CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-520

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-520
Brand Name:	SYMBYAX
Generic Name:	Olanzapine-Fluoxetine
Type of Dosage Form:	Capsules
Strengths:	[ ] mg; 6 mg/25 mg; 6 mg/50 mg; 12 mg/25 mg; 12 mg/50 mg
Indications:	Bipolar Depression
Type of Submission:	Complete Response to Approvable Letter
Sponsor:	Eli Lilly & Co.
Submission Dates:	June 24, 2003
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This review evaluates the Sponsor's response to the recommendations made by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in the approvable action letter for NDA 21-520.

In the review of the original NDA (see OCPB review of 4/1/03), the Office of Clinical Pharmacology and Biopharmaceutics recommended the following:

- A change in the *in vitro* dissolution specification
- [ ]
- Specific revisions of the proposed label's text

The Sponsor has provided responses as follows:

- The Sponsor has provided justification for and requests retention of the originally submitted dissolution specification of Q=[ ] at 30 minutes.

The Office of Clinical Pharmacology and Biopharmaceutics agrees with the Sponsor's proposed dissolution specification, and recommends that this specification be adapted.

[ ]

- The Sponsor has made most of the changes recommended in the Clinical Pharmacology sections of the labeling.

OCPB suggests the following change (OCPB change highlighted) to the Sponsor's proposed language on line 691-692 (of proposed clean word.doc) to increase the usefulness of this information for prescribing physicians:

The effect of CYP1A2 inhibitors such as fluvoxamine and some fluoroquinolone antibiotics on SYMBYAX has not been evaluated.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has the following recommendations.

1) The proposed *in vitro* dissolution specification is acceptable.
2) [
3) The OCPB recommends some revisions of the proposed label's text regarding listing examples of CYP1A2 inhibitors to increase the usefulness of this information for prescribing physicians.

Please forward the comments above and the labeling comments in Section 3.2.3 (p. 6 of this review) to the Sponsor.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 21-520
CSO/ D. Bates
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta, C. Sahajwalla

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

NDA 21-520 (November 4, 2002) for SYMBYAX, a combination of olanzapine and fluoxetine for use in the treatment of depressive episodes associated with bipolar disorder, received an approvable letter on May 5, 2003.

The Clinical Pharmacology and Biopharmaceutics Recommendations for that submission were that the submitted data were acceptable, pending the outcome of the DSI inspection report of the pivotal bioequivalence study (HDAK). The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommended the following:

- A change in the *in vitro* dissolution specification
- [ ]
- Specific revisions of the proposed label's text

The Sponsor has submitted a complete response to the approvable letter. The response to the OCPB recommendations will be addressed here.

3.2 Current Submission

3.2.1 Dissolution Specifications

Is the proposed dissolution specification acceptable?

The Sponsor originally proposed the dissolution specification of Q=' — at 30 minutes. OCPB recommended changing to Q=—— at — minutes, since the proposed method discriminated between different formulations at — minutes and all formulations were more than — dissolved at 30 minutes.

The Sponsor requests retention of the originally submitted dissolution specification of Q= — at 30 minutes. The Sponsor proposes that this specification provides ample quality assurance control, noting that this control strategy is supported by the control strategy for similarly formulated single entity capsules used in the pivotal clinical efficacy trials. The Sponsor also notes that the specification for single entity fluoxetine capsules is Q=' — at 30 minutes and for the single entity olanzapine capsules is Q=' —— at 30 minutes.

In addition, the Sponsor notes that the rate of dissolution does not influence the rate or extent of absorption. This is in agreement with the OCPB consideration in the original review of NDA 21-520 that absorption rather than dissolution is the rate limiting step in exposure to either olanzapine or fluoxetine. This, however, does not directly pertain to the use of dissolution specifications for quality assurance, although it is noted that the tmax for both olanzapine and fluoxetine occurs at approximately 4-5 hours. Thus, a

rapidly dissolving formulation would not be expected to alter the tmax. A poorly dissolving formulation would be apparent at the 30 minute time point.

Therefore, OCPB finds that the specification of Q=[redacted] at 30 minutes is acceptable.

3.2.3 Labeling Changes

The Sponsor has made most of the changes recommended in the Clinical Pharmacology sections of the labeling. We suggest the following change (OCPB change highlighted) on line 691-692 of the "proposed clean word.doc", to increase the usefulness of this information for prescribing physicians:

The original paragraph (lines 687-698 in the "proposed clean word.doc" provided by the Sponsor) in which that sentence is found in the **Drug Interactions** section of the label, is copied below.

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/s/

Sally Yasuda
11/7/03 01:50:24 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
11/7/03 01:54:59 PM
BIOPHARMACEUTICS

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-520
Brand Name:	SYMBIAX
Generic Name:	Olanzapine-Fluoxetine
Type of Dosage Form:	Capsules
Strengths:	[redacted], 6 mg/25 mg; 6 mg/50 mg; 12 mg/25 mg; 12 mg/50 mg
Indications:	Depressive Episodes Associated with Bipolar Disorder
Type of Submission:	New NDA/ 4 Priority
Sponsor:	Eli Lilly & Co.
Submission Dates:	11/4/02, 11/21/02, 12/4/02, 12/9/02, 12/16/02, 12/18/02, 1/27/03, 2/3/03
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD
PM Reviewer:	Meiyu Shen, PhD
PM Team Leader:	Jogarao Gobburu, PhD

1 Executive Summary

This NDA review evaluates *in vivo* and *in vitro* data regarding olanzapine/fluoxetine combination capsules in different strengths to be indicated for depressive episodes associated with bipolar disorder. Clinical trials were conducted to evaluate the use of the two drugs in combination in the treatment of depressive episodes associated with bipolar disorder. The to-be-marketed OFC capsules were not used in the clinical trials.

The pivotal clinical trial used a combination of olanzapine and fluoxetine in individual capsules. The highest strength of SYMBIAX was found to be bioequivalent to the individual clinical trial capsules. The Sponsor has requested a biowaiver for lower strengths of SYMBIAX capsules. The SYMBIAX capsules are not rapidly dissolving *in vitro* and the dissolution profiles of different strengths are not considered similar based on the f2 value. The lower strengths show faster dissolution than the highest strength in pH 4.5 and pH 6.8 buffers. Data from other formulations of olanzapine and of fluoxetine showed that rapidly dissolving olanzapine formulations are bioequivalent to slower dissolving tablets, and fluoxetine solution was bioequivalent to a capsule, suggesting that absorption, rather than dissolution (especially in pH 4.5 and 6.8), is the rate-limiting step in exposure. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics recommends a biowaiver for the lower strengths of SYMBIAX.

Fluoxetine given with olanzapine results in higher Cmax (approximately 16%) and AUC (approximately 17%) of olanzapine than observed with olanzapine alone. Since olanzapine is metabolized by CYP1A2 and CYP2D6 to a lesser extent, the potential for interaction with CYP1A2 inhibitors now given in combination with a CYP2D6 inhibitor, fluoxetine, may be of

concern. Therefore, the OCPB recommends evaluation of olanzapine pharmacokinetics when the highest strength of SYMBIAX is administered with a potent inhibitor of CYP1A2.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA-21-520 for SYMBIAX acceptable, pending the outcome of the DSI inspection report of the pivotal bioequivalence study (HDAK). The OCPB recommends some revisions of the proposed label's text (please refer to Section 5).

The proposed *in vitro* dissolution method is acceptable. The OCPB recommends that the specification be changed to Q=' —— at ¯ minutes.

Please forward the comments above and the labeling comments in Section 5, as well as the recommendations for a Phase IV commitment to the Sponsor.

1.2 Phase IV Commitment

The Office of Clinical Pharmacology and Biopharmaceutics recommends that the Sponsor agree to conduct the following study as a Phase IV commitment:

Since olanzapine is metabolized by CYP1A2 and CYP2D6 to a lesser extent, the potential for interaction with CYP1A2 inhibitors now given with olanzapine as SYMBIAX (in combination with a CYP2D6 inhibitor fluoxetine) may be of concern. Therefore, we recommend that you conduct a drug interaction study with the highest strength of SYMBIAX and a potent CYP1A2 inhibitor.

Clinical Pharmacology & Biopharmaceutics Required Interdivision Briefing:
March 27, 2003
Attendees: Mehul Mehta, Chandra Sahajwalla, John Hunt, Hank Malinowski, John Lazor, Paul Andreason, Li Shan Hsieh, Sally Yasuda, Ramana Uppoor, Abi Adebowale, Chandra Chaurasia, Jogarao Gobburu, Meiyu Shen

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

SYMBIAX is a combination of two previously approved agents, olanzapine and fluoxetine. Olanzapine (ZYPREXA) is approved for use in schizophrenia and in bipolar mania. It binds with high affinity to serotonin $5HT_{2A/2C}$, dopamine D_{1-4}, muscarinic cholinergic M_{1-5}, histamine-H_1, and α_1-adrenergic receptors. Fluoxetine (PROZAC) is an antidepressant that inhibits neuronal uptake of serotonin. The dosing range for olanzapine is 5-20 mg daily. The dosing range for fluoxetine is 20-80 mg/day.

Olanzapine displays linear kinetics over the dosing range of up to 20 mg/day. It has an elimination half-life of 21-54 hours, allowing for once daily dosing. It is extensively hepatically metabolized, with approximately 7% of the dose recovered in urine as unchanged drug following a single oral dose. Its P450 mediated metabolism is primarily via CYP1A2 with CYP2D6 being a minor pathway.

Fluoxetine displays nonlinear kinetics. It has an elimination half-life of 1-3 days after acute administration and 4-6 days after chronic administration. It is metabolized to norfluoxetine, an active metabolite with an elimination half-life of 4-16 days. Fluoxetine metabolism is mediated by CYP2D6. In addition, it inhibits CYP2D6.

3.2 Current Submission

The present NDA (21—520) has been submitted to support the approval of SYMBIAX for depressive episodes associated with bipolar disorder. The strengths are (mg olanzapine/mg fluoxetine)—, 6/25, 6/50, 12/25, and 12/50. The proposed dosing will range from olanzapine 6-12 mg and fluoxetine 25-50 mg, given by mouth once daily in the evening. It is suggested that the beginning dose be 6/25 mg. The sponsor has requested a biowaiver for the lower strengths of SYMBIAX.

The following clinical pharmacology and biopharmaceutics studies have been submitted and reviewed:

- HP-FW-HDAK – Pivotal bioequivalence study
- F1D-MS-HGCI – Olanzapine/fluoxetine pharmacokinetic interaction study
- F1D-MC-HGFR – Safety and efficacy of olanzapine/fluoxetine vs. olanzapine or fluoxetine in treatment resistant depression
- F1D-MD-HGIE – Olanzapine/fluoxetine dose ranging study in treatment resistant depression

The bioanalytical methods were validated and documented appropriately. HGFR and HGIE used population pharmacokinetics to assess the fluoxetine/olanzapine pharmacokinetic interaction, and have been evaluated by the Pharmacometrics reviewer. In addition, a Pharmacometrics

consult was requested to determine whether a dose-response relationship could be characterized in the pivotal clinical study F1D-MD-HGGY in bipolar depression.

The key findings with respect to the clinical pharmacology of SYMBIAX are as follows:

- Bioequivalence was demonstrated between the highest strength (12/50) SYMBIAX capsule and the clinical trial individual capsule formulation of the olanzapine/fluoxetine combination when given as a single dose under fasting conditions.

- A dose-response relationship could not be characterized in the pivotal clinical study.

- Fluoxetine (60 mg) given in combination with olanzapine (5 mg) results in a 16% increase in olanzapine Cmax, an approximate 17% increase in AUC compared to administration of olanzapine alone in healthy volunteers. This is supported by findings in a clinical study in patients with treatment resistant depression in which the Sponsor showed a decrease in olanzapine clearance of 14% with olanzapine doses from 6-12 mg given with fluoxetine doses of 25 mg or more. Pharmacometrics review suggests this most likely reflects an increase in bioavailability, rather than a decrease in systemic clearance. The effect of olanzapine on fluoxetine pharmacokinetics was evaluated in population PK studies. An effect could not be detected, but a drug interaction could not be ruled out.

Administration of SYMBIAX with a potent inhibitor of CYP1A2 is likely to result in blockade of both of the Phase I elimination pathways for olanzapine. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics recommends a drug interaction study in humans with SYMBIAX in the highest strength with a potent inhibitor of CYP1A2 to assist with recommendations for dosing in that situation. This could be done as a Phase IV commitment.

The key findings with respect to the request for biowaiver of lower strengths of SYMBIAX are as follows:

- The composition of the lower strengths of SYMBIAX differs substantially in the percentage of pregelatinized starch compared to the 12/50 capsule. However, the percent of starch in the lower strength capsules is bracketed by the percent of starch in the 12/50 capsules and the clinical trial formulations.

- Dissolution studies in multiple media showed that the formulation could not be considered rapidly dissolving in pH 6.8 and pH 4.5 dissolution media across the dosage strengths. Therefore, BCS principles cannot be used to grant a biowaiver. The f2 factor comparing test and reference products was less than 50 in those buffers. Hence, dissolution profiles are not similar.

- The sponsor has provided data from NDA-21-086 demonstrating bioequivalence of a rapidly orally dissolving olanzapine tablet (ZYPREXA ZYDIS) to standard olanzapine tablets. OCPB review of that NDA found that ZYDIS tablets are more rapidly dissolving *in vitro* than standard olanzapine tablets in 0.1 N HCl.

- The Sponsor has provided additional olanzapine ZYDIS dissolution data in pH 4.5 and pH 6.8 showing rapid dissolution. The dissolution profiles for olanzapine from the highest strength SYMBIAX capsules and the olanzapine ZYDIS tablets bracket the profiles of the lower strengths of SYMBIAX in these media.

- The sponsor has provided data from fluoxetine NDA 20-101 in which fluoxetine oral solution and fluoxetine capsules were bioequivalent.

The additional data showed that the rapidly dissolving formulations are bioequivalent to the regular dissolving tablet, suggesting that absorption, rather than dissolution (especially in pH 4.5 and 6.8) is the rate-limiting step in exposure to either olanzapine or fluoxetine. The Office of Clinical Pharmacology and Biopharmaceutics recommends that a biowaiver for the lower strengths be granted.

The proposed *in vitro* dissolution method is acceptable. The Office of Clinical Pharmacology and Biopharmaceutics recommends the specification be changed to Q= — at — minutes.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends some revisions in the proposed text. Please refer to Section 5.

The Division of Scientific Investigations (DSI) has been requested to inspect the clinical site (Lilly-NUS Centre for Clinical Pharmacology, Singapore) and bioanalytical facilities [redacted], formerly [redacted] and [redacted], of the pivotal bioequivalence study ("Bioequivalence of Olanzapine Fluoxetine Combination Commercial Capsule Formulation versus the Clinical Trial Individual Capsule Formulations", study # H6P-FW-HDAK). The DSI inspection report is pending.

The OCPB finds that the submitted data in NDA 21-520 is acceptable pending the outcome of the DSI inspection report. In addition we recommend the consideration of a drug interaction study with a potent inhibitor of CYP1A2 as a Phase IV commitment.

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4 Question-Based Review

4.1 General Attributes

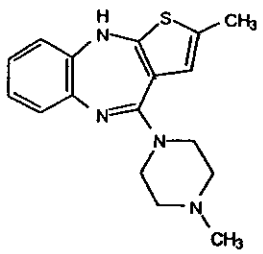
4.1.1 What are the highlights of the chemistry and physical-chemical properties of SYMBIAX, and the formulation of the drug product?

SYMBIAX is a combination of two previously approved agents, olanzapine and fluoxetine. The following information has been extracted from the proposed labeling.

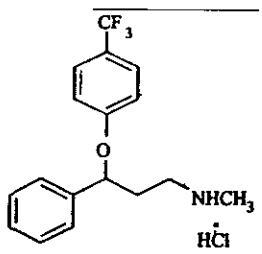
Olanzapine is chemically designated as 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3- *b*][1,5]benzodiazepine. The empirical formula of olanzapine is $C_{17}H_{20}N_4S$ and its molecular weight is 312.44. Olanzapine is a yellow crystalline solid that is practically insoluble in water.

Fluoxetine hydrochloride is chemically designated as (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro- *p* -tolyl)oxy]propylamine hydrochloride. The empirical formula of fluoxetine hydrochloride is $C_{17}H_{18}F_3NO \cdot HCl$ and its molecular weight is 345.79. Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility in water of 14 mg/mL.

The structural formulas of olanzapine and fluoxetine are shown below:



olanzapine



fluoxetine hydrochloride

The olanzapine-fluoxetine combination is an immediate release capsule for oral administration. SYMBIAX capsules will be available in the following strengths (olanzapine equivalent/fluoxetine base equivalent): — mg, 6/25 mg, 6/50 mg, 12/25 mg, and 12/50 mg. Each capsule also contains starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. Details of the pharmaceutical composition are shown in Section 6.2.6 of the Appendix. Capsules of different strength will be differentiated by color.

4.1.2 What is the proposed mechanism of drug action and what is the proposed therapeutic indication?

The proposed indication for the olanzapine-fluoxetine combination is for treatment of depressive episodes associated with bipolar disorder.

Olanzapine is a psychotropic drug of the thienobenzodiazepine class. Its mechanism of action for the proposed indication is unknown. It binds with high affinity to serotonin $5HT_{2A/2C}$, dopamine D_{1-4}, muscarinic cholinergic M_{1-5}, histamine-H_1, and α_1-adrenergic receptors. It is thought that antagonism of muscarinic cholinergic M_{1-5} may be responsible for anticholinergic effects, antagonism of histamine-H_1 receptors may be associated with somnolence, and that antagonism of α_1-adrenergic receptors may be responsible for observed orthostatic hypotension.

Fluoxetine is an antidepressant that is chemically unrelated to tricyclic and tetracyclic antidepressants. Its mechanism is thought to be due to inhibition of neuronal uptake of serotonin in the CNS.

It has been proposed that the combination of olanzapine and fluoxetine produces synergistic increases in norepinephrine, dopamine, and serotonin.

4.1.3 What is the proposed dosage and route of administration?

The proposed dosing for SYMBIAX will range from olanzapine 6 mg to 12 mg and fluoxetine 25mg to 50 mg, given by mouth once daily in the evening, without regard to meals. It is suggested that the beginning dose be 6/25 mg, with dosage adjustments, if needed, made according to efficacy and tolerability.

