA	1.14	3.57	NA	0.774
	012	3.56	0.781	0.853	2.61	0.308	0.33
6	005	3.96	0.633	0.872	3.32	0.247	0.559
	006	3.8	1.16	0.819	3.46	0.993	0.653

- Source: Table 2 on page 1959 of study report

Figure 2: Dopamine D2/D3 Receptor Occupancy-Plasma Concentration of OPC-34712 Following a Single Oral Dose of OPC-34712 to Healthy Subjects



Source: Figure 9.4.1-1 of the study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Conclusions:**
  1) OPC-34712 and DM-3411 metabolite C_{max} and AUC PK parameters increased with the dose administered after single dosing of OPC-34712 (0.25 to 6 mg).
  2) After single-dose administration of OPC-34712 to healthy subjects, plasma concentrations up to 60 ng/mL corresponded to more than 80% and 90% dopamine D2/D3 receptors occupancies in the putamen and caudate nucleus, respectively.
- **Reviewer's Comment:** PK results from this trial seemed to be similar to those obtained from other trials.

Reference ID: 3779909

2. Receptor Occupancy (2) - in Schizophrenia Patients

Report # 331-08-209 **Study Period**:11/19/2009-07/30/2010
Title: A Phase 1b, Multicenter, Randomized, Double-blind, Active-controlled Pilot Polysomnography Study of the Effects of OPC-34712 on Sleep in Adult Subjects with Stable Schizophrenia

- **Objective:** To examine if OPC-34712 has a better sleep profile compared with aripiprazole as measured by polysomnography (PSG) in adult subjects with stable schizophrenia during 4 weeks of treatment.
- **Study Design:** This was a phase 1b, multicenter, randomized, double-blind, active-controlled pilot PSG trial to examine if OPC-34712 has a better sleep profile compared with aripiprazole in adult subjects with stable schizophrenia. A total of 75 subjects were enrolled at 10 US sites and randomized to one of two treatment groups (OPC-34712 or aripiprazole). To assess biophysiological changes that occur during sleep, 9 PSG recordings were completed during the trial. The trial consisted of 3 phases: Screening Phase, 4-week Double-blind Treatment Phase, and Safety follow-up phase. The double-blind treatment phase consisted of a 7-day titration period and a 21-day fixed dose period. The initial titration was administered as follows: OPC-34712: 2 mg × 3 days, 3 mg × 2 days, reaching 4 mg by Day 6
  Aripiprazole: 10 mg × 3 days, 15 mg × 2 days, reaching 20 mg by Day 6.
- **PK Sampling times:** Day 1 prior to randomization, Day 14 just prior to leaving for the sleep clinic, Day 15 upon returning from the sleep clinic, Day 28 just prior to leaving for the sleep clinic, and Day 29 upon returning from the sleep clinic. Serial PK samples were also taken on Day 21 as follows: predose and then postdose at 1, 2, 3, 4, 5, 6, 8, 12 hours (or prior to laying down for sleep) and 24 hours (or right after waking up on Day 22).
- **PSG Scan Times:** Total 9 PSG recordings were done. A screening PSG (PSG no.1) was done on the night of Day −8; Subjects had PSG no. 2 and no. 3 on the nights of Day −2 and Day −1. Subjects had PSG no. 4 and no. 5 on the nights of Day 6 and 7 (Week 1), followed by PSG no. 6 and no. 7 on the nights of Day 13 and 14 (Week 2), and PSG no. 8 and no. 9 on the nights of Day 27 and 28, respectively (Week 4).
- **Analytical Method:**

Analyte	Brexpiprazole & DM-3411	Aripiprazole & dehydro-aripiprazole
Method	LC-MS/MS	LC-MS/MS
Matrix	Plasma	Plasma
Range (ng/mL)	0.3 to 100	0.5 to 500
Performance	Acceptable	Acceptable

- **Results:**

1. Study population:

	Brexpiprazole	Aripiprazole
Randomized/Completed/ Discontinued Due to AE	39/33/2	36/29/1
Age [Mean±SD]	39.8±11	42.3±8.8
Male/Female	29/10	28/8

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Race (Caucasian/black/asian)	13/25/1	7/29/0

2. Pharmacokinetics

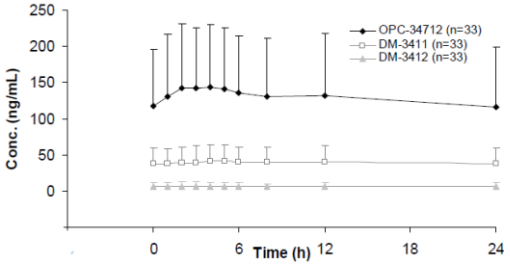
Table 1: Mean (SD) OPC-34712, DM-3411, and DM-3412 Pharmacokinetic Parameters Following 4 mg Daily Dose of OPC-34712 to Subjects with Schizophrenia on Day 21

PK Parameter	OPC-34712 (n = 33)	DM-3411 (n = 33)	DM-3412 (n = 33)
C_{max} (ng/mL)	158 (92.4)	46.4 (23.2)	7.58 (5.97)
t_{max} (h)[a]	4.00 (0.00-23.95)	5.00 (0.00-24.00)	3.00 (0.00-24.00)
AUC_{τ} (ng·h/mL)	2970 (1760)[b]	968 (474)[c]	171 (125)[d]
C_{min} (ng/mL)	109 (75.1)	33.5 (20.3)	5.57 (4.23)
C_{avg} (ng/mL)	124 (73.4)[b]	40.3 (19.8)[c]	7.13 (5.20)[d]

[a]Median (minimum-maximum). [b]n = 29. [c]n = 27. [d]n = 21.

-Source: Table 10.2.1-1 of study report

Figure 1: Mean Concentration-time Profiles of OPC-34712, DM-3411, and DM-3412 Following 4 mg Daily Dose of OPC-34712 to Subjects with Schizophrenia on Day 21



3. Pharmacodynamics:

Table 2: Summary of Mean Change From Baseline in Objective Sleep Parameters as Determined by Polysomnography (OC-MMRM)

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Sleep Parameter Statistic	OPC-34712 4 mg			Aripiprazole 20 mg		
	Week 1 (N = 37)	Week 2 (N = 36)	Week 4 (N = 34)	Week 1 (N = 33)	Week 2 (N = 31)	Week 4 (N = 29)
SWS (minutes)						
Baseline mean (SD)	49.15 (39.01)			37.44 (28.09)		
LS mean change[a]	−1.49	−5.33	−5.64	−2.23	−3.02	0.44
Treatment difference	0.74	−2.31	−6.08			
95% CI	−7.23, 8.72	−11.0, 6.37	−15.8, 3.61			
p-value	0.8525	0.5963	0.2141			
TST (minutes)						
Baseline mean (SD)	371.46 (63.12)			347.42 (59.24)		
LS mean change[a]	1.04	15.27	0.01	−4.66	0.24	−16.35
Treatment difference	5.71	15.03	16.36			
95% CI	−22.1, 33.55	−13.0, 43.04	−12.1, 44.81			
p-value	0.6833	0.2871	0.2531			
Sleep efficiency						
Baseline mean (SD)	77.39 (13.15)			72.52 (12.10)		
LS mean change[a]	0.17	3.14	−0.06	−0.05	1.30	−2.10
Treatment difference	0.23	1.83	2.05			
95% CI	−5.04, 5.50	−3.65, 7.32	−3.32, 7.42			
p-value	0.9316	0.5067	0.4473			
WASO (minutes)						
Baseline mean (SD)	65.21 (40.64)			80.87 (49.40)		
LS mean change[a]	19.04	12.95	26.71	31.02	19.80	29.60
Treatment difference	−11.98	−6.85	−2.89			
95% CI	−30.8, 6.80	−27.7, 14.01	−26.1, 20.33			
p-value	0.2068	0.5138	0.8044			
NAW						
Baseline mean (SD)	11.90 (7.45)			13.60 (6.52)		
LS mean change[a]	0.77	0.13	−0.81	1.91	−0.42	−1.07
Treatment difference	−1.14	0.55	0.26			
95% CI	−3.84, 1.56	−2.13, 3.23	−2.00, 2.53			
p-value	0.4008	0.6821	0.8172			
LPS (minutes)						
Baseline mean (SD)	49.22 (57.71)			56.34 (61.58)		
LS mean change[a]	−20.05	−31.22	−26.54	−38.52	−28.71	−24.86
Treatment difference	18.47	−2.50	−1.68			
95% CI	−2.36, 39.31	−19.5, 14.54	−12.9, 9.52			
p-value	0.0812	0.7698	0.7637			

CI = confidence interval; LPS = latency to persistent sleep; MMRM = mixed model repeated measurements; NAW = number of awakenings; OC = observed cases; SD = standard deviation; SWS = slow wave sleep; TST = total sleep time; WASO = wake after sleep onset.
-source: Table 9.3-1 of study report

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusions:** No statistically significant differences between 4 mg OPC-34712 and 20 mg aripiprazole were observed for the objective sleep parameters as determined by PSG at Week 1, 2, or Week 4
- **Reviewer's comment:** Brexpiprazole and DM-3411 PK parameters seemed to be comparable with previous data obtained in subjects with schizophrenia (Trial 331-08-205).

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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 Do the E-R relationships support evidence of effectiveness in major depressive disorder (MDD) patients and schizophrenia patients?

With regard to the proposed indication of adjunctive treatment of MDD, the exposure-response relationship was consistent with the dose-response relationship. Although there was a trend of MADRS Total Score reduction in brexpiprazole-treated patients compared to placebo, there was no significant increase of efficacy with the increase of AUC within brexpiprazole-treated patients.

For the schizophrenia indication, the exposure-response relationship was also consistent with the dose-response relationship. There was a significant PANSS Total Score reduction in brexpiprazole-treated patients compared with placebo and there was a trend of increase of efficacy with an increase of AUC of brexpiprazole.

MDD Indication:

Sponsor claimed the efficacy of brexpiprazole was supported at doses of 2 mg/day and 3 mg/day (Table 1). Based on the primary analysis (change in MADRS Total Score), greater improvement was observed for fixed 2 mg/day (Trial 331-10-228) and 3 mg/day (Trial 331-10-227) doses. However, the p-values in Trials 331-10-227 did not meet the prespecified threshold due to multiplicity correction (ie, Hochberg correction p<0.01).

Table 1. MDD primary efficacy results

Trt group	N	Baseline	ΔMADRS	ΔΔMADRS	P-value
331-10-228					
Brex 2mg +ADT	187	26.6	-8.3	-3.1	0.0001
Placebo +ADT	191	27.1	-5.2		
331-10-227					
Brex 1mg +ADT	225	26.7	-7.7	-1.2	0.09
Brex 3mg +ADT	226	26.3	-8.0	-1.5	0.03
Placebo +ADT	218	26.2	-6.5		

Source: Sponsor's summary-clin-efficacy-mdd.pdf, Table C

We merged two fixed dose Phase 3 trials Trial 331-10-228 and Trial 331-10-227 together.There was a trend of MADRS Total Score reduction with higher Brexpiprazole exposure compared

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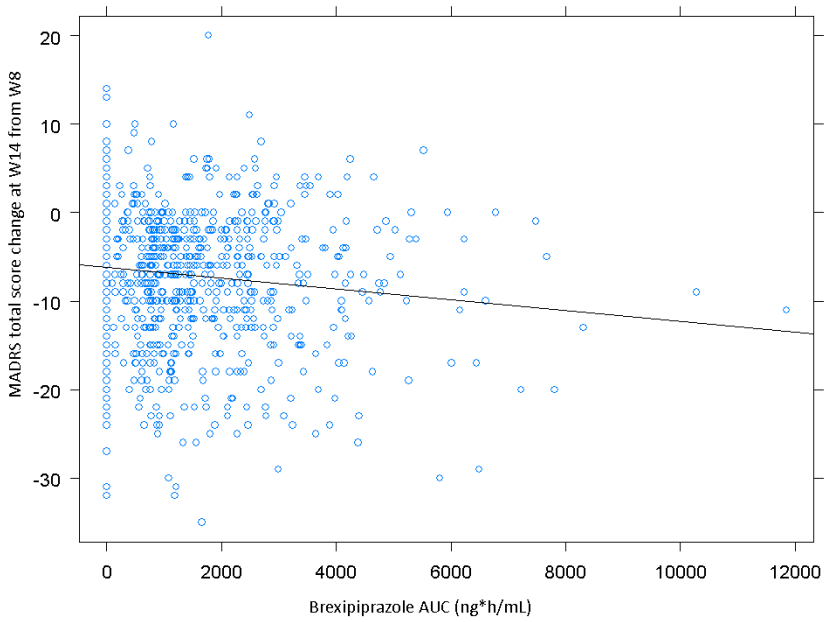
with placebo (P=0.0001, Figure 1). But there was no significant MADRS reduction within Brexpiprazole-treated patients .

Figure 1 Trend of MADRS reduction with in Brexpiprazole-treated groups compared with placebo



Source: Reviewer's analysis

In both Phase 3 trials Trial 331-10-228 and Trial 331-10-227, clinical response was defined as >= 50% reduction in MADRS Total Score at week 14 from the end of Phase A (Week 8). The proportion of responders treated with brexpiprazole was higher than patients with placebo (23% vs 15%). However, there was not a significant increase of responder rate with the increase of AUC in brexpiprazole-treated patients (Figure 2).

Figure 2. No significant increase of responder rate with the increase of AUC in Brexpiprazole treated patients

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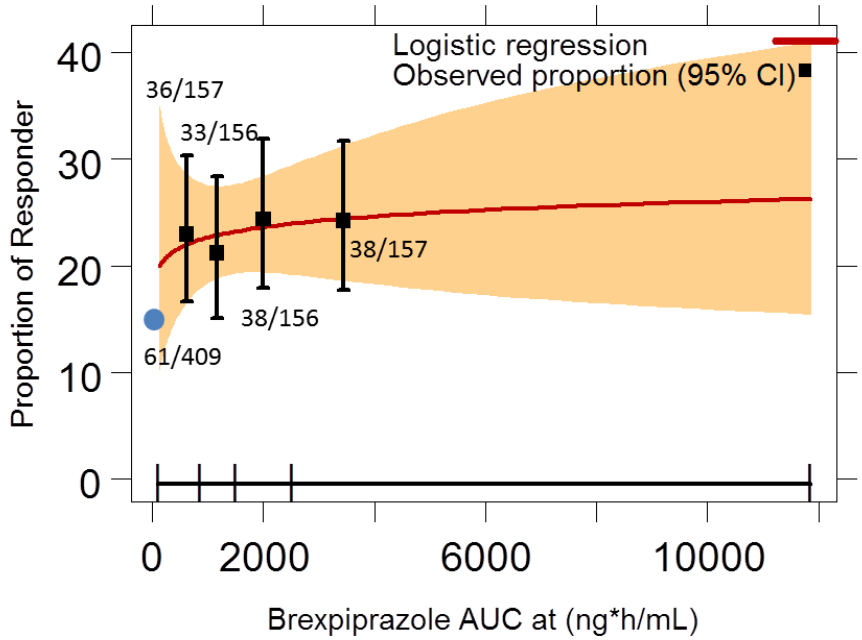

Source: Reviewer's analysis

Schizophrenia Indication:

Sponsor claimed the efficacy of brexpiprazole was supported at doses of 2 mg/day and 4 mg/day (Table 2). Based on the primary analysis (change in PANSS Total Score at Week 6), superiority of 4 mg/day was replicated in both phase 3 trials, whereas superiority for 2 mg/day was only seen in one trial (Trial 331-10-231).

Table 2. Schizophrenia primary efficacy results

Trt group	N	Baseline	ΔPANSS	ΔΔPANSS	P-value
331-10-230					
Brex 1 mg	117	93.2	-16.9	-3.37	0.1588
Brex 2mg	179	96.3	-16.6	-3.1	0.1448
Brex 4mg	181	95.0	-20.0	-6.5	0.0022
Placebo	180	94.6	-13.5		
331-10-231					
Brex 0.25 mg	87	93.6	-14.9	-2.89	0.291
Brex 2mg	180	95.9	-20.7	-8.7	<0.0001
Brex 4mg	178	94.7	-19.7	-7.7	0.0006
Placebo	178	95.7	-12.0		

Source: Sponsor's summary-clin-efficacy-scz.pdf, Table 2.7.3.2.1.1-1 & Table 2.7.3.2.1.2-1

We merged two fixed dose Phase 3 trials Trial 331-10-230 and Trial 331-10-231together. There was a significant PANSS Total Score reduction with higher Brexpiprazole exposure compared with placebo (P= 0.00005,Figure 1) and there was a trend of PANSS reduction with the increase of AUC within brexpiprazole-treated patients (P= 0.03).

Figure 3 Trend of PANSS reduction with higher Brexpiprazole exposure compared with placebo

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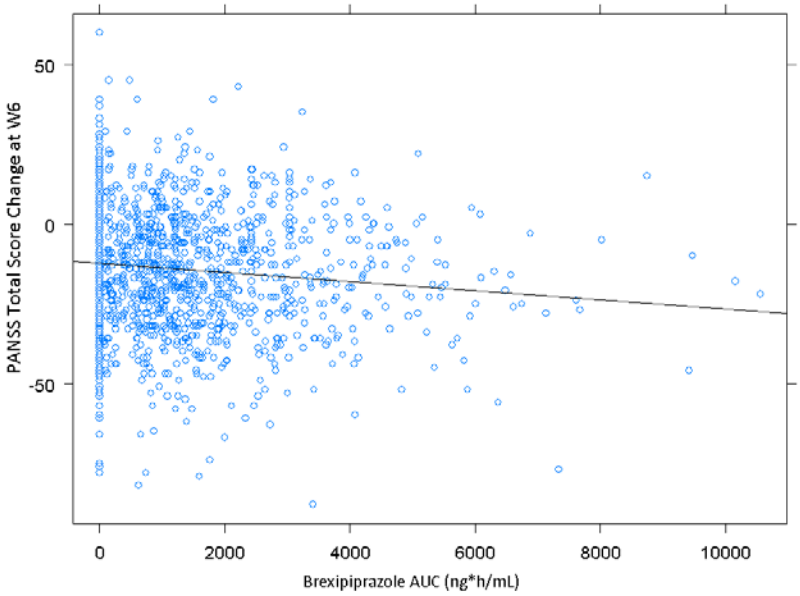
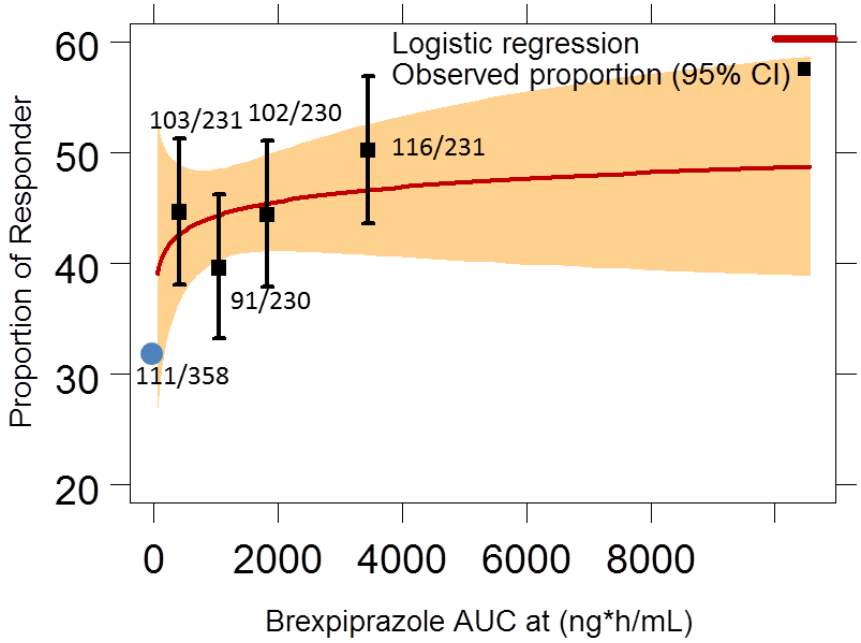


Source: Reviewer's analysis

In both Phase 3 trials Trial 331-10-230 and Trial 331-10-231, clinical response was defined as : >= 30% PANSS reduction at week 6/ET or CGI-I value of 1 or 2 at week 6/ET. The proportion of responders treated with Brexpiprazole was higher than patients with placebo (45% vs 31%). In addition, there was trend of increase of responder rate with the increase of AUC in Brexpiprazole treated patients (Figure 4).

Figure 4. Trend of increase of responder rate with the increase of AUC in Brexpiprazole treated patients



Source: Reviewer's analysis

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1.1.2 What are the characteristics of the E-R relationship for safety in MDD patients and schizophrenia patients?

The incidence of akathisia is dose-related in both MDD and schizophrenia patients treated with Brexpiprazole. The exposure-safety relationship was consistent with the dose-safety relationship. For both MDD and Schizophrenia indications, there are significant increases of Akathisia incidence rate with the increase of Brexpiprazole exposure.

The incidence of Akathisia is dose-related in both MDD and schizophrenia patients treated with Brexpiprazole (Table 3).

Table 3 Incidence of Akathisia is dose-related

MDD	1 mg (N=226)	2 mg (N=188)	3 mg (N=229)	Placebo (N=411)
Akathisia	10 (4.4)	14 (7.4)	31 (13.5)	7 (1.7)

Schizophrenia	0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	Placebo (N=368)
Akathisia	0	5 (4.2)	17 (4.6)	25 (6.9)	17 (4.6)

Source: summary-clin-safety-mdd.pdf, Table 2.7.4.2.1.1.1.3-1 & summary-clin-safety-scz.pdf, Table 2.7.4.2.1.1.1.3-1

There is higher incidence of akathisia in patients receiving a concomitant potent CYP2D6 inhibitor. With paroxetine or fluoxetine, the incidences of akathisia are 4.3%, 10.2%, and 24.0% at 1, 2, and 3 mg/day, compared to all other ADTs 4.5%, 6.5%, and 10.6%. However, the higher incidence of akathisia did not result in an imbalance of discontinuation.

The exposure-safety relationship was consistent with dose-safety relationship in both MDD and schizophrenia population. For MDD indication, there is a significant increase of Akathisia incidence rate with the increase of Brexpiprazole exposure (P = 0.002, Figure 5); for the Schizophrenia indication, there is also a significant increase of Akathisia incidence rate with the increase of Brexpiprazole exposure (P = 0.008, Figure 6).

Figure 5 Significant increase of Akathisia incidence rate with the increase of Brexpiprazole exposure in MDD Population

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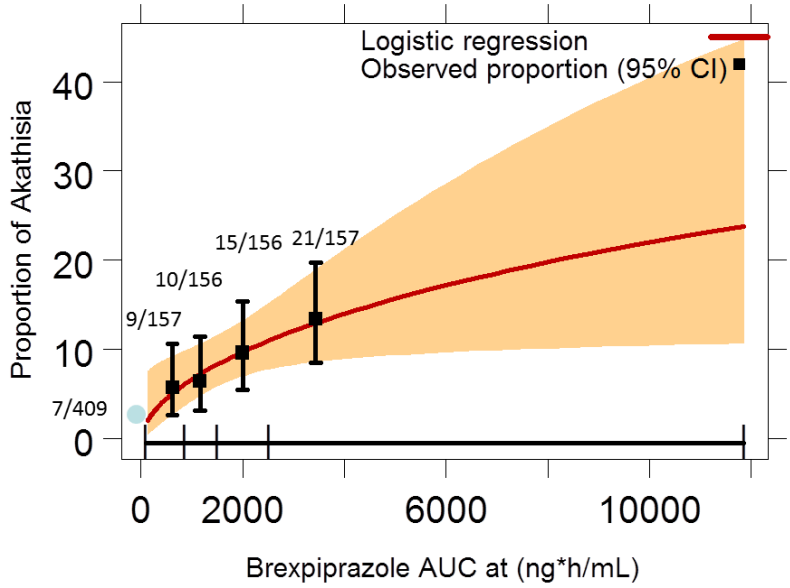
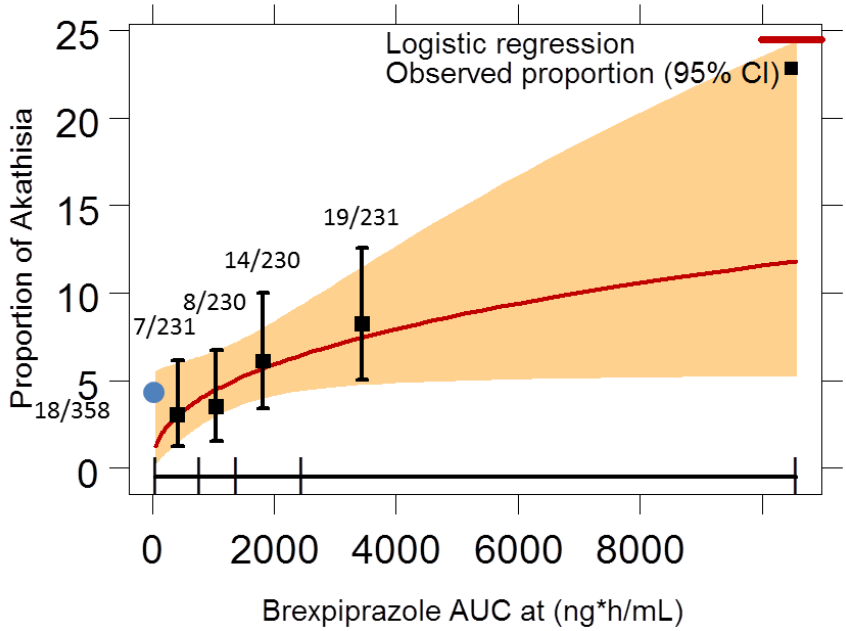


Source: Reviewer's analysis

Figure 6 Significant increase of Akathisia incidence rate with the increase of Brexpiprazole exposure in Schizophrenia Population



Source: Reviewer's analysis

1.1.3 Is the proposed dosage adjustment for brexpiprazole appropriate when co-administered with strong CYP3A4 inhibitors, or strong CYP2D6 inhibitors, or in CYP2D6 PMs?

No. Sponsor's proposed dosage adjustments for brexpiprazole when co-administered with strong CYP3A4 inhibitors, or strong CYP2D6 inhibitors, or in CYP2D6 PMs are not acceptable. Given our review of the dose/exposure-response

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relationships for both efficacy and safety, it is recommended for patients to receive half of the usual dose under certain scenarios of increased exposure, such as CYP2D6 PM status or concomitant medication with strong CYP3A or 2D6 inhibitors.

Based on our review of the dose/exposure-response relationships for both efficacy and safety, and adopting similar logic used for Aripiprazole (approved in 2002), half of the usual dose under certain scenarios of increased exposure, such as CYP2D6 PM status or concomitant medication with strong CYP3A or 2D6 inhibitors, would not compromise the efficacy but would reduce the incidence of akathisia.

Table 4 Aripiprazole vs. Brexpiprazole dose adjustment

Factors	Moiety	AUC ratio (GMR, 90%CI)	Dosage Adjustment
Strong CYP3A inhibitor (ketoconazole)	Aripiprazole[a] Active metabolite	1.63 1.77	Half of the usual dose
	Brexpiprazole	1.97(1.63-2.37)	Half of the usual dose[b]
Strong CYP2D6 inhibitor(quinidine)	Aripiprazole Active metabolite	2.12 0.66	half of the usual dose
	Brexpiprazole	1.94(1.49-2.53)	Half of the usual dose[b]
CYP2D6 PM(PM/EM)	Aripiprazole Active metabolite	1.82 0.66	Half of the usual dose
	Brexpiprazole	1.5 (simulation)	Half of the usual dose[b]
Strong CYP3A inhibitor	Aripiprazole	4.5 (simulation)	A quarter of the usual dose
& strong CYP2D6 inhibitor	Brexpiprazole	5.1 (simulation)	A quarter of the usual dose

Source: a. from original OCP review of Aripiprazole (2012); b. recommended dose adjustment.

1.1.4 Should brexpiprazole dose be adjusted in patients with moderate renal impairment?

Yes, brexpiprazole dose should be adjusted by half for patients with moderate renal impairment. We pooled 4 Phase 3 trials (Trial 331-10-228, 331-10-227, 331-10-230 and 331-10-231). In total, 909 patients are normal renal function, 633 patients have mild renal impairment, and 29 patients have moderate renal impairment (Figure 7). No severe renal impairment patient was included in the Phase 3 trials. The individual brexpiprazole concentration-time profiles were simulated using the sponsor's final PPK model. The normalized AUC was calculated with a reference dose of 2 mg. The exposures between normal renal function and mild renal impairment are similar. But Brexpiprazole exposure in patients with moderate renal dysfunction was significantly increased (i.e., 71% increase in mean $AUC_{0\text{-}inf}$). Therefore, brexpiprazole dose should be adjusted by half for patients with moderate renal impairment.

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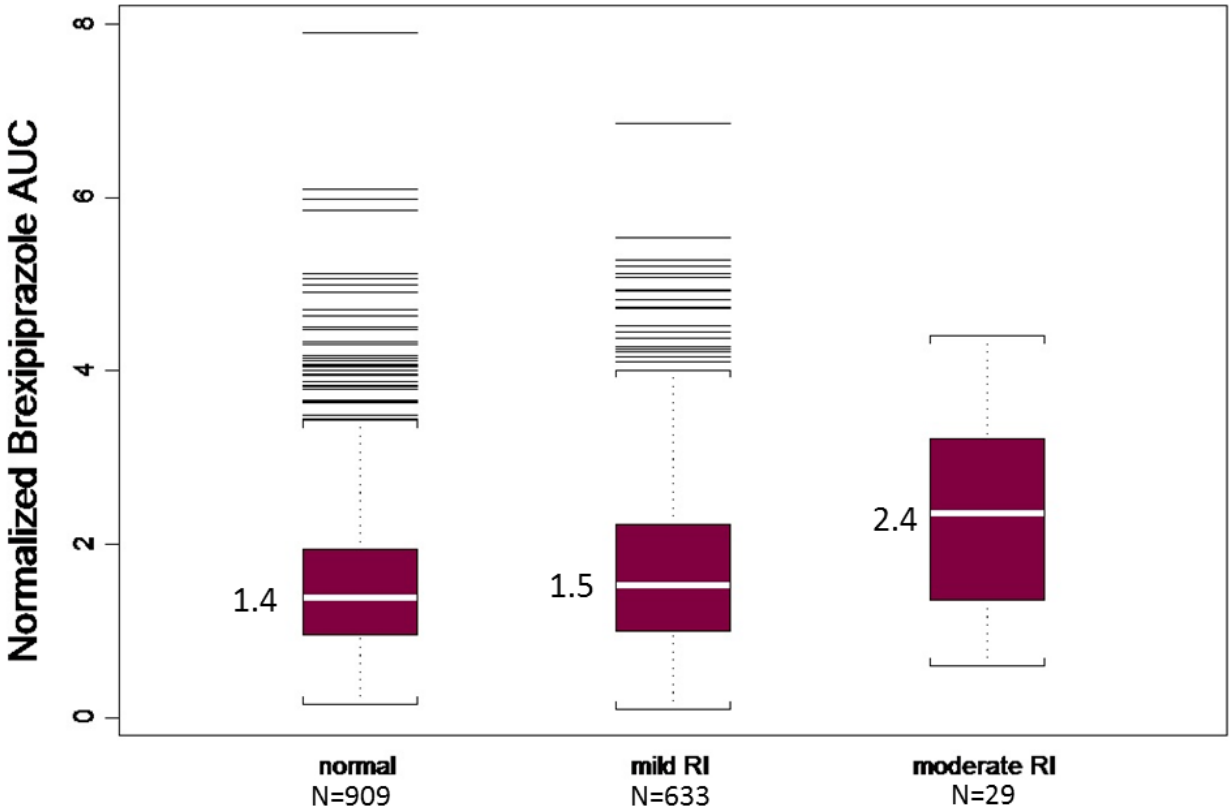
Figure 7 Brexpiprazole exposure comparisons between renal impairment patients



Source: Reviewer's analysis

1.2 Recommendations

Given our review of the dose/exposure-response relationships for both efficacy and safety, it is recommended for patients to receive half of the usual dose under certain scenarios of increased exposure, such as CYP2D6 PM status or concomitant medication with strong CYP3A or 2D6 inhibitors.

1.3 Label Statements

(b) (4)

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Reference ID: 3779909

(b) (4)

[redacted]

2 Pertinent regulatory background

OTSUKA submitted a new original NME NDA application for Brexpiprazole (OPC-34712). This is a split NDA for the following indications: (i) Adjunctive treatment of MDD (2 to 3 mg administered orally once daily) & (ii) treatment of Schizophrenia (2 to 4 mg administered orally once daily). The submission contains 12 Phase 2/3 trials utilized in population pharmacokinetic (PPK) and pharmacokinetic/pharmacodynamic (PK/PD) analysis (Table 6).

Table 6. Overview of clinical trials utilized in PPK and exposure-response analyses

Phase	Trial	Patient Population	Number of Subjects (%)	Dosing Regimen (Dose Range)	Endpoints
Phase 1	331-07-201	Healthy	42 (1.8%)	Single-dose (0.2-8 mg)	PK
	331-09-221	MDD	21 (0.9%)	Multiple, once-daily (1.5-4 mg)	PK
	331-09-225	Hepatic impaired	45 (1.9%)	Single-dose (2 mg)	PK
	331-09-226	Renal impairment	19 (0.8%)	Single-dose (3 mg)	PK
	331-10-244	Elderly	48 (2.0%)	Single-dose (2 mg)	PK
Phase 2	331-08-211	MDD	259 (11.0%)	Multiple, once-daily (0.15-2 mg)	PK [b] and PD
	331-09-222	MDD	172 (7.3%)	Multiple, once-daily (1-3 mg)	PK [b] and PD
	331-07-203	SCHZ	303 (12.9%)	Multiple, once-daily (0.25-6 mg)	PK [c] and PD
Phase 3 [a]	331-10-227	MDD	414 (17.6%)	Multiple, once-daily (1-3 mg)	PK [b] and PD
	331-10-228	MDD	167 (7.1%)	Multiple, once-daily (2 mg)	PK [b] and PD
	331-10-230	SCHZ	457 (19.4%)	Multiple, once-daily (1-4 mg)	PK [c] and PD
	331-10-231	SCHZ	410 (17.4%)	Multiple, once-daily (2-4 mg)	PK [c] and PD

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2.2.2.7-1.

Reference ID: 3779909

3 Results of Sponsor's Analysis

The main objectives of sponsor's population pharmacokinetic (PPK) analysis include:

1) Estimate brexpiprazole population exposure based on covariate effects:

– CYP2D6 phenotypes

– CYP2D6 EMs co-administered strong CYP2D6 inhibitors [fluoxetine (FLX) and paroxetine (PRX)]

2) Simulate brexpiprazole exposures :

– CYP2D6 EMs co-administered strong CYP3A4 inhibitors

– CYP2D6 PMs co-administered strong CYP3A4 inhibitors

– CYP2D6 EMs co-administered strong CYP2D6 inhibitor (FLX and PRX) ADTs and strong CYP3A4 inhibitors (dual inhibition).

A total of 2654 quantifiable brexpiprazole plasma concentrations from 154 healthy subjects and 3114 quantifiable brexpiprazole plasma concentrations from 1140 subjects with MDD and 5072 PK samples from 1247 schizophrenia subjects (2541 total subjects) were available for the population PK analysis. The evaluable dataset included 2357 subjects, who had at least one measurable brexpiprazole concentration.

3.1 Analytical Methodologies

The PPK model included two compartments with inter-individual variability on apparent clearance (CL/F), apparent volume of distribution in central compartment (V_c/F), and absorption rate constant (k_a). The following covariate effects were included in the final PPK model: (i) the effects of age, body weight, and sex on Vc/F and the effect of sex on CL/F; (ii) the effect of CYP2D6 metabolism status (poor, intermediate, and ultra-rapid relative to extensive) on CL/F; (iii) the effects of adjunctive co-administration of strong CYP2D6 inhibitor ADTs (FLX/PRX) and non-protocol mandated strong CYP2D6/3A4 inhibitors on CL/F; and (iv) a scaling factor on F1 where the relative bioavailability in MDD phase 2/3 was also estimated as compared to MDD phase 1, healthy and subjects with schizophrenia.
The expressions in the final population PK model for apparent volume of the central compartment (V_c/F) and apparent clearance (CL/F) are shown

$$\frac{V_c}{F}(L) = 105 * \left(\frac{BodyWeight}{78.2}\right)^{0.314} * \left(\frac{Age}{42}\right)^{0.352} * (0.779)^{Sex}$$

$$\frac{CL}{F}(L/hr) = 1.65 * (0.798)^{Sex} * (0.678)^{Poor} * (0.796)^{Inter} * (1.18)^{Ultra} * (0.655)^{Adj_ext} * (0.762)^{NP_Inh}$$

where Age is in years, Sex is 1 for females and 0 for males, Poor is 1 for poor CYP2D6 metabolizers and 0 otherwise, Inter is 1 for intermediate CYP2D6 metabolizers and 0 otherwise, Ultra is 1 for ultra-rapid CYP2D6 metabolizers and 0 otherwise, Adj_ext is 1 for extensive/ultra-rapid metabolizers that received strong CYP2D6 inhibitors and 0 otherwise, and NP_Inh is 1 for

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more than one non-protocol mandated moderate/strong CYP2D6/CYP3A4 inhibitor and 0 otherwise.

The final brexpiprazole population PK model equation for the phase 2/3 scaling factor, F1, is described by $F1 = (0.788)^{PhII_III}$, where PhII_III is 1 for Phase 2/3 studies in MDD and 0 for phase 1 studies in MDD.

PK data were analyzed using nonlinear mixed-effects modeling, as implemented by the NONMEM software 7.2. Diagnostic graphics and post-processing of NONMEM output was produced with PSN 3.1.0, XPose 4.1, R 2.15.3, and/or S-PLUS 8.2.

3.2 *PPK Model Parameters*

The final population PK parameter estimates are presented in Table 7.

Table 7. Final Population PK Parameters for Brexpiprazole

Reference ID: 3779909

Parameter	Parameter Description	Population Estimate (%SE)	Inter-Individual Variability (%SE)
θ_1	Apparent clearance, CL/F (L/h)	1.65 (2.1%)	61.1% (2.6%)
θ_2	Apparent volume of distribution in central compartment, Vc/F (L)	105 (2.8%)	51.4% (4.2%)
θ_3	Absorption rate constant, k_a (h^{-1})	0.635 (5.1%)	87.6% (4.1%)
θ_4	Apparent inter-compartmental clearance, Q/F (L/h)	0.701 (20.6%)	-
θ_5	Apparent volume of distribution in peripheral compartment, V_p/F(L)	28.4 (6.4%)	-
θ_7	Effect of more than one non protocol mandated CYP2D6/CYP3A4 Inhibitor on CL/F	-0.238 (20.5%)	-
θ_9	Effect of Intermediate CYP2D6 inferred metabolic status on CL/F	-0.204 (12.5%)	-
θ_{10}	Effect of Poor CYP2D6 inferred metabolic status on CL/F	-0.322 (15.9%)	-
θ_{11}	Effect of Ultra rapid CYP2D6 inferred metabolic status on CL/F	0.175 (55.1%)	-
θ_{14}	Effect of Female Sex on CL/F	-0.202 (11.4%)	-
θ_{15}	Effect of Age on V_c/F	0.352 (12.8%)	-
θ_{16}	Effect of Female Sex on V_c/F	-0.221 (13.6%)	-
θ_{17}	Effect of Body Weight on V_c/F	0.314 (22.9%)	-
θ_{18}	Effect of Strong CYP2D6 Inhibitor Adjunctive therapy on CL/F in extensive CYP2D6 metabolizers	-0.345 (11.9%)	-
θ_{19}	MDD Phase 2/3 scaling factor (vs. all other subjects	-0.212 (11.4%)	-
σ_1	Phase 1 proportional residual error	0.166 (3.7%)	-
σ_2	Phase 1 additive residual error (ng/mL)	0.15 FIXED [a]	-
σ_3	Phase 2/3 MDD proportional residual error	0.272 (4.2%)	-
σ_4	Phase 2/3 MDD additive residual error (ng/mL)	2.32 (23.9%)	-
σ_5	Phase 2/3 schizophrenia proportional residual error	0.231 (3.2%)	-
σ_6	Phase 2/3 schizophrenia Additive residual error (ng/mL)	1.10 (22.1%)	-

Source: 331-12-208-report-body.pdf, Table 4.3.2.3-1.

3.3 *Model Evaluation*

The final PPK model was mainly evaluated with standard diagnostic goodness of fit plots, bootstrapping method and prediction corrected visual predictive checks (pcVPCs).

Figure 8 presented goodness-of-fit (GOF) plots for the final brexpiprazole PPK model. Lines of identity, zero lines, and trend lines were overlaid as appropriate. The individual predictions fit well along the identity line, and the conditionally weighted residuals were relatively low and well distributed along the zero line relative to population predictions and time.

Figure 8 General Goodness-of-Fit for the Final Brexpiprazole PPK Model (Loess Smoothing Line in Red)

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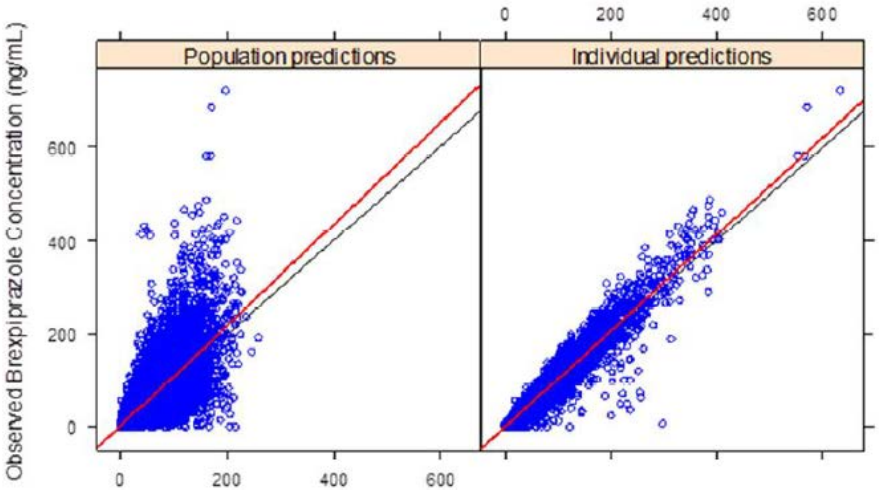

Source: 331-12-208-report-body.pdf, Figure 4.3.4.1-1.

One thousand bootstrapped data sets were generated using the same set of subjects as in the analysis dataset. Table 8 compares the final PK parameter estimates with the median and 90% confidence intervals (CIs) derived from the bootstrap runs. The median values of all parameters from bootstrapping were consistent with the original PPK estimates.

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Table 8 Point Estimates and 90% CIs for the Final Population PK Parameter Estimates From the Bootstrap

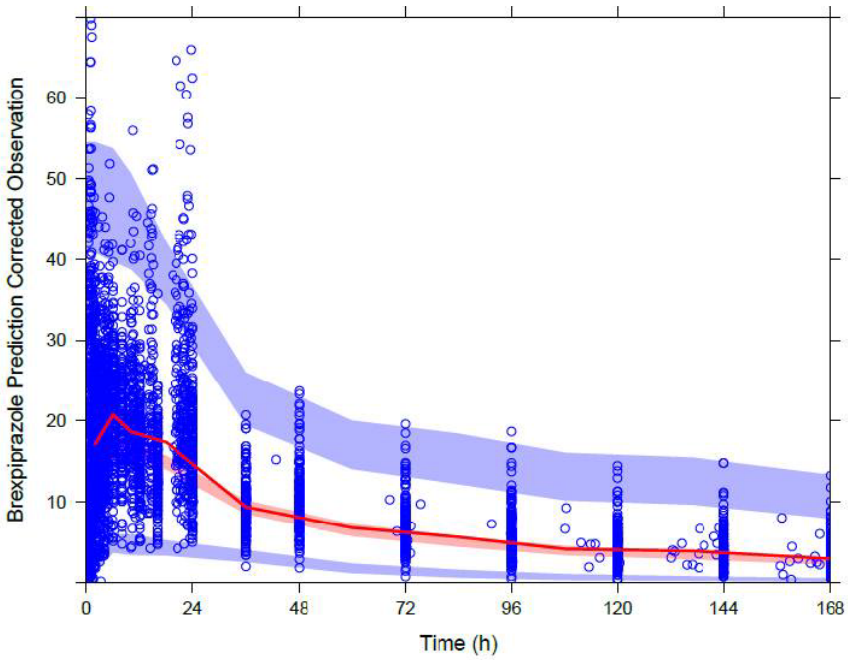
Parameter	Parameter Description	Point Population Estimate	Bootstrap Final Population PK Model Median (5th, 95th Percentiles)
θ_1	Apparent Clearance, CL/F (L/h)	1.65	1.65 (1.59, 1.71)
θ_2	Apparent Volume of distribution in central compartment, V_c/F (L)	105	104 (99.8, 109)
θ_3	Absorption Rate Constant, k_a (h^{-1})	0.635	0.629 (0.576, 0.683)
θ_4	Apparent Inter-compartmental clearance, Q/F (L/h)	0.701	0.708 (0.526, 1.07)
θ_5	Apparent Volume of distribution in peripheral compartment, V_p (L)	28.4	28.7 (25.6, 31.8)
θ_7	Effect of more than one non protocol mandated CYP2D6/CYP3A4 Inhibitor on CL/F	-0.238	-0.237 (-0.308, -0.152)
θ_9	Effect of Intermediate CYP2D6 inferred metabolic status on CL/F	-0.204	-0.203 (-0.243, -0.162)
θ_{10}	Effect of Poor CYP2D6 inferred metabolic status on CL/F	-0.322	-0.325 (-0.404, -0.228)
θ_{11}	Effect of Ultra rapid CYP2D6 inferred metabolic status on CL/F	0.175	0.173 (0.019, 0.352)
θ_{14}	Effect of Female Sex on CL/F	-0.202	-0.203 (-0.239, -0.160)
θ_{15}	Effect of Age on V_c/F	0.352	0.352 (0.273, 0.428)
θ_{16}	Effect of Female Sex on V_c/F	-0.221	-0.219 (-0.270, -0.171)
θ_{17}	Effect of Body Weight on Vc/F	0.314	0.312 (0.192, 0.438)
θ_{18}	Effect of Strong CYP2D6 Inhibitor Adjunctive therapy on CL/F in extensive CYP2D6 metabolizers	-0.345	-0.344 (-0.405, -0.275)
θ_{19}	MDD Phase 2/3 scaling factor (vs. all other subjects	-0.212	-0.212 (-0.250, -0.170)

Source: 331-12-208-report-body.pdf, Table 4.3.4.2-1

Prediction-corrected visual predictive checks of the final brexpiprazole PPK model for the first week of data are shown in Figure 9. There is reasonable agreement between the simulated and observed median lines except for a slight underestimation of early data. This may represent an inability to estimate the absorption as a first-order process, which is consistent with the fact that there was limited or no absorption data from phase 2/3 subjects.