4.1.4 What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., can disparate efficacy measurements or adverse events reports be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The pivotal clinical study supporting efficacy and safety of SYMBIAX for the treatment of Depressive Episodes Associated with Bipolar Disorder is Study F1D-MC-HGGY. The primary efficacy endpoint was the Montgomery-Asberg Depression Rating Scale (MADRS). A Pharmacometrics review (Section 6.3 of the Appendix) attempted to use this efficacy endpoint to evaluate whether a dose-response relationship exists, but was not able to detect a relationship.

Extrapyramidal symptoms and somnolence have previously been noted to be dose-dependent effects of olanzapine. Although these were monitored in the pivotal clinical study, the Sponsor did not report the relationship between dose and this adverse effect.
Other safety measures in the clinical pharmacology and biopharmaceutics studies were vital signs and electrocardiographic measurements. Three subjects were discontinued from the pivotal bioequivalence study (HDAK) due to symptomatic hypotension during the first treatment period.

One of these subjects had the highest reported fluoxetine C_{max} and AUC $_{0-\infty}$ in this study. This individual had a CYP2D6 genotype of *2/*5 and would be predicted to have an extensive metabolizer phenotype. (Thus, the elevated plasma concentrations would not be explained by the predicted phenotype). The remaining 2 subjects were not outliers with respect to pharmacokinetic parameters for either fluoxetine or olanzapine.

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The Montgomery-Asberg Depression Rating Scale (MADRS) is an investigator-performed rating scale for severity of depressive mood symptoms. Change from baseline to endpoint was used as the primary efficacy measure in the pivotal clinical study HGGY.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active parent moieties, olanzapine and fluoxetine, as well as the active metabolite norfluoxetine, were appropriately identified and measured in the plasma. Please refer to the Bioanalytical Section (4.6).

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

- *Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship for olanzapine and for fluoxetine?*

It has previously been shown, according to the approved olanzapine label, that olanzapine displays linear kinetics over the dosing range of up to 20 mg/day. According to the labeling for fluoxetine, nonlinearity was observed for fluoxetine, although norfluoxetine has linear pharmacokinetics.

- *Do PK parameters change with time following chronic dosing?*

According to the approved labeling for fluoxetine, the PK parameters for fluoxetine change with time following chronic dosing. Fluoxetine has an elimination half-life of 1-3 days after acute administration and 4-6 days after chronic administration.

- *How long is the time to onset and offset of the pharmacological response or clinical endpoint?*

According to the Sponsor, a statistically significant clinical response was observed as early as Week 1. The maximum effect was seen by 4 weeks, and was maintained through the 8 weeks of study in the pivotal clinical study F1D-C-HGGY.

- *Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

The Pharmacometrics consult (Section 6.3 in the Appendix) evaluated whether there was a dose-response relationship in MADRS score changes from baseline that could be identified in the pivotal clinical study F1D-C-HGGY. In that study, patients were randomized to receive either olanzapine, placebo or olanzapine plus fluoxetine in combination (6/25, 6/50, or 12/50) and therapy was initiated with the lowest dose. The Pharmacometrics reviewer reports that the dose-response relationship cannot be well characterized. A relationship between dose and adverse reactions has not been characterized.

The once daily dosage regimen is consistent with the long elimination half-lives of olanzapine and fluoxetine. SYMBIAX is to be initiated at the dose of 6/25 with dosage adjustments made according to efficacy and tolerability. It would be useful to include guidance in the dosing recommendation on when the dose should be titrated up, if needed, based on the pharmacokinetics and the expected time course for response.

4.2.4 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics of olanzapine/fluoxetine OFC were studied in healthy volunteers in study HDAK (the pivotal bioequivalence study) at the highest dosage strength (12/50) that will be marketed. The pharmacokinetic parameters following administration of both the OFC formulation (test) and the individual capsules of the same strength (reference) are shown in the table below. The pharmacokinetics after OFC administration have not been evaluated in the target patient population.

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Pharmacokinetic parameters (arithmetic mean) for olanzapine and fluoxetine

	Test (% CV) n=20	Reference (% CV) n=20
Olanzapine		
t_{max} (h)[a]	4.00	4.50
C_{max} (ng/mL)	28.24 (24.9)	26.78 (31.7)
λ_Z (h^{-1})	0.0244 (16.2)	0.0240 (22.2)
$t_{1/2}$ (h)	29.70 (16.73)	30.49 (20.37)
AUC $_{0-\infty}$ (ng*h/mL)	882.9 (23.1)	881.0 (27.2)
AUC $_{0-t}$ (ng*h/mL)	828.5 (21.9)	818.9 (25.5)
Cl/F (L/kg/h)	0.217 (26.9)	0.220 (28.6)
Fluoxetine		
t_{max} (h)[a]	5.50	6.50
C_{max} (ng/mL)	39.73 (16.8)	39.74 (21.2)
λ_Z (h^{-1})	0.0185 (30.1)	0.0184 (30.1)
$t_{1/2}$ (h)	44.69 (50.54)	43.26 (35.29)
AUC $_{0-\infty}$ (ng*h/mL)	2300.2 (37.7)	2322.8 (34.9)
AUC $_{0-t}$ (ng*h/mL)	2165.3 (35.2)	2196.4 (32.5)
Cl/F (L/kg/h)	0.378 (39.2)	0.370 (39.7)

[a] median (range)

It has previously been demonstrated that both olanzapine and fluoxetine are extensively hepatically metabolized. Approximately 7% of the dose of olanzapine was recovered in urine as unchanged drug following a single oral dose. For fluoxetine, the primary route of elimination is hepatic metabolism followed by renal excretion of inactive metabolites.

4.2.5 What is the inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In healthy volunteers (studies HDAK and HGCI), inter-subject variability after administration of olanzapine alone, SYMBIAX OFC, or olanzapine and fluoxetine administered together as individual capsules was approximately 24.9-40.5 % for Cmax and 23.1-45.4% for AUC for olanzapine, and approximately 16.8 – 39.41% for Cmax and 37.7% for AUC for fluoxetine. Inter-subject variability for Cl was approximately 26.9-28.6% for olanzapine and 39.2-39.7% for fluoxetine. Pharmacokinetic parameters were not determined in the target patient population. Potential causes for variability include CYP2D6 phenotype, since fluoxetine, and to some extent olanzapine, are metabolized by CYP2D6. An additional source of variability in PK could be due to variability in expression of CYP1A2, the major P450-mediated pathway for olanzapine. CYP1A2 is influenced by gender, smoking, and age.

In study HDAK, subjects were genotyped for CYP2D6. One subject was predicted to have a poor metabolizer phenotype, and had Cmax and AUC representing the lower end of the observed ranges for olanzapine. In both HDAK and HGCI, smoking was an exclusion criterion. In HGCI, genotype for CYP2D6 was not determined. In the population PK studies, neither genotype nor smoking status were evaluated.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

The pharmacokinetics of olanzapine and of fluoxetine have previously been studied in special populations and the influence on exposure can be found in the labels for each, as outlined below.

Age - The elimination half-life of olanzapine was 1.5 times greater in elderly (> 65 years old) than in non-elderly healthy volunteers. The disposition of single doses of fluoxetine in healthy elderly did not differ significantly from that in younger normal subjects. No unusual age-associated pattern of adverse events was observed in elderly patients who received 20 mg fluoxetine for 6 weeks.

Gender - Clearance of olanzapine is approximately 30% lower in women than in men, although no apparent differences in effectiveness or adverse effects are reported.

Race - No specific pharmacokinetic studies have evaluated the effect of race. Cross-study comparisons suggest that olanzapine exposure may be about 2-fold greater in Japanese than in U.S. populations. Clinical trial safety and efficacy data did not suggest clinically significant differences among Caucasian patients, patients of African descent, or a pooled category of Asian and Hispanic patients.

Renal Impairment - Pharmacokinetics of olanzapine were similar in patients with severe renal impairment and normal subjects. Steady state plasma concentrations of fluoxetine and norfluoxetine were similar in patients on dialysis as compared to patients with normal renal function.

Hepatic Impairment - A study of the effect of impaired liver function in subjects with clinically significant cirrhosis showed little effect on the pharmacokinetics of olanzapine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to 2-3 days in subjects without liver disease. Norfluoxetine half-life was also prolonged to 12 days compared to 7-9 days in normal subjects.

Genetic Polymorphisms – Fluoxetine is metabolized in part by CYP2D6. However, at steady state, the sum of the four active enantiomers of fluoxetine and norfluoxetine measured in the plasma was not significantly greater in poor metabolizers than in normal metabolizers, and the net pharmacodynamic activities were the same. According to the olanzapine label, clearance of olanzapine is not reduced in subjects deficient in CYP2D6.

4.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these subgroups?

Age – Caution should be used in dosing olanzapine in the elderly, according to the labeling. This caution is extended to SYMBIAX.

Gender – Based on previous labeling for fluoxetine and for olanzapine, there are no dosage modifications of SYMBIAX recommended for gender alone.

Race – Dosage modifications for race are not routinely required for either olanzapine or fluoxetine. This recommendation has been extended to SYMBIAX.

Renal Impairment – Dosage adjustment in renal impairment has not been required for either olanzapine or fluoxetine and this has been extended to SYMBIAX.

Hepatic Impairment – Based on the pharmacokinetics of olanzapine and fluoxetine, it is recommended that the lowest starting dose of SYMBIAX be considered for patients with hepatic impairment. This is consistent with the labeling of fluoxetine, although the label for fluoxetine recommends either a lower or less frequent dose in patients with cirrhosis. It would be prudent to recommend a longer titration period for SYMBIAX in patients with hepatic disease due to the longer half-life of fluoxetine and norfluoxetine compared to that in patients without hepatic disease.

Genetic polymorphisms – As in the labels for olanzapine and for fluoxetine, no recommendations have been made for adjusting the dose of SYMBIAX in patients deficient in CYP2D6.

Combined Effects – The proposed labeling suggests that dosage modification of SYMBIAX may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component.

Pediatric – The Sponsor states that a deferral of studies in the pediatric population has been granted. The proposed label states that SYMBIAX has not been studied in patients less than 18 years of age.

Pregnancy and Lactation – Pharmacokinetic studies have not been reported in pregnancy. Based on pharmacology/toxicology data it is recommended in the proposed labeling that SYMBIAX be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. According to the proposed labeling, adequate and well-controlled studies with SYMBIAX in nursing mothers or infants are not available. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in breast milk following SYMBIAX treatment, although fluoxetine has been measured in human breast milk. It is recommended that women not breast-feed when receiving SYMBIAX.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

According to the labeling for olanzapine, olanzapine clearance is 40% higher in smokers than nonsmokers. Carbamazepine causes an approximate 50% increase in olanzapine clearance, thought to be due to induction of CYP1A2. Fluvoxamine, a CYP1A2 inhibitor, decreases clearance of olanzapine, resulting in a 54% increase in Cmax in female nonsmokers and 77% in male smokers, with 52% and 108% increases, respectively, in olanzapine AUC. The impact of these factors on pharmacodynamics is not stated in the label.

According to the proposed label, co-administration of ethanol with SYMBIAX may potentiate sedation and orthostatic hypotension.

4.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

The proposed labeling recommends lower doses of the olanzapine component of SYMBIAX in patients receiving fluvoxamine. The proposed labeling does not require dosage modifications dependent on smoking status alone. A general guideline in the proposed label is that a dosage increase for drugs that induce olanzapine metabolism or a dosage decrease for drugs that inhibit olanzapine metabolism may need to be considered with specific drugs. It is recommended in "Information for Patients" that alcohol be avoided. These recommendations are consistent with the labeling of olanzapine.

4.4.3 Drug-Drug Interactions

4.4.3.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug- interactions mediated by CYP enzymes?

The P450-mediated metabolism of olanzapine and of fluoxetine have previously been evaluated and are outlined in the approved labels for each. Olanzapine is metabolized primarily by CYP1A2 and to a lesser extent by CYP2D6. Fluoxetine, in addition to being a substrate for CYP2D6, is an inhibitor of CYP2D6. The labels for both olanzapine and fluoxetine identify the potential for P450-mediated interactions. This includes a warning regarding a potential for fluoxetine interaction with thioridazine that is reflected in the proposed SYMBIAX label. In addition, the olanzapine label states that fluoxetine "causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance".

4.4.3.2 Since SYMBIAX is a combination of olanzapine and fluoxetine has the interaction potential between these drugs been evaluated?

Study F1D-MS-HGCI evaluated the influence of fluoxetine (single 60 mg dose and repeated oral administration of 60 mg daily) on the pharmacokinetic characteristics and the safety of a single 5 mg oral dose of olanzapine given 1 hour after fluoxetine in healthy volunteers (n=15; 11 M/4 F; mean age 32 (range 23-40) years of age). The review of the study can be found in the

Appendix, Section 6.2.3. This was an open-label, one-sequence crossover (fixed sequence) study. The treatment sequence is shown in the Table below. There was an interval of at least 10 days between the day of dosing olanzapine in Period 1 and Period 2, and at least 7 days between the day of dosing olanzapine in Period 2 and Period 3.

Treatment Sequence in HGCI

Period 1	Period 2	Period 3
Olanzapine 5 mg	Fluoxetine 60 mg	Fluoxetine 60 mg daily on Days 1-8
	Olanzapine 5 mg (1 hour later)	Olanzapine 5 mg (1 hour after last fluoxetine dose on day 8)

Fluoxetine Cmax (mean, % CV) was 54.42 ng/ml after a single dose and 275.81 ng/ml after chronic administration (as calculated by reviewer). Norfluoxetine Cmax (mean, % CV) was 30.59 (37.10) ng/ml after a single fluoxetine dose and 161.13 (31.13) ng/ml after chronic exposure to fluoxetine (as calculated by reviewer). Therefore, exposure to fluoxetine and norfluoxetine has been documented.

The plasma concentration time course for olanzapine (as provided by Sponsor) during the three study periods is shown in the figure at right. The pharmacokinetic parameters for olanzapine are shown in the Table below. There was an increase in Cmax of approximately 14-16%, an increase in AUC of approximately 15-18%, and a decrease in Cl/F of approximately 11-16% in Periods 2 and 3, compared to Period 1.

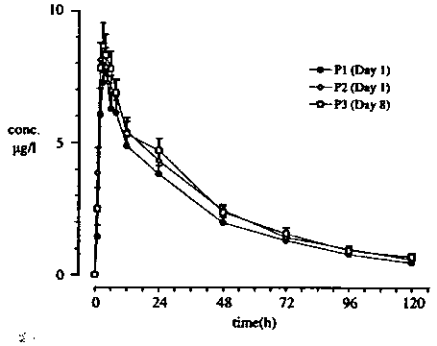

Figure HGCL5.6.1.1. Plasma concentration of olanzapine (means and SEM of the 15 subjects who participated in the three study Periods) after a single oral dose of olanzapine (5 mg) given alone (—○—), with a single dose of fluoxetine (60 mg) (—△—) and after 8 daily oral doses of fluoxetine (60 mg) (— —).

Pharmacokinetic parameters (arithmetic mean) for olanzapine

	Period 1 (% CV) n=15	Period 2 (% CV) n=15	Period 3 (% CV) n=15
Olanzapine			
t_{max} (h)	3.7 (40.5)	3.5 (57.1)	3.0 (36.7)
C_{max} (ng/mL)	8.15 (40.5)	9.47 (30.3)	9.30 (34.2)
AUC $_{0-24}$ (ng*h/mL)	118.5 (33.4)	135.8 (30.8)	138.6 (34.3)
AUC $_{0-\infty}$ (ng*h/mL)	293.3 (40.6)	343.7 (37.8)	347.3 (45.4)
Cl/F (L/ /h)	19.8 (38.9)	16.7 (41.9)	17.7 (48.6)
$t_{1/2}$ (h)	32.21 (19.8)	32.32 (17.5)	31.21 (30.1)

With respect to the drug interaction, the 90% CI for the ratio of geometric means falls outside of the 80-125% equivalence range for Cmax in periods 2 and 3, AUC0-inf in period 2, and Cl/F in Period 2 compared to Period 1. It should be noted that as terminal half-life is not affected, the increase in clearance reflects the increase in bioavailability, rather than a decrease in systemic clearance.

Study HGCI has therefore demonstrated a pharmacokinetic interaction between olanzapine and fluoxetine resulting in increased exposure to olanzapine. This study did not evaluate the effect of olanzapine on fluoxetine.

4.4.3.3 Has the pharmacokinetic interaction between olanzapine and fluoxetine been confirmed in the target patient population?

This interaction was not evaluated in the target population, although it has been evaluated in patients with treatment resistant major depressive disorder using population pharmacokinetics. This has been reviewed in the Pharmacometrics consult (Section 6.3 in the Appendix).

Study F1D-MC-HGFR was designed to evaluate safety and efficacy of fluoxetine (20-60mg/day) plus olanzapine (5-20 mg/day) versus fluoxetine (20-60 mg/day) or olanzapine (5-20 mg/day) alone in treatment resistant major depressive disorder. Olanzapine, fluoxetine, and norfluoxetine concentrations were used to assess potential drug-drug interaction between olanzapine and fluoxetine using sparse sampling. The sponsor concluded that no interaction was detected. However, the 95% confidence intervals of the difference in mean plasma concentrations between monotherapy and combination treatment for both fluoxetine and olanzapine are wide. The Pharmacometrics consult suggested that the study was not powered to demonstrate an interaction.

Study F1D-MC-HGIE was designed to characterize the pharmacokinetic interaction of olanzapine and fluoxetine and to characterize pharmacodynamics in patients with treatment-resistant depression. The study was prospectively designed to include a sparse sampling strategy for evaluation using population pharmacokinetic analysis techniques. Concomitant administration of fluoxetine of 25 mg or more decreased the olanzapine clearance by 13.6% compared to olanzapine monotherapy. However, the Pharmacometrics review points out that this most likely reflects an increase in bioavailability, rather than a decrease in systemic clearance.

The effect of olanzapine on fluoxetine was evaluated in both HGFR and HGIE. In HGFR the mean fluoxetine concentrations were slightly higher when fluoxetine was given with olanzapine, although the difference was not statistically significant. As discussed above, the Pharmacometrics consult suggested that the study was not powered to demonstrate an interaction. In study HGIE, fluoxetine clearance was 3x greater in the olanzapine 1 mg/fluoxetine 5 mg group than in the other patient groups. However, the 5 mg fluoxetine dose was lower than the fluoxetine dose in any other group (in which the doses were 25 or 50 mg of fluoxetine given either alone or with olanzapine). Therefore, this observation could be due to the nonlinearity of fluoxetine metabolism at the higher doses. In addition, the Pharmacometrics review suggests that the Sponsor's model has several flaws. Therefore, it is not possible to interpret this finding.

Based on these studies, a drug-drug interaction between olanzapine and fluoxetine cannot be ruled out.

4.4.3.4 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Since both olanzapine and fluoxetine are CNS active drugs, SYMBIAX would be expected to have additive effects with other CNS depressants, including alcohol. There is a potential for a pharmacodynamic interaction with other drugs that increase serotonin levels. The label for fluoxetine describes adverse reactions in patients receiving fluoxetine in combination with tryptophan, and refers to adverse reactions following the use of an SSRI with sumatriptan. In addition, orthostatic hypotension may be potentiated by other medications that produce hypotension.

Fatal reactions have been reported in patients with a combination of fluoxetine and monoamine oxidase (MAO) inhibitors. Consistent with the labeling for fluoxetine, this is addressed in the proposed labeling for SYMBIAX.

4.4.3.5 What is the potential for drug-interactions between olanzapine and fluoxetine due to protein binding?

Olanzapine and fluoxetine have previously been found to be highly protein bound, as reflected in their current labeling. In the present submission, ADME Report 01 evaluated the *in vitro* binding to human plasma proteins of [14C]olanzapine, fluoxetine, and norfluoxetine when incubated alone versus in combination. The study review can be found in Section 6.2.1 in the Appendix. The results are summarized in the Table below, as provided by the Sponsor. The results confirm that olanzapine, fluoxetine, and norfluoxetine are highly protein bound. There is unlikely to be an interaction mediated by altered protein binding by any of these compounds when they are given together in humans.

	Mean % Bound (n=9) ± SEM	
Component	Alone[a]	In Combination[b]
Olanzapine[c]	94.4 ± 0.3	94.0 ± 0.5
Fluoxetine[d]	96.1 ± 0.1	96.5 ± 0.2
Norfluoxetine[d]	97.1 ± 0.3	97.9 ± 0.2[e]

[a] Protein binding determined for each component after incubation with the single component.
[b] Protein binding determined for each component after incubation with all three components.
[c] Olanzapine concentration determined by liquid scintillation counting.
[d] Fluoxetine and norfluoxetine concentrations determined by LC/MS assay.
[e] = Mean of 8 observations.

4.4.4 What issues related to dose, dosing regimen, or administration are unresolved, and represent significant omissions?

The pharmacokinetic interaction between fluoxetine and olanzapine results in a small increase in exposure to olanzapine. The magnitude of the increase reflects the minor contribution of CYP2D6 to olanzapine elimination relative to the contribution of CYP1A2. Concomitant

administration of SYMBIAX, in which CYP2D6 is blocked, with an inhibitor of CYP1A2 would be expected to result in absence of the primary metabolic pathways for Phase I elimination of olanzapine. Fluvoxamine is a CYP1A2 inhibitor that has previously been shown to decrease the clearance of olanzapine. There is a precaution in the proposed labeling that lower doses of the olanzapine component of SYMBIAX should be considered in patients receiving concomitant therapy with fluvoxamine. Other inhibitors of CYP1A2 that are commonly used include the fluoroquinolone antibiotics ciprofloxacin and ofloxacin, available by prescription, and the over-the-counter H2-antagonist cimetidine. These medications are usually given for short-term use. It would be useful to conduct a drug-interaction study between SYMBIAX and a potent CYP1A2 inhibitor to determine the magnitude of the increased exposure, in order to make specific recommendations regarding concomitant use. In addition, precautions in the label regarding CYP1A2 inhibitors should be stronger, even in the absence of specific data.

4.5 General Biopharmaceutics

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

Both olanzapine and fluoxetine have been previously characterized (NDA 20-592 and NDA 18-936, respectively) as highly soluble, with the highest strengths (12 mg and 50 mg respectively) dissolving in less than 250 ml of different media. These data are shown in the Dissolution Method Development report in the Appendix, Section 6.2.5. However, when all proposed strengths were evaluated for dissolution in multiple media, the results showed that —— or more of the labeled amount of the drug was not consistently dissolved in 30 minutes in pH 6.8 and pH 4.5 dissolution media across the dosage strengths, and therefore the formulation is not considered to be rapidly dissolving. In addition, the f2 factor comparing the test and reference products was less than 50 in the pH 4.5 and pH 6.8 buffers. Dissolution data are reviewed in detail in the Biowaiver report in the Appendix, Section 6.2.6. Based on the dissolution data, BCS principles cannot be used to grant a biowaiver, and BCS-related information has not been further reviewed.

4.5.2 What is the in vivo relationship of the proposed to be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure? What data support a waiver of in vivo bioequivalence data? Is this data sufficient to support a biowaiver of SYMBIAX OFC?

The pivotal bioequivalence study (HP-FW-HDAK) assessed the relative oral bioavailability of olanzapine and fluoxetine when administered as a single capsule formulation (commercial image formulation 12/50) compared to the capsules (co-administration of two 6 mg capsules of olanzapine and two 25 mg of fluoxetine) used in clinical trials (reference formulations) that contain individual ingredients. The full study review can be found in the Appendix, Section 6.2.2. This was a randomized, 2-sequence cross-over study that was performed under fasting conditions. The study was completed in 20 healthy subjects (15 M/ 5 F; mean age 23 (21-27) years of age). The plasma concentration time course and pertinent pharmacokinetic parameters are shown in Figures and Table below.

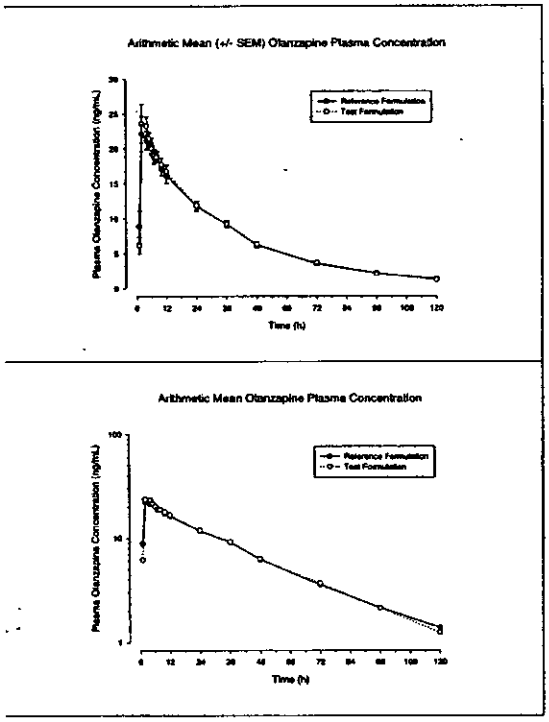

Figure HDAK.11.1. Arithmetic mean plasma concentration time profiles of olanzapine following the Reference and Test Formulations. Upper panel: cartesian scale. Lower panel: logarithmic scale.

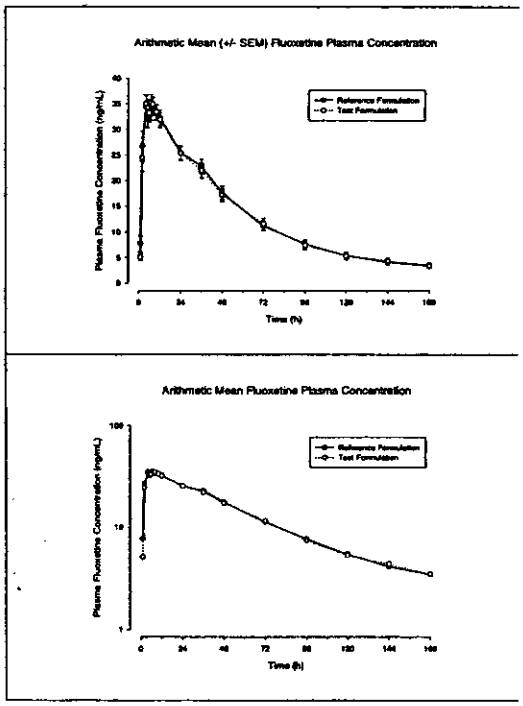

Figure HDAK.11.2. Arithmetic mean plasma concentration time profiles of fluoxetine following the Reference and Test Formulation Upper panel: cartesian scale. Lower panel: logarithmic scale.

Pharmacokinetic parameters (arithmetic mean) for olanzapine and fluoxetine

	Test (% CV) n=20	Reference (% CV) n=20
Olanzapine		
t_{max} (h)[a]	4.00	4.50
C_{max} (ng/mL)	28.24 (24.9)	26.78 (31.7)
λ_Z (h^{-1})	0.0244 (16.2)	0.0240 (22.2)
$t_{1/2}$ (h)	29.70 (16.73)	30.49 (20.37)
AUC $_{0-\infty}$ (ng*h/mL)	882.9 (23.1)	881.0 (27.2)
AUC $_{0-t}$ (ng*h/mL)	828.5 (21.9)	818.9 (25.5)
Cl/F (L/kg/h)	0.217 (26.9)	0.220 (28.6)
Fluoxetine		
t_{max} (h)[a]	5.50	6.50
C_{max} (ng/mL)	39.73 (16.8)	39.74 (21.2)
λ_Z (h^{-1})	0.0185 (30.1)	0.0184 (30.1)
$t_{1/2}$ (h)	44.69 (50.54)	43.26 (35.29)
AUC $_{0-\infty}$ (ng*h/mL)	2300.2 (37.7)	2322.8 (34.9)
AUC $_{0-t}$ (ng*h/mL)	2165.3 (35.2)	2196.4 (32.5)
Cl/F (L/kg/h)	0.378 (39.2)	0.370 (39.7)

[a] median (range)

The 90% confidence intervals on the geometric means of the Cmax and AUC $_{0\text{-inf}}$ ratios of the test and reference formulations were within the bioequivalence interval of 0.8 to 1.25. Therefore this study has demonstrated bioequivalence between the OFC (test) capsule and the clinical trial

individual capsule formulation (reference) of the olanzapine/fluoxetine combination (12/50 mg) when given as a single dose under fasting conditions.

What data support a biowaiver for the lower strengths of SYMBIAX?.

The Sponsor has requested a biowaiver for the lower strengths of SYMBIAX OFC. The following information has been provided in support of the biowaiver request:

- Composition of the lower strength OFC capsules – As shown in the review of the Biowaiver request (Appendix, Section 6.2.6), the percentage of the pregelatinized starch in the —— 6/25 capsules varies from the 12/50 capsule by more than the +/- 10% allowed in SUPAC-IR (level II). However, the percent of starch in these lower strength capsules is bracketed by the percent of starch in the higher strength (12/50) OFC capsules and the clinical trial formulations.
- Dissolution studies in multiple media showed that the formulation could not be considered rapidly dissolving in pH 6.8 and pH 4.5 dissolution media across the dosage strengths. The f2 factor comparing test and reference products was less than 50 in those buffers. The profile for OFC 12/50 has slower dissolution compared to the lower strengths. The concern would be whether more rapid dissolution of the lower strengths would result in increased bioavailability.
- The Sponsor has provided data from NDA 21-086 for the rapidly orally dissolving tablets Zyprexa Zydis olanzapine that undergoes rapid disintegration when placed on the tongues. Study F1D-EW-LOAL demonstrated bioequivalence of Zydis olanzapine to standard olanzapine tablets. The OCPB review of that NDA shows that Zydis tablets are more rapidly dissolving *in vitro* than the standard olanzapine tablet in 0.1 N HCl. However, based on the bioavailability data, *in vitro* differences in dissolution of olanzapine did not preclude bioequivalence of olanzapine tablets even when one formulation was more rapidly dissolving than another. The Sponsor has provided additional olanzapine ZYDIS dissolution data in pH 4.5 and pH 6.8 showing rapid dissolution. The dissolution profiles for olanzapine from the highest strength SYMBIAX capsules and the olanzapine ZYDIS tablets bracket the profiles of the lower strengths of SYMBIAX in these media.
- The Sponsor has provided data from fluoxetine NDA 20-101, study HCEZ, in which fluoxetine oral solution and fluoxetine capsules were considered to be bioequivalent. This suggests that a fluoxetine formulation with a faster rate of dissolution would not necessarily have an altered pharmacokinetic profile compared to a fluoxetine formulation with a slower rate of dissolution.

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Is this data sufficient to grant a biowaiver for lower strengths of SYMBIAX OFC?

- Bioequivalence has been shown for the highest strength of SYMBIAX OFC and the individual trial capsules.
- Lower strengths of the OFC capsule have the same dissolution profile in 0.1 N HCl that is the approved medium for the individual entities for olanzapine tablets and for fluoxetine tablets.
- There could be a potential effect of differences in dissolution at pH 4.5 and pH 6.8.

One concern related to rapid dissolution of the lower strengths of SYMBIAX could be orthostatic hypotension due to unexpected increased exposure when therapy is initiated at the lower doses or due to use of the same doses (given as multiple units of lower strengths). The additional data provided for olanzapine and fluoxetine, as described above, suggest that absorption, rather than dissolution at least in pH 4.5 and 6.8, is the rate limiting step in exposure to either olanzapine or fluoxetine. This supports the consideration that the more rapidly dissolving lower strengths of the OFC capsule at pH 4.5 and pH 6.8 would not be expected to result in exposure to olanzapine or fluoxetine that would be greater than the more slowly dissolving higher strength OFC capsule. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics recommends that a biowaiver be granted for the lower strengths of OFC.

4.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The current approved labeling of fluoxetine capsules states that "food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant." The current approved labeling of olanzapine tablets states that "food does not affect the rate or extent of olanzapine absorption". Therefore, food does not affect the bioavailability of marketed formulations.

The effect of food on the bioavailability of fluoxetine and olanzapine from SYMBIAX OFC has not been evaluated. The pivotal clinical trials were conducted without regard to meals. Since each of these drugs are highly soluble, the currently approved Prozac and Zyprexa have shown no significant food effect, and the SYMBIAX OFC is bioequivalent to individual capsules used in clinical trials, it seems reasonable to allow administration of SYMBIAX without regard to meals. However the clinical division should evaluate whether the specific claim in the label "without regard to meals" should be allowed in the absence of a food effect study on SYMBIAX. The Clinical Pharmacology section of the label should state that the food effect on OFC has not been evaluated.

4.5.4 When would a fed BE study be appropriate and was one conducted?

A fed BE study is not necessary in this case.

4.5.5 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Dissolution method development is reviewed in the Appendix, Section 6.2.5. *In vitro* dissolution specifications were based on lots from primary stability and large scale demonstration batches as well as the lot used in the pivotal bioequivalence study HDAK. The sponsor has proposed the following dissolution method and specifications:

Apparatus: USP Apparatus 2 (Paddle)
Medium: 0.1 N HCl
Volume: 900 ml
Rotation Speed: 50 rpm
Specification: Q=[redacted] at 30 minutes.

The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed dissolution method acceptable. We recommend that the specification be changed to Q=[redacted] at [redacted] minutes.

4.5.6 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Different strength olanzapine/fluoxetine combinations of the individual capsules, rather than the SYMBIAX to-be-marketed product, were used in the pivotal clinical study. Therefore, there is no available clinical safety and efficacy data with the to-be-marketed product supporting its approval in the various strengths. However, data to support bioequivalence have been provided.

4.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable to Symbiax OFC, an immediate release formulation.

4.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

No active control was used in the pivotal efficacy and safety study.

4.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

A DSI inspection of study H6P-FW-HDAK, the pivotal BE study, has been requested and the results are pending.

4.5.10 If replicate design studies were conducted and individual BE was analyzed, what were the outcomes with respect to variability and subject-by-formulation interactions?

These studies were not conducted for SYMBIAX OFC.

4.6 Bioanalytical Method

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

Olanzapine was detected in plasma samples from all clinical pharmacology and biopharmaceutics studies using [redacted] (HPLC) method with [redacted] detection. For the pivotal BE study HDAK, and for HGFR, and HGIE, fluoxetine and norfluoxetine were measured using an HPLC-MS/MS method. For HGCI, the analysis of fluoxetine and norfluoxetine were performed using gas liquid chromatography. The two methods for determination of fluoxetine and norfluoxetine were cross-validated. Detailed descriptions of the methods are found in the Appendix, Section 6.2.4.

4.6.2 Which metabolites have been selected for analysis and why?

The pharmacokinetic analysis for the pivotal bioequivalence study and for the drug interaction study HGCI evaluate only the parent compound. This is the recommended approach for bioequivalence studies since the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite. (Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, July 2002). The drug interaction study HGCI evaluated change in olanzapine concentrations in the presence of fluoxetine. Since olanzapine is metabolized to inactive metabolites, this approach is appropriate. The population PK studies HGFR and HGIE analyzed olanzapine, fluoxetine, and norfluoxetine.

4.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total olanzapine, total fluoxetine, and total norfluoxetine were measured. These moieties are highly protein bound. However, this approach has been used for the previous evaluations of olanzapine, fluoxetine, and norfluoxetine and it is acceptable to continue to measure total concentrations. This continuity would allow for inter-study comparisons.

4.6.4 What bioanalytical methods are used to assess concentrations?

For the HPLC method for olanzapine, linearity was established over the range of [redacted] to [redacted] For the HPLC-MS/MS method, linearity was established in the range of [redacted] to [redacted] for both fluoxetine and norfluoxetine. For the [redacted] method, linearity was established in the range of [redacted] to [redacted] and from [redacted] to [redacted] for both fluoxetine and

norfluoxetine. The bioanalytical methods are adequately documented and validated, and the performance of the assays for the clinical pharmacology studies are considered acceptable.

5 Detailed labeling recommendations (only the changed sections are included here)

In addition to the specific recommendations made in the text below, it may be useful to provide guidance in the dosing recommendations regarding how often the dose can be titrated up. This can be based on the long half-life of fluoxetine as well as the time course for observation of effect.

Pharmacokinetics

Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17 %) and a small decrease in mean apparent clearance of olanzapine (-16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

Following a single oral 12/50 mg dose of , peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of

Olanzapine — Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption, when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine — Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Drug Interactions

The risks of using in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions of the individual components are applicable to As with all drugs, the potential for interaction by a variety of mechanisms (eg, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. Caution is advised if the concomitant administration of and other

CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Antihypertensive agents — Because of the potential for olanzapine to induce hypotension, [redacted] may enhance the effects of certain antihypertensive agents (*see* Orthostatic hypotension).

Anti-Parkinsonian — The olanzapine component of [redacted] may antagonize the effects of levodopa and dopamine agonists.

The effect of other drugs on olanzapine Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. [redacted] Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs. [redacted]

Dosage and Administration

[redacted]

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

6.2 Clinical Pharmacology and Biopharmaceutics Individual Study Review

6.2.1 PLASMA PROTEIN BINDING STUDIES

THE EFFECT ON THE IN VITRO BINDING OF [^{14}C]OLANZAPINE, FLUOXETINE, AND NORFLUOXETINE TO HUMAN PLASMA PROTEINS WHEN INCUBATED IN COMBINATION

The purpose of this study was to evaluate *in vitro* binding to human plasma proteins of [14C]olanzapine, fluoxetine, and norfluoxetine when incubated alone versus in combination.