Reference ID: 3779909

Figure 9 Prediction Corrected Visual Predictive Checks for the Final Brexpiprazole Population PK Model



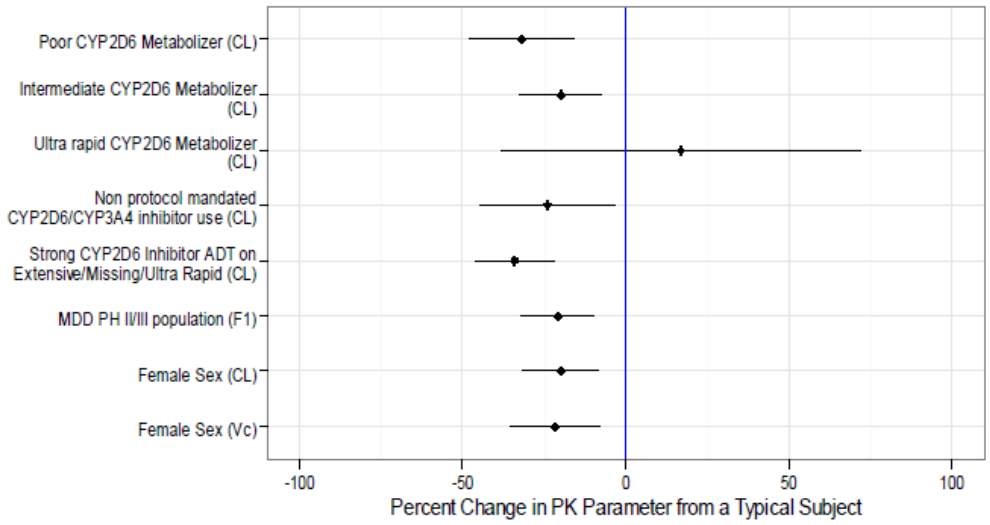
Source: 331-12-208-report-body.pdf, Figure 4.3.4.3-1

Reviewer's Comments: The final PPK model had no significant biases and represented an adequate fit to the data.

3.4 Magnitude of Covariate Effects

Percent changes in PK parameters (population average, standard errors) of statistically significant covariates are shown Figure 10.

Figure 10 Percent Change in PK Parameters (Population Average, Standard Errors) due to Categorical Covariates in the Final PPK Model



Source: 331-12-208-report-body.pdf, Figure 4.3.2.4-1

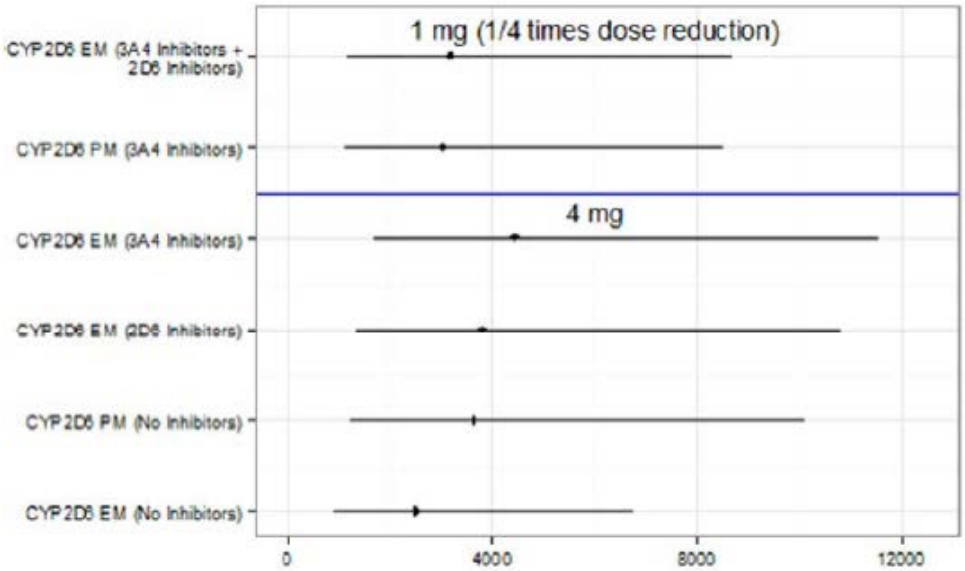
Reference ID: 3779909

The effect of age and weight (within 5th and 95th percentiles) on Vc/F was less than 20% each. In females, CL/F and Vc/F were estimated to be 20% and 22% lower than respective values in males, resulting in an estimated 25% higher brexpiprazole AUC in females compared with males. In CYP2D6 PM subjects, ultra-rapid and intermediate CYP2D6 metabolizer subjects, CL/F was estimated to be -32%, +18% and -20% than the value estimated for CYP2D6 EM subjects, corresponding to +47%, -21% and +25% change in AUC in these subjects, respectively. Co-administration of protocol-allowed strong inhibitors of CYP2D6 ADTs (FLX/PRX) in CYP2D6 EM subjects reduced the CL/F by 35%, corresponding to a 53% increase in AUC. The effect of the scaling factor of MDD phase 2/3 vs. all other subjects was estimated to be -21%, which may be explained by a slight lack of adherence to treatment in this group of subjects.

3.5 *Simulated Brexpiprazole Exposure in Subpopulations of Interest*

The final PPK model was used to simulate and compare steady-state AUC. Plots of median and SE of simulated steady-state AUC after 4 mg once daily administration of brexpiprazole in populations of interest is provided in Figure 11. Of note, an additional simulation of a dose of 1 mg (1/4 times dose reduction from 4 mg) was also included in the simulations to serve as a possible dosing reduction option in CYP2D6 PM subjects co-administered strong CYP3A4 inhibitors, and CYP2D6 EM subjects co-administered strong CYP2D6 inhibitor (FLX, PRX) ADTs and strong CYP3A4 inhibitors (dual inhibition).

Figure 11 Simulated AUC (Median and SE) in Populations of Interest



Source: 331-12-208-report-body.pdf, Figure 4.3.5-1

Simulated median brexpiprazole AUC ratios and CL/F changes after once-daily doses of 4 mg in phase 3 populations of interest change are provided in Table 9.

Table 9 Simulated Brexpiprazole CL/F Decrease and AUC Increase in Populations of Interest

Reference ID: 3779909

Population	Median CL/F (L/h)	Decrease in Median CL/F from Reference (%)	Fold Increase in Exposure (AUC_τ)
CYP2D6 EM Subjects [a]	1.46	0 (reference)	1 (reference)
CYP2D6 EM Subjects Administered CYP3A4 Inhibitors [a, b]	0.81	45	1.8
CYP2D6 PM Subjects Administered CYP3A4 Inhibitors [a, c]	0.31	79	4.8
CYP2D6 EM Subjects Administered CYP3A4 and CYP2D6 Inhibitors (Dual Inhibition) [a, d]	0.28	81	5.1

Source: 331-12-208-report-body.pdf, Table 4.3.5-1

Reviewer's Comments: The dose reduction based on simulated DDI exposure for CYP2D6 PM subjects co-administered strong CYP3A4 inhibitors, and CYP2D6 EM subjects co-administered strong CYP2D6 inhibitor (FLX, PRX) ADTs and strong CYP3A4 inhibitors (dual inhibition) are acceptable.

3.6 Exposure-Response Analysis

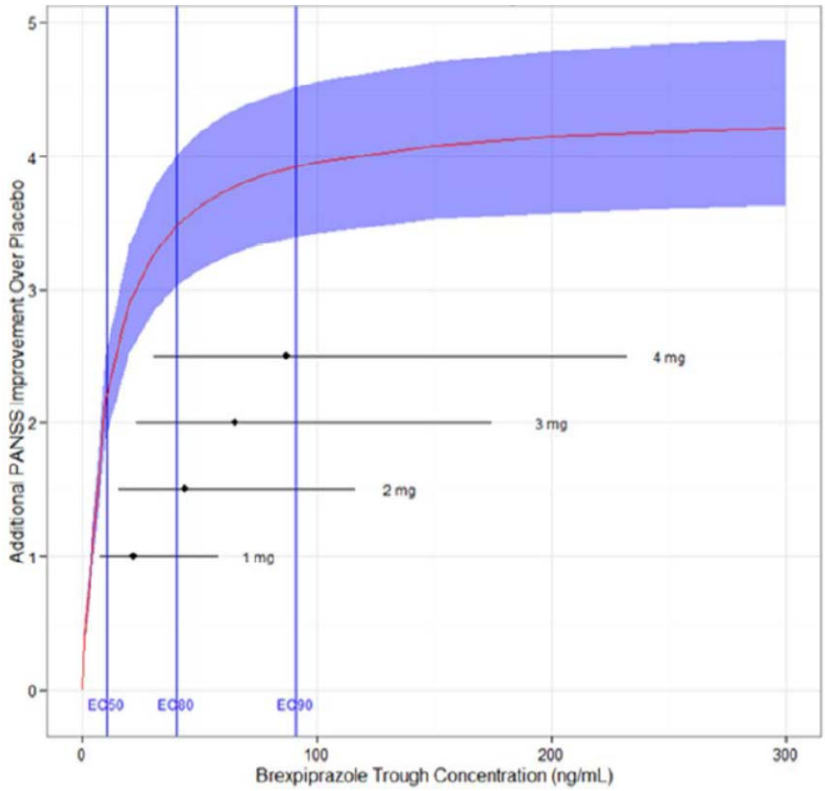
Sponsor conducted exposure-response analyses using efficacy data from all phase 2/3 trials and safety data from phase 3 trials only.

For subjects with MDD, a total of 1848 (1128 active and 720 placebo) subjects with MDD (12389 MADRS scores) from phase 2/3 trials were included in brexpiprazole exposure-MADRS response analyses, and brexpiprazole doses ranged from 0.5 mg to 3 mg once daily. A flat exposure relationship (improvement over placebo) between estimated brexpiprazole concentrations and change in MADRS score from baseline was observed in the range of measured concentrations.

For subjects with schizophrenia, a total of 1719 (1256 active and 463 placebo) subjects with schizophrenia (9967 PANSS scores) from phase 2/3 trials were available for the exposure-PANSS response analysis, and brexpiprazole doses ranged from 0.25 mg to 5 mg once daily. Results from exposure-efficacy response analyses suggested that brexpiprazole doses were associated with PANSS improvement over placebo, and an apparent relationship between brexpiprazole exposure and change in PANSS existed, which was described with a simple Emax model. Maximum drug-related effect on PANSS (Emax) on top of placebo was estimated to be 4.37 points. Brexpiprazole concentrations that exhibit 50% (EC50), 80% (EC80), and 90% (EC90) of Emax were estimated to be 10.1, 40.4, and 90.9 ng/mL, respectively. Model-predicted changes in PANSS scores from baseline over placebo versus simulated brexpiprazole trough concentrations in phase 3 trial subjects with schizophrenia are shown in Figure 12. Median brexpiprazole simulated trough concentrations achieved by daily brexpiprazole administration of 1 mg were above EC50, 2 mg at EC80, and 4 mg well above EC80 values.

Reference ID: 3779909

Figure 12 Model-Predicted Changes in PANSS Scores From Baseline Over Placebo Versus Brexpiprazole Trough Concentrations



Source:summary-clin-pharm.pdf, Figure 2.7.2.2.2.7.3-1

In subjects with MDD, a total of 1039 (629 active and 410 placebo) subjects from phase 3 trials were included in the primary exposure-safety analysis, and brexpiprazole doses ranged from 0.5 mg to 3 mg administered once daily. In subjects with schizophrenia, a total of 1310 (942 active and 368 placebo) subjects from phase 3 trials were included in the primary exposure-safety analysis, and brexpiprazole doses ranged from 0.5 mg to 4 mg administered once daily. By splitting the simulated exposure metrics into tertiles and using Kaplan-Meier plots, in subjects with MDD (co-administered with ADTs) or schizophrenia, no exposure-dependent increase in insomnia, change in body weight, or akathisia (except for a slight effect of Cmax on akathisia in MDD subjects) was observed during 42 days of treatment with brexpiprazole.

4 Reviewer's Analysis

Because of flexible dose reductions in Phase 3 trials, the reviewer conducted dose/exposure-efficacy analysis from phase 3 trials only (exposure-efficacy analysis result was demonstrated in the Section 1.1.1) and results were consistent with sponsor's analysis. However, FDA exposure-safety analysis (exposure-safety analysis result was demonstrated in the Section 1.1.2) demonstrated a significant increase of Akathisia incidence rate with the increase of Brexpiprazole exposure, which was consistent with the dose-safety relationship.

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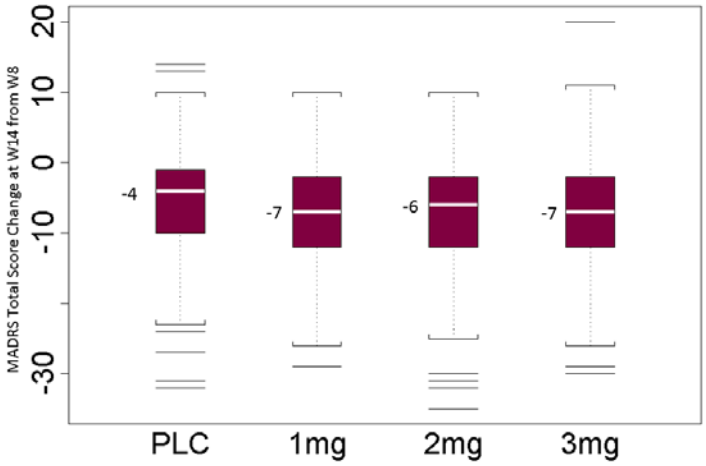
In FDA exposure-response analysis, the logistic regression model was applied. The individual brexpiprazole concentration-time profiles were simulated using the sponsor's final PPK model. Individual AUC was calculated with dose divided by clearance.

Dose-efficacy Analysis for MDD Indication:

We merged two fixed dose Phase 3 trials Trial 331-10-228 and Trial 331-10-227 together. There was no significant dose-response (change in MADRS Total Score) relationship in MDD population. But 3 arms (1mg, 2mg and 3mg) showed noticeable decrease of MADRS Total Score compared with placebo (Figure 13).

Figure 13 Dose-MADRS Relationship in MDD population



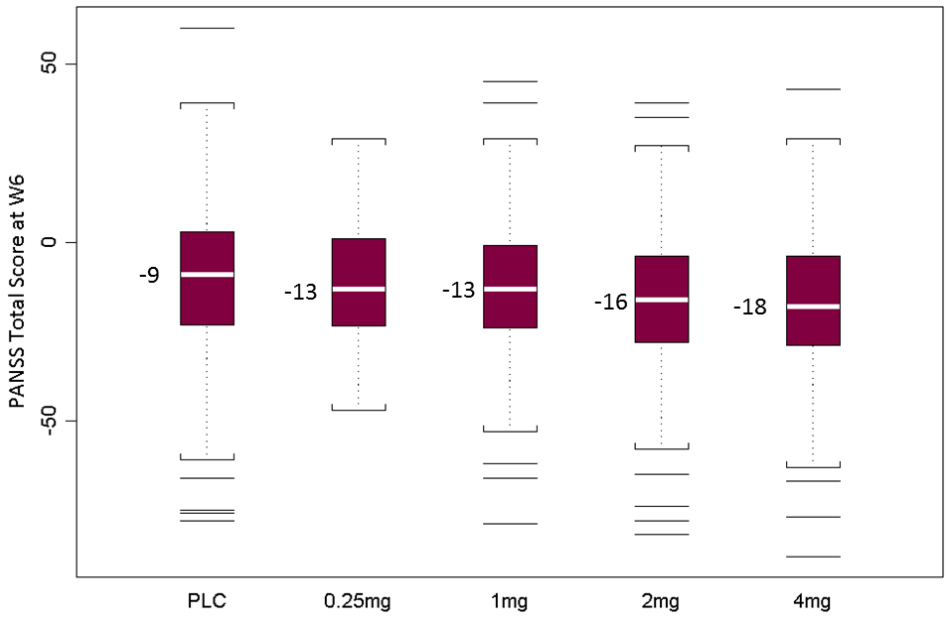
Source: Reviewer's analysis

Dose-efficacy Analysis for Schizophrenia Indication:

We merged two fixed dose Phase 3 trials Trial 331-10-230 and Trial 331-10-231together. There was a trend of dose-response (change in PANSS Total Score) relationship in Schizophrenia population. 4 arms (0.25mg, 1mg, 2mg and 3mg) showed noticeable decrease of PANSS Total Score compared with placebo (Figure 14).

Figure 14 Dose-PANSS Relationship in Schizophrenia population

Reference ID: 3779909



Source: Reviewer's analysis

Data sets used are summarized in Table 10. Analytic softwares include SAS 9.3 and SPLUS 8.0.

Table 10. Analysis Data Sets

Study Number	Name	Link to EDR
331-10-227, 331-10-228, 331-10-230 and 331-10-231	3-mar-2014-brexnm.xpt	\\Cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\11142014\Exposure-Efficacy for SCHZ\Dataset
	covppk-tab.xpt	
331-10-227	S227_admadrs.xpt	\\Cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\10262014\Exposure-efficacy for MDD\Dataset
331-10-228	S228_admadrs.xpt	
331-10-230	S230_adpanss.xpt	\\Cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\10262014\Exposure-efficacy for SCHZ\Dataset
331-10-231	S231_adpanss.xpt	
331-10-227	S227_adae.xpt	\\Cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\10262014\Exposure-safety for MDD\Dataset
331-10-228	S228_adae.xpt	
331-10-230	S230_adae.xpt	\\Cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\Brexipiprazole_NDA

Reference ID: 3779909

331-10-231	S231_adae.xpt	205422__LZ\Analysis\10262014\Exposure-safety for SCHZ\Dataset

5 Listing of Analyses Codes

File Name	Description	Location in \\cdsnas\pharmacometrics\
Brexi E-E MDD.ssc	Exposure-Efficacy for MDD	Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\11142014\Exposure-Efficacy for MDD\Code
Brexi E-E SCHZ.ssc	Exposure-Efficacy for SCHZ	Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\11142014\Exposure-Efficacy for SCHZ\Code
Brexi E-S MDD.ssc	Exposure-Safety for MDD	Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\11142014\Exposure-Safety for MDD\Code
Brexi E-S SCHZ.ssc	Exposure-Safety for SCHZ	Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\11142014\Exposure-Safety for SCHZ\Code
Exposure-RI.SSC	Exposure comparison for renal impairment patients	Reviews\Ongoing PM Reviews\Brexipiprazole_NDA 205422__LZ\Analysis\11142014\Renal Impairment\Code

Reference ID: 3779909

PHARMACOGENOMICS REVIEW

NDA/BLA Number	205422
Submission Date	07/11/2014
Applicant Name	Otsuka Pharmaceutical
Generic Name	Brexpiprazole
Proposed Indication	Schizophrenia; Major Depressive Disorder
Primary Reviewer	Jeff Kraft, Ph.D.
Secondary Reviewer	Christian Grimstein, Ph.D.

EXECUTIVE SUMMARY

The sponsor's classification of subjects as Ultra-rapid (UM), Extensive (EM), Intermediate (IM), or Poor (PM) metabolizers based on the haplotype of the genotype alleles is acceptable. Concordance between the sponsor's assignments and the reviewer's is greater than 99%. In the reviewer's assessment, most discordant subjects were reclassified from EM to IM or from IM to EM, and it is unlikely that this reclassification of CYP2D6 metabolizer status for a limited number of subjects will affect the findings of the PopPK analysis demonstrating that CYP2D6 metabolizer status has a significant impact on brexpiprazole exposures.

1 Background

Brexpiprazole is an orally administered small molecule modulator of multiple monoaminergic receptors. Its activity is thought to be primarily through modulatory activity at the serotonin and dopamine systems. The receptor binding profile shows that it has high affinity for multiple monoaminergic receptors including serotonin 5-HT1A, 5-HT2A, 5-HT2B, 5-HT7, dopamine D2, D3, and noradrenergic α1A, α1B, α1D, and α2C receptors. Brexpiprazole also acts as a partial agonist at the 5-HT1A, D2, and D3 receptors and as an antagonist at 5-HT2A, 5-HT2B, 5-HT7, α1A, α1B, α1D, and α2C receptors. The proposed indications are Major Depressive Disorder (MDD, adjunctive therapy) and Schizophrenia (monotherapy).

The sponsor, based on the results of the drug-drug interaction (DDI) trials performed, has determined that CYP3A4 and CYP2D6 were primarily responsible for the metabolism of brexpiprazole. Furthermore, the sponsor estimates the contributions of CYP3A4 and CYP2D6 metabolic pathways to the total apparent clearance of brexpiprazole to be 90% (46.7% and 43.3%, respectively), with the remainder (10%) attributed to other minor pathways. The sponsor has not proposed dosing recommendations for CYP2D6 PMs, despite an apparent $AUC_{0-\tau}$ increase of 47%.

The purpose of this review is to evaluate the CYP2D6 genotype information submitted by the sponsor and confirm the metabolizer status of subjects utilized in the PopPK analysis.

Reference ID: 3779909

2 Submission Contents Related to Genomics

The sponsor submitted the following reports and datasets related to the pharmacogenetic (PGx) analysis of brexpiprazole:

Table 1: Reports and Datasets Pertaining to Pharmacogenetic Analyses of Brexpiprazole

ID	***Report Description***	***Datasets***
---	Subject Level Genotypes	brex2d6.xpt
331-12-208	Population Pharmacokinetic and Exposure-Response Analyses of Brexpiprazole (OPC-34712) in Schizophrenia and as an Adjunct Treatment in Major Depressive Disorder	---
AVP02-00-00	Validation Plan for CYP2D6 Multiplex PCR	---
AVP039-27-02	Detection of CYP2D6 *2 (rs16947), *2L (rs1985842), *3 (rs35742686), *4 (rs3892097), *6 (rs5030655), *7 (rs5030867), *8 (rs5030865), *9 (rs5030656), *10 (rs1065852), *14 (rs5030865), *17 (rs28371706), *19 (rs72549353), *21 (rs72549352), *25 (rs-N/A), *29 (rs59421388), *38 (rs72549351), *41 (rs28371725), *45 (rs28371710), and *46 (rs28371696) using Sanger Sequencing Technology	---
AVP068-00-02	Cross Validation of CYP2D6 *5(Gene Deletion) and GD (Gene Duplication) Gel Based Genotyping Procedure	---
AVP120-00	Detection of CYP2C19*17 (rs12248560), and CYP2D6 *2 (rs16947) and *41 (rs28371725) using TaqMan Chemistry	---

A summary of the studies included in the PopPK analysis which investigated the effects of CYP2D6 metabolizer status on brexpiprazole PK is provided in table 2 below. Data from a total of twelve clinical trials were included in the analysis, which consisted of five phase 1 trials, two phase 2 trials in subjects with MDD, two phase 3 trials in subjects with MDD, one phase 2 trial in subjects with schizophrenia, and two phase 3 trials in subjects with schizophrenia.