Methods

Human plasma samples were spiked with [14C]olanzapine, fluoxetine, or norfluoxetine at concentrations of 100, 500, and 1000 ng/ml alone or in combination. Samples were incubated for approximately 1 hour at approximately 37° C. Aliquots were then transferred to ultracentrifuge tubes and centrifuged at approximately [ ] rpm for 3 hours and 14 minutes at 37° C. For analysis of olanzapine samples, aliquots of the radiolabeled spiked plasma samples and the protein free fraction from the centrifuged plasma were diluted and radioactivity determined using liquid scintillation counting. For determination of fluoxetine and norfluoxetine, aliquots of the spiked plasma samples and the protein free fraction from the centrifuged plasma were [ ] and analyzed using liquid chromatography/mass spectrometry (LC/MS). Standard curves for fluoxetine, norfluoxetine, and olanzapine at concentrations of 2, 50, 100, 200, and 400 ng/ml, quality control (QC) samples at concentrations of 2 and 400 ng/ml, and dilution validation samples of 500 ng/ml (2x dilution) and 1000 ng/ml (4x dilution) were also included. For the LC/MS assay the % RSD was [ ] to [ ] for fluoxetine and [ ] (at 2 ng/ml) to [ ] for norfluoxetine, and %RE was [ ] to [ ] for fluoxetine and [ ] to [ ] for norfluoxetine, at the low (2 ng/ml) and high (400 ng/ml) standards, respectively. % protein binding was calculated as

% Protein Binding = (1-Cf/Cp)x100

where Cf is the amount of radioactivity or concentration in the protein-free fraction and Cp is the amount of radioactivity or concentration in plasma.

Results

The results are summarized in Table 1 below (reproduced from ADME Report 01 in the NDA).

	Mean % Bound (n=9) ± SEM	
Component	Alone[a]	In Combination[b]
Olanzapine[c]	94.4 ± 0.3	94.0 ± 0.5
Fluoxetine[d]	96.1 ± 0.1	96.5 ± 0.2
Norfluoxetine[d]	97.1 ± 0.3	97.9 ± 0.2[e]

[a] Protein binding determined for each component after incubation with the single component.
[b] Protein binding determined for each component after incubation with all three components.
[c] Olanzapine concentration determined by liquid scintillation counting.
[d] Fluoxetine and norfluoxetine concentrations determined by LC/MS assay.
[e] = Mean of 8 observations.

It can be seen that olanzapine, fluoxetine, and norfluoxetine are more than 94% protein bound, when incubated alone or in combination with all three components. In addition, the sponsor evaluated non-specific binding of olanzapine to the ultracentrifuge tubes, and reports recovery of radioactivity as 101.9 ± 7.7% (SD), suggesting negligible nonspecific binding of olanzapine. The sponsor also reports that nonspecific binding of [14C]R-fluoxetine, similarly evaluated previously , was negligible.

Conclusions

The results of this study confirm that olanzapine, fluoxetine, and norfluoxetine are highly protein bound. There is unlikely to be an interaction mediated by altered protein binding by any of these compounds, when they are given together in humans.

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6.2.2 BIOEQUIVALENCE STUDY

BIOEQUIVALENCE OF OLANZAPINE/FLUOXETINE COMBINATION COMMERCIAL CAPSULE FORMULATION VERSUS THE CLINICAL TRIAL INDIVIDUAL CAPSULE FORMULATIONS

Study Investigators and Site:

[ ]

Lilly NUS Centre for Clinical Pharmacology Pte. Ltd.
Singapore

Protocol Number: H6P-FW-HDAK

OBJECTIVES:

To assess the relative oral bioavailability (bioequivalence) of olanzapine and fluoxetine when administered as a single capsule formulation (commercial image formulation 12/50) which contains both ingredients (OFC) compared to the capsules used in clinical trials (reference formulations) that contain individual ingredients.

FORMULATIONS:

Table 1. Products used in H6P-FW-HDAK

	Package Lot Number	Dose Form Lot Number	Manufacture Date (Dates of Clinical Study)
Test Product (T) Olanzapine and Fluoxetine Combination Capsule (OFC) 12/50 mg	CT19191	D40337	10/9/00 (2/01-4/01)
Reference Product (R) Olanzapine Capsule 6 mg Fluoxetine Capsule 25 mg	CT19192 CT19194	00390218 CT18482	7/3/00 (2/01-4/01) 9/28/00 (2/01-4/01)

The batch size for the test product was ——— capsules and was approximately — of the intended ——— batch size. For a comparison of the composition of the test and reference products, please refer to "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Lower Strengths of the Olanzapine/Fluoxetine Combination (OFC) Capsules" in this review.

STUDY DESIGN:

This study was an open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study, as shown in Table 1, below. Subjects received a single dose of one OFC 12/50 mg capsule (treatment period T) and co-administration of two 6 mg capsules of olanzapine and two 25 mg capsules of fluoxetine (treatment period R) on two separate occasions. There was a minimum interval of 35 days between dosing periods.

Table 2. Treatment Sequence in HDAK

Sequence Number	Treatment Period 1	Treatment Period 2
1	T	R
2	R	T

Inclusion criteria included healthy males or females, 21-50 years of age inclusive. Exclusion criteria included electrocardiographic (ECG) QTc (Bazett correction) > 430 msec in males or > 450 msec in females, intention to use concomitant drug therapy, including nonprescription medication on a regular basis apart from vitamin/mineral supplements, use of prescription medication within 14 days and over-the-counter medication within 7 days prior to the study, exposure to a monoamine oxidase inhibitor within the last 2 weeks, and history of smoking during the 6 months prior to the study.

Study drugs were administered after overnight fast with approximately 120 ml of water. Subjects fasted until at least 4 hours after dosing, and neither alcohol nor caffeine-containing foods were allowed from 3 days prior to dosing and throughout each study period. In addition, caffeine-containing foods were not allowed. Following administration of study drug, blood samples were drawn at 0 (predose), 1, 2, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours (5 days) for olanzapine and fluoxetine, with additional samples collected at 144, 168, and 216 hours for fluoxetine. Plasma was separated by centrifugation and plasma samples were stored at approximately –20° C until analysis.

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ASSAY:

Table 3. Performance of Analytical Method

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-day CV (%)	Inter-day Accuracy (%)
Olanzapine	HPLC	[				6.7	]
						8.7	
						7.8	
Fluoxetine	LC/MS/MS					3.73	
						2.90	
		L				1.93	]

Analysis was completed within the time period for which stability data are available for olanzapine and for fluoxetine. The performance of the assays for both olanzapine and fluoxetine are considered acceptable.

RESULTS:

Demographics

Twenty-four healthy subjects (18 males and 6 females) were enrolled in the study. The mean age of the subjects was 23 y.o. and the age range was 21 to 27 years old. Four subjects discontinued from the study (3 due to adverse events, and 1 due to failure to report to the CRC for dosing). Statistical analyses were only performed in subjects who completed both periods of the crossover study (n=20) and are summarized in the table below. One subject (#10) was predicted to be a poor metabolizer of CYP2D6, based on a genotype of *5/*5. The sponsor noted that there was subject non-compliance with respect to caffeine-containing beverages (green tea, lemon tea), but did not consider this violation to alter the study conclusions.

Table 4. Demographics of Subjects Completing the Study

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
23 (21-27)	15 males	67.0 ± 7.5 kg (n=20)	Chinese 11
	5 females	68.4 ± 8.1 kg (male)	Indian 5
		62.7 ± 2.7 kg (female)	Caucasian 3
			Malay 1

Pharmacokinetics

Pharmacokinetic parameters were determined using noncompartmental analysis. The plasma concentration time course and the pertinent pharmacokinetic parameters for olanzapine and for fluoxetine are shown in Figure 1 and Tables 5 and 6, below.

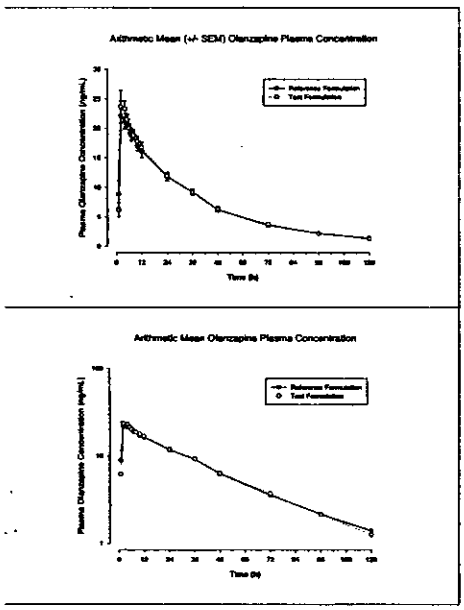

Figure HDAK.11.1. Arithmetic mean plasma concentration time profiles of olanzapine following the Reference and Test Formulations. Upper panel: cartesian scale. Lower panel: logarithmic scale.

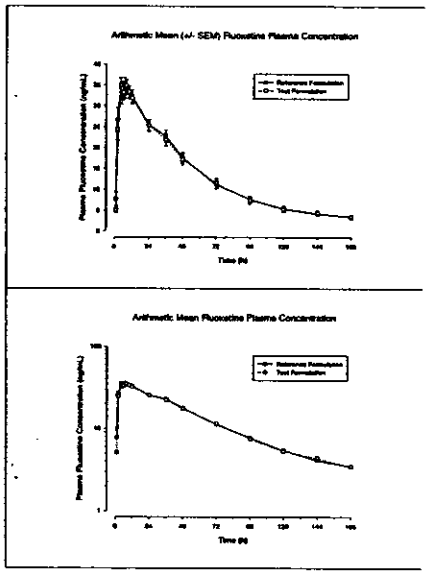

Figure HDAK.11.2. Arithmetic mean plasma concentration time profiles of fluoxetine following the Reference and Test Formulation Upper panel: cartesian scale. Lower panel: logarithmic scale.

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Figure 1. Mean Plasma Concentration Time Course for Olanzapine and Fluoxetine after Administration of Test or Reference Formulations

Table 5. Pharmacokinetic parameters (arithmetic mean) for olanzapine and fluoxetine

	Test (% CV) n=20	**Reference** (% CV) n=20
Olanzapine		
t_{max} (h)[a]	4.00	4.50
C_{max} (ng/mL)	28.24 (24.9)	26.78 (31.7)
λ_Z (h^{-1})	0.0244 (16.2)	0.0240 (22.2)
$t_{1/2}$ (h)	29.70 (16.73)	30.49 (20.37)
AUC $_{0-\infty}$ (ng*h/mL)	882.9 (23.1)	881.0 (27.2)
AUC $_{0-t}$ (ng*h/mL)	828.5 (21.9)	818.9 (25.5)
Cl/F (L/kg/h)	0.217 (26.9)	0.220 (28.6)
Fluoxetine		
t_{max} (h)[a]	5.50	6.50
C_{max} (ng/mL)	39.73 (16.8)	39.74 (21.2)
λ_Z (h^{-1})	0.0185 (30.1)	0.0184 (30.1)
$t_{1/2}$ (h)	44.69 (50.54)	43.26 (35.29)
AUC $_{0-\infty}$ (ng*h/mL)	2300.2 (37.7)	2322.8 (34.9)
AUC $_{0-t}$ (ng*h/mL)	2165.3 (35.2)	2196.4 (32.5)
Cl/F (L/kg/h)	0.378 (39.2)	0.370 (39.7)

[a] median (range)

Table 6. Bioequivalence Assessment

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Reference	Test		
Olanzapine				
C_{max} (ng/ml)	25.7	27.1	1.06	(0.948, 1.182)
AUC $_{0-\infty}$ (ng*h/ml)	851	857	1.01	(0.946, 1.071)
AUC $_{0-t}$ [a] (ng*h/ml)	805	820	1.02	(0.963, 1.071)
Fluoxetine				
Cmax (ng/ml)	38.9	39.2	1.01	(0.950, 1.070)
AUC $_{0-\infty}$ (ng*h/ml)	2175	2145	0.99	(0.958, 1.015)
AUC $_{0-t}$ [a] (ng*h/ml)	2085	2054	0.98	(0.959, 1.007)

[a] Calculated by reviewer

Reanalysis of the data by the reviewer was in agreement with that provided by the sponsor regarding the bioequivalence of the test and reference compounds.

The 90% confidence intervals on the geometric means of the C_{max} and $AUC_{0-\infty}$ ratios are within the bioequivalence interval of 0.8 to 1.25. This suggests that the rate and extent of absorption are similar for the commercial image formulation (test) and the combined capsules (reference) that were used in pivotal clinical trials.

The sponsor has noted that the C_{max} of olanzapine in the present study was higher than would be predicted based on results of previous pharmacokinetic studies.

Of note, the subject with CYP2D6 genotype *5/*5 had a lower C_{max} and $AUC_{0-\infty}$ than the mean for olanzapine, and a higher AUC than the mean for fluoxetine.

Safety

Three subjects were discontinued from the study due to symptomatic hypotension during the first treatment period. One of these subjects had the highest reported fluoxetine C_{max} and AUC $_{0-\infty}$ in this study. This individual had a CYP2D6 genotype of *2/*5 which would be predicted to be an extensive metabolizer phenotype. (Thus, his predicted phenotype would not explain the higher plasma concentrations). The remaining 2 subjects were not outliers with respect to pharmacokinetic parameters for either fluoxetine or olanzapine. Hypotension and bradycardia were reported in 8 and 7 subjects, respectively. Other commonly reported adverse events included somnolence (23 subjects), dizziness and pallor (8 subjects and 5 subjects, respectively), and nausea, nervousness, akathisia, asthenia, headache, and dry mouth.

CONCLUSIONS:

This study demonstrated bioequivalence between the OFC (test) capsule and the clinical trial individual capsule formulation (reference) of olanzapine/fluoxetine combination (12/50mg) when given as a single dose under fasting conditions.

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6.2.3 PHARMACOKINETIC INTERACTION STUDY F1D-MS-HGCI

PHARMACOKINETIC INTERACTION STUDY OF FLUOXETINE ON OLANZAPINE AFTER SINGLE AND REPEATED ADMINISTRATION OF FLUOXETINE IN HEALTHY VOLUNTEERS

Study Investigators and Site:

Protocol Number: F1D-MS-HGCI

OBJECTIVES:

1. To assess the influence of fluoxetine (single and repeated oral administration) on the pharmacokinetic characteristics of olanzapine after a single 5 mg oral dose.
2. To assess the safety of a single oral dose of olanzapine 5 mg when given with a single dose of fluoxetine and after multiple-dose administration of fluoxetine.

FORMULATIONS:

Table 1. Products used in F1D-MS-HGCI

	Lot Number	Expiration Date
Olanzapine 5 mg tablets	BO456	8/96
Fluoxetine Capsule 20 mg pulvules	95C27	3/97

STUDY DESIGN:

This study was an open-label, one-sequence crossover study consisting of three treatment periods, as shown in Table 2, below.

Table 2. Treatment Sequence in HGCI

Period 1	Period 2	Period 3
Olanzapine 5 mg	Fluoxetine 60 mg	Fluoxetine 60 mg daily on Days 1-8
	Olanzapine 5 mg (1 hour later)	Olanzapine 5 mg (1 hour after last fluoxetine dose on day 8)

Inclusion criteria included healthy males or females between 18 and 45 years of age. Exclusion criteria included clinically significant abnormality of the 12-lead ECG, subjects who smoked or who used nicotine substitutes and were unable to refrain from nicotine during the study, subjects who received fluoxetine within 12 weeks prior to study entry, any medication (including oral contraceptives) within 4 weeks of the first study day, or any medication that needed to be continued during the study.

Study drugs were administered with 100 ml of water following overnight fast on Day 1 of Periods 1 and 2 and on Day 8 of Period 3. Subjects reported to the clinic on the mornings of Day 1 to Day 7 of Period 3 to receive the daily fluoxetine dose. Following administration of each dose of olanzapine, blood samples were obtained at 0 (predose), 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours for determination of olanzapine plasma concentrations. Fluoxetine and norfluoxetine plasma concentrations were monitored concomitantly with olanzapine during Periods 2 and 3 immediately prior to fluoxetine dosing, and at times corresponding to olanzapine sampling times. There was an interval of at least 10 days between the day of dosing olanzapine in Period 1 and Period 2, and at least 7 days between the day of dosing olanzapine in Period 2 and Period 3.

ASSAY:

Table 3. Performance of Analytical Method for HGCI

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-day CV (%)	Inter-day Accuracy (%)
Olanzapine	HPLC	[redacted]			[redacted]	15.3 8.8 4.2	[redacted]
Fluoxetine	GC					14.6 4.9 3.8	
Norfluoxetine	GC					12.4 5.4 3.6	[redacted]

*Calculated by reviewer.

Analysis was completed for olanzapine within 5 months of beginning the study and for fluoxetine/norfluoxetine within 6 months of beginning the study. This is within the time period for which stability data are available.

Several samples from this study could not be assayed for fluoxetine or norfluoxetine due to sample consistency. Subject 7 could not be analyzed at all. Eleven samples from subject 16 and 3 samples from subject 13 could not be analyzed. In run # 9, both of the high QC standards for fluoxetine as well as for norfluoxetine deviated from the nominal concentration by more than 15%. However, the low and medium QC samples for that run were acceptable as was each point on the standard curve for each analyte.

The performance and documentation of the assays for olanzapine, as well as for fluoxetine and norfluoxetine, are acceptable.

RESULTS:

Demographics

Seventeen subjects (11 males and 6 females) were enrolled in the study. Two female subjects (subjects 8 and 11) discontinued due to protocol violations and were not included in the pharmacokinetic analysis. Genotype for CYP2D6 was not reported.

Table 4. Demographics of Subjects Completing Study HGCI

Mean Age (Range)	Gender	Weight (mean ± SD)	Race	
32 (23-40)	11 males	71.0 ± 13.4 kg (n=15)	Caucasian	11
	4 females	74.24 ± 10.9 kg (male)	Hispanic	3
		62.3 ± 17.4 kg (female)	Asian	1

Pharmacokinetics

Pharmacokinetic parameters in the subjects completing all three periods were determined using noncompartmental analysis. The scheduled time was used to calculate the pharmacokinetic parameters. The actual time of blood collection was within 10% of the scheduled time. Fluoxetine and norfluoxetine pharmacokinetics following single and multiple dosing are shown in Table 5 (calculated by the reviewer). This documents exposure to fluoxetine and norfluoxetine in the present study. The plasma concentration time course and the pertinent pharmacokinetic parameters for olanzapine are shown in Figure 1 and Tables 6 and 7, below.

Table 5. Pharmacokinetic parameters for fluoxetine and norfluoxetine*

	Period 2 (% CV) n=14	Period 3 (% CV) n=14
Fluoxetine		
t_{max} (h)	4.21 (45.77)	5.43 (108.31)
C_{max} (ng/mL)	54.42 (39.41)	275.81 (28.70)
Norfluoxetine		
t_{max} (h)	90.14 (26.48)	73.07 (48.00)
C_{max} (ng/mL)	30.59 (37.10)	161.04 (31.13)

*Calculated by reviewer.

Figure 1. Mean Plasma Concentration Time Course for Olanzapine After Administration in the Test (P1) and Reference Periods (P2 and P3)

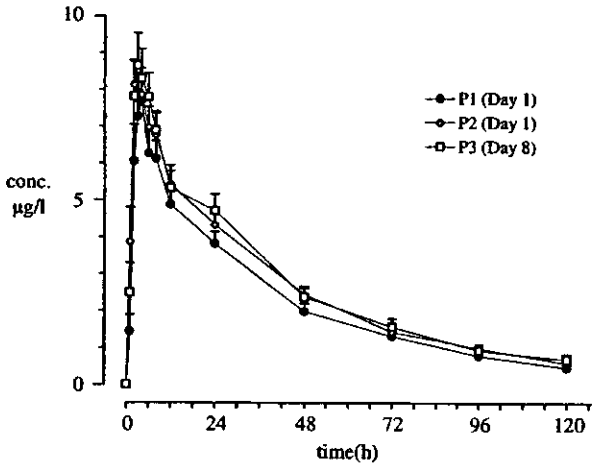


Figure HGCL5.6.1.1. Plasma concentration of olanzapine (means and SEM of the 15 subjects who participated in the three study Periods) afte a single oral dose of olanzapine (5 mg) given alone (—●—), with a single dose of fluoxetine (60 mg) (—◇—) and after 8 daily oral doses of fluoxetine (60 mg) (— —).

Table 6. Pharmacokinetic parameters (arithmetic mean) for olanzapine

	Period 1 (% CV) n=15	Period 2 (% CV) n=15	Period 3 (% CV) n=15
Olanzapine			
t_{max} (h)	3.7 (40.5)	3.5 (57.1)	3.0 (36.7)
C_{max} (ng/mL)	8.15 (40.5)	9.47 (30.3)	9.30 (34.2)
AUC $_{0\text{-}24}$ (ng*h/mL)	118.5 (33.4)	135.8 (30.8)	138.6 (34.3)
AUC $_{0\text{-}\infty}$ (ng*h/mL)	293.3 (40.6)	343.7 (37.8)	347.3 (45.4)
Cl/F (L/ /h)	19.8 (38.9)	16.7 (41.9)	17.7 (48.6)
$t_{1/2}$ (h)	32.21 (19.8)	32.32 (17.5)	31.21 (30.1)

For olanzapine pharmacokinetics, reanalysis of the data (arithmetic mean) by the reviewer (using WINNONLIN) was generally in agreement with that provided by the sponsor. Exceptions were $AUC_{0\text{-}\infty}$ that differed from that reported by the sponsor by less than 4%, and the elimination half-life that was calculated by the reviewer as 31.4 h, 34.9 h, and 37.0 h for Periods 1, 2, and 3, respectively.

Using the results as provided by the sponsor, an increase in C_{max} of approximately 14-16%, an increase in AUC of approximately 15-18%, and a decrease in Cl/F of approximately 11-16% were observed in Periods 2 and 3 compared to Period 1. Since the half-life was similar in the

presence or absence of fluoxetine, the change in Cl/F is most likely due to an increase in bioavailability rather than a decrease in systemic clearance.

T_{max} values for olanzapine did not differ between Period 1 and 2, or between Periods 2 and 3, with P-values (determined by Sponsor using Wilcoxon signed rank test) greater than 0.1.

Table 7. Bioequivalence Assessment

	Geometric Mean			*Period 2: Period 1*	*Period 3: Period 1*
	Period 1 (Reference)	Period 2 (Test)	Period 3 (Test)	**Ratio of Geometric Means (90% CI for the Ratio of Geometric Means)**	**Ratio of Geometric Means (90% CI for the Ratio of Geometric Means)**
	n=15	n=15	n=15		
Olanzapine					
C_{max} (ng/mL)	7.61	8.98	8.79	118.0 (107.8, 129.1)	115.5 (105.5, 126.4)
AUC_{0-24}	113.0	129.9	130.8	115.0 (108.0, 122.4)	115.8 (108.7, 123.3)
(ng*h/mL)	272.2	321.4	314.2	118.1 (110.3, 126.4)	115.5 (107.9, 123.5)
$AUC_{0-\infty}$ (ng*h/mL)	19.8	16.7	17.7	84.6 (77.3, 91.9)	89.4 (82.2, 96.7)
Cl/F (L/ h)	32.21	32.32	31.21	100.3 (91.3, 109.4)	96.9 (87.8, 106.0)
$t_{1/2}$ (h)					

For olanzapine pharmacokinetic parameters, with respect to the bioequivalence of the test and reference periods, according to the results reported by the sponsor, the 90% CI for the ratio of geometric means, falls outside of the 80-125% equivalence range for C_{max} in Periods 2 and 3, AUC_{0-inf} in Period 2, Cl/F in Period 2 compared to Period 1 (olanzapine alone). Reanalysis of the data by the reviewer found ranges outside of the 80-125% equivalence range for AUC_{0-inf} (upper 90% CI 125.70) and for Cl/F (lower 90% CI 79.55) in Period 3 as well. The differences found by the reviewer, in comparison to the values reported by the Sponsor, do not change the overall conclusions from the study. Changes of less than 20% were observed in the pharmacokinetic parameters when olanzapine was given with fluoxetine compared to olanzapine alone.

Safety

The sponsor states that there were no serious or unexpected adverse events. An episode of severe vagal syncope occurred 4 hours after olanzapine administration in Period 1, but was not experienced in Periods 2 or 3.

CONCLUSIONS:

An increase in olanzapine C_{max} and AUC, and a decrease in olanzapine Cl/F were observed when olanzapine was given with fluoxetine. The changes, in comparison to olanzapine given alone, were less than 20%.

6.2.4 BIOANALYTICAL METHOD

Olanzapine

A [redacted] High Performance Liquid Chromatography (HPLC) method with [redacted] detection [redacted] was used for analysis of olanzapine in human plasma samples following [redacted] Compound [redacted] was used as the internal standard. The method was developed and performed by [redacted], for all of the *in vivo* studies. Assay revisions 001-003 were used for Clinical Studies HGFR, HGIE, and HGCI. Revision 000 was used for the pivotal BE study HDAK. Revision 000 differed from 001-003 only by an [redacted] method, but not in the analytical method

Standard operating procedures (SOPs) were in place for sample preparation, for the analytical procedure, and for acceptance.

Selectivity, Accuracy, and Precision

Selectivity was determined by analysis of blank samples from 6 lots of control plasma with respect to olanzapine and internal standard, and with respect to the lower limit of quantification (LLOQ). In the assay for HGIE, it was determined that there was no interference from fluoxetine and norfluoxetine.

For assay revision 000, accuracy and precision, analyzed for 6 replicates for each of 3 concentrations [redacted], were acceptable. Accuracy (% relative error) was [redacted] for intra-day and [redacted], for inter-day. Precision (% relative standard deviation) was [redacted] for intra-day (it did not exceed 15% except for the LLOQ) and [redacted] for inter-day. Accuracy and precision were also acceptable for the dilution standards for a dilution factor of [redacted] Extraction efficiency, for high and low standards, was more than [redacted] for olanzapine and more than [redacted] for the internal standard.

A calibration curve consisted of 9 non-zero standards, as well as a blank sample and a zero sample. Linearity was established for olanzapine in the range of [redacted] ng/ml (LLOQ) to [redacted] ng/ml [redacted] 1/concentration weighted least squares linear regression of peak height ratio vs concentration, 5 standard curves). The accuracy and precision ranged from [redacted] and [redacted], respectively for each of the non-zero standards.

For assay revisions 001-003, accuracy and precision, analyzed for 5 replicates for each of 3 concentrations, [redacted] ng/ml, [redacted] ng/ml, and [redacted] ng/ml) were acceptable. Accuracy (% relative error) was [redacted], for inter-day and [redacted], for intra-day. Precision (% relative standard deviation) was [redacted], for inter-day and [redacted] for intra-day. Linearity was established in the range of [redacted] ng/ml (LLOQ) to [redacted] ng/ml ([redacted] 3 standard curves) with accuracy of [redacted] and precision of [redacted] for each of the non-zero standards.

Stability

Stability of olanzapine in plasma was tested using QC samples (ng/ml, ng/ml, and ng/ml) at room temperature for 48 hours. Accuracy ranged from for the low concentration ng/ml) to for the high concentration ng/ml). After freeze-thaw cycles accuracy ranged from The freeze thaw samples were refrozen for at least 1 hour, rather than the recommended 12-24 hours. Long-term stability was determined at 8.5 months at –80° C, with accuracy ranging from During the analysis of study HGIE, long-term stability was shown at –60° C for 12 months (accuracy ranged from to , and precision ranged from), and at –20° C for 12 months (accuracy ranged from and precision ranged from . Extracted samples were stable at room temperature for 6 days, with accuracy (% relative error) ranging from Stability of stock solutions is reported to be at least 3 months at –60° C.

In conclusion, the bioanalytical method used for olanzapine analysis in plasma samples is adequately documented and validated. This method was previously used for studies reviewed in NDA 20-592.

Fluoxetine and Norfluoxetine

For the pivotal BE study HDAK and for HGFR, and HGIE, fluoxetine and norfluoxetine analysis in plasma was performed by , using an HPLC-MS/MS method. For HGCI, the analysis in plasma was performed by , using gas liquid chromatography (GLC).

HPLC-MS/MS Method

For the HPLC-MS/MS analysis, samples were mixed with internal standard (and) prior to . SOPs are in place for sample preparation and for the analytical method.

Selectivity, Accuracy, and Precision

Selectivity was determined using plasma blanks from 6 lots of control plasma with respect to fluoxetine, norfluoxetine, and the internal standards, in which no interfering peaks were noted. In addition, no interference is observed in the presence of olanzapine.

Accuracy and precision, analyzed with 5 replicates at each of 3 concentrations (ng/ml ng/ml, and ng/ml), were acceptable. For fluoxetine, accuracy ranged from to for intra-day and to for inter-day, and precision ranged from to for intra-day and from to for inter-day. For norfluoxetine, accuracy ranged from to for intra-day and to for inter-day, and precision ranged from to for

intra-day and —— to —— for inter-day. It should be noted that on 2 dates for norfluoxetine and on 1 date for fluoxetine in the validation report, a signal from the ng/ml sample was not detected in 1 of the replicates, resulting in 4 replicates for the low QC sample on those dates. However, sufficient accuracy and precision was demonstrated with the LLOQ ng/ml) in other assays using QC samples.

Extraction efficiencies (mean +/- SD of 5 replicates each of ng/ml and ng/ml) were 99 +/- 24% for fluoxetine and 89 +/- 20% for norfluoxetine. Mean extraction efficiencies (mean +/- SD) were 125 +/- 24% for fluoxetine internal standard (ng/ml replicates) and 148 +/-22 % for norfluoxetine internal standard ng/ml, 9 replicates).

Calibration curves for fluoxetine and for norfluoxetine consisted of 7 nonzero standards. Linearity was established in calibration curves for both fluoxetine and norfluoxetine with 7 nonzero standards in the range of ng/ml (LLOQ) to ng/ml (3 standard curves). The accuracy and precision ranged from to and from to , respectively for fluoxetine and from to and from to , respectively for norfluoxetine.

Stability

Stability (QC samples of ng/ml, ng/ml, and ng/ml) was tested as follows:

1) with regard to bench top where unprocessed samples were stable up to 5 hours at room temperature (accuracy for fluoxetine ranged from to and for norfluoxetine from to)
2) with regard to processed samples that were stable for up to 36 hours at room temperature (accuracy for fluoxetine ranged from to , and for norfluoxetine from to) and up to 21 hours at 4° C (accuracy for fluoxetine ranged from to and for norfluoxetine from to)
3) through of freeze/thaw at –20° C and room temperature, respectively (accuracy was to for fluoxetine and to for norfluoxetine.
4) long-term storage stability at –20° C and at –70° C was tested with QC samples of ng/ml, ng/ml, and ng/ml. For samples stored at -20° C for 18 months, accuracy was from - to for fluoxetine and from - for norfluoxetine. For samples stored at – 70° C for 18 months, accuracy ranged from to for fluoxetine and from - to for norfluoxetine.

In conclusion, the HPLC-MS/MS method for fluoxetine and norfluoxetine is adequately documented and validated.

GLC Method

A GLC method with electron capture detection (EC) was used for determining fluoxetine and norfluoxetine in human plasma in Clinical Study HGCI.

Selectivity, Accuracy, and Precision

Selectivity was determined in control blank plasma samples run as blanks in the validation study that showed no major interfering peaks. To determine accuracy and precision, QC control samples— ng/ml,— ng/ml, and ' ng/ml) were assayed in duplicate with each of three standard curves. The inter-day CV ranged from % for fluoxetine and from .% for norfluoxetine. The intra-day accuracy and precision and inter-day accuracy were not calculated in the material provided, but were calculated by the reviewer as follows: the inter-day accuracy ranged from to % for fluoxetine and from to for norfluoxetine, the intra-day precision ranged from to for fluoxetine and from to for norfluoxetine, and the intra-day accuracy ranged from- to for fluoxetine and from to for norfluoxetine. These values are acceptable.

Calibration curves consisted of 12 nonzero points ng/ml to ng/ml) in addition to a blank sample and a zero sample. The LLOQ is ng/ml. The curves were split into a low curve (ng/ml ng/ml) and a high curve (ng/ml – ng/ml). For the low curve, the precision for the nonzero standards ranged from to for inter-day (3 standard curves on each day, 5 nonzero points) with linearity demonstrated (The value of was for the LLOQ. For the high curve the inter-day precision ranged from to (3 standard curves on each day, 9 nonzero points) with linearity demonstrated (The ng/ml standard had a CV of but was not more than for any other standard. Thus 8 out of the 9 nonzero points met the conditions for deviation. For norfluoxetine for the low curve, the CV ranged from to with linearity demonstrated (and for the high curve the inter-day CV ranged from to with linearity demonstrated (. The CV for the ng/ml standard was ', with the CVs for the remaining standards for that curve ranging from to

Intra-day precision ranged from to for the fluoxetine low curve, where the value of was for the LLOQ based on data provided in Table 3 of the validation report. For the high curve, intra-day precision ranged from to The ng/ml standard had a CV of (, on the three validation days), but was not more than for any other standard, according to data provided in Table 3. Intra-day precision ranged from , for the norfluoxetine low curve and from to for the norfluoxetine high curve according to data provided in Table 4. The value of was for the ng/ml standard (to on the three validation days), but was not more than for any other standard. (, provided slightly different data in Tables 5 and 6 for intra-day precision that was generally in agreement with these calculations and met the requirements for precision). Based on this, the standard curve used for validation meets the criteria for inter-day and intra-day precision.

Accuracy for the calibration curve was not calculated in the data provided by the sponsor. However, the reviewer has calculated accuracy based on data provided in Tables 3 and 4. For fluoxetine inter-day accuracy ranged from to for the low curve and from to for 7 of 9 points in the high curve (disregarding ng/ml and ng/ml standards for which accuracy was and respectively). Intra-day accuracy ranged from to for the fluoxetine low curve, in which the value was for the LLOQ (from to on the

three validation days), but was not more than ——— for any other standard. For the norfluoxetine low curve intra-day accuracy ranged from —— to —— For the norfluoxetine high curve ranged intra-day accuracy ranged from —— to —— for 7 of 9 standards (disregarding the —— ng/ml and —— ng/ml standards for which it ranged from —— to —— and from —— to —— respectively). Based on this, the standard curve used for validation meets the criteria for inter-day and intra-day accuracy.

Stability

Freeze/thaw stability was determined using 6 aliquots of QC samples stored at –20° C through —— freeze-thaw cycles on 3 different days. These QC standards were —— ng/ml —— ng/ml, and —— ng/ml. For the low standard for fluoxetine, the CV was —— and accuracy was —— after the third cycle, and for the high standard those values were —— and —— respectively. For the low standard for norfluoxetine the CV was —— and accuracy was —— after the third cycle, and for the high standard those values were —— and —— , respectively. Therefore, the samples are stable through —— freeze-thaw cycles.

Bench top stability of extracted samples was evaluated to demonstrate that the extracted samples are stable under injection conditions. This was performed using only a medium QC standard (—— ng/ml). After 8 days at room temperature the results were as follows: for fluoxetine the CV was —— and accuracy was —— and for norfluoxetine the CV was —— and the accuracy was —— Thus the extracted samples are stable for 8 days at room temperature.

In conclusion, the GLC method for fluoxetine and norfluoxetine is adequately documented and validated.

Cross-Validation Between Fluoxetine/Norfluoxetine GC/MS Method and the LC/MS/MS Method

Cross-validation was performed using pooled samples from previous bioanalytical reports (B1Y-SP-0004 and B1Y-MC-HCIT) at fluoxetine concentrations and norfluoxetine concentrations of approximately ——— (BLQ), ——— and —— ng/ml. For each method, a duplicate standard curve and QC samples in replicates of 5 at ———, and —— ng/ml were extracted. Sample pools were extracted in replicates of 5.

For the LC and GC Validation Runs, the standard curves were linear with a correlation coefficient of —— for fluoxetine and for norfluoxetine. Accuracy for each point ranged from —— to —— Accuracy and precision for the QC standards were acceptable, as was inter-method accuracy. The accuracy of the pooled sample results was acceptable for fluoxetine. For norfluoxetine the accuracy was acceptable except for the concentrations of approximately —— and —— where accuracy was ——— and ——— , respectively. Since the QC samples were acceptable at —— ng/ml, it was hypothesized that the pools were not sufficiently mixed prior to extraction.

The GC/MS and LC/MS/MS Methods can be considered to be cross-validated.