The PopPK dataset included 2541 subjects, of which 1140 subjects were from MDD trials and 1247 subjects from schizophrenia trials. Only 2357 subjects were evaluable, subjects who had at least one measurable brexpiprazole concentration. DNA samples were collected from subjects who consented to optional participation in PGx research during each study. Of the 2541 subjects who were utilized for the PopPK analyses, 1706 (67%) subjects were also listed in the genotype dataset.

Reference ID: 3779909

Table 2: Clinical Trials Utilized for PopPK Analyses

Study	***Description***	***Number of Subjects in PopPK Dataset***	***PGx N***
33107201	A Phase 1, Randomized, Double-blind, Placebo-controlled Study to Assess the Tolerability, Safety, and Pharmacokinetics of Ascending Single Oral Doses of OPC-34712 in Healthy Subjects	56	42
33107203	A Phase 2, 6-Week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 Once Daily and Aripiprazole Once Daily for Treatment of Hospitalized Adult Patients with Acute Schizophrenia	409	173
33108211	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of OPC-34712 as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder	429	233
33109221	A Phase 1, Multi-center, Randomized, Double-blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ascending High Doses of OPC-34712 as Adjunctive Therapy in the Treatment of Subjects with Major Depressive Disorder	40	24
33109222	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of OPC-34712 (1 to 3 mg/day) as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder	372	140
33109225	A Single-dose, Open-label, Parallel Group, Matched Study valuating the Pharmacokinetics of Oral OPC-34712 Tablet in Subjects with Normal Hepatic Function and Hepatically Impaired Subjects	45	45
33109226	A Single-dose, Open-label, Parallel-group, Matched Trial Evaluating the Pharmacokinetics of Oral OPC-34712 Tablets in Subjects with Normal Renal Function and Renally Impaired Subjects	19	18
33110227	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of OPC-34712 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder (Pivotal #1)	667	308
33110228	Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Fixed-dose OPC-34712 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder, the Pyxis Trial	372	133
33110230	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Fixed-dose OPC-34712 (4, 2, and 1 mg/day) in the Treatment of Adults With Acute Schizophrenia	660	291
33110231	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Three Fixed Doses of OPC-34712 in the Treatment of Adults With Acute Schizophrenia	630	251
33110244	An Open-label, Single-dose Trial of the Tolerability, Safety, and Pharmacokinetics of Orally Administered OPC-34712 Tablets in Healthy Adult and Elderly Male and Female Subjects	48	48
TOTAL		**2541**	**1706**

Reference ID: 3779909

Source: PK/PD study report (#331-12-208), Page 94, Table 8-1.

DNA samples were analyzed for genetic variants in the genes encoding CYP2D6. Table 3 lists the variants investigated, methods utilized, and functional consequences of these variants.

(b) (4)

3 Key Questions and Summary of Findings

3.1 Is the sponsor's predicted metabolizer status classification accurate based on reported genotype data?

Yes. While the sponsor's assigned metabolizer status categories were not completely concordant with the reviewer's assignments, concordance rates were greater than 99%.

Sponsor's Analyses:

Subjects were classified as Ultra-rapid (UM), Extensive (EM), Intermediate (IM), or Poor (PM) metabolizers based on haplotype of the genotyped variants. Subjects were classified as UMs if they had had 2 normal functioning alleles and possessed the gene duplication, PMs if they possessed 2 non-functioning alleles, IMs if they had one non-functioning and one normal unction alleles or 2 decreased function alleles, or EMs for any other combination. If genotype for a SNP could not be determined or was missing, then the metabolizer status was unknown unless it could be extrapolated from the know genotypes. A summary of the sponsor's assigned metabolizer status for all subjects in the PopPk dataset are provided in table 4.

Reference ID: 3779909

Table 4: Sponsor's Assignment of CYP2D6 Metabolizer Status

Metabolizer Status	***Number of Subjects***	***Percentage of Genotyped Subjects***
Extensive	976	57%
Inconclusive	17	1%
Intermediate	592	35%
Poor	71	4%
Ultra Rapid	52	3%

Reviewer's Analyses:

Subjects were re-classified using identical methodologies as listed above using the sponsor's provided subject level genotype dataset. The reviewer noticed that two subjects were duplicated in the genotype dataset. In one case both subject entries were listed by the sponsor as intermediate metabolizers (IM) despite discordant genotypes (*1/*5 vs. *4/*10) and in the other case both subject entries differed in genotype (*1/*2 vs. *2/*4) and metabolizer status (EM vs. IM).

Concordance between the reviewer generated metabolizer status assignments and those of the sponsor were high, at greater than 99%. Table 5 summarizes the concordance of CYP2D6 metabolizer status between the sponsor and the reviewer. The two discordant subjects that the sponsor had classified as IMs but the reviewer as EMs had haplotypes of *2/*41 and *2/*41 which both should be classified as EMs (one normal function and one decreased function allele). The 12 subjects classified as EMs by the sponsor and IMs by the reviewer all had haplotype with one normal function and one non-functional allele and should be classified as IMs. The one subject the sponsor classified as EM and the reviewer classified as UM had a haplotype of *1/*2xN and therefore should be classified as a UM based on the presence of two normal functioning alleles and a gene duplication.

Table 5: Sponsor and Reviewer Concordance of CYP2D6 Metabolizer Status

		Reviewer				
		Extensive	*Inconclusive*	*Intermediate*	*Poor*	*Ultra Rapid*
Sponsor	*Extensive*	963	--	12	--	1
	Inconclusive	--	17	--	--	--
	Intermediate	2	--	590	--	--
	Poor	--	--	--	71	--
	Ultra Rapid	--	--	--	--	52

Reference ID: 3779909

4 Summary and Conclusions

Overall, the sponsor's classification of subjects as UM, EM, IM, or PM based on the haplotype of the genotype alleles is acceptable. Concordance between the sponsor's assignments and the reviewer's was greater than 99%. All subjects in the extreme groups (UMs and PMs) were confirmed by the reviewer. Most discordant subjects were reclassified from EM to IM or from IM to EM which is likely to have little effect on phenotype guided dosing recommendations in the label, as these pertain to differences between EM and PM subjects.

Incorrect assignment of CYP2D6 metabolizer status for a limited number of subjects (i.e., <1%) is unlikely to affect the findings of the PopPK analysis demonstrating that CYP2D6 metabolizer status has a significant impact on brexpiprazole exposures.

5 Recommendations

None.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

Reference ID: 3779909

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Reference ID: 3779909

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06/18/2015

Office of Clinical Pharmacology Review

NDA#/eCTD	205,422/0000
NDA Type	Standard
Related INDs	IND101,871; IND103,958
Proposed Brand Name	REXULTI
Generic Name	Brexpiprazole
Dosage Form	Immediate-Release Tablet
Dosage Strength (mg)	0.25, 0.5, 1, 2, 3, 4
Indications	Adjunctive Major Depressive Disorder & Schizophrenia
Sponsor	Otsuka
Submission Type	505(b)(1) NME
Submission Date	July 11, 2014
OCP Review Team	Huixia Zhang, Li Zhang, Praveen Balimane, Kofi Kumi, Jeffrey Kraft, Christian Grimstein, Kevin Krudys, Hao Zhu

OCP Required Office-Level Briefing was held on February 19, 2015.

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Reference ID: 3713053

1. EXECUTIVE SUMMARY

Otsuka is seeking approval of brexpiprazole immediate release tablet for the treatment of (1) major depressive disorder (MDD) as adjunctive therapy, and (2) schizophrenia in adult patients, via 505(b)(1) route. Brexpiprazole is thought to have modulatory activity at the serotonin-dopamine system that combines partial agonist activity at serotonergic 5-hydroxytryptamine-1A (5-HT_{1A}) and dopaminergic D_2 receptors with antagonist activities at serotonergic 5-HT2A and noradrenergic $\alpha_{1/2}$ receptors, and actions on several other central monoaminergic receptor subtypes.

The proposed starting dose for brexpiprazole as adjunctive treatment for Major Depressive Disorder (MDD) is 0.5 mg/day or 1 mg/day. Dose titration to 1 mg/day and up to the target dose of 2 mg/day should occur at intervals of up to 1 week based on the patient's clinical response and tolerability. The proposed maximum recommended dose is 3 mg/day.

The proposed starting dose for brexpiprazole in the treatment of patients with schizophrenia is 1 mg/day. The dose should be increased to 2 mg after Day 4 and may subsequently be increased to 4 mg after Day 7 based on the patient's clinical response and tolerability. The proposed target dose range is 2 to 4 mg/day.

The efficacy and safety of brexpiprazole as an adjunctive therapy for MDD was evaluated in two 6-week controlled studies in adult patients at doses of 1 to 3 mg administered once daily, with one trial showing statistical superiority of brexipiprazole over placebo. The efficacy and safety of brexpiprazole in schizophrenia was demonstrated in two 6-week controlled studies in adult patients at doses of 2 to 4 mg administered orally once daily.

Pharmacokinetics (PK) of brexpiprazole and its major metabolite (DM-3411) was characterized in healthy volunteers and patients. The effects of intrinsic factors (i.e., hepatic impairment, renal impairment, age, and gender) and extrinsic factors (e.g., quinidine, ketoconazole, and food) on PK of brexpiprazole and DM-3411 were evaluated.

The findings from the Office of Clinical Pharmacology are summarized as follows:

- Brexpiprazole can be taken with or without food.
- In general, no dose adjustment is necessary in patients based on age or gender.
- For schizophrenia and MDD patients with renal or hepatic dysfunction (moderate impairment or worse), the maximum recommended dose is 3 mg/day and 2 mg/day, respectively. Close monitoring of patients with renal or hepatic dysfunction during dose initiation is highly recommended.
- Brexpiprazole dose should be reduced by half in patients coadministered with a strong CYP3A4 inhibitor or a CYP2D6 inhibitor, or in patients with known CYP2D6 poor metabolizer (PM) status.
- Brexpiprazole dose should be reduced to a quarter (25%) in patients coadministered with a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor, or in patients with known CYP2D6 PM status concomitantly taking a strong CYP3A4 inhibitor.
- Brexpiprazole dose should be doubled in patients coadministered with a strong CYP3A inducer. Further dose adjustments on the basis of clinical response maybe needed.

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- No significant QTc prolongation effect of brexpiprazole at the doses of 12 mg was detected in a thorough QT study.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of brexpiprazole. The acceptability of specific drug information is provided below.

Decision	**Acceptable to OCP?**	**Comment**
Overall	☒ Yes ☐ No ☐ NA	Pending labeling
Evidence of effectiveness-Schizophrenia	☒ Yes ☐ No ☐ NA	Two positive registration trials
Evidence of effectiveness-MDD	☐ Yes ☒ No ☐ NA	Only ONE positive trial. Result from the second registration trial is considered marginal.
Proposed doses for adult patients-Schizophrenia	☒ Yes ☐ No ☐ NA	The proposed starting dosing regimen is 1 mg/day. Dose should be increased to 2 mg after Day 4 and may subsequently be increased to 4 mg after Day 7. The target dose range is 2 to 4 mg/day.
Proposed dose for subgroups of patients or patients receiving comedications	☐ Yes ☒ No ☐ NA	--Findings: 1. In general, no dose adjustment is necessary in patients based on age or gender. 2. Brexpiprazole dose should be reduced to a quarter (25%) in patients coadministered with a strong CYP3A4 inhibitor **AND** a strong CYP2D6 inhibitor. 3. Brexpiprazole dose should be doubled in patients coadministered with a strong CYP3A4 inducer, and further dosage adjustment maybe needed based on clinical response. -- OCP Recommendations: 1. For schizophrenia and MDD patients with renal or hepatic dysfunction (moderate impairment or worse), the maximum recommended dose is 3 mg/day and 2 mg/day, respectively. Close monitoring of patients with renal or hepatic dysfunction during dose initiation is recommended. 2.Coadministration of strong CYP2D6 inhibitor or strong CYP3A4 inhibitor doubled the exposure of brexpiprazole. Given the benefit-risk profile, brexpiprazole dose should be reduced by half:

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		1) in patients coadministered with a strong CYP3A4 inhibitor **OR** a strong CYP2D6 inhibitor. 2) in patients with known CYP2D6 PM status.
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with sponsor

1.2 Post-Marketing Studies

None.

Recommendation to DPP:

Given the information of doubled exposure of brexpiprazole in the presence of a strong CYP2D6 or CYP3A4 inhibitor, and risk-benefit profile for brexpiprazole, OCP recommends that the dose of brexpiprazole be reduced by half when a strong CYP2D6 or CYP3A4 inhibitor is coadministered, or in patients with known CYP2D6 poor metabolizer status. In addition, for patients with renal or hepatic dysfunction (moderate impairment or worse), the maximum recommended dose is 3 mg/day and 2 mg/day in schizophrenia and MDD, respectively. Close monitoring of these patients during dose initiation is recommended.

1.3 Summary of Clinical Pharmacology Findings

In the current submission, the sponsor has submitted 26 clinical pharmacology studies (19 in healthy subjects and 7 in patients), and 20 in vitro studies. The submitted studies include 6 PK studies (2 single ascending dose PK studies in healthy volunteers, 2 multiple dose PK studies in healthy volunteers, and 2 multiple dose PK studies in patients), 3 intrinsic factor studies (hepatic impairment, renal impairment, race and gender studies), 7 extrinsic studies (effect of food, activated charcoal with sorbitol, and increased gastric pH, rifampin, ketoconazole, quinidine and ticlopidine on brexpiprazole PK; effect of brexpiprazole on CYP3A4, CYP2D6, and CYP2B6 substrates as well as BCRP and P-gp substrates), 2 receptor binding studies, and 1 thorough QT study. Population PK and ER analyses were also performed. Below summarizes the key findings from these studies:

- Absolute bioavailability of brexpiprazole is about 95%.
- Administration of brexpiprazole with food (high-fat meal) does not affect its rate and extent of absorption.
- Even though aqueous solubility of brexpiprazole is pH dependent, co-administration of brexipiprazole with omeprazole does not result in clinically relevant changes in bioavailability of brexpiprazole. Gastric acid pH modifiers (including antacids, H2 receptor antagonists, and PPIs) are not expected to significantly affect the absorption of brexpiprazole.
- Brexpiprazole is highly bound (greater than 99%) to plasma proteins. Brexpiprazole protein binding is not affected by renal or hepatic impairment.

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- Brexpiprazole is extravascularly distributed. Brexpiprazole (0.25 mg, 1 hour IV infusion) volume of distribution is 1.56 (±0.418) L/kg.

- Hepatic clearance is the major route of elimination, and brexpiprazole (0.25 mg, 1 hour IV infusion) clearance is 19.8 (±10.0) mL/h/kg.

- Brexpiprazole is mainly metabolized by CYP3A and CYP2D6; about 14% and less than 1% of the dose is excreted as unchanged parent drug in the feces and urine, respectively.

- After single-dose and multiple-dose (once-daily) administration, brexpiprazole and its metabolite DM-3411, are the major moieties with greater than 10% of the total exposure in systemic circulation. DM-3411 is not considered as an active metabolite

- The steady state median brexpiprazole T_{max} is 3.0 hours, and the mean terminal T1/2 is about 91 hours. The overall median T_{max} of DM-3411 is 5.0 hours, and the mean terminal T1/2 is about 86 hours.

- Brexpiprazole steady state is reached after 10 to 12 days of once daily administration, and the accumulation ratio is about 4fold. At steady state, DM-3411 represents 23-48% of brexpiprazole exposure in plasma.

- Brexpiprazole C_{max} and AUC increase approximately in proportion to the dose after either single-dose or multiple-dose (once-daily) oral administration.

- Intrinsic factors:
  - Age: Elderly (≥ 65 years) and adult (18 to 45 years) subjects exhibited similar brexpiprazole PK parameters (C_{max} and AUC).
  - Gender: Female subjects exhibited approximately 40% to 50% higher brexpiprazole systemic exposure (C_{max} and AUC) compared with male subjects.
  - Hepatic impairment: Subjects with mild, moderate, and severe hepatic impairment exhibited 26%, 73%, and 4% increases in brexpiprazole exposure (AUC), respectively. Subjects with mild, moderate, and severe hepatic impairment exhibited 10%, 15%, and 47% reduction in brexpiprazole C_{max} values, respectively.
  - Renal impairment: In subjects with severe renal impairment, brexpiprazole exposure (AUC) was increased by 72% compared with matched subjects with normal renal function, while brexpiprazole C_{max} was unchanged. Population PK analysis indicated that brexpiprazole exposure (AUC) in patients with mild or moderate renal dysfunction was increased by 7% and 71%, respectively.

- Drug-drug interactions – effect of other drugs on brexpiprazole
  - Co-administration of a potent CYP3A4 inhibitor (ketoconazole) or CYP2D6 inhibitor (quinidine) with brexpiprazole resulted in about 100% increase in brexpiprazole exposure (AUC) and about a 1.5-fold increase in the terminal $T_{1/2}$ of brexpiprazole.

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- Co-administration of a potent CYP3A4 inducer (rifampin) with brexpiprazole resulted in approximately a 73% decrease in brexpiprazole exposure and a 50% decrease in the terminal $T_{1/2}$ of brexpiprazole.
- Co-administration of food, omeprazole, or ticlodipine did not cause clinically meaningful change of brexpiprazole exposure.

- Drug-drug interactions – effect of brexpiprazole on other drugs
  - Based on the results of in-vitro studies, brexpiprazole and metabolite DM-3411 showed mild-to-negligible potential to inhibit CYP enzymes (CYPs 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). Results of a drug-drug interaction trial also showed that administration of brexpiprazole had no effect on the PK parameters of probe substrates of CYP3A4, CYP2D6, CYP2B6, P-gp, or BCRP.
  - Brexpiprazole was a weak or non-inhibitor of OAT1, OAT3, OCT2, MATE1, MATE2-K, OATP1B1, OATP1B3, or OCT1.

- Exposure/Dose-Response relationship was demonstrated for both efficacy and safety in schizophrenia patients. However, there was no clear exposure/dose-response relationship for efficacy shown in MDD patients, whereas it was evident that the risk of adverse events increased as exposure/dose increased.

2. QUESTION BASED REVIEW

2.1 Specific Questions

2.1.1 Is there adequate evidence of effectiveness to support the proposed indications for brexpiprazole?

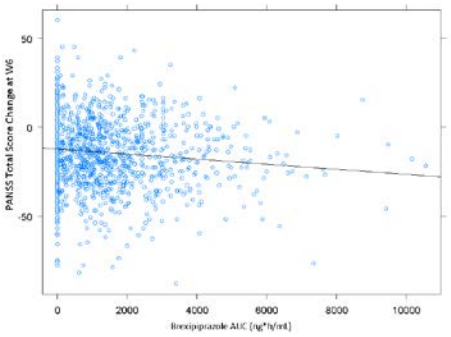
-Schizophrenia

The efficacy of brexpiprazole was established at doses of 2 mg/day and 4 mg/day. Based on the primary analysis (change in PANSS Total Score at Week 6), superiority of 4 mg/day dose over placebo was replicated in two phase 3 trials (Trial 331-10-230 and Trial 331-10-231), whereas superiority of 2 mg/day dose over placebo was only seen in one trial (Trial 331-10-231).

Exposure-Response analysis based on change in PANSS score indicated that there was a significant PANSS Total Score reduction with pooled brexpiprazole exposures in the treated group compared with placebo (P= 0.00005, Figure 1), and there was a significant reduction of PANSS total score with an increase of AUC in brexpiprazole-treated patients (P=0.03).

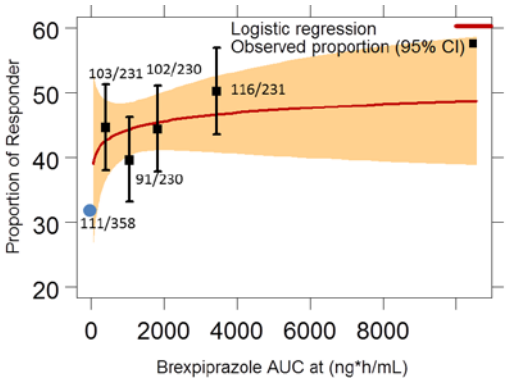
Reference ID: 3713053

Figure 1: PANSS Reduction with Higher Brexpiprazole Exposure Compared with Placebo



Exposure-responder relationship was further explored. Responder was defined as patients shown≥30% PANSS reduction at week 6/ET or CGI-I value of 1 or 2 at week 6/ET. The data from two phase 3 clinical trials (Trial 331-10-230 and Trial 331-10-231) demonstrated that the proportion of responders treated with brexpiprazole was higher than patients treated with placebo (45% vs 31%). In addition, there was a significant increase in responder rate with the increase of AUC in brexpiprazole treated patients (Figure 2).

Figure 2: Increase in Responder Rate with the Increase of AUC in Brexpiprazole Treated Patients



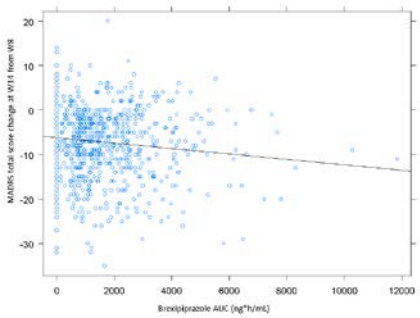
-Adjunctive MDD

The efficacy of brexpiprazole was evaluated at doses of 2 mg/day and 3 mg/day. Based on the primary analysis (change in MADRS Total Score), greater improvement was observed for 2 mg/day (Trial 331-10-228) and 3 mg/day (Trial 331-10-227) doses. However, the p-values in Trial 331-10-227 did not meet the pre-specified threshold due to multiplicity correction (i.e., Hochberg correction p<0.01). Hence, the findings from Trial 331-10-227 are currently considered negative.

Exposure-Response analysis using MADRS total score indicated that there was a significant reduction of MADRS Total Score with the pooled brexpiprazole exposures in the treatment groups compared with placebo (P=0.0001, Figure 3). However, there was no significant MADRS reduction between brexpiprazole treatment groups (P=0.2027).

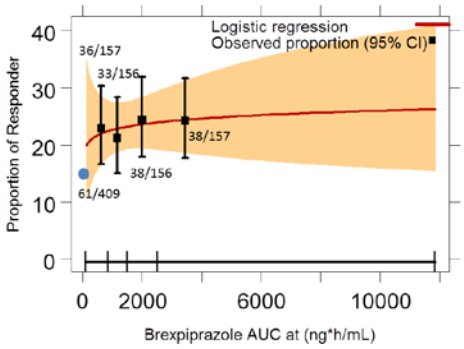
Reference ID: 3713053

Figure 3: MADRS reduction with Higher Brexpiprazole Exposure



Exposure-responder analysis was further explored. Responder was defined as patients shown ≥ 50% reduction in MADRS Total Score at week 14 from the end of Phase A (Week 8). The proportion of responders treated with brexpiprazole was higher than patients treated with placebo (23% vs 15%). However, there was no significant increase in responder rate with the increase of AUC in brexpiprazole-treated patients (Figure 4).

Figure 4: No significant increase of Responder Rate with the Increase of AUC in Brexpiprazole Treated Patients



In conclusion, there is sufficient evidence to demonstrate the effectiveness of brexpiprazole in treating patients with schizophrenia. However, only marginal evidence is demonstrated for the effectiveness of brexpiprazole in adjunctive treatment of MDD.