6.2.5 SYMBIAX DISSOLUTION METHOD DEVELOPMENT

Rationale for Selection of Dissolution Method and Media for SYMBIAX (OFC) Capsules

The established dissolution method and specification for the marketed tablet formulation of olanzapine (Zyprexa) is USP Apparatus 2, in 900 ml of 0.1 N HCl, at an agitation speed of 50 rpm, Q=[redacted] in 30 minutes. The established dissolution method and specification for the 10 mg, 20 mg, 40 mg, and 60 mg marketed capsules of fluoxetine is USP Apparatus 2, in 900 ml of water, at an agitation speed of 50 rpm, Q = [redacted] in [redacted] minutes. According to the OCPB review of fluoxetine (Prozac) tablets (NDA 20-974) recommended dissolution method and specification for fluoxetine tablets is USP Apparatus I, in 1000 ml of 0.1 N HCl, at an agitation speed of 100 rpm, Q=[redacted] at 15 minutes.

Both olanzapine and fluoxetine have been previously characterized (NDA 20-592 and NDA 18-936, respectively) as highly soluble, with the highest strengths (12 mg and 50 mg respectively) dissolving in less than 250 ml of different media. This is shown in Tables 1 and 2 below, as provided by the sponsor.

Table 1. Aqueous Solubility of Olanzapine at Room Temperature

Medium	pH of Medium at Saturation	Solubility (mg/mL)	Minimum Volume to Dissolve 12 mg[a] of Olanzapine (mL)
Buffer 0.05M pH 2	5.87	[redacted]	[redacted]
Buffer 0.05M pH 4	5.97		
Buffer 0.05M pH 6	6.04		
Buffer 0.05M pH 7	7.08		
Buffer 0.05M pH 10	9.92		
0.1N HCl	5.38		
0.1N NaOH	12.83	[redacted]	[redacted]

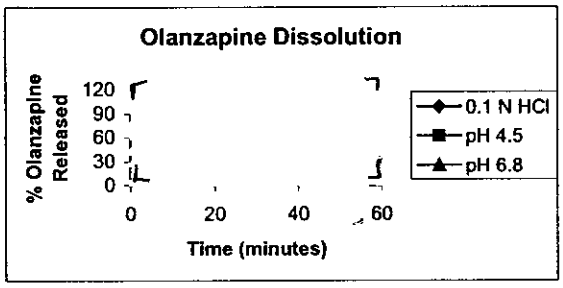
[a] 12 mg of Olanzapine represents the highest dose in the OFC capsules. None of the media require more than 250 mL to dissolve the highest strength. Therefore, the drug substance is considered highly soluble according to the guidance document.

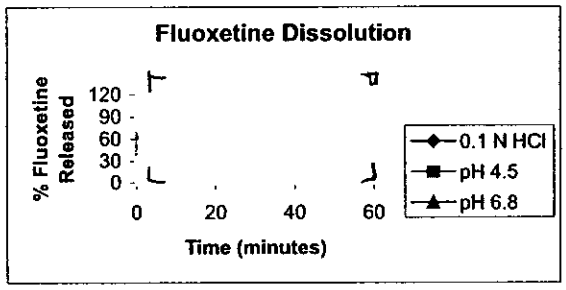
Table 2. Aqueous Solubility of Fluoxetine HCl at Room Temperature

Medium	pH of Medium at Saturation	Solubility (mg/mL)	Minimum Volume to Dissolve 50 mg[a] of Fluoxetine (mL)
0.1N HCl, pH 1.1	--	[redacted]	[redacted]
0.1M Acetate Buffer, pH 4.5	4.49		
Deionized Water	6.80		
0.05M Phosphate Buffer, pH 6.8	6.11		
0.1M Phosphate Buffer, pH 7.5	7.29	[redacted]	[redacted]

[a] 50 mg of Fluoxetine represents the highest dose in the OFC capsules. None of the media require more than 250 mL to dissolve the highest strength. Therefore, the drug substance is considered highly soluble according to the guidance document.

Based on the solubility of olanzapine and fluoxetine in 0.1 N HCl, 0.1 N HCl was used as the dissolution media, according to the Sponsor in the method validation for Method ~~~ (CMC validation report). Dissolution profiles (mean of 12 replicates) for the 12/50 OFC capsules in 0.1 N HCl, pH 4.5, and pH 6.8 media are shown below (as plotted by reviewer from data provided by Sponsor). The % dissolved did not reach ~~~in the pH 4.5 and pH 6.8 buffers. Therefore, the use of 0.1 N HCl media is justified.





Dissolution Results

This methodology was used to test olanzapine/fluoxetine combination (OFC) capsules (at least 6 replicates) including lots from primary stability and large scale demonstration batches. Additional studies were performed with the lot used in the pivotal bioequivalence study HDAK (lot D40337). Testing was performed at 15, 20, and 30 minutes. Dissolution was at least ~~~ by ~~~ minutes, although there was more variability at 15 minutes. Results from the OFC capsule primary stability and large scale demonstration batches, as well as from the pivotal bioequivalence study, are shown in the Table at right (as provided by Sponsor).

Table 3. Minimum Percent Dissolved for Olanzapine and for Fluoxetine from OFC Capsule Primary Stability and Large Scale Demonstration Batches.

Use of Lot	Lot Number	Minimum % Olanzapine Dissolved 15 min	20 min	30 min	Minimum % Fluoxetine Dissolved 15 min	20 min	30 min	Number of Replicates (n[a])
Olanzapine/Fluoxetine Combination Capsules 6/25								
Primary Stability								12
Primary Stability								12
Primary Stability								12
Olanzapine/Fluoxetine Combination Capsules 12/25								
Primary Stability								12
Primary Stability								12
Primary Stability								12
Olanzapine/Fluoxetine Combination Capsules 6/50								
Primary Stability								12
Primary Stability								12
Primary Stability								12
~~ Scale								6
Olanzapine/Fluoxetine Combination Capsules 12/50								
Primary Stability								12
Primary Stability								12
Prim. Stab, Bioeq								12
~~ Scale								24
~~ Scale								12
~~ Scale								6

NOTE: All batches above are manufactured at the commercial site and are representative of the commercial process.

[a] Dissolution sample sizes varied during development for selected experiments to demonstrate the robustness of specific unit operations. The testing of more than six replicates was due to collection of additional development data throughout processing and not due to second or third stage testing.

Dissolution profiles from those batches are shown in the figures

below. It can be seen that this method can discriminate between different formulations at — minutes, and that all formulations were more than — dissolved at 30 minutes.

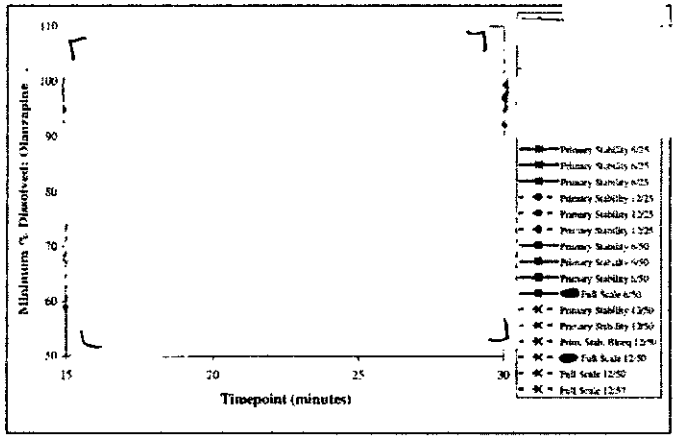


Figure F.3. **Minimum dissolution profiles for olanzapine from OFC capsule primary stability and demonstration batches.**

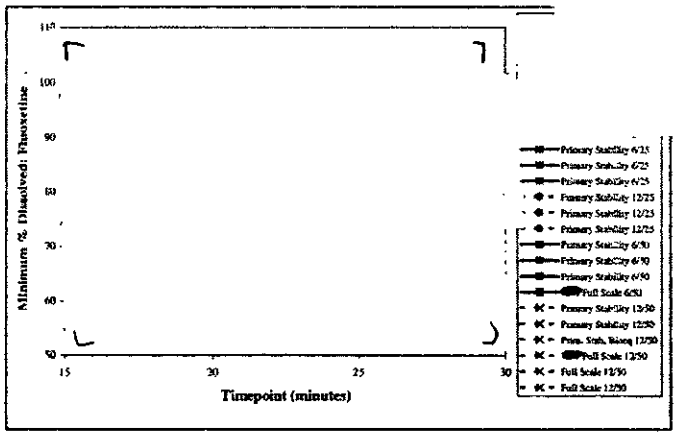


Figure F.4. **Minimum dissolution profiles for fluoxetine from OFC capsule primary stability and demonstration batches.**

Proposed Dissolution Method and Specifications

The Sponsor has proposed the following dissolution method and specifications:

Apparatus: USP Apparatus 2 (Paddle)
Medium: 0.1 N HCl
Volume: 900 ml
Rotation Speed: 50 rpm
Specification: Q = — at 30 minutes

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed dissolution method of USP Apparatus 2 (paddle) at 50 rpm and 900 ml of 0.1 N HCl dissolution media acceptable. It is recommended that the specification be changed to Q=‘—— at ‾ minutes.

APPEARS THIS WAY
ON ORIGINAL

6.2.6 REQUEST FOR A BIOWAIVER OF SYMBIAX LOWER STRENGTHS

WAIVER OF IN VIVO BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR LOWER STRENGTHS OF THE OLANZAPINE/FLUOXETINE COMBINATION (OFC) CAPSULES

The sponsor has demonstrated bioequivalence between the highest strength OFC capsule (12/50 mg olanzapine/fluoxetine) and concomitantly administered individual capsules of equal dose used in the clinical trials. A biowaiver for lower strengths of the OFC capsules has been requested.

Composition of OFC Capsules

All of the drug products are manufactured using a [redacted] manufacturing process. The excipients are pregelatinized starch (diluent), dimethicone (lubricant), and empty gelatin capsules (vehicle). The composition of the OFC capsules and the individual olanzapine capsules and fluoxetine capsules used in the clinical trials are shown in Tables G13 through G15 below (as provided by the sponsor). Note that the percentages shown in the table are based on the total weight of each strength capsule, not on the reference (12/50) target weight. Using the weight of the 12/50 capsules as the reference as for SUPAC type computations, the dimethicone change for [redacted] 6/25, and 12/25 strengths is [redacted] which falls within SUPAC level I for lubricant. It can be seen that the percentage of pregelatinized starch in the [redacted] 6/25 capsules varies from the 12/50 capsule by more than the ±10 % allowed in SUPAC-IR for diluent (level II). However the amount of starch in the clinical trial capsules was [redacted] for the 25 mg fluoxetine capsules and was [redacted] for the 6 mg olanzapine capsules, the strengths of the individual capsules used in the pivotal bioequivalence study. Therefore, the percent of starch in the lower strengths is bracketed by the higher strength and the clinical trial formulations [redacted].

Table G.13. Theoretical Commercial Unit Formulas of Olanzapine/Fluoxetine Combination Capsule Formulations

OFC Capsule Strength	6/25 mg/cap (%/cap)	12/25 mg/cap (%/cap)	6/50 mg/cap (%/cap)	12/50 mg/cap (%/cap)
Olanzapine	6.000	12.00	6.000	12.00
Fluoxetine HCl [Fluoxetine Base]	[redacted]	[redacted]	[redacted]	[redacted]
Pregelatinized Starch	[redacted]	[redacted]	[redacted]	[redacted]
Dimethicone	[redacted]	[redacted]	[redacted]	[redacted]
Fill Weight (mg)	230.0	230.0	300.0	300.0
Capsule Size	3	3	2	2
Capsule Shell Colors (Cap/Body)	Opaque Mustard Yellow/ Opaque Light Yellow	Opaque Red/ Opaque Light Yellow	Opaque Mustard Yellow/ Opaque Light Grey	Opaque Red./ Opaque Light Grey

Table G.14. **Theoretical Clinical Trial Unit Formulas for Olanzapine Capsules**

Olanzapine Capsule Strength	1	2.5	5	6
	mg/cap (%/cap)	mg/cap (%/cap)	mg/cap (%/cap)	mg/cap (%/cap)
Olanzapine	1.00	2.5	5.00	6.00
Pregelatinized Starch				
Dimethicone				
Fill Weight (mg)	290	290	290	290
Capsule Size	2	2	2	2
Capsule Shell Colors: Cap/Body	Blue/ Blue	Blue/ Blue	Blue/ Blue	Blue/ Blue

ible G.15. **Theoretical Clinical Trial Unit Formulas for Fluoxetine Capsules**

Fluoxetine Capsule Strength	5	10	20	25
	mg/cap (%/cap)	mg/cap (%/cap)	mg/cap (%/cap)	mg/cap (%/cap)
Fluoxetine HCl	5.59	11.18	22.36	27.95
[Fluoxetine Base]				
Pregelatinized Starch				
Dimethicone				
Fill Weight (mg)	230	230	230	195
Capsule Size	3	3	3	3
Capsule Shell Colors: Cap/Body	White/ White	White/ White	White/ White	White/ White

Biopharmaceutics Classification System (BCS)

The sponsor has submitted data regarding the solubility, permeability, and dissolution of olanzapine and of fluoxetine for consideration of a biowaiver based on BCS. However, the OFC capsules demonstrated neither rapid dissolution in all three dissolution media, nor similar dissolution based on the f_2 value, as reviewed below. Since a biowaiver for lower strengths of OFC capsules cannot be granted based on dissolution alone, the data for BCS classification will not be reviewed.

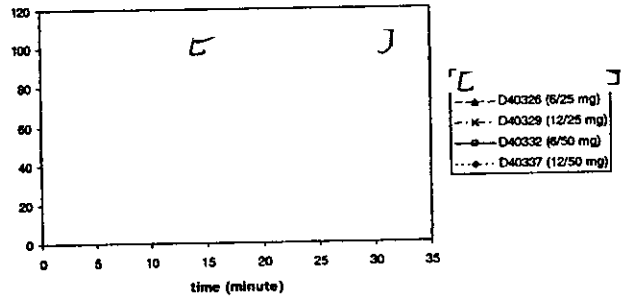
Dissolution

Dissolution testing, using 12 individual units each of test and reference products, was carried out in USP Apparatus II at 50 rpm using 900 ml of the following dissolution media: a 0.1 N HCl, a pH 4.5 acetate buffer, and a pH 6.8 buffer, as recommended in the FDA guidance for Industry " Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System". Olanzapine and fluoxetine were detected using an isocratic, reversed phase HPLC method with UV detection using a validated method.

The mean percent dissolved in 0.1 N HCl was at least — (range of dissolution ———), with the coefficient of variation (CV) less than 1.8% at 15, 20, and 30 minutes for all strengths of OFC for both olanzapine and fluoxetine. The mean percent dissolved in pH 4.5 at 15 minutes was less than — for olanzapine at all strengths and for fluoxetine in OFC 12/25, 6/50, and 12/50 (range of dissolution ——— for olanzapine in OFC 12/50 to ——— for fluoxetine in OFC 3/25), with CV for both olanzapine and fluoxetine exceeding 10% at 15 minutes for OFC 12/25, 6/50, and 12/50. In 30 minutes at pH 4.5, the mean percent dissolved was more than — except for olanzapine in OFC — and for olanzapine and fluoxetine in OFC 12/50 (range of dissolution ———, for fluoxetine in OFC 12/50 to ——— for fluoxetine in OFC 12/25), with the CV for both olanzapine and fluoxetine greater than 10% in OFC 12/50. The mean percent dissolved in pH 6.8 at 15 minutes was less than — for both olanzapine and fluoxetine at all OFC strengths (range of dissolution — for olanzapine in OFC 12/50 to ———, for fluoxetine in OFC —), with CV exceeding 10% at 15 minutes for both olanzapine and fluoxetine at all

OFC strengths. At 30 minutes in pH 6.8, the mean percent dissolved did not exceed [redacted] (range of dissolution [redacted] for olanzapine in OFC 12/50 to [redacted] for fluoxetine in OFC 6/25), with the CV exceeding 10% except for olanzapine in OFC [redacted] The results are shown in the Figures below, as provided by the sponsor.

A review of the graphic representation of the mean dissolution profiles for the test (OFC [redacted], 6/25, 12/25, and 6/50) and reference (OFC 12/50) products in the three media demonstrate that in pH 4.5 and pH 6.8, the profile for OFC 12/50 has slower dissolution compared to the test products.



e G.4. Profiles of the average percent fluoxetine dissolved in 0.1N HCl for the reference product (OFC 12/50) and the test products (OFC [redacted] OFC 6/25, OFC 12/25, & OFC 6/50).

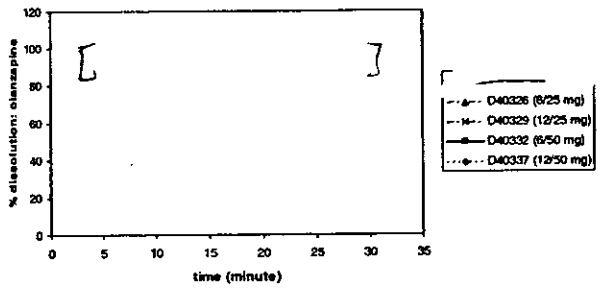
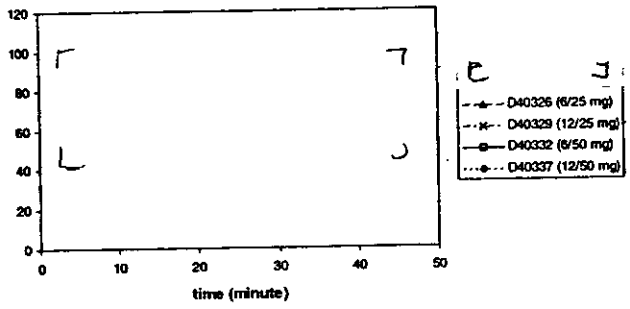
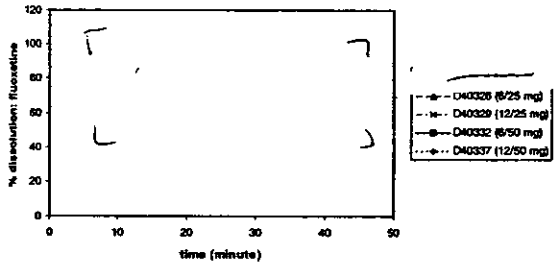


Figure G.3. Profiles of the average percent olanzapine dissolved in 0.1N HCl for the reference product (OFC 12/50) and the test products (OFC [redacted] OFC 6/25, OFC 12/25, & OFC 6/50).



re G.5. Profiles of the average percent olanzapine dissolved in pH 4.5 acetate buffer for the reference product (OFC 12/50) and the test products (OFC [redacted] OFC 6/25, OFC 12/25, & OFC 6/50).



ure G.6. Profiles of the average percent fluoxetine dissolved in pH 4.5 acetate buffer for the reference product (OFC 12/50) and the test products (OFC [redacted] OFC 6/25, OFC 12/25, & OFC 6/50).

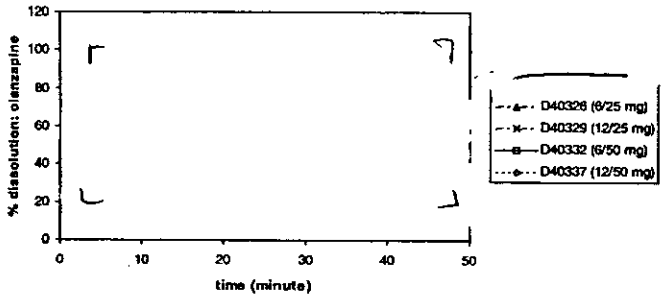
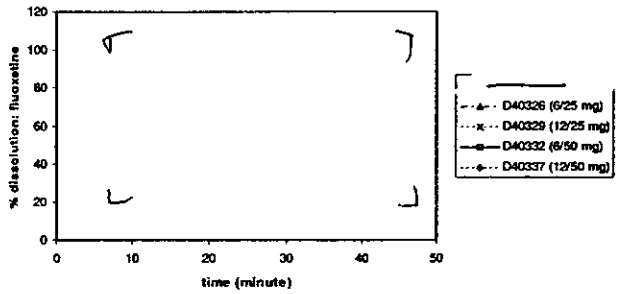


Figure G.7. Profiles of the average percent olanzapine dissolved in pH 6.8 simulated intestinal fluid without enzyme for the reference product (OFC 12/50) and the test products (OFC —, OFC 6/25, OFC 12/25, & OFC 6/50).



gure G.8. Profiles of the average percent fluoxetine dissolved in pH 6.8 simulated intestinal fluid without enzyme for the reference product (OFC 12/50) and the test products (OFC —, OFC 6/25, OFC 12/25, & OFC 6/50).

Since —or more of the label amount of the drug was not consistently dissolved in 15 minutes in the pH 6.8 and pH 4.5 dissolution media across the dosage strengths, the profile comparison with an f_2 test is necessary.

Similarity factors (f2) for olanzapine and for fluoxetine are shown in the tables below (as provided by the sponsor). Comparing the test and reference products, the f2 factor was greater than 50 for all of the test products in 0.1 N HCl, but less than 50 in the pH 4.5 and pH 6.8 buffers.

Table G.7. Similarity factors (f_2) for olanzapine

		f_2 Values[a]		
Lot Number	Dose	0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
D40326	6/25	81	27	22
D40329	12/25	89	26	22
D40332	6/50	81	30	26

[a] Dissolution profiles are considered similar if the f_2 value is greater than or equal to 50

Table G.8. Similarity factors (f_2) for fluoxetine

		f_2 Values[a]		
Lot Number	Dose	0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
D40326	6/25	97	19	17
D40329	12/25	92	23	16
D40332	6/50	91	26	24

[a] Dissolution profiles are considered similar if the f_2 value is greater than or equal to 50

Influence of Dissolution on *In Vivo* Absorption

Olanzapine:

The Sponsor has provided additional data comparing relative bioavailability of Zyprexa oral olanzapine tablets and Zyprexa Zydis olanzapine orally disintegrating tablets (NDA 21-086). The Zydis tablet undergoes rapid disintegration when placed on the tongue. Study F1D-EW-LOAL demonstrated the bioequivalence of 20 mg olanzapine Zydis formulation to four, 5 mg oral tablets of olanzapine in a randomized crossover study in healthy male subjects. These results are shown in the Table below (as provided by the Sponsor).

Results of Bioequivalence Assessment for Study LOAL (as provided by Sponsor)

Bioavailability Variable	Treatment [a] (N=20)	Least Square Mean	Separation in Means	p Value	Ratio of Means	90% Confidence Interval [b]	
C_{max} [c] (ng/mL)	A: Standard	38.4					
	B: Zydis™	38.4	-0.04%	0.991	0.99	0.94 to 1.06	P
t_{max} (hr)	A: Standard	3.00					
	B: Zydis™	3.20	0.2 hr	0.459	na	na	
AUC(0-t)[c] (ng•hr/mL)	A: Standard	1001					
	B: Zydis™	1030	2.94%	0.230	1.02	0.98 to 1.07	P
AUC(0-∞)[c] (ng•hr/mL)	A: Standard	1030					
	B: Zydis™	1062	3.05%	0.219	1.02	0.98 to 1.07	P

[a] Treatments: A = Olanzapine Standard Oral 5 mg Tablet (4×5 mg) (REFERENCE)
B = Olanzapine Zydis™ 20 mg Tablet (1×20 mg) (TEST).

[b] Lower and Upper Bounds. P = pass F = fail, Bioequivalence Criterion 0.8 to 1.25.
na = not applicable.

[c] Ratio of Means and 90% Confidence Interval analysis performed on the log-transformed variables, based on N=20 subjects (completers).

Dissolution of the Zydis tablet (also referred to as RTD) has been compared to dissolution of the standard oral tablet (STD) using the specification approved by OCPB for the Zydis tablet (NDA 21086). The results (as provided in the OCPB review of NDA 21086), shown in the table below, show that the Zydis tablets are more rapidly dissolving in vitro than the STD in 0.1 N HCl.

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Apparatus: USP Apparatus 2 (paddle) rotated at 50 rpm
Media: 900 ml of 0.1N HCL at 37±0.5°C
Specification: NLT ___ ___) in 10 minutes

What dissolution results are provided?

Formulation	Lot #	Time (min)	Mean (range) (%, n=6)	CV (%)
SDT 5-mg	B5121*	30	100	3.3
RDT 5-mg	97C03OG*	5	101	0.7
	98C07OG*	10	103	1.5
RDT 10-mg	97C01OH*	5	101	0.9
RDT 15-mg	97C01OK	5	102	0.9
	97E01LK	10	103	1.0
RDT 20-mg	97C03OM*	5	103	0.9

*Lots used in bioequivalence studies. SDT is standard oral tablet and RDT is rapid dissolving tablet.

The bioavailability data considered with the *in vitro* dissolution data support the suggestion that in the case of olanzapine, the *in vitro* dissolution does not affect the bioavailability even when one formulation is more rapidly dissolving than another.

The Sponsor has provided additional data showing rapid dissolution of olanzapine Zydis tablets in pH 4.5 acetate buffer and in pH 6.8 phosphate buffer, as shown in the figures below. The dissolution profiles of the olanzapine Zydis tablets and the 12/50 SYMBIAX capsule in these media bracket the profiles of the lower strength SYMBIAX capsules.

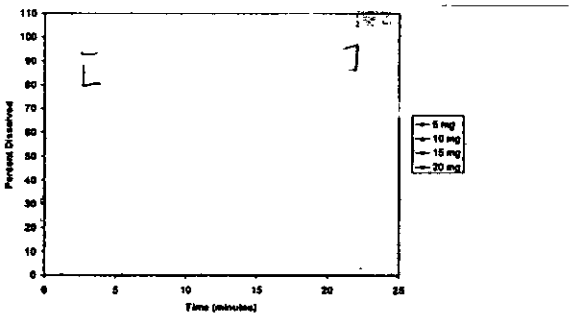

Figure 2. Profiles of the average (n=12) percent olanzapine dissolved in 900 mL of pH 4.5 acetate buffer at 37°C using USP apparatus 2 at 50 rpm for olanzapine Zydis tablets (5 mg, 10 mg, 15 mg, and 20 mg)

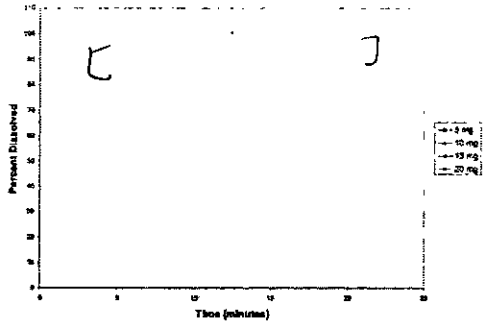

Figure 3. Profiles of the average (n=12) percent olanzapine dissolved in 900 mL of pH 6.8 phosphate buffer at 37°C using USP apparatus 2 at 50 rpm for olanzapine Zydis tablets (5 mg, 10 mg, 15 mg, and 20 mg)

Fluoxetine:

The Sponsor has also provided additional information (NDA 20-101) from study HCEZ in which fluoxetine oral solution (20 mg/5 ml) and fluoxetine capsules (20 mg) were considered to be bioequivalent. Those results, shown in the Table below, suggest that a fluoxetine formulation with a faster rate of dissolution would not necessarily have an altered pharmacokinetic profile compared to a formulation with a slower rate of dissolution (e.g., the OFC capsule).

Results of Bioequivalence Assessment for Study HCEZ (as provided by Sponsor)

Recommendation:

Fluoxetine PK Parameter	Formulation	Mean (n_{PK}=28)	Solution/Capsule	p-value
C_{max} (ng/mL)	Solution	7.93		0.419
	Capsule	8.07		
AUC(0-∞) (ng•hr/mL)	Solution	343.3		0.458
	Capsule	335.6		
t_{max} (hr)	Solution	7.11		0.123
	Capsule	7.54		

OFC capsules cannot be considered rapidly dissolving (no less than —of the labeled amount of the drug substance dissolves within 30 minutes) in all three dissolution media. The dissolution profiles are not considered similar based on the f_2 value. Therefore a biowaiver for lower strengths of OFC capsules cannot be granted based on BCS.

Previously approved formulations of olanzapine have demonstrated a range of dissolution profiles that did not result in altered exposure to olanzapine. In addition, the dissolution profiles of the rapidly dissolving olanzapine ZYDIS tablets and the highest strength SYMBIAX capsules bracket the dissolution profiles for olanzapine in the lower strength SYMBIAX capsules. Previously evaluated formulations of fluoxetine (capsules vs oral solution) similarly did not result in altered exposure *in vivo*. Based on these data, it appears that absorption, rather than dissolution at least in pH 4.5 and 6.8, is the rate limiting step in exposure to either olanzapine or fluoxetine. This supports the consideration that the more rapidly dissolving lower strengths of the OFC capsule would not be expected to result in exposure to olanzapine or fluoxetine that would be greater than the more slowly dissolving higher strength OFC capsule.

Therefore, the Office of Clinical Pharmacology and Biopharmaceutics recommends that a biowaiver be granted for the lower strengths of OFC.

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6.3 Pharmacometrics Consult Review

Pharmacometrics Review

NDA:	21520
Compound:	Olanzapine Fluoxetine
Submission Dates:	11/04/2002
Sponsor:	Eli Lilly and Company

Background:

Overview of this report

This is a pharmacometric review. The purpose of this review is to evaluate the population pharmacokinetic studies F1D-MC_HGFR and F1D-MC-HGIE, to explore whether there is pharmacokinetic and pharmacodynamic relationship, and to explore whether there is a dose-response relationship from the clinical study F1D-C-HGGY. These three studies are summarized here:

Study F1D-MC-HGFR: Study of Olanzapine in Treatment Resistant Major Depressive Disorder without Psychotic Features
Pharmacokinetic and Statistical Report

Study F1D-MC-HGIE: Population Pharmacokinetic and Pharmacodynamic Analysis of Study F1D-MC-HGIE

Olanzapine Plus Fluoxetine Combination Therapy in Treatment-Resistant Depression: A Dose Ranging Study

Study F1D-C-HGGY: Placebo-Controlled Olanzapine Monotherapy in Treatment of Bipolar I Depression

Review of the clinical pharmacokinetics of Olanzapine and Fluoxetine

Review of Olanzapine clinical pharmacokinetics [*2002 Physician's Reference Desk*]

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption.

Olanzapine displays linear kinetics over the 5 mg to 20 mg/day clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age. Olanzapine is extensively distributed throughout the body.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs IA2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo.

Review of Fluoxetine clinical pharmacokinetics [*2002 Physician's Reference Desk*]

Fluoxetine is well absorbed from the gastrointestinal tract after oral administration and its bioavailability is not affected by the presence of food.

Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine.

The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species on chronic use and delayed attainment of steady state, even when a fixed dose is used.

Plasma concentrations of fluoxetine at the steady state were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics.

Drug-drug interaction of Olanzapine and Fluoxetine

Gossen D, de Suray J-M, Vandenhende F et al (Eli Lilly and Co., 1998) indicated that olanzapine plasma CL/F decreased approximately 15% and Cmax increased approximately 18% following administration of fluoxetine. The t1/2β of olanzapine was not significantly affected. Fluoxetine inhibits CYP2D6, which may affect the minor metabolic pathway forming 2-hydroxymethyl olanzapine.

Sponsor's methods

Study HGFR

Data

Figure 4 displayed the concentration difference between the monotherapy and combination therapy.

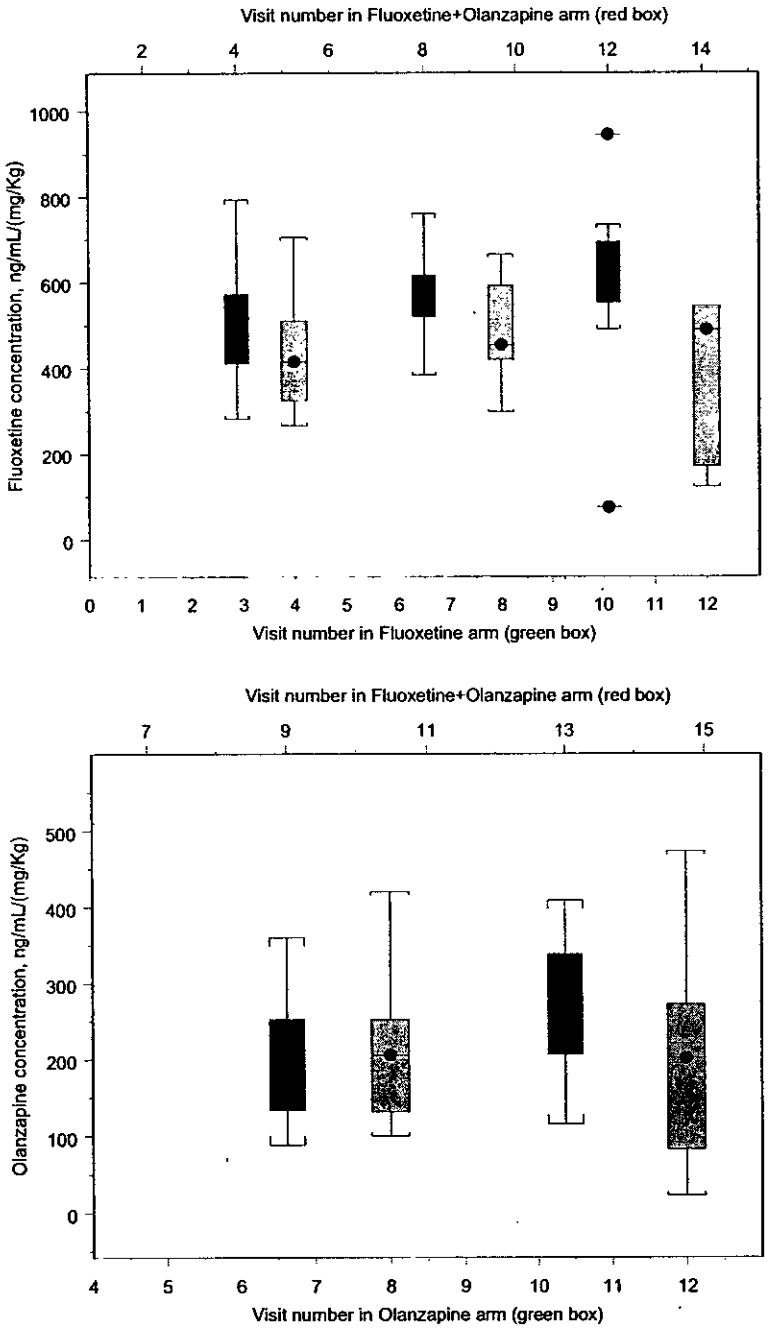

Figure 4 Box plots of fluoxetine concentration and olanzapine concentration in montherapy and combination therapy

Modeling

Steady-state concentrations were dose-weight-normalized and then the dose-weight-normalized concentrations were compared between treatments and between visits for

each of the analytes: fluoxetine, norfluoxetine, and olanzapine. The statistical analyses were conducted via a linear mixed-effects model based on a crossed-nested design. In the statistical model, treatment and visits formed fixed factors and subjects within treatment a random factor.. In the case of fluoxetine and norfluoxetine, the plasma concentration at visit 4 (at the beginning of Period II) for each subject was incorporated as a covariate in the model. Since the data were imbalanced, least square means were assessed and least square means differed from the ordinary means. Each group at the last visit had at most 10 subjects since each arm started with 12 subjects in the screening phase.

Missing data

For various reasons, 11 quantifiable plasma concentrations were excluded from the analysis (Table 13). Two subjects (1015 and 1007 fluoxetine group) had concentrations recorded for both visit 8 and visit 9. The protocol called for blood sampling at visits 4, 8, and 12. Since the visit 8 and 9 concentrations for the two mentioned individuals were not significantly different from one-another, the visit 9 fluoxetine and norfluoxetine data were excluded from the final analysis.

Baseline plasma concentrations were excluded for two individuals. The fluoxetine concentration for subject 1038 was above the limit of quantification ([ ] ng/mL) and the sample was not reanalyzed. The norfluoxetine concentration for this individual was within the limits of detection and therefore included in the analysis. The fluoxetine and norfluoxetine samples for subject 1005 were obtained at visit 5, after the subject had been receiving olanzapine treatment for two days. Since olanzapine treatment may affect baseline fluoxetine and norfluoxetine levels, these concentrations were excluded from the analysis.

To assume steady-state concentrations with once daily dosing, the interval between dosing and sampling should not be considerably greater than 24 hours. This was true for all concentrations with 4 exceptions (Subjects 1020, 1022, 1026, and 1038) which are listed in Table 13 (Sponsor's report) and which were excluded from the analysis.

Two subjects (1002 and 1038) had blood drawn on an unscheduled visit date (visit 9). Since samples were not collected on visit 8 and since there had been no dose adjustments for several weeks prior to the sample collections, visit 9 data for these subjects were included in the analysis.

Study HGIE

Data

Figure 5 shows the olanzapine concentrations in individual patients for each treatment arm.