2.1.2 Should brexpiprazole dose be adjusted with concomitant use of a strong CYP3A4 inhibitor, a strong CYP2D6 inhibitor or in CYP2D6 PMs?

Yes. The dose of brexpiprazole should be reduced by half when brexpiprazole is coadministered with a strong CYP3A4 inhibitor (e.g., itraconazole, clarithramicin), or a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine), or in patients with known CYP2D6 poor metabolizer (PM) status. The impact of mild or moderate CYP3A4 inhibitors or CYP2D6 inhibitors has not been evaluated.

In vivo data showed that a strong CYP3A4 inhibitor (i.e., ketoconazole) or a strong CYP2D6 inhibitor (i.e., quinidine) increased the brexpiprazole exposure by about 100%, and exposure to brexpiprazole in CYP2D6 PM was about 120% higher compared with CYP2D6 Ems (Trial 331-08-208).

Reference ID: 3713053

Dose-response analysis for safety indicated that the incidence of akathisia is dose-related in both MDD and schizophrenia patients treated with brexpiprazole (Table 1). For both indications, there are significant increases of akathisia incidence rate with the increase of brexpiprazole exposure. In addition, there is higher incidence of akathisia in patients receiving a concomitant strong CYP2D6 inhibitor. With the presence of paroxetine or fluoxetine, the incidences of akathisia are 4.3%, 10.2%, and 24.0% at 1, 2, and 3 mg/day, compared to all other ADTs 4.5%, 6.5%, and 10.6%. However, the higher incidence of akathisia did not result in an imbalance of discontinuation.

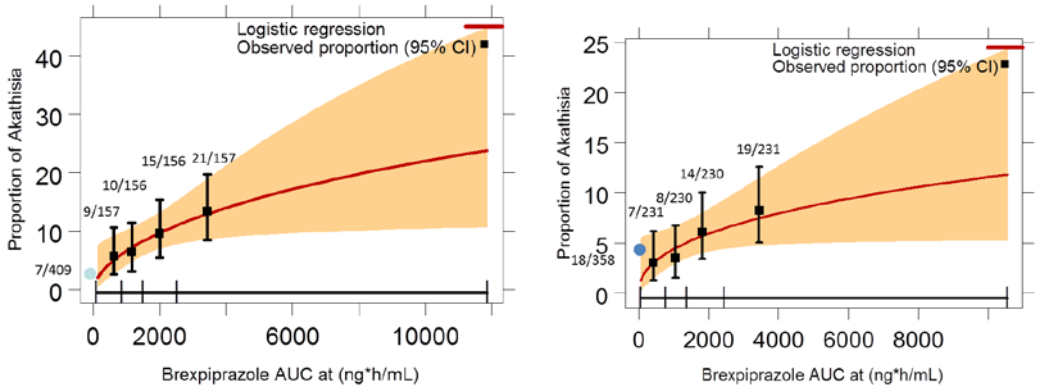
Table 1: Dore-Dependent Incidence of Akathisia

MDD	1 mg (N=226)	2 mg (N=188)	3 mg (N=229)	Placebo (N=411)
Akathisia	10 (4.4)	14 (7.4)	31 (13.5)	7 (1.7)

Schizophrenia	0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	Placebo (N=368)
Akathisia	0	5 (4.2)	17 (4.6)	25 (6.9)	17 (4.6)

The exposure-safety relationship was consistent with the dose-safety relationship. There is a significant increase of akathisia incidence rate with the increase of brexpiprazole exposure from trials conducted in MDD patients (P = 0.002, Figure 5) and from trials conducted in schizophrenia patients (P = 0.008, Figure 5).

Figure 5: Significant Increase of Akathisia Incidence Rate with the Increase of Brexpiprazole Exposure in MDD (Left Panel) and Schizophrenia (Right Panel) Populations



In conclusion, given the relatively steep Exposure-safety profiles (Figure 5) in both schizophrenia and MDD patients, the dose of brexpiprazole should be reduced to compensate brexpiprazole exposure increase when brexpiprazole is coadministered with a strong CYP3A4 inhibitor (e.g., itraconazole, clarithramicin), or a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine), or in patients with known CYP2D6 poor metabolizer status. Half of the usual dose under abovementioned scenarios is expected to manage the increased risk or incidence of the adverse event (i.e., akathisia).

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2.1.3 Should brexpiprazole dose be adjusted in patients with moderate or worse renal or hepatic impairment?

For schizophrenia and MDD patients with renal or hepatic dysfunction (moderate impairment or worse), the maximum recommended dose is 3 mg/day and 2 mg/day, respectively. Close monitoring of patients with renal or hepatic dysfunction during dose initiation is highly recommended.

Brexpiprazole is mainly metabolized with less than 1% of the parent excreted unchanged in the urine. Compared to patients with normal renal or hepatic function, the exposure (unbound AUC) of brexpiprazole was found to be increased about 70% in patients with moderate renal or hepatic impairment, and in patients with severe renal dysfunction (Table 2), though minimal effect of severe hepatic impairment was observed on the AUC of brexpiprazole. In addition, a large variability was observed in these patients. For instance, the upper limit of 90% confidence interval calculated geometric mean ratio based on inter-subject variability in patients with moderate hepatic impairment is 3. The maximum recommended dose in patients with normal renal or hepatic function is 4 mg/day and 3 mg/day for schizophrenia and MDD indication, respectively. Considering the risk/benefit profiles of brexpiprazole as shown in Question 2.1.2, the maximum recommended dose for schizophrenia and MDD patients with moderate to severe renal or hepatic dysfunction should be 3 mg/day and 2 mg/day, respectively.

Table 2: Effect of Organ Dysfunction on the Exposure (Unbound AUC) of Brexpiprazole

AUC ratio (Impaired/Normal) (GMR, 90% CI)	Mild	Moderate	Severe
Hepatic Impairment	1.26 (0.70-2.24)	1.73 (0.98-3.05)	1.04 (0.51-2.14)
Renal Impairment	1.07*	1.71*	1.72 (1.26-2.35)

* Observed data from 4 Phase 3 trials, total concentration of brexpiprazole.

2.2 Standard Questions

2.2.1 PK Characteristics

2.2.1.1 What are the general ADME (Absorption, Distribution, Metabolism and Elimination) characteristics of brexpiprazole and its major metabolite?

• What are the characteristics of drug absorption?

Brexpiprazole is highly bioavailable, with an absolute bioavailability of about 95%.

Based on a pooled analysis of the PK data from single-dose trials in healthy subjects, the median T_{max} of brexpiprazole after administration of a single oral dose (0.2 mg to 8 mg) was about 4.0 hours, and the mean terminal $T_{1/2}$ was about 79 hours. For the major metabolite, DM-3411, the median T_{max} was about 12.0 hours, and the mean terminal $T_{1/2}$ was about 74 hours.

Based on a pooled analysis of the PK data from multiple-dose trials with brexpiprazole in healthy subjects (0.5 mg to 2 mg), subjects with schizophrenia (1 mg to 12 mg), and as an

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adjunct treatment in subjects with MDD (1 mg to 4 mg), the steady state median brexpiprazole T_{max} was 3.0 hours, and the mean terminal $T_{1/2}$ was about 91 hours. The overall median T_{max} of DM-3411 was 5.0 hours, and the mean terminal $T_{1/2}$ was about 86 hours.

Food and omeprazole did not significantly affect the absorption of brexpiprazole. Administration of activated charcoal with sorbitol one hour after administration of a single-2-mg-oral-dose of brexpiprazole resulted in 5% to 23% lower C_{max} and 31% to 39% lower AUC (based on historical data comparison).

• **What are the characteristics of drug distribution?**
Plasma protein binding for brexpiprazole and DM-3411 were greater than 99% and 90%, respectively. Brexpiprazole does not preferentially bind to red blood cells. Brexpiprazole is extravascularly distributed (Vd = 1.56±0.418 L/kg) following a single dose (0.25-mg, 1-hour IV infusion) of brexpiprazole. Based on population PK analysis, brexpiprazole Vc/F was 105 L (CSR 331-12-208).

• **Does the mass balance study suggest renal or hepatic clearance as the major route of elimination?**
Brexpiprazole is mainly hepatically eliminated. Following a single oral dose of [^{14}C]-labeled brexpiprazole administration, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% and about 14% of the oral dose was excreted as unchanged brexpiprazole in the urine and feces, respectively.

• **What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**
Following a single oral dose of [^{14}C]-labeled brexpiprazole administration, the majority of plasma radioactivity (about 80%) was accounted by the unchanged parent drug and two metabolites (DM-3411 and DM-3412). Brexpiprazole was the major circulating moiety (about 57%) in human plasma, followed by DM-3411 (19%) and DM-3412 (3.7%).

• **What are the characteristics of drug metabolism?**
Brexpiprazole is mainly metabolized in humans. CYP3A4 and CYP2D6 are the major enzymes involved in its metabolism, with minor contributions from FMO3 and other CYP enzymes (Figure 6).

Figure 6: Metabolic Scheme of Brexpiprazole

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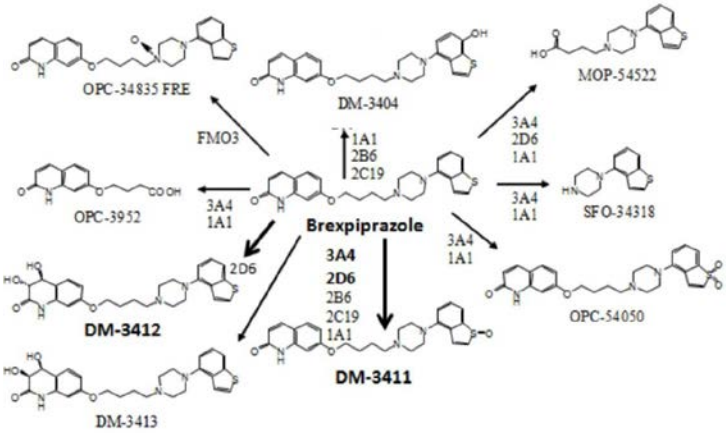

2.2.1.2 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy volunteers?

Single Dose

Pharmacokinetic data after single dose administration in healthy subjects are available up to 8 mg (0.2 mg to 8 mg, Trial 331-07-201) dose. There was also a major metabolite DM-3411 identified in the systemic circulation. PK parameters of brexpiprazole and DM-3411 are summarized in Table 3.

Table 3: Mean (SD) Brexpiprazole and DM-3411 Plasma Pharmacokinetic Parameters Following Single-dose Administration of Brexpiprazole (0.2 mg to 8 mg) in Healthy Subjects

Parameters	**0.25 mg (n=6)**	**0.5 mg (n=6)**	**1 mg (n=6)**	**2 mg (n=6)**	**4mg (n=6)**	**6mg (n=5)**	**8mg (n=5)**
Brexpiprazole							
C_{max} (ng/mL)	2.8 (0.7)	6.6 (1.2)	12.1 (3.8)	24.6 (5.6)	47.3 (16.4)	72.7 (17.0)	93.0 (48.9)
T_{max} (hr)	2 (2-4)	2.1 (1.5-4.0)	6 (2.1-6.3)	4.0 (4-6.1)	6 (4-6)	4 (2.1-6.0)	6 (1.5-12)
$AUC_{0-\infty}$ (hr.ng/mL)	143 (56.5)	387 (239)	612 (222)	1940 (989)	2690 (1710)	5040 (2520)	7950 (3310)
Cl/F (ml/hr)	1550 (496)	1580 (595)	1860 (796)	1280 (622)	1970 (1020)	1490 (796)	1190 (594)
$T_{1/2}$ (hr)	50.4 (13.2)	54.9 (20.9)	55.4 (14.0)	66.0 (16.2)	48.3 (15.8)	64.8 (25.1)	80.8 (31.7)
DM-3411							
C_{max} (ng/mL)	1.1 (0.5)	2.6 (1.0)	5.9 (3.3)	8.8 (3.4)	22.5 (8.9)	25.6 (17.0)	24.3 (20.6)
T_{max} (hr)	16 (4-36)	10 (2-24)	12 (6-24)	24 (6-24)	24 (8-24)	16 (12-24)	24 (24-36)
$AUC_{0-\infty}$ (hr.ng/mL)	110 (44.4)	208 (61.3)	370 (147)	950 (489)	1790 (479)	2420 (167)	2900 (1870)
$T_{1/2}$ (hr)	66.5 (15.1)	49.1 (16.3)	55.6 (15.4)	63.8 (15.2)	48.6 (13.6)	63.2 (22.3)	77.5 (33.1)

[a]T_{max} is median (range). -Source: Table 1.9.2.3.1.2-1 and 1.9.2.3.1.3-1 of study report 331-07-201

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Multiple Dose

PK of brexpiprazole and metabolite DM-3411 were evaluated at three dose levels after multiple dosing in healthy subjects (Table 4) for 14 days.

Table 4: Mean (SD) Pharmacokinetic Parameters for Brexpiprazole and DM-3411 after Administration of Brexpiprazole for 14 Days in Healthy Volunteers.

Parameters	**0.5 mg (n=11)**	**1 mg (n=11)**	**2 mg (n=4)**
Brexpiprazole			
C_{max} (ng/mL)	27.9 (14.3)	44.7 (18.8)	69.3 (15.3)
T_{max} (hr)	4 (1-16)	4 (3-8)	4 (4-24)
AUC_{0-24} (hr.ng/mL)	506 (299)	827 (351)	1377 (365)
Cl/F (L/hr)	1220 (511)	1500 (666)	1548 (489)
$T_{1/2}$ (hr)	84.8 (39.6)	73.6 (20.1)	78.5 (13.3)
DM-3411			
C_{max} (ng/mL)	9.8 (3.3)	19.4(9.3)	29.9 (11.4)
T_{max} (hr)	6 (3-35)	4 (4-8)	5.5 (3-24)
AUC_{0-24} (hr.ng/mL)	191 (73.2)	395 (207)	631 (244)
$T_{1/2}$ (hr)	76.4 (32)	85 (33.2)	76.2 (15.3)

- Source: Tables 9.2.3.1-1, 9.2.3.2-1, 9.2.3.1-2, and 9.2.3.2-2 in Trial 331-08-206 study report

2.2.1.3 Is there any PK difference for brexpiprazole between healthy volunteers and patient populations?

No. No significant PK difference was observed between healthy volunteers and targeted patient populations. Multiple dose PK of brexpiprazole was characterized in healthy volunteers (Trial 331-08-206), patients with schizophrenia or schizoaffective disorder (Trial 331-08-205), and patients with major depressive disorder (Trial 331-09-221). No significant difference in PK was observed between schizophrenia patients and healthy volunteers (Table 5). The PK of brexipiprazole looks different in MDD patients as compared to healthy subjects. It is to note that MDD patients received fluoxetine or paroxetine as concomitant medication. It is anticipated that brexipiprazole exposure should be approximately doubled with decreased clearance due to drug-drug interaction. After adjusting the drug-drug interaction effect, the PK in MDD patients is not expected to be different from healthy volunteers.

Table 5: Mean (SD) Pharmacokinetic Parameters for Brexpiprazole and DM-3411 on Day 14 after Daily Administration of 2 mg Brexpiprazole in Patients with Schizophrenia, MDD, or Healthy Volunteers

Parameters	**MDD* (n=4)**	**Schizophrenia (n=11)**	**Healthy Volunteers (n=4)**
Brexpiprazole			
C_{max} (ng/mL)	125 (28.2)	81.2 (28.3)	69.3 (15.3)
T_{max} (hr)	4.5 (1-24)	2 (2-3)	4 (4-24)
AUC_{0-24} (hr.ng/mL)	2406 (629)	1620 (594)	1377 (365)
Cl/F (L/hr)	874 (220)	1390 (517)	1548 (489)

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$T_{1/2}$ (hr)	120 (61.6)	104.7 (25.5)	78.5 (13.3)
DM-3411			
C_{max} (ng/mL)	23.7 (6.12)	17.3(2.9)	29.9 (11.4)
T_{max} (hr)	4.5 (1-8)	3(0.5-24)	5.5 (3-24)
AUC_{0-24} (hr.ng/mL)	470 (134)	374 (65.7)	631 (244)
$T_{1/2}$ (hr)	107 (17.3)	127 (24.7)	76.2 (15.3)

*patients were on fluoxetine or paroxetine; exposure was expected to be doubled for brexpiprazole

2.2.1.4 Based on PK parameters, what is the degree of linearity or non-linearity in the dose-concentration relationship?

Based on a pooled analysis of the PK data collected in the clinical pharmacology program, brexpiprazole PK parameters (C_{max} and AUC) are found to be approximate dose proportional after single- (0.2 mg to 8 mg) or multiple-dose (0.5 mg to 4 mg) once-daily administration (Figure 7).

Figure 7: Dose Proportionality Analysis of Brexpiprazole PK Parameters After Single- and Multiple-Dose Administration

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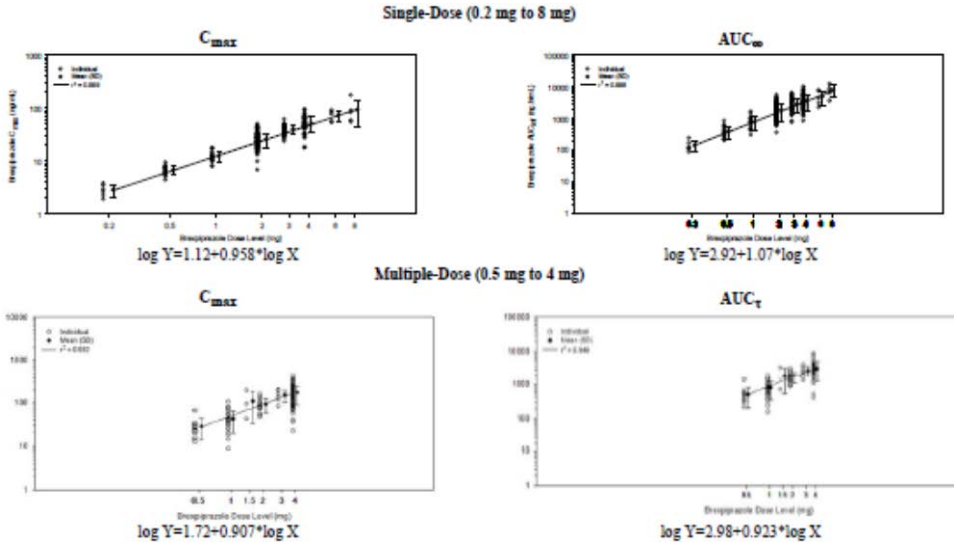

-Source: Figure 3-1 in Clin-Pharm-reviewers-guide

Population PK analysis using data from Phase 3 trials also indicated PK proportionality of brexpiprazole at the therapeutic doses.

Figure 8: Brexpiprazole Exposure in Schizophrenia Patients from Phase 3 Trials

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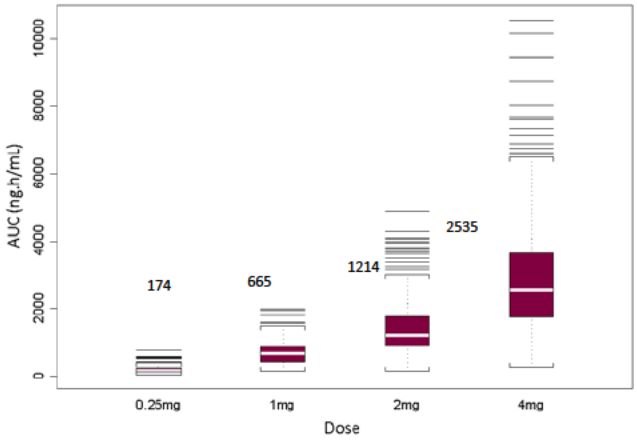

2.2.1.5 How do the PK parameters change with time following chronic dosing?

There was no evidence of time-dependent pharmacokinetics for brexpiprazole. Brexpiprazole exposure was generally comparable following single-dose administration ($AUC_{0-\infty}$) and after multiple once daily dosing of brexpiprazole (AUC_{0-24}) (Table 6).

Table 6: Comparison of Brexpiprazole Exposure between Single-Dose and Multiple-Dose Administration of Brexpiprazole at Different Dose Levels

Trials	# Subjects	Dose[a]	AUC (ng•h/mL)
331-07-201 331-08-206 331-10-241 331-10-243 331-10-244	137	2 mg SD	1870 ± 1030
331-08-205 331-08-206 331-09-221	14	2 mg MD	1780 ± 663
331-10-243 331-13-209	77	3 mg SD	2730 ±1290
331-09-221	6	3 mg MD	2670 ± 993
331-07-201 331-09-224 331-10-240 331-10-246	53	4 mg SD	3760 ± 2050
331-08-205 331-08-209 331-09-221 331-10-242	106	4 mg MD	3160 ± 1880

[a].SD is single dose administration, MD is once daily multiple dosing.

2.2.1.6 What is the inter- and intra-subject variability of the PK parameters in volunteers and targeted patients?

Pooled analysis indicated that the inter-subject variability of brexpiprazole PK parameters is high, and its intra-subject variability is considered low. The inter- and intra-subject variability

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ranges of brexpiprazole C_{max} and AUC are provided in Table 7. Based on the results of the population PK analysis (CSR 331-12-208, Table 4.3.2.3-1), the inter-subject variability (%SE) for brexpiprazole CL/F, Vc/F, and Ka was 61% (2.6%), 51% (4.2%), and 88% (4.1%).

Table 7: Inter- and Intra-Subject Variability of Brexpiprazole Pharmacokinetic Parameters

Variability	C_{max}	AUC_{∞}
Inter-subject Variability	19-32%	40-55%
Intra-subject Variability	12-16%	11-15%

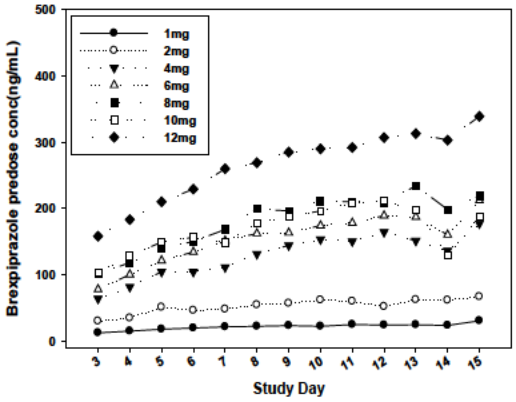
Note: The range for inter-subject variability is based on pooled analysis of single-dose (0.2-mg to 4-mg) trials while the range for intra-subject variability is based on the data from pivotal bioequivalence trials (Trial 331-10-243, Trial 331-10-245, and Trial 331-13-209).

2.2.1.7 Are steady state PK well characterized for brexpiprazole and DM-3411?

Steady state PK for brexpiprazole and DM-3411 were characterized in healthy volunteers and patient populations. No significant difference in PK was observed amongst the different populations (Table 5, Section 2.2.1.3).

After multiple once daily dosing, steady state of brexpiprazole seemed to be reached after 10-12 days (Figure 9).

Figure 9: Mean Predose Concentrations of Brexpiprazole after Multiple Dosing in Patients with Schizophrenia or Schizoaffective Disorder (Trial 331-08-205)



After multiple once-daily oral administration of brexpiprazole (1 mg to 4 mg), the median T_{max} of brexpiprazole and major metabolite DM-3411 ranged from 2 to 8 hours and 3 to 8 hours, respectively; mean terminal $T_{1/2}$ was in the range of 81-107 hours and 72 to 127 hours, respectively. Steady state accumulation was about 4-fold for brexpiprazole (Table 8).

Table 8: Mean (SD) Brexpiprazole and DM-3411 Plasma PK Parameters Following Multiple Daily Administration of 1 mg to 12 mg of Brexpiprazole to Subjects with Schizophrenia or Schizoaffective Disorder

Parameters	**1 mg (n=12)**	**2 mg (n=6)**	**4 mg (n=5)**	**6 mg (n=6)**	**8 mg (n=5)**	**10 mg (n=6)**	**12 mg (n=4)**
Brexpiprazole Day 1							

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C_{max} (ng/mL)	11.9 (3.9)	23.1 (5.3)	55.1 (12.4)	64 (14.1)	86.3 (15.3)	98.5 (43)	115 (23.2)
T_{max} (hr)[a]	4.6 (2.3-8.3)	4.5 (2.3-8)	4.1 (3-5)	6 (2.3-8)	5.1 (2-12.3)	7 (3-16)	7 (4-12)
AUC_{0-24} (hr.ng/mL)	191 (58.4)	416 (97.9)	943 (281)	1070 (217)	1450 (226)	1830 (876)	2050 (397)
Brexpiprazole Day 14							
$C_{ss,\ max}$ (ng/mL)	39.2 (26.0)	81.2 (28.3)	199 (134)	228 (93.9)	276 (80.7)	200 (185)	382 (30.3)
$C_{ss,\ min}$ (ng/mL)	21.2 (10.9)	56.8 (23.0)	112 (75.3)	143 (52.3)	171 (59.7)	112 (93.1)	205 (51.7)
$T_{ss,max}$ (hr)[a]	3 (0.5-8)	2 (2-3)	8 (3-24)	14.5 (3-24)	4.3 (0.5-12)	7.5 (0-24)	3 (2-6)
AUC_{0-24} (hr.ng/mL)	728 (493)	1620 (594)	3950 (2860)	4530 (1910)	5280 (1790)	4040 (3890)	6950 (797)
Cl/Fss (ml/hr)[b]	2110 (1650)	1390 (517)	1390 (730)	1620 (876)	1800 (1050)	10700 (17700)	1740 (215)
$T_{1/2}$ (hr)	81.1 (32.6)	104.7 (25.5)	86.9 (14.5)	96.0 (37.1)	106.8 (11)	104.8 (44.2)	100.2 (32.0)
$R_{ac}(C_{max})$[c]	3.6 (2.7)	3.5 (0.6)	3.3 (1.3)	3.6 (1.4)	3.2 (1.2)	1.9 (1.4)	3.5 (0.4)
R_{ac}(AUC)	4.1 (3.4)	3.7 (0.8)	3.5 (1.6)	4.1 (1.3)	3.7 (1.6)	1.6 (1.2)	3.7 (0.6)
DM-3411 Day 14							
$C_{ss,max}$ (ng/mL)	15.2 (8.8)	17.3 (2.9)	64.3 (28.4)	57.6 (16.3)	103 (25.9)	71.1 (68.2)	209 (89.9)
$T_{ss,max}$ (hr)[a]	6 (0-24)	3 (0.5-24)	8 (3-24)	24 (8-24)	8 (0.5-24)	8 (2-24)	4 (2-16)
AUC_{0-24} (hr.ng/mL)	299 (170)	374 (65.7)	1280 (508)	1190 (381)	1900 (463)	1390 (1390)	4240 (1730)
$T_{1/2}$ (hr)	72 (22.9)	127 (24.7)	55 (ND)	85.2 (34.5)	87.4 (13.9)	99 (39.7)	88.9 (49.9)

[a]median(range) [b]CL/Fss for Day 14 calculated as dose/AUC0-24h. [C] accumulation ratio calculated as the ratio of AUC_{0-24hr} on Day 1 and Day 14. ND: not determined

-source: Table 9.2.31-1& Table 9.2.3.2-1 in Trial report 331-08-205

2.2.2 Exposure-Response

2.2.2.1 What are the design features of the clinical studies used to support dosing or claims?

The effectiveness of brexpiprazole in the treatment of MDD was established in one 6-week controlled study and one supportive 6-week study of adult patients at doses of 2 to 4 mg administered orally once daily. The efficacy and safety of brexpiprazole in the treatment of schizophrenia was established in two 6-week controlled studies in adult patients at doses of 2 to 4 mg administered orally once daily. Design features for these trials were shown in Table 9.

Table 9: Design Features of Pivotal Clinical Trials

Pivotal Trials	Design Features	Drugs/Dose/Duration

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Schizophrenia		
331-10-230	Phase 3, randomized, double-blind, placebo-controlled, fixed-dose, efficacy and safety study	Brexpiprazole 1 mg/day Brexpiprazole 2 mg/day Brexpiprazole 4 mg/day 6 weeks duration
331-10-231	Phase 3, randomized, double-blind, placebo- controlled, parallel-group, fixed-dose, efficacy and safety study	Brexpiprazole 0.25 mg/day Brexpiprazole 2 mg/day Brexpiprazole 4 mg/day 6 weeks duration
Adjunctive Treatment for Major Depressive Disorder		
331-10-228	Phase 3, randomized, double-blind, placebo-controlled, fixed-dose, efficacy and safety study in MDD patients on antidepressant treatment	Brexpiprazole 2 mg/day Phase A: 8 weeks duration Phase B: 6 week duration
331-10-227	Phase 3, randomized, double-blind, placebo-controlled, fixed-dose, efficacy and safety study in MDD patients on antidepressant treatment	Brexpiprazole 1 mg/day Brexpiprazole 3 mg/day Phase A: 8 weeks duration Phase B: 6 week duration

2.2.2.2 What are the design features of the clinical pharmacology and biopharmaceutics studies?

Clinical pharmacology studies were conducted following both single dose and multiple dose administration. Except for three multiple dose PK studies, thorough QT, and effect of brexpiprazole on sleep trials, all other studies were conducted after single dose administration. The longest blood sampling was up to 312 hr post dose, which is considered adequate to reliably evaluate the PK parameters for brexpiprazole and its major metabolite DM-3411.

2.2.2.3 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The endpoints for Clinical Pharmacology studies were PK measures (plasma, and/or urine/feces concentrations of brexpiprazole and its major metabolite DM-3411) or PD measures (QT, receptor binding). No biomarkers for the intended indications were evaluated in clinical pharmacology studies.

Standard endpoints for schizophrenia and major depressive disorder were employed in the efficacy and safety studies. The primary efficacy endpoint for the phase 2/3 trials in subjects with schizophrenia was the change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score. The primary efficacy endpoint for the phase 2/3 trials in subjects with MDD (adjunct treatment to ADTs) was the change from the end of 8 weeks of adequate prospective treatment with an ADT (Phase A, Week 8) to Week 14 in Montgomery Asberg Depression Rating Scale (MADRS) total score.

2.2.2.4 What are the characteristics of the exposure-response relationship for efficacy?

Schizophrenia

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Exposure-Response analysis indicated that there was a significant PANSS Total Score reduction with higher brexpiprazole exposure compared with placebo (P= 0.00005, Figure 1), and there was a significant reduction of PANSS with the increase of AUC within brexpiprazole-treated patients (P=0.03).

In both Phase 3 trials, Trial 331-10-230 and Trial 331-10-231, clinical response was defined as : >= 30% PANSS reduction at week 6/ET or CGI-I value of 1 or 2 at week 6/ET. The proportion of responders treated with brexpiprazole was higher than patients with placebo (45% vs 31%). In addition, there was a significant increase in responder rate with the increase of AUC in brexpiprazole treated patients (Figure 2).

Adjunctive Major Depressive Disorder
There was a trend of MADRS Total Score reduction with higher brexpiprazole exposure compared with placebo (P=0.0001, Figure 3). However, there was no significant MADRS reduction between Brexpiprazole treatment groups (P=0.2027).

In both Phase 3 trials Trial 331-10-228 and Trial 331-10-227, clinical response was defined as >= 50% reduction in MADRS Total Score at week 14 from the end of Phase A (Week 8). The proportion of responders treated with brexpiprazole was higher than patients with placebo (23% vs 15%). However, there was no significant increase of responder rate with the increase of AUC in brexpiprazole-treated patients (Figure 4).

2.2.2.5 What are the characteristics of the exposure-response relationships for safety?
For safety, the most commonly occurred adverse event, namely akathisia, was analyzed. Exposure-response analysis indicated that the incidence of akathisia is dose-related in both MDD and schizophrenia patients treated with brexpiprazole (Table 1). There are significant increases of akathisia incidence rate with the increase of brexpiprazole exposure. In addition, there is higher incidence of akathisia in patients receiving a concomitant potent CYP2D6 inhibitor. With paroxetine or fluoxetine, the incidences of akathisia are 4.3%, 10.2%, and 24.0% at 1, 2, and 3 mg/day, compared to all other ADTs 4.5%, 6.5%, and 10.6%. However, the higher incidence of akathisia did not result in an imbalance of discontinuation in Phase 3 trials.

The exposure-safety relationship was consistent with the dose-safety relationship. There is a significant increase of akathisia incidence rate with the increase of brexpiprazole exposure in MDD patients (P = 0.002, Figure 5) and in schizophrenia patients (P = 0.008, Figure 5).

2.2.2.6 Does this drug prolong QT/QTc Interval?
No significant QTc prolongation effect of brexpiprazole was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between brexpiprazole (4 mg and 12 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines except for at one time point (6 hours post-dose) for the 4-mg dose. The findings were considered negative.

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2.2.3 Intrinsic Factors

2.2.3.1 What intrinsic factors influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

(b) (4)

[redacted]

Gender

Female subjects had about 42% and 46% (C_{max} and AUC, respectively) higher exposure of brexpiprazole than males (Table 10) in young healthy subjects (18-45 years of age). This is likely due to differences in body weight. Similar gender effect was observed in elderly patients (≥ 65 years of age) as well.

Table 10: PK Parameters (Mean ±SD) for Brexpiprazole and DM-3411 after Single Dose Administration of 2 mg Brexpiprazole to Young Healthy Subjects (18-45 Years Old) Under Fasted Conditions.

Parameters	Female (n=12)	Male (n=12)	Geometric Mean Ratio (90% CI) (Female/male)
Brexpiprazole			
C_{max} (ng/mL)	34.6 ±11.4	23.6 ± 6.0	1.42 (1.17-1.72)
$AUC_{0-\infty}$(hr.ng/mL)	1830 ± 759	1300 ±706	1.46 (1.07-2.00)
DM-3411			
C_{max} (ng/mL)	11.5 ± 6.7	8.2 ± 2.6	-
$AUC_{0-\infty}$(hr.ng/mL)	985 ± 450	689 ±245	-

Population PK analysis found that in females, CL/F and Vc/F were estimated to be 20% and 22% lower than respective values in males, resulting in an estimated 25% higher brexpiprazole AUC in females compared with males.

The impact of gender on the PK of brexpiprazole is not considered clinically relevant.

Age

Elderly male subjects (≥ 65 years of age) had about 18% lower C_{max}, and 5% higher AUC, respectively, of brexpiprazole than younger subjects (18-45 years of age) (Table 11). Similar age effect was observed in female patients as well.

Table 11: PK Parameters (Mean ±SD) for Brexpiprazole and DM-3411 after Single Dose Administration of 2 mg Brexpiprazole to Male Subjects (18-45 Years Old) Under Fasted Conditions.

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Parameters	Elderly (n=12)	Young (n=12)	Geometric Mean Ratio (90% CI) (Female/male)
Brexpiprazole			
Cmax (ng/mL)	19.3 ± 4.8	23.6 ± 6.0	0.82 (0.67-0.99)
$AUC_{0-\infty}$(hr.ng/mL)	1290 ± 430	1300 ±706	1.05 (0.74-1.48)
DM-3411			
Cmax (ng/mL)	7.1 ± 3.2	8.2 ± 2.6	-
$AUC_{0-\infty}$(hr.ng/mL)	974 ± 322	689 ±245	-

The impact of age on the PK of brexpiprazole is not considered clinically relevant.

Organ Impairment
Section 2.2.3.2 (hepatic impairment), section 2.2.3.3 (renal impairment)

2.2.3.2 Effect of Hepatic Impairment
The effect of hepatic impairment on the PK of brexpiprazole and DM-3411 was evaluated after a single dose administration of 2 mg brexpiprazole.

Brexpiprazole exposure (unbound AUC) was increased about 26%, 73%, and 4% in patients with mild, moderate, and severe hepatic impairment, respectively, compared with their respective control (Table 12).

Table 12: Geometric Mean Ratio (90% CI) for Unbound Brexpiprazole in Patients with Hepatic Impairment and Normal Hepatic Function After 2 mg Single Dose Administration of Brexpiprazole

	Mildly Impaired/Normal	Moderately Impaired/ Normal	Severely Impaired/ Normal
$C_{max,u}$ (ng.mL)	0.90 (0.71-1.16)	0.85 (0.67-1.09)	0.53 (0.40-0.71)
$AUC_{0-\infty,u}$ (hr.ng/mL)	1.26 (0.70-2.24)	1.73 (0.98-3.05)	1.04 (0.51-2.14)

Given the benefit/risk profiles of brexpiprazole, the maximum recommended dose for schizophrenia and MDD patients with moderate or severe hepatic dysfunction is 3 mg/day and 2 mg/day, respectively. Close monitoring of patients is recommended during dose initiation, especially in patient with moderate or severe hepatic dysfunction.

2.2.3.3 Effect of Renal Impairment
The effect of renal impairment on the PK of brexiprazole and DM-3411 was evaluated in subjects with severe renal dysfunction after 3 mg single dose administration of brexpiprazole.

Exposure of brexpiprazole (unbound AUC) was increased 72% in subjects with severe renal dysfunction, and unbound C_{max} was only minimally increased (Table 13).

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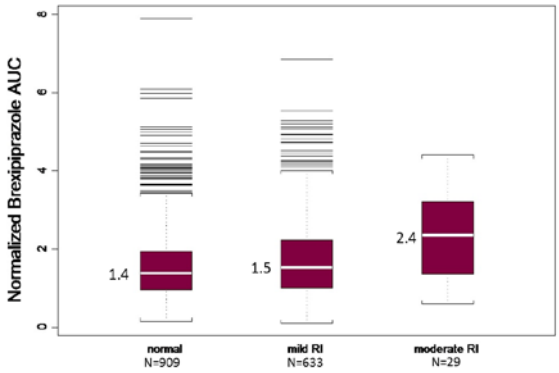
Table 13: Mean (SD) PK Parameters of Brexpiprazole and DM-3411 in Patients with Severe Renal Impairment and Normal Renal Function After 3 mg Single Dose Administration of Brexpiprazole

	Severe Renal Dysfunction (n=10)	Normal Renal Function (n=9)	Geometric Mean Ratio (90% CI) Severely Impaired/ Normal
Brexpiprazole			
$C_{max,u}$ (ng.mL)	0.20 (0.07)	0.20 (0.07)	1.01 (0.77-1.34)
$AUC_{0-\infty,u}$ (hr.ng/mL)	18.0 (8.7)	9.6 (2.3)	1.72 (1.26-2.35)
DM-3411			
Cmax (ng.mL)	19.8 (12.3)	18.2 (6.2)	-
$AUC_{0-\infty}$ (hr.ng/mL)	ND	1730 (566)	-

In addition, population PK analysis using pooled 4 Phase 2 trials (Trial 331-10-228, 331-10-227, 331-10-230 and 331-10-231) indicated that brexpiprazole exposures between patients with normal renal function and mild renal impairment are similar (Figure 10), but exposure in patients with moderate renal dysfunction was significantly increased (i.e., 71% increase in mean AUC_{0-inf}).

Figure 10: Brexpiprazole exposure comparisons between renal impairment patients



Given the benefit/risk profiles of brexpiprazole, the maximum recommended dose for schizophrenia and MDD patients with moderate or worse renal dysfunction is 3 mg/day and 2 mg/day, respectively. Close monitoring of patients with renal dysfunction during dose initiation is highly recommended.

2.2.4 Extrinsic Factors

2.2.4.1 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?

Food

Refer to Section 2.2.4.1.1

Strong CYP3A4 inhibitor

Refer to Section 2.2.4.4.1

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Strong CYP2D6 inhibitor
Refer to Section 2.2.4.4.2
Strong CYP3A4 inducer
Refer to Section 2.2.4.4.3
Strong CYP2B6 inhibitor
Refer to Section 2.2.4.4.4
Gastric pH modifier
Refer to Section 2.2.4.4.5
Activated Charcoal with sorbitol
Refer to Section 2.2.4.4.6

2.2.4.1.1 What is the effect of food on bioavailability of brexpiprazole?
The effect of food on brexpiprazole exposure was evaluated in LTSS formulation (to-be-marketed formulation). High-fat food had minimal effect on the rate and extent of absorption for brexpiprazole (Table 14). Brexpiprazole can be administered without regard to food.

Table 14: PK Parameters (Mean ± SD) for Brexpiprazole and DM-3411 after A Single Dose Administration of 4 mg Brexpiprazole under Fasting and Fed Conditions.

Parameters	Treatment A (fed, n=13)	Treatment B (fasting, n=13)	Ratio of Geometric Means (A/B, 90% CI)
Brexpiprazole			
Cmax (ng/mL)	47.3±14.8	49.3±19.3	0.99 (0.86-1.13)
T_{max} (hr)#	5.5 (2-16)	5.0 (2.0-6.0)	-
$AUC_{0-\infty}$(hr.ng/mL)	3440±1730	3400±1390	1.01 (0.87-1.18)
DM-3411			
Cmax (ng/mL)	18.3±8.6	19.1±8.0	-
$AUC_{0-\infty}$(hr.ng/mL)	1710±844	1820±930	-
# median(min-max)			

2.2.4.2 Is there an in vitro basis to suspect in vivo drug-drug interactions?
In vitro metabolism studies indicated that CYP3A4 and CYP2D6 appear to be the two major enzymes involved in the metabolism of brexpiprazole. So there are potential interactions between brexpiprazole and inhibitors and/or inducers of CYP3A4 and CYP2D6.

2.2.4.3 Effect of brexpiprazole on other drugs
In vitro studies indicated that brexpiprazole and its major metabolite DM-3411are not potent inhibitors and/or inducers of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/3A5. Clinical studies showed that oral brexpiprazole (2 mg/day, 11 days) had no effect on the metabolism of lovastatin (a CYP3A4 substrate), bupropion (a CYP2B6 substrate), or dextromethorphan (a CYP2D6 substrate) (Table 15). Coadministration of brexpiprazole with drugs that are substrates of those enzymes is not likely to affect the PK of those drugs. No dosage adjustment of CYP2D6, CYP3A4, or CYP2B6 substrates is required when administered concomitantly with brexpiprazole.

In vitro studies indicated that the potential for transporter-mediated drug interactions with brexpiprazole and DM-3411 is low, as they are not or weak substrates or inhibitors of P-gp,

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BCRP, OATP1B1, OATP1B3, OAT3 or OCT2, MATE1, MATE2-K. Clinical studies showed that brexpiprazole did not affect absorption of fexofenadine (P-gp substrate, Table 15), or rosuvastatin (BCRP substrate, Table 16). No dosage adjustment of BCRP and P-gp substrates is required when administered concomitantly with brexpiprazole.

Table 15: PK Parameters (Mean ± SD) for Lovastatine, Bupropion, Dextramethorphan, and Fexofenadine after A Single Dose Administration Alone or With Multiple Oral Doses of Brexpiprazole (Brex) to Healthy Male Subjects

Parameters	Treatment A (with Brex)	Treatment B (without Brex)	Arithmetic Mean Ratio A/B
Lovastatin (80 mg, n=5)			
C_{max} (ng/mL)	8.5 ± 6.1	8.9 ± 7.9	0.96
AUC_{0-t}(hr.ng/mL)	107 ± 74.1	97.6 ± 47.3	1.10
Bupropion (150 mg, n=5)			
C_{max} (ng/mL)	115 ± 31.9	120 ± 42.5	0.96
$AUC_{0-\infty}$(hr.ng/mL)	1090 ± 407	1070 ± 418	1.02
Dexmethorphan (30 mg, n=12)			
Ae_{48} (mg) Dexmethorphan	0.2 ± 0.38	0.2 ± 0.46	
Ae_{48} (mg) Dextrorphan	9.9 ± 4.9	8.6 ± 2.6	
Fexofenadine (60 mg, n=5)			
C_{max} (ng/mL)	181 ± 49.2	196 ± 61.8	0.92
$AUC_{0-\infty}$(hr.ng/mL)	1180 ±283	1130 ± 211	1.04

Table 16: PK Parameters (Mean ± SD) for Rosuvastatin after A Single Dose Administration Alone or With Multiple Oral Doses of Brexpiprazole (Brex) to Healthy Male Subjects

Parameters	Treatment A (with Brex, n=25)	Treatment B (without Brex, n=24	Ratio of Geometric Means (A/B, 90% CI)
C_{max} (ng/mL)	2.4 ± 1.1	3.3 ± 1.6	0.76 (0.69-0.84)
$AUC_{0-\infty}$ (hr.ng/mL)	28.1 ± 12.4	25.2 ± 12.5	1.10 (0.95-1.28)

2.2.4.4 Effect of other drugs on brexpiprazole

2.2.4.4.1 Strong CYP3A4 Inhibitor

Coadministration of ketoconazole with brexpiprazole increased plasma exposure of brexpiprazole by 1.19-fold and 1.97-fold for C_{max} and $AUC_{0-\infty,}$ respectively (Table 17).

Dose adjustment is recommended for brexpiprazole in the presence of strong CYP3A4 inhibitors. For patients on a stable brexpiprazole dose at the time when a strong CYP3A4 inhibitor (e.g., itraconazole) is initiated, to achieve similar plasma levels, brexpiprazole dose is recommended to be reduced by half.

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Table 17: Plasma PK Parameters (Mean ±SD) for Brexpiprazole (brex) and DM-3411Following A Single 2-mg Dose of Brexpiprazole Alone or With Ketoconazole (keto) in Healthy Subjects

PK Parameters	Treatment A (Keto+brex) N=12	Treatment B (brex alone) N=12	Geometric Mean Ratio (A/B, 90% CI)
Brexpiprazole			
Cmax (ng/mL)	29.9±8.1	25.3±7.2	1.19 (1.10-1.27)
AUC_0-∞ (hr.ng/mL)	3520±2777	1624±735	1.97 (1.63-2.37)
DM-3411			
Cmax (ng/mL)	9.7±5.7	9.7±4.0	0.98 (0.85-1.12)
AUC_0-∞ (hr.ng/mL)	1500±887	888±508	1.46 (1.34-1.60)

-source: excerpted from Table 9.2.3.2.1-1 and Table 9.2.3.2.2-1 in Study report of Trial 331-08-208

2.2.4.4.2 Strong CYP2D6 inhibitor

Coadministration of quinidine with brexpiprazole increased plasma exposure of brexpiprazole by 1.11-fold and 1.94-fold for C_{max} and $AUC_{0-\infty}$, respectively (Table 18).

Dose adjustment is recommended for brexpiprazole in the presence of strong CYP2D6 inhibitors. For patients on a stable brexpiprazole dose at the time when a strong CYP2D6 inhibitor (e.g., quinidine) is initiated, to achieve similar plasma levels, brexpiprazole dose is recommended to be reduced by half.

Table 18: Plasma PK Parameters (Mean ±SD) for Brexpiprazole (brex) and DM-3411 Following A Single 2-mg Dose of Brexpiprazole Alone or With Quinidine in Healthy Subjects

PK Parameters	Treatment A (Quinidine+brex) N=11	Treatment B (brex alone) N=11	Geometric Mean Ratio (A/B, 90% CI)
Brexpiprazole			
Cmax (ng/mL)	25.7±6.7	22.9±5.1	1.11 (1.01-1.22)
AUC_0-∞ (hr.ng/mL)	2995±1305	1479±630	1.94 (1.49-2.53)
DM-3411			
Cmax (ng/mL)	5.0±1.7	8.6±4.5	0.63 (0.50-0.81)
AUC_0-∞ (hr.ng/mL)	815±429	822±391	0.97 (0.83-1.13)

-source: excerpted from Table 9.2.3.2.1-1 and Table 9.2.3.2.2-1 in Study report of Trial 331-08-208

2.2.4.4.3 Strong CYP3A4 Inducer

Coadministration of rifampin with brexpiprazole decreased plasma exposure of brexpiprazole by 40 % and 73% for C_{max} and $AUC_{0-\infty}$, respectively (Table 19).

Dose adjustment is recommended for brexpiprazole in the presence of strong CYP3A4 inducers. For patients on a stable brexpiprazole dose at the time when a strong CYP3A4

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inducer (e.g., rifampin) is initiated, to achieve similar plasma levels, brexpiprazole dose is recommended to be doubled, and further dose adjustment based on clinical response.

Table 19: Plasma PK Parameters (Mean ±SD) for Brexpiprazole (brex) and DM-3411 Following A Single 4-mg Dose of Brexpiprazole Alone or With rifampin (rif) in Healthy Subjects

PK Parameters	Treatment A (rif+brex) N=16	Treatment B (brex alone) N=16	Geometric Mean Ratio (A/B, 90% CI)
Brexpiprazole			
Cmax (ng/mL)	37.4±10.0	53.9±12.6	0.59 (0.61-0.78)
AUC_0-∞ (hr.ng/mL)	999±289	4190±2380	0.27 (0.23-0.33)
DM-3411			
Cmax (ng/mL)	9.7±5.7	9.7±4.0	-
AUC_0-∞ (hr.ng/mL)	1500±887	888±508	-

-source: excerpted from Table 9.2.3.2.1-1 and Table 9.2.3.2.2-1 in Study report of Trial 331-09-224

2.2.4.4.4 Strong CYP2B6 Inhibitor

Coadministration of ticlopidine with brexpiprazole had minimal effect on the PK of brexpiprazole or DM-3411 (Table 20). Dose adjustment is not necessary for brexpiprazole when a CYP2B6 inhibitor is coadministered.

Table 20: Plasma PK Parameters (Mean ±SD) for Brexpiprazole (brex) and DM-3411 Following A Single 2-mg Dose of Brexpiprazole Alone or with Ticlopidine (tic) in Healthy Subjects

PK Parameters	Treatment A (tic+brex) N=11	Treatment B (brex alone) N=11	Geometric Mean Ratio (A/B, 90% CI)
Brexpiprazole			
Cmax (ng/mL)	22.7±7.5	24.8±11.0	0.97 (0.80-1.17)
$AUC_{0-\infty}$ (hr.ng/mL)	1652±921	1769±1158	1.00 (0.85-1.19)
DM-3411			
Cmax (ng/mL)	8.8±4.8	8.2±4.7	1.12 (0.92-1.37)
$AUC_{0-\infty}$ (hr.ng/mL)	627±231	690±264	0.84 (0.70-1.00)

-source: excerpted from Table 9.2.3.2.1-1 and Table 9.2.3.2.2-1 in Study report of Trial 331-08-208

2.2.4.4.5 Gastric pH modifier

Coadministration of omeprazole with brexpiprazole decreased C_{max} of brexpiprazole by 2 % and increased $AUC_{0-\infty}$ by 18%, respectively (Table 21). These changes are not considered clinically relevant. Dose adjustment is not necessary for brexpiprazole in the presence of gastric acid pH modifiers (including antacids, H2 receptor antagonists, and PPIs).

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Table 21: Plasma PK Parameters (Mean ±SD) for Brexpiprazole (brex) and DM-3411 Following A Single 4-mg Dose of Brexpiprazole Alone or with Omeprazole (omp) in Healthy Subjects

PK Parameters	Treatment A (omp+brex) N=15	Treatment B (brex alone) N=15	Geometric Mean Ratio (A/B, 90% CI)
Brexpiprazole			
Cmax (ng/mL)	50.8±17.9	53.1±20.0	0.98 (0.83-1.16)
$AUC_{0-\infty}$ (hr.ng/mL)	4970±2970	3710±2970	1.18 (1.06-1.32)
DM-3411			
Cmax (ng/mL)	15.2±58.8	18.4±8.5	-
$AUC_{0-\infty}$ (hr.ng/mL)	1950±557	1740±751	-

-source: excerpted from Table 9.2.3.2.1-1 and Table 9.2.3.2.2-1 in Study report of Trial 331-10-240

2.2.4.4.6 Activated Charcoal with Sorbitol

When 50 g/240 mL oral activated charcoal/sorbitol was administered 1 hour after dosing with brexpiprazole, the mean C_{max} and $AUC_{0-\infty}$ of brexpiprazole were reduced by approximately 5% to 23% and 31% to 39%, respectively, as compared with historical trial data (Table 22). Activated charcoal/sorbitol combination can be of some use to reduce brexpiprazole absorption in overdose situations.

Table 22: Mean (SD) Brexpiprazole Pharmacokinetic Parameters Following Administration of 2 mg Brexpiprazole Followed by 50 g/240 mL Oral Activated Charcoal/Sorbitol or 2 mg Brexpiprazole Alone (Historical Trials) to Healthy Subjects

PK Parameter	Brexpiprazole (2 mg) With Activated Charcoal/Sorbitol	Brexpiprazole Alone (Historical Trials, 2-mg Single Oral Dose)			
	331-10-239 (N = 10)	331-08-208 (N = 12)	331-10-241 (N = 16)	331-10-243 (N = 37)	331-10-244 (N = 24)
C_{max} (ng/mL)	5.50 (2.16)	9.17 (3.98)	7.50 (4.70)	7.91 (3.28)	9.82 (5.23)
t_{max} (h)[a]	7.00 (6.00-24.00)	10.01 (6.00-24.00)	12.00 (3.00-24.00)	8.02 (2.00-48.00)	8.00 (6.00-24.00)
AUC_t (ng·h/mL)	434 (199)	753 (371)	601 (302)	728 (318)	738 (341)
AUC_∞ (ng·h/mL)	475 (237)[b]	888 (508)[c]	726 (357)[d]	783 (334)[e]	844 (389)[f]
$t_{1/2,z}$ (h)	68.6 (24.9)[b]	58.1 (16.4)[c]	68.1 (24.9)[d]	81.0 (34.1)[e]	61.9 (21.0)[f]

-source: Table 9.2.3.2.1-1 of study report 331-10-239

2.2.5 General Biopharmaceutics

2.2.5.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation?

Brexpiprazole is likely to be Biopharmaceutic Classification System (BCS) Class 2, (i.e., a low solubility, high permeability). Formal determination of BCS class will be decided by the BCS Classification Committee if requested.

(b) (4)

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(b) (4) For the purpose of the BCS, orally administered brexpiprazole is likely to be highly permeable.

2.2.5.2 How is the proposed to-be-marketed formulation linked to the clinically used formulation?

The to-be-marketed formulation and the clinically used formulation (clinical tablet) are both tablets. The Clinical tablet dose strengths evaluated in the phase 3 trials are the same as the commercial tablet/LTSS (long-term stability study) dose strengths (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg). For each dose strength, the composition of the clinical tablets (b) (4) was the same as the LTSS/commercial tablets. The manufacturing methods and scale for the clinical phase 3 tablets were the same as for the LTSS/Commercial tablets, and the manufacturing process parameters were similar between the Clinical and LTSS/Commercial tablets. In addition, bioequivalence of the 3-mg brexpiprazole Clinical phase 3 tablets to the 3-mg brexpiprazole LTSS/Commercial tablets was established in a clinical trial (Refer to ONDQA/ONDP review).

2.2.6 General Attributes of the Drug

2.2.6.1 What are the highlights of the chemistry and physical-chemical properties of brexpiprazole?

The empirical formula for brexpiprazole is C25H27N3O2S, and its chemical name is 7-[4-(4-Benzo[b]thiophen-4-ylpiperazin-1-yl)butoxy]quinolin-2(1H)-one (Figure 11). The key physicochemical properties of brexpiprazole are summarized in Table 23.

Figure 11: Chemical Structure of Brexpiprazole

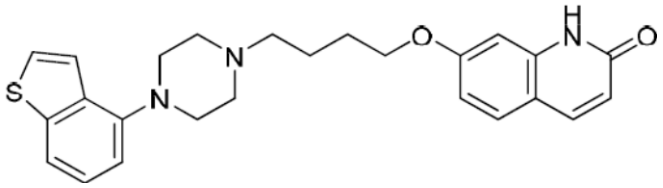

Table 23: Key Physicochemical Properties of Brexpiprazole

Description	(b) (4)
Molecular Weight	
Solubility at 25°C	
Melting Point	
pKa	

(b) (4)

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Table 24: Brexpiprazole pH-Solubility Profile

(b) (4)

[redacted]

2.2.6.2 What are the proposed mechanism of action and therapeutic indications?

Brexpiprazole binds with high affinity to multiple serotonin, dopamine and noradrenergic receptors. Brexpiprazole is a partial agonist at serotonin 5-HT1A and dopamine D2 receptors and an antagonist at serotonin5-HT2A, noradrenergic α1/2 receptors and several other monoaminergic receptor sub-types (Table 25). Metabolite DM-3411 binding affinity at D_2/D_3 and 5-$HT_{2A/2B}$ receptors is about 9 to 17 times and 2 to 5 times, respectively, lower than that of brexpiprazole.

Table 25: Brexpiprazole Human Receptor Affinities (Ki, nM)

Receptor	Binding affinity
Serotonin $5HT_{1A}$	0.12*
Serotonin $5HT_{2A}$	0.47#
Serotonin $5HT_{2B}$	1.88#
Serotonin $5HT_7$	3.66#
Dopamine D_2	0.30*
Dopamine D_3	1.14*
Adrenergic α_{1A}	3.78#
Adrenergic α_{1B}	0.17#
Adrenergic α_{1D}	2.60#
Adrenergic α_{2C}	0.59 #

* = partial agonist; #=antagonist; –source: Table 2.6.2.2.1-19 Pharmacol written summary

The proposed indications for brexpiprazole are adjunctive therapy for the treatment of adult patients with MDD and the treatment of adult patients with schizophrenia.

2.2.6.3 What are the proposed dosing regimens for the targeted indications?

-Schizophrenia

The proposed starting dose is 1 mg/day. The dose should be increased to 2 mg/day after day 4 and may subsequently be increased to 4 mg/day after day 7 based on the patient's clinical response and tolerability. The efficacy of brexpiprazole in the treatment of schizophrenia was established at doses of 2 mg/day and 4 mg/day.

-Major Depressive Disorder

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The proposed starting dose is 0.5-1 mg/day. Dose titration to 1 mg/day and up to the target dose of 2 mg/day should occur at intervals of up to 1 week based on the patient's clinical response and tolerability. The efficacy of brexpiprazole as an adjunctive therapy for MDD was established at doses of 2 mg/day and 3 mg/day.

The proposed commercial strengths of brexpiprazole tablets are 0.25, 0.5, 1, 2, 3, and 4 mg.

2.2.7 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

The current submission consisted of 27 clinical pharmacology studies and 20 in vitro studies (Refer to Section 3: OCP NDA Filing and Review Form).

2.2.8 Analytical Section

2.2.8.1 Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Major moieties in the circulation, including brexpiprazole and its major metabolite DM-3411 are appropriately identified and measured to assess PK parameters in the development program of brexpiprazole.

2.2.8.2 What bioanalytical methods are used to assess concentrations and is the validation complete and acceptable?

LC-MS/MS assay methods were developed to determine the concentrations of brexpiprazole and its major metabolite DM-3411 in human biomatrix samples. The analytical methods were adequately validated and acceptable. For detailed information, refer to individual study review under Appendix I (to be amended).

SIGNATURES

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Cc: NDA 205,422, DPP, DCP1 (Mehta, Uppoor, Zhu, Zhang)

3. NDA FILING FORM

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205,422**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**DCPI**	**Generic Name**	**Brexpiprazole**
Medical Division	**Division of Psychiatry Product**	**Drug Class**	**Antipsychotics**
OCP Reviewer	**Huixia Zhang**	**Indication(s)**	**1)Adjunctive treatment of MDD; 2)Treatment of schizophrenia**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**IR tablet**
Pharmacometrics Reviewer	**Li Zhang**	**Dosing Regimen**	**QD**
Date of Submission	**7/11/2014**	**Route of Administration**	**PO**
Estimated Due Date of OCP Review	**03/11/2015**	**Sponsor**	**Otsuka**
Medical Division Due Date	**03/19/2015**	**Priority Classification**	**Standard**
PDUFA Due Date	**7/11/2015**		

Reference ID: 3713053

Summary

OTSUKA submitted a new original NME NDA application for Brexpiprazole (OPC-34712). This is a split NDA for the following indications: (i) adjunctive treatment of Major Depressive Disorder (MDD) (2 to 3 mg administered orally once daily) & (ii) treatment of Schizophrenia (2 to 4 mg administered orally once daily).

The submission contains 27 in vivo clinical pharmacology and biopharmaceutics studies, 1 population pharmacokinetic (PopPK) and pharmacokinetic/pharmacodynamic (PK/PD) analysis and 20 in vitro studies. The sponsor stated that efficacy for schizophrenia and MDD was each established in two 6-week controlled studies in adult patients.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	4		
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	5		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	2		
Pharmacokinetics (e.g., Phase I) -	x	8		
Healthy Volunteers-				
single dose:	x	1		
multiple dose:	x	1		
Patients-				
single dose:				
multiple dose:	x	4		
Dose proportionality -				
fasting / non-fasting single dose:	x	2		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	5		
In-vivo effects of primary drug:	x	1		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	x	1		
pediatrics:				
geriatrics:	x	1		
renal impairment:	x	1		
hepatic impairment:	x	1		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	4		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	1		

Reference ID: 3713053

II. Biopharmaceutics				
Absolute bioavailability	**x**	**1**		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**3**		
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**2**		
Bio-waiver request based on BCS				
BCS class	**x**			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**	**1**		
Literature References	**x**	**87**		
Total Number of Studies		**48**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
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	X			

Reference ID: 3713053

	studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Huixia Zhang 9/2/2014
Reviewing Clinical Pharmacologist Date

Hao Zhu 9/2/2014
Team Leader/Supervisor Date

Reference ID: 3713053

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUIXIA ZHANG
03/09/2015

PRAVEEN BALIMANE
03/09/2015

KOFI A KUMI
03/09/2015

JEFFREY B KRAFT
03/09/2015

CHRISTIAN GRIMSTEIN
03/09/2015

KEVIN M KRUDYS
03/09/2015
I am also signing on behalf of Li Zhang, the primary pharmacometrics reviewer.

HAO ZHU
03/09/2015

BIOPHARMACEUTICS REVIEW Division of Biopharmaceutics/Office of New Drug Products			
Application No.:	NDA 205422	**Primary Reviewer:** Minerva Hughes, Ph.D.	
Sub. Date:	9 July 2014		
Division:	Division of Neurology Products	**Secondary Reviewer:** Angelica Dorantes, Ph.D.	
		Biopharmaceutics Division Director: Paul Seo, Ph.D. (acting)	
Sponsor:	Otsuka		
Trade Name:	Rexulti	**Date Assigned:**	16 Jul 2014
		Primary Review:	15 March 2015
		PDUFA Date:	15 July 2015
Generic Name:	Brexpiprazole	**Date of Review:**	25 February 2015
Indication:	Major Depressive Disorder and Schizophrenia	**Type of Submission:** **505(b)(1)** **NME**	
Dosage Form/Strengths	Tablet 0.25, 1, 2, 3, and 4 mg		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- Dissolution method and acceptance criterion.
- Bridging bioequivalence studies (Study 209 and 243)
- Biowaiver requests
- Drug product process and dissolution effects
- Drug product dissolution stability (shelf life)

EXECUTIVE SUMMARY

SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

General

NDA 205422 was submitted in accordance with Section 505(b)(1) of the FDC Act for the use of brexpiprazole, a new chemical entity, in the treatment of adult patients with major depressive disorder (MDD) and schizophrenia. For MDD, the recommended starting dose is 0.5-1 mg/day. Dose titration to 1 mg/day and up to the target dose of 2 mg/day should occur at intervals of up to 1 week based on the patient's clinical response and tolerability. The efficacy of brexpiprazole as an adjunctive therapy for MDD is considered by the Applicant to be established at doses of 2 mg/day and 3 mg/day. For schizophrenia, the recommended starting dose is 1 mg/day. The dose should be increased to 2 mg/day after day 4 and may subsequently be increased to 4 mg/day after day 7 based on the patient's clinical response and tolerability.

The proposed drug product is an immediate release [redacted] (b) (4) tablet in the following strengths: 0.25, 0.5, 1, 2, 3, and 4 mg.

Reference ID: 3794027

Bioequivalence Studies

Study 331-13-209 ("Study 209") was conducted to demonstrate bioequivalence between the clinical phase 3 tablets and the proposed commercial tablets. There is no difference in the qualitative and quantitative composition of the clinical and commercial tablets. However, the clinical phase 3 tablets exhibited [redacted] (b) (4) a change in the drug product manufacturing process, which triggered the need for in vivo studies. Bioequivalence was satisfactorily demonstrated between the clinical phase 3 and proposed commercial tablets.

Dissolution Method and Acceptance Criterion

The following dissolution method and acceptance criterion are acceptable for product quality assurance for batch release and stability testing.

Parameter	Criteria
Apparatus	USP 2
Dissolution medium	pH 4.3 USP acetate buffer (0.05 mol/L), 900 mL
Paddle speed	50 rpm
Acceptance Criterion	Q = (b) (4) at 30 minutes
Assay	UV for 3 and 4 mg tablets HPLC for 0.25 and 2 mg tablets

Risk Assessment Evaluation

Refer to the Product Quality review by Thomas Wang for a comprehensive drug product risk assessment evaluation.

Biowaiver Requests

The Applicant's request for a biowaiver for the 0.25, 1, 2, and 4 mg tablets is granted.

CONSULTS

None.

PHASE 4 COMMITMENTS

None.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 205422, brexpiprazole tablets for the treatment of adult patients with major depressive disorder (MDD) and for the treatment of adult patients with schizophrenia is recommended for ***APROVAL.***

Signature Block

Minerva A. Hughes -S

Digitally signed by Minerva A. Hughes -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000389946, cn=Minerva A. Hughes -S
Date: 2015.02.25 15:30:28 -05'00'

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Angelica Dorantes -S

Digitally signed by Angelica Dorantes -S
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Date: 2015.02.25 19:24:35 -05'00'

Angelica Dorantes, Ph.D.
Biopharmaceutics Branch Chief (Acting)
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Reference ID: 3794027

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4 DISSOLUTION APPLICATIONS 17
5 LABELING 20
6 INFORMATION REQUESTS DURING THE REVIEW 21

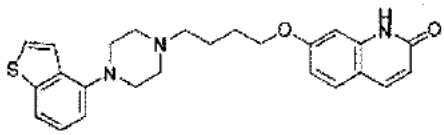
Reference ID: 3794027

BIOPHARMACEUTICS REVIEW

1 GENERAL ATTRIBUTES

1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

The drug substance brexpiprazole is a new dopamine D2 receptor partial agonist with the following structure and formula.



Molecular formula: $C_{25}H_{27}N_3O_2S$; Molecular weight: 433.57 g/mol

(b) (4)

The proposed drug product is formulated as an immediate-release tablet and will be available in six strengths (0.25, 0.5, 1, 2, 3, and 4 mg). All tablet strengths are qualitatively and quantitatively similar with respect to all excipients except (b) (4) for differences in (b) (4) color (b) (4)

Table 2.7.1.1.2.2.3-1 Composition of Brexpiprazole LTSS/Commercial Tablets

Component (Dose [mg]/ Ingredient [mg/unit])	Function	0.25-mg	0.5-mg	1-mg	2-mg	3-mg	4-mg
Brexpiprazole	Active ingredient	0.25	0.5	1.0	2.0	3.0	4.0
Lactose monohydrate	(b) (4)						
Corn starch							
Microcrystalline cellulose							
Hydroxypropyl cellulose							
Low-substituted hydroxypropyl cellulose							
Magnesium stearate							
(b) (4)							
Tablet Color		Light Brown	Light Orange	Light Yellow	Light Green	Light Purple	White
Total Tablet Weight		**93.0**	**93.0**	**93.0**	**93.0**	**93.0**	**93.0**

Reference ID: 3794027

1.2 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Brexpiprazole binds with high affinity to multiple serotonin, dopamine and noradrenergic receptors. The exact mechanisms of the antipsychotic and adjunctive antidepressant effects of brexpiprazole are unknown but are thought to be mediated through modulation of monoaminergic neurotransmitter systems in the brain. Brexpiprazole is a partial agonist at serotonin 5-HT1A and dopamine D2 receptors and an antagonist at serotonin 5-HT2A, noradrenergic α1/2 receptors and several other monoaminergic receptor sub-types.

The proposed indication is for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and for the treatment of schizophrenia.

1.3 *What are the proposed dosage(s) and route(s) of administration?*

The drug product is intended for oral administration. The proposed dose for MDD is 2 mg/day with a starting dose of 0.5 mg or 1 mg/day, not to exceed 3 mg/day. The proposed dose for schizophrenia is 2 to 4 mg/day, with a starting dose of 1 mg/day, not to exceed 4 mg/day.

1.4 *Is there any information on BCS classification? What claim does the applicant make based on BCS classification? What data are available to support this claim?*

A BCS Class 2 designation is reported. (b) (4)

(b) (4)

2 GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 CLINICAL STUDIES

2.1.1 What are the design features of the biopharmaceutics studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided.

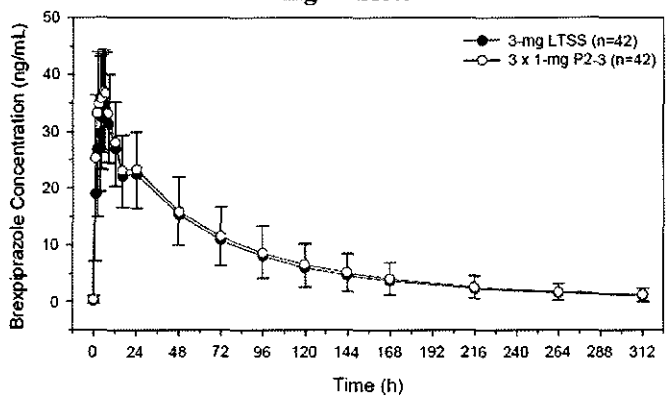
The biopharmaceutics development program included 6 clinical studies evaluating the bioavailability, food effect, dose equivalence, and bioequivalence of brexpiprazole formulations. The following biopharmaceutics studies are evaluated in this review.

- Study 331-10-243: bioequivalence of brexpiprazole commercial and phase 2 clinical trial material
- Study 331-13-209: bioequivalence of brexpiprazole commercial and phase 3 clinical trial material

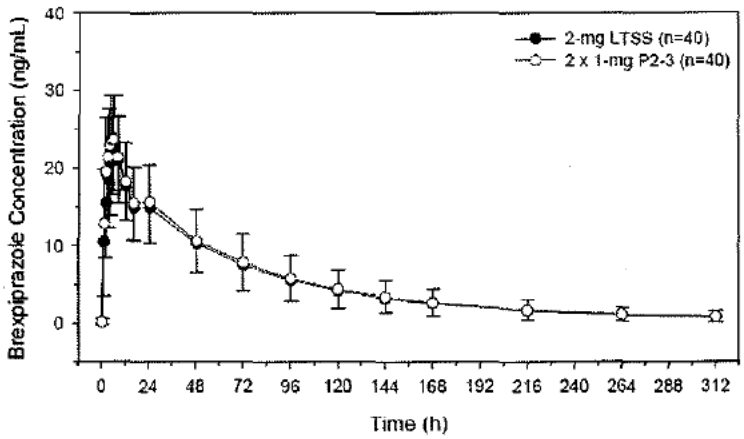
All other biopharmaceutics studies will be evaluated by the assigned Clinical Pharmacology Reviewer as per the division of review responsibilities between Biopharmaceutics and Clinical Pharmacology.

Reference ID: 3794027

Study 331 -10-234

Relative BA Study 234 (Phase 2 and LTSS)	
STUDY DESIGN	An open-label, randomized, two-arm, two-way, crossover trial of the bioequivalence commercial brexpiprazole and phase 2 clinical trial tablets in healthy subjects
METHODOLOGY	This study was a two-arm study. The 2 arms were as follows: • Arm 1: A 3-mg dose of brexpiprazole was administered to each subject as one 3-mg LTSS tablet (test) or three 1-mg P2-3 tablets (reference) on Days 1 and 16 according to the randomization schedule. • Arm 2: A 2-mg dose of brexpiprazole was administered to each subject as one 2-mg LTSS tablet (test) or two 1-mg P2-3 tablets (reference) on Days 1 and 16 according to the randomization schedule. Brexpiprazole and metabolite DM-3411 plasma concentrations were analyzed by noncompartmental methods.
NUMBER OF SUBJECTS/DEMOGRAPHICS	Overall, 100 subjects were enrolled (49 subjects in Arm 1 and 51 subjects in Arm 2), and 96 subjects completed the trial (48 subjects [98.0%] in Arm 1 and 48 subjects [94.1%] in Arm 2).
SUMMARY OF RESULTS	Predose concentrations greater than 5% of Cmax during Period 2 were observed for 6 of 48 subjects for Arm 1 and 8 of 49 subjects for Arm 2 for brexpiprazole and 12 of 48 subjects for Arm 1 and 11 of 49 subjects for Arm 2 for DM-3411. Given the number of subjects falling into this category, the Applicant included supplementary noncompartmental analyses with corrections to C_{max} and AUC. In addition, there were three subjects who experienced vomiting and diarrhea, but these events were not deemed to impact the PK profile and thus, no subjects were excluded from the PK analysis due to an adverse event. The mean plasma concentration profiles for each arm (excluding the subjects noted previously) are presented below. **Mean Plasma Concentration Profiles – Commercial 3-mg vs. Phase 2, 1 mg Tablets** 

Reference ID: 3794027

Relative BA Study 234 (Phase 2 and LTSS)	
	Mean Plasma Concentration Profiles – Commercial 2-mg vs. Phase 2, 1 mg Tablets  The bioequivalence analysis results reported by the Applicant when subjects with predose concentrations >5% of Cmax was excluded or when these data were corrected met the bioequivalence criterion of (b) (4) 90% CI).
SUMMARY OF SAFETY[1]	No serious TEAEs occurred, and no subjects discontinued trial medication due to a TEAE.
Reviewer's Evaluation	*The study results suggest that an adequate washout period was not employed for this study, leading to a large number of patients with drug carryover into period two. Additionally, subjects also experienced vomiting at a critical time post dose. Given these complications, the study would warrant a more thorough independent review to ensure that the statistical analysis included the appropriate subjects for review. However, after communication with the Clinical Review team, the information generated from Phase 2 studies will not be leverage upon for efficacy and thus, Study 243 is deemed NOT critical for review. Therefore, the data from this study are acknowledged only as part of the Applicant's overall bridging strategy supporting the CMC changes throughout the product's development.*

Study 331-13-209

Relative BA Study 209 (Phase 3/Commercial)	
STUDY DESIGN	Single center, open-label, 2-way, randomized, crossover trial evaluating the relative bioavailability of the Phase 3 and commercial (LTSS) tablet formulations.
METHODOLOGY	Subjects received 3-mg brexpiprazole as one 3-mg LTSS tablet (lot number 10K74A003A) and one 3-mg P3 tablet (lot number 10L76A003).

[1] Drug safety is fully evaluated by the assigned Clinical Reviewer.

Reference ID: 3794027

Relative BA Study 209 (Phase 3/Commercial)

Doses were administered orally on Days 1 and 22 (crossover) with 240 mL of room temperature still water. All doses were administered after at least 8 hours of fasting and lunch was served 4 hours after dose administration. Blood samples were collected for the determination of brepiprazole and metabolite DM-3411. Pharmacogenomic sampling was also done.[2]

NUMBER OF SUBJECTS/DEMOGRAPHICS

A total of 31 subjects were enrolled in the study. Twenty-eight of the 31 (90.3%) subjects completed the trial; 15 of the 16 (93.8%) subjects in Sequence 1, and 13 of the 15 (86.7%) subjects in Sequence 2. The mean age of the 31 subjects enrolled in this trial was 32.5 ± 7.8 years, and their mean BMI was 26.1 ± 3.1 kg/m^2. The demographic information by sequence is tabulated below.

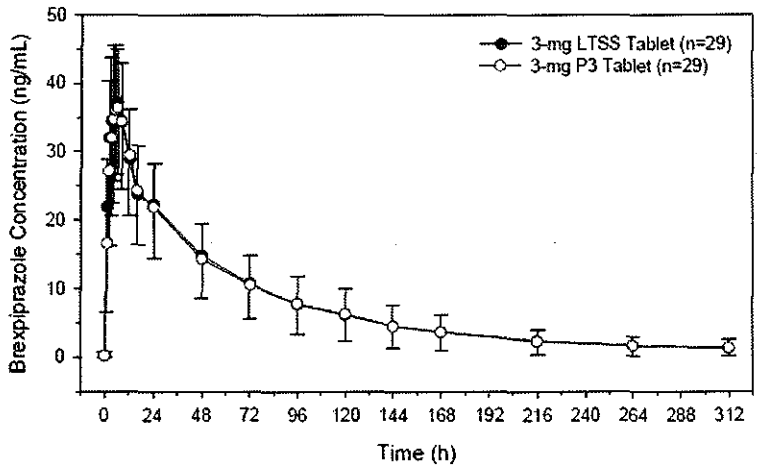
Table 11.2-1 Demographics by Treatment Sequence

Demographic	Sequence 1 LTSS/PS 3 mg (N=16) n (%)[a]	Sequence 2 P3/LTSS 3 mg (N=15) n (%)[a]	Total (N=31) n (%)[a]
Sex			
Male	8 (50.0)	7 (46.7)	15 (48.4)
Female	8 (50.0)	8 (53.3)	16 (51.6)
Race			
White	4 (25.0)	3 (20.0)	7 (22.6)
Black or African American	12 (75.0)	11 (73.3)	23 (74.2)
Other	0 (0.0)	1 (6.7)	1 (3.2)
Ethnicity			
Hispanic or Latino	2 (12.5)	3 (20.0)	5 (16.1)
Not Hispanic or Latino	14 (87.5)	12 (80.0)	26 (83.9)

[a] Percentages based on number of enrolled subjects.

SUMMARY OF RESULTS

Mean Plasma Concentration Profiles Following Single Oral Doses of 3 mg LTSS and 3 mg Phase 3 Tablets



[2] Pharmacogenomic analyses are evaluated by Clinical Pharmacology.

Reference ID: 3794027

Relative BA Study 209 (Phase 3/Commercial)

Mean Brexpiprazole Pharmacokinetic Parameters

PK Parameter	3-mg LTSS Tablet (n=29)	3-mg P3 Tablet (n=29)
C_{max} (ng/mL)	40.8 (11.8)	38.9 (10.0)
t_{max} (h)[a]	4.00 (1.00-8.00)	4.00 (1.00-8.00)
AUC_t (ng·h/mL)	2335 (1055)	2310 (912)
AUC_{72h} (ng·h/mL)	1415 (474)	1387 (393)
AUC_∞ (ng·h/mL)	2508 (1202)	2488 (1074)
$t_{1/2,z}$ (h)	82.0 (23.3)	80.4 (18.2)
CL/F (mL/h/kg)	19.7 (8.74)	20.1 (10.4)

[a]Median (minimum-maximum).
Source: PKT-6 and PKT-7.

Brexpiprazole Bioequivalence Analyses (Reported)

Table 11.5.2.3.3.1-1 Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole Pharmacokinetic Parameters Following Administration of 30-mg Brexpiprazole as One 3-mg LTSS Tablet and One 3-mg P3 Tablet to Healthy Subjects

Comparison	PK Parameter	GMR	90% CI
3-mg LTSS Tablet (T) versus 3-mg P3 Tablet (R)	C_{max}	1.0464	0.9591-1.1417
	AUC_t	1.0133	0.9604-1.0692
	AUC_{72h}	1.0177	0.9594-1.0796
	AUC_∞	1.0154	0.9626-1.0710

GMR=geometric mean ratio; T=test.; R=reference
Source: Section 14.5.4 and PK-1.1.

Brexpiprazole Bioequivalence Analyses (Reviewer's Analyses)

The following subjects were excluded from the Applicant's analyses:
Subj 19 – early termination at Day 23
Subj 22 – early termination at Day 33
Subj 23 - early termination at Day 32
Subj 29 – predose concentration >5% of Cmax

There were three subjects who experienced either emesis or diarrhea after dosing. One subject (Subj 29) was excluded because of the amount of drug at pre-dose in the second period; however, all other subjects were included in the analysis because the PK profile appeared similar to other subjects in the study. The rationale for including/excluding PK data in the statistical analysis appears reasonable. Although Subj 22 and 23 were excluded for early termination, this reviewer's analysis estimated that ~ 90% or more of the estimated AUC was captured with the available data. The sensitivity of the bioequivalence analysis to these subjects was explored.

This Reviewer's results applying the Applicant's inclusion/exclusion criteria are as following.

GMR and 90% Confidence Intervals for Brexpiprazole (Independent Analysis)

PK Parameter	GMR	90% CI
Cmax	1.04	0.9591 – 1.1417
AUC_{last}	1.01	0.9604 – 1.0692
AUC_{inf}	1.02	0.9700 – 1.0729

Additional analyses including Subj 22 and Subj 23 are summarized below.

Reference ID: 3794027

Relative BA Study 209 (Phase 3/Commercial)	
GMR and 90% Confidence Intervals for Brexpiprazole (Independent Analysis – w/Subj 22 and Subj 23)	

PK Parameter	GMR	90% CI
Cmax	1.05	0.9707 – 1.1433
AUC_{last}	1.02	0.9695 – 1.0719
AUC_{inf}	1.03	0.9789 – 1.0758

SUMMARY OF SAFETY[3]	No deaths or SAEs occurred in subjects during this trial. One subject in the LTSS/P3 sequence discontinued from the trial on Day 23 due to an AE of viral upper respiratory tract infection that was not related to the drug. The most frequently occurring TEAEs reported in 4 or more subjects were dizziness, nausea, weight increased, vomiting, and orthostatic hypotension reported in 13 (41.9%), 9 (29.0%), 8 (25.8%), 4 (12.9%), and 4 (12.9%) subjects, respectively.
Reviewer's Evaluation	*Bioequivalence was satisfactorily demonstrated in Study 209* (b) (4) (b) (4) (b) (4). *The proposed study included a more appropriate washout period to minimize the issues with drug carryover, as observed in Study 243. As such, a satisfactory bridge has been demonstrated between the proposed commercial product/process and the phase 3 clinical trial material.*

2.1.2 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.

2.1.3 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?

Refer to the Clinical Pharmacology Review

2.2 BIOANALYTICAL METHOD SECTION

2.2.1 How are the active moieties and/or metabolites identified and measured in the plasma in the biopharmaceutics studies?

Brexpiprazole and its major metabolite DM-3411 were extracted from human plasma using a protein precipitation extraction and analyzed using HPLC/MC with internal standards.

2.2.2 What bioanalytical methods are used to assess concentrations?

A validated HPLC-MS/MS method was used to assess concentrations.

2.2.2.1 What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower

[3] Drug safety is fully evaluated by the assigned Clinical Reviewer.

Reference ID: 3794027

and upper limits of quantification (LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?

The HPLC bioanalytical method was validated for use over the linear concentration range of 0.300 to 100 ng/ml. Results were calculated using peak area ratios, and calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression.

For each batch of samples processed, the calculated concentrations of at least two-thirds of the QC samples were within 15% of nominal concentrations. Over the course of the trial (Study 209), at each QC sample concentration, the percent relative standard deviation (%RSD) values were within 8.3%, and the percent accuracy values were within ± 2.0% for brexpiprazole and DM-3411. Also, based on QC sample performance, there were no apparent stability problems encountered during the sample analysis. The incurred sample reassay (ISR) test, in which a total of 121 samples from 31 subjects were chosen for reassay, demonstrated adequate reproducibility in that for at least two-thirds of the ISR samples, the difference between the initial and ISR results were within 20% of the mean of the 2 results.

2.2.2.2 Are the Inspection reports of the BE study acceptable?

It is noted that the clinical site inspections were not performed for the bioequivalence studies covered in this review based on a risk assessment of the studies' impact and prior inspections at the same or related sites by the Office of Scientific Investigations.

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION INFORMATION

3.2 DISSOLUTION METHOD

3.2.1 What is the proposed dissolution method?

The proposed dissolution method and acceptance criterion are summarized below.

Table 2.7.1.1.2.4-1 Proposed Dissolution Method and Acceptance Criterion for Release Testing for Brexpiprazole Tablets

Tablet Strength	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg
Apparatus	USP Apparatus 2 (Paddle Method)
Dissolution Medium	pH 4.3 USP acetate buffer (0.05 mol/L)
Volume of Dissolution Medium	900 mL
Paddle Speed	50 rpm
Sampling Time Points (minutes)	10, 20, 30, 45, 60
Acceptance Criteria	Q= (b) (4) in 30 minutes
Assays [a]	UV for 3-mg and 4-mg tablets HPLC for 0.25-mg to 2-mg tablets

(b) (4)

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3.2.4 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The analytical method validation information will be addressed by the drug product CMC Reviewer.

3.2.5 Is the proposed dissolution method biorelavant? What data are available to support this claim?

No, the proposed dissolution method is not biorelavant.

3.2.6 Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the proposed dissolution method is acceptable.

3.3 ACCEPTANCE CRITERIA

3.3.1 What are the proposed dissolution acceptance criteria for this product?

The proposed dissolution acceptance criterion is Q = (b) (4) at 30 minutes for all tablet strengths.

3.3.2 What data are available to support the criteria?

The Applicant states in Section 3.2.P.5.6 of the NDA that the dissolution acceptance criterion is justified because the range of dissolution results during long-term stability studies up to 18 months and accelerated studies up to 6 months were (b) (4). No additional discussion or analyses were provided.

The complete dissolution profile data for a representative commercial lot for each tablet strength and mean dissolution at 30 minutes for representative clinical lots are included in the dissolution method development report. Using the proposed dissolution method, the commercial product performance is as illustrated in the following figure.

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(b) (4)

[redacted]

3.3.3 *Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?*

The clinical lots were evaluated using an earlier dissolution method [redacted] (b) (4) Lot retains were evaluated using the proposed regulatory test method in 2013 (> 2 years later); however, the registration QC release data were primarily used to assessed the appropriateness of the proposed acceptance criterion.

3.3.4 *Are mean (n =12) dissolution profile data used for the setting of the acceptance criteria?*

Yes.

3.3.5 *Are the acceptance criteria acceptable? If not, what are the recommended criteria?*

Yes, the proposed acceptance criterion is acceptable.

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4 DISSOLUTION APPLICATIONS

4.1 FORMULATION CHANGES

4.1.1 Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?

There have been no changes to the tablet formulation during development; however, the clinical batches for the phase 2 trials were initially manufactured at a pilot scale [redacted] (b) (4) The process parameters used [redacted] (b) (4) were different from those used to manufacture the long term stability study (LTSS) and commercial batches. Later stage phase 2 batches [redacted] (b) (4) were manufactured at the Tokushima factory and did use similar process parameters and equipment as the commercial product, [redacted] (b) (4) [redacted] (b) (4)

Phase 3 clinical trial material was manufactured at production scale [redacted] (b) (4) [redacted] (b) (4) but the process parameters [redacted] (b) (4) changed slightly for initial batches [redacted] (b) (4) [redacted] (b) (4)

Despite the manufacture of additional phase 3 clinical trial material using the final commercial process, these batches were not utilized in any significant quantity in the clinical study [redacted] (b) (4) across the entire program). Thus, in spite of the formulation consistency throughout development; drug product representative of the commercial process was not used in the pivotal clinical studies in any appreciable way. Both bioequivalence and in vitro dissolution studies were completed to bridge the manufacturing process changes throughout development. An overview of the formulation bridging strategy, including phase 2 clinical trial material, is illustrated below.

[redacted] (b) (4)

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(b) (4)

4.2 BIOWAIVERS

4.2.1 *Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?*

Yes. A waiver is requested for bioequivalence studies comparing the Phase 3 clinical and commercial 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 4 mg tablets. The justification for the proposed waiver is as follows.

- Bioequivalence was established between the 3-mg P3 Clinical versus 3-mg LTSS/Commercial tablets (Trial 331-13-209).
- Brexpiprazole exhibits dose-proportional pharmacokinetics after single-dose (0.2 mg to 8 mg) and multiple-dose (0.5 mg to 12 mg), once-daily administration.
- Brexpiprazole tablets are (b) (4) 0.25-mg through 4 mg dose strengths.
- Based on the dissolution testing in three pH media (b) (4) (b) (4) the 0.25-mg, 0.5-mg, 1-mg, 2-mg, and 4-mg LTSS/Commercial tablets met the similarity (f2 similarity ≥50) criterion when compared with the corresponding P3 Clinical tablet at each dose level.
- Based on the dissolution testing conducted in three pH media (b) (4) (b) (4) the 1-mg, 2-mg, and 4-mg LTSS/Commercial tablets met the similarity (f2 similarity ≥50) criterion when compared with the 3-mg LTSS/Commercial tablet.
- Based on the dissolution testing conducted in three pH media (b) (4) (b) (4) the 0.25-mg and 0.5-mg LTSS/Commercial tablets met the similarity (f2 similarity ≥50) criterion when compared with the 1-mg LTSS/Commercial tablets.

The Phase 3 and commercial tablets (b) (4) are manufactured using a similar process. (b) (4) (b) (4) Similarity f2 testing failed to demonstrate dissolution profile similarity of the 3 mg clinical and commercial tablet (b) (4). This outcome triggered the need for bioequivalence testing between the phase 3 and commercial tablets and the 3 mg tablet strength was used for the study. As discussed in Section 2.0 of this review, bioequivalence was satisfactorily demonstrated between the Phase 3 and commercial tablets.

From this Reviewer's perspective, the comparative in vivo and in vitro data, (b) (4)

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(b) (4) adequately support granting a biowaiver for the 0.25, 1, 2, and 4 mg tablet strengths.

4.2.2 ***Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?***

Not applicable.

4.3 SURROGATES IN LIEU OF DISSOLUTION

4.3.1 ***Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?***

Not applicable.

4.4 DISSOLUTION AND QBD

4.4.1 ***Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?***

Yes. A design space was developed and used (b) (4) Dissolution is identified as a CQA for defining the design space.

(b) (4)

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(b) (4)

4.4.2 *Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?*

(b) (4)

(b) (4) Following the DOE studies, the Applicant notes that the risks for all parameters have been appropriately mitigated. Reference is made to the CMC Drug Product Quality Review for a full evaluation of the manufacturing process and control strategy.

(b) (4)

4.4.3 *What biopharmaceutics information is available to support the clinical relevance of the proposed design space?*

Although a design space was developed, the design space is not proposed for regulatory flexibility (verified in the 30 January 2015 NDA Amendment). The Applicant plans to operate at set points and seek FDA approval for any changes to the operating parameters. Therefore, a critical review is not warranted.

4.4.4 *Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?*

Not applicable.

5 LABELING

The biopharmaceutics labeling information is addressed by the assigned Clinical Pharmacology Reviewer.

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6 INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses are incorporated into the QBR above. There are no outstanding review issues.

1. Provide the PK parameter analysis datasets as SAS transport files for bioequivalence studies 209 and 243, preferably in stacked column format.

   Adequate responses were received in the 14 October 2014 NDA Amendment.

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205,422	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	DCPI	Generic Name	Brexpiprazole
Medical Division	Division of Psychiatry Product	Drug Class	Antipsychotics
OCP Reviewer	Huixia Zhang	Indication(s)	1)Adjunctive treatment of MDD; 2)Treatment of schizophrenia
OCP Team Leader	Hao Zhu	Dosage Form	IR tablet
Pharmacometrics Reviewer	Li Zhang	Dosing Regimen	QD
Date of Submission	7/11/2014	Route of Administration	PO
Estimated Due Date of OCP Review	03/11/2015	Sponsor	Otsuka
Medical Division Due Date	03/19/2015	Priority Classification	Standard
PDUFA Due Date	7/11/2015		

Summary

OTSUKA submitted a new original NME NDA application for Brexpiprazole (OPC-34712). This is a split NDA for the following indications: (i) adjunctive treatment of Major Depressive Disorder (MDD) (2 to 3 mg administered orally once daily) & (ii) treatment of Schizophrenia (2 to 4 mg administered orally once daily).

The submission contains 28 in vivo clinical pharmacology and biopharmaceutics studies, 1 population pharmacokinetic (PopPK) and pharmacokinetic/pharmacodynamic (PK/PD) analysis and 20 in vitro studies. The sponsor stated that efficacy for schizophrenia and MDD was each established in two 6-week controlled studies in adult patients..

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	4		
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	5		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	2		
Pharmacokinetics (e.g., Phase I) -	x	8		
Healthy Volunteers-				
single dose:	x	1		
multiple dose:	x	1		

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Patients-				
single dose:				
multiple dose:	**x**	**4**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**2**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**5**		
In-vivo effects of primary drug:	**x**	**1**		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	**x**	**1**		
pediatrics:				
geriatrics:	**x**	**1**		
renal impairment:	**x**	**1**		
hepatic impairment:	**x**	**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**4**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability	**x**	**1**		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**3**		
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**2**		
Bio-waiver request based on BCS				
BCS class	**x**			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**	**1**		
Literature References	**x**	**87**		
Total Number of Studies		**48**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

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4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Huixia Zhang	9/2/2014
Reviewing Clinical Pharmacologist	Date
Hao Zhu	9/2/2014
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUIXIA ZHANG
09/03/2014

HAO ZHU
09/03/2014