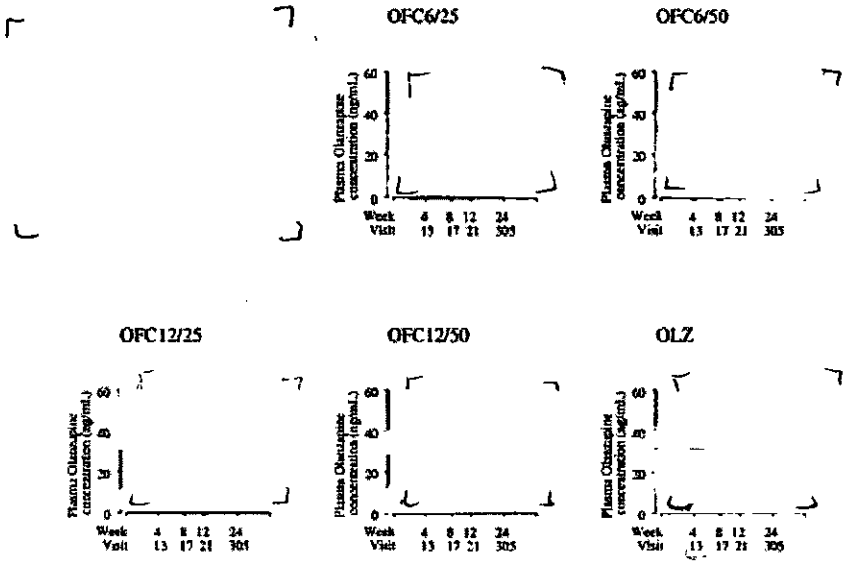

Figure 5 Steady-state plasma olanzapine concentrations at various visits for individual patients receiving olanzapine daily as monotherapy or in combination with fluoxetine in study HGIE.

Note: Visits 13,17, and 21 represent a double-blind phase of the study where olanzapine and fluoxetine doses in the combination arms were supposed to be fixed and to be equal to the assigned dose combination. Visit 305 represents an open label phase of the study, where doses varied.

Abbreviations of treatment arms: OFC 1/5=olanzapine 1 mg/day plus fluoxetine 5 mg/day; OFC 6/25= olanzapine 6 mg/day plus fluoxetine 25 mg/day; OFC 6/50= olanzapine 6 mg/day plus fluoxetine 50 mg/day; OFC 12/25=olanzapine 12 mg/day plus fluoxetine 25 mg/day; OFC 12/50=olanzapine 12 mg/day plus fluoxetine 50 mg/day; Olz=olanzapine 6 or 12 mg/day

Figure 6 shows steady-state plasma fluoxetine concentrations at various visits for individual patients receiving fluoxetine daily as monotherapy or in combination with olanzapine.

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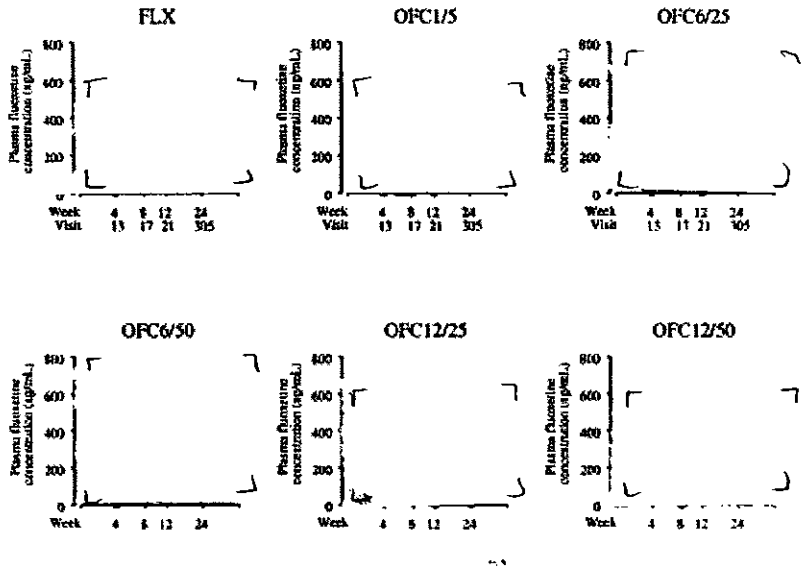

Figure 6 Steady-state plasma fluoxetine concentrations at various visits for individual patients receiving fluoxetine daily as monotherapy or in combination with olanzapine in study HGIE.

Note: Visits 13,17, and 21 represent a double-blind phase of the study where olanzapine and fluoxetine doses in the combination arms were supposed to be fixed and to be equal to the assigned dose combination. Visit 305 represents an open label phase of the study, where doses varied.

Population pharmacokinetic modeling for olanzapine

Base Model Development

Previous population pharmacokinetic analysis of an earlier Study HGAJ (Patel et al. 1995, documentation acquired from sponsor) established an olanzapine pharmacokinetic model when olanzapine was administered as monotherapy. The final model from this analysis was a one-compartment mixture model with first-order absorption (Ka) and first-order elimination, and with different clearance (CL) for each of two populations in the mixture. The structural model was parameterized in terms of total CL and volume of distribution (V). Clearance of the first population and volume of both populations depended on smoking and gender. The value of the rate constant for absorption of olanzapine was fixed at 0.543 hr^{-1}. A separate exponential inter-subject variability term was included for clearance of each of two populations and for volume of distribution, and a proportional residual error term was used. In this report, population 1 was defined as a "low" clearance group where the typical value of the clearance was 13.4 L/hr, and population 2 was defined as a "high" clearance group where the typical value of clearance was 26.4 L/hr. The population model was developed by NONMEM with the first-order condition method with interaction.

This model was adopted for the olanzapine analysis of Study HGIE as the starting base model. Although smoking has been established as a covariate in olanzapine pharmacokinetics, smoking habits were not collected during the course of this study.

Therefore smoking as a covariate could not be used in the model. In the Study HGIE, the first-order estimation (FO) method was used for the population analysis.

Covariate Model Development

The only covariate (in addition to gender present in the base model) explored for olanzapine was fluoxetine dose administered concomitantly. Dose of fluoxetine was not constant for many patients even in the fixed dose portion of the trial, therefore two different covariate variables were tested: the last dose of fluoxetine before the blood sample (DDIO), and fluoxetine dose to which patient was randomly assigned (TRT). In the Study HGIE, the first-order estimation (FO) method was used for the population analysis.

The model with DDIO as a factor variable for clearance of the Population 1 (Run 015, covariate levels: DDIO=0,5, 25, 50, 75) was better than the model with TRT (Run 020, covariate levels: OLZ, OFC1/5, OFC12/50, OFC6/25, OFC6/50, OFC12/25), though the former model had one less estimated parameter (MOF=3101.86 versus OF=3103.45). Among all the models, the model where clearance of Population 1 was different when DDIO was 25 or 50 mg (Run 018) and the model with different clearance when DDIO was > 25 (Run 026), best described the data. Though the former model had a slightly lower value of the objective function (difference = 4.95), having the same clearance for 0, 5 and 75 mg of fluoxetine, and different clearance for 25 and 50 mg was not logical. Also, there were no patients assigned to 75 mg of fluoxetine, so the number of patients who actually got that dose was relatively small. Therefore, the model with change in clearance when fluoxetine dose was > 25 mg was chosen.

Final Model Development

An additional model was tested after identification of the covariate. It aimed to check the variance-covariance structure of the random inter-individual effects (excluding a random effect). A value of either 0 or 1 assigned for levels of a categorical covariate.

Model Evaluation

Parameter Sensitivity Analysis and a leverage analysis technique were used to evaluate the robustness of the final population pharmacokinetic model.

<u>Population pharmacokinetic modeling for fluoxetine</u>

Base Model Development

A one-compartment model with first-order absorption (Ka) and first-order elimination was selected as the starting base structural model based on the previous analyses. The structural model was parameterized in terms of CL and V. An exponential inter-subject variability term (η) was included for CL, and a proportional residual error term was used. Modifications of the statistical model (addition of an exponential for V, a correlation

term, and an additive residual error term) were tried to optimize the base model. The first-order conditional estimation method with interaction (FOCEI) was used for the analysis.

Covariate Model Development

Covariate model development was implemented in two steps. First, all covariates except ones that represented interaction with olanzapine were introduced ("no olanzapine interaction" models). After the final "no olanzapine interaction" covariate model was established, interaction with olanzapine was explored to arrive at the final population PK model.

Covariate Identification ("no olanzapine interaction" models)
Table 1 summarizes the results of the NONMEM analyses of individual covariates.

Table 1 **Identification of Possible Significant Covariates**

Covariates Tested [a]		Parameter [b]	NONMEM Run # [c]	Change in MOF[d]
	Base model		110	
GEND	Gender	CL	235	6.885
GEND	Gender	V	236	9.399
AGE	Age at entry	V	237	7.699
AGE	Age at entry	CL	238	8.591
WT	Weight	CL	239	14.133
WT	Weight	V	240	20.068

[a] Covariates tested in NONMEM by adding individually to the base model. Unless noted otherwise, the exponential model for continuous covariates was used.

[b] Pharmacokinetic parameter (CL or V) accounting for the effect of the covariate

[c] NONMEM model causing a significant effect on the base model when added individually. Model number was unique for each covariate analysis.

[d] Minimum objective function value.

Full and Final "No Interaction" Model

All three covariates (gender, age, and weight) were identified as statistically significant when added individually to CL or V parameters of the base model. A full model contained AGE, WT (weight) and GEND (gender) on both CL and V. Additive residual variability was tested again in the full model, and was dropped from the subsequent model development. All covariates on CL and, AGE and GEND on V were eliminated in the reduction from the full model. The final model contained only WT on V.

Olanzapine interaction models

The final "no olanzapine interaction" model was further explored for interaction with olanzapine.

Since olanzapine dose was not constant for many patients even in the fixed dose portion of the trial, the last dose of olanzapine before the blood sample (DDIO) was

used as a covariate. DDIO was tested as a categorical covariate with different dose levels grouped together, as a continuous variable with linear dependence on CL, and as a combination of both. Among all the models, the model with separate CL for 1 mg dose of olanzapine and with a slight linear increase in CL with all other increasing doses of olanzapine (Run 283), best described the data. Elimination of the linear dependence (Run 288) did not significantly increase the objective function. Therefore, the latter model was chosen. Elimination of correlation between CL and V, and of the inter-individual variability term in V (Runs 290, 291) did not change the objective function. Thus, the final model (Run 291) did not include the inter-individual variability in V.

Final Model Development

Potentially significant covariates were then added to the base model in combination so that a full model containing all possible covariates (except olanzapine interaction) was established. The process was then reversed, with potential covariates being removed individually from the full model. A least significant covariate, removal of which did not cause a significant increase in the minimal value of the objection function (MOF) (10.828 points for 1 degree of freedom, $p<0.001$) was removed from the full model. The elimination procedure was repeated until no covariates could be eliminated. The resulting model was the final "no interaction" model.

Next, interaction with olanzapine was examined. Since olanzapine dose was not constant for many patients even in the fixed dose portion of the trial, the last dose of olanzapine before the blood sample (DDIO) was used as a covariate. DDIO was tested as a categorical covariate with different dose levels grouped together, as a continuous variable with linear dependence on CL, and as a combination of both. Groupings were based on the obtained parameter values (levels with similar parameter values were lumped together), and on the questions at hand (monotherapy versus combination therapy).

Several additional models were tested after establishing the "interaction model" to check the variance-covariance structure of the random inter-individual effects (deleting a correlation and a random effect).

Model Evaluation

Parameter Sensitivity Analysis and leverage analysis technique were used to evaluate the robustness of the final population pharmacokinetic model.

Study HGGY

The sponsor did not explore any dose-response relationship.

Sponsor's analysis

Design/Data

Study F1D-MC-HGFR:

Study HGFR was designed to evaluate the safety and efficacy of fluoxetine plus olanzapine versus fluoxetine or olanzapine alone in the treatment of patients with recurrent major depressive disorder (MDD) without psychotic features who are nonresponsive to conventional therapy. Olanzapine, fluoxetine, and its metabolite norfluoxetine concentration data from this study were used to assess the potential drug drug interaction between olanzapine and fluoxetine in this patient population.

This was a single-center study of 34 patients conducted in the United States. Following a six week period of fluoxetine dose escalation (20 to 60 mg/day, Study Period I), patients were randomized at visit 4 to one of three treatment groups: fluoxetine (20 to 60 mg/day) plus placebo, olanzapine (5 to 20 mg/day) plus placebo or fluoxetine (20 to 60 mg/day) plus olanzapine (5 to 20 mg/day). Table 1 shows the demographic summary of the twenty-eight (28) patients who were enrolled in the study.

Patients were treated in a double-blind manner during Study Period II with visits occurring approximately weekly from visits 4 through 12. During Study Period III, the open-label treatment period, all patients received olanzapine (5 to 20 mg/day) plus fluoxetine (20 to 60 mg/day). A single blood sample (approximately 10 mL) for determination of drug concentrations was collected at the scheduled visits 4, 8, and 12 which occurred over the course of approximately 8 weeks for all study groups. MADRS scores and other efficacy variables were rated at each visit.

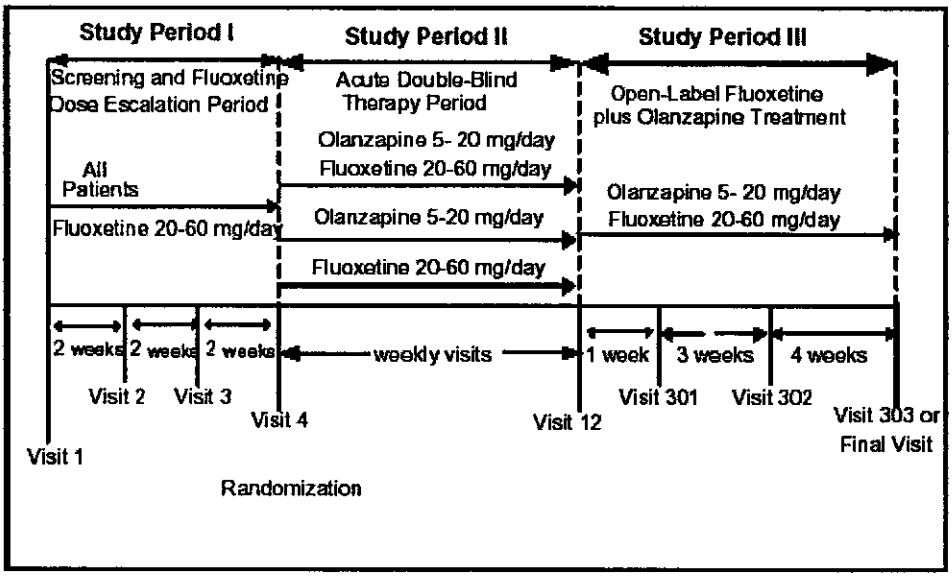

Figure 1. Overview of Design of Study HGFR

Table 2 Descriptive summary of patient characteristics by study period II treatment

Patient Subgroup	Fluoxetine	Olanzapine	Fluoxetine + Olanzapine
Total [a]	10	8	10
Males	3	2	2
Females	7	6	8
20-34 years	4	2	0
35-49 years	4	5	7
50-64 years	2	1	3
50-73 kg [b]	5	5	5
74-97 kg [b]	3	2	4
98-121 kg [b]	2	1	1
Caucasian	9	8	10
African American	1	0	0
Fluoxetine Conc. (N[c])	27	7	28
Norfluoxetine Conc.	27	7	28
Olanzapine Conc. (N[c])	0	14	19

[a] Total number of patients enrolled in each treatment group.
[b] Weight (kg) at date of randomization (visit 4).
[c] N represent the number of plasma fluoxetine, norfluoxetine and olanzapine concentrations reported for each treatment group.

Study F1D-MC-HGIE

The purpose of this analysis was to characterize the pharmacokinetic interaction of olanzapine and fluoxetine when two drugs were administered in combination and to compare steady state concentrations of each drug given as monotherapy versus in combination with the other drug.

This was a randomized, double-blind, multicenter pharmacokinetic and pharmacodynamic study in patients with treatment-resistant depression. During the double-blind phase of the study (Study Period IV), subjects received one of eight treatments: (1) olanzapine 1 mg/day plus fluoxetine 5 mg/day, (2) olanzapine 6 mg/day plus fluoxetine 25 mg/day, (3) olanzapine 12 mg/day plus fluoxetine 25 mg/day, (4) olanzapine 6 mg/day plus fluoxetine 50 mg/day, (5) olanzapine 12 mg/day plus fluoxetine 50 mg/day, (6) olanzapine 6 or 12 mg/day, (7) fluoxetine 25 or 50 mg/day, (8) venlafaxine 75 to 375 mg/day. During the 52-week open-label combination treatment period of the study (Study Period V), subjects received the combination therapy at any of the possible dose combinations (OFC) of olanzapine 6, 12, or 18 mg/day plus fluoxetine 25, 50, or 75 mg/day.

A total of 807 patients were enrolled by 33 US and 65 non-US study sites. Of these subjects, 57 subjects were randomized to the OFC 12/50 combination group, 59 subjects were randomized to each of the OFC 1/5 combination and venlafaxine groups, 60 subjects were randomized to each of the OFC 12/25 combination and fluoxetine groups, 62 subjects were randomized to olanzapine group, 63 subjects were randomized to each of the OFC 6/25 and OFC 6/50 combination groups, and 324 subjects were randomized to placebo.

The study was prospectively designed to include a sparse sampling strategy for evaluation using population pharmacokinetic analysis techniques. Blood samples were obtained from subjects at scheduled time points throughout the study for determination of the olanzapine and fluoxetine (and norfluoxetine) concentrations in plasma. One blood sample per subject was taken at Visits 13, 17, 21, 305 and at the subject's final study visit, if subject discontinued after Visit 7. The actual date and time of the blood draws were recorded. In addition, the actual dates and times of the last two doses prior to the blood draw were recorded. Furthermore, subject demographics such as age and body weight were recorded.

Table 3 Descriptive summary of patient characteristics in Study HGIE

	Age (yr)	Body Weight (kg)	Gender Males/Females
Olanzapine			
Range	19.2 - 84.6	37.5 - 159	
Mean (%CV)	46.7 (22.9%)	78.4 (26.3%)	
Median (10th/90th percentile)	47.3 (32.9 / 59.6)	75.5 (55.0 / 109)	
Count			196 / 83
Percent (%)			70.3 / 29.7
Fluoxetine [a]			
Range	18.8 - 84.6	41.0 - 159	
Mean (%CV)	46.1 (23.4%)	78.7 (27.3%)	
Median (10th/90th percentile)	47.2 (31.4 / 58.9)	75.3 (55.2 / 108)	
Count			201 / 86
Percent (%)			70.0 / 30.0

Abbreviations: CV = coefficient of variation.

[a] For 8 fluoxetine observations from 7 subjects, weight was imputed using LOCF or backward propagation.

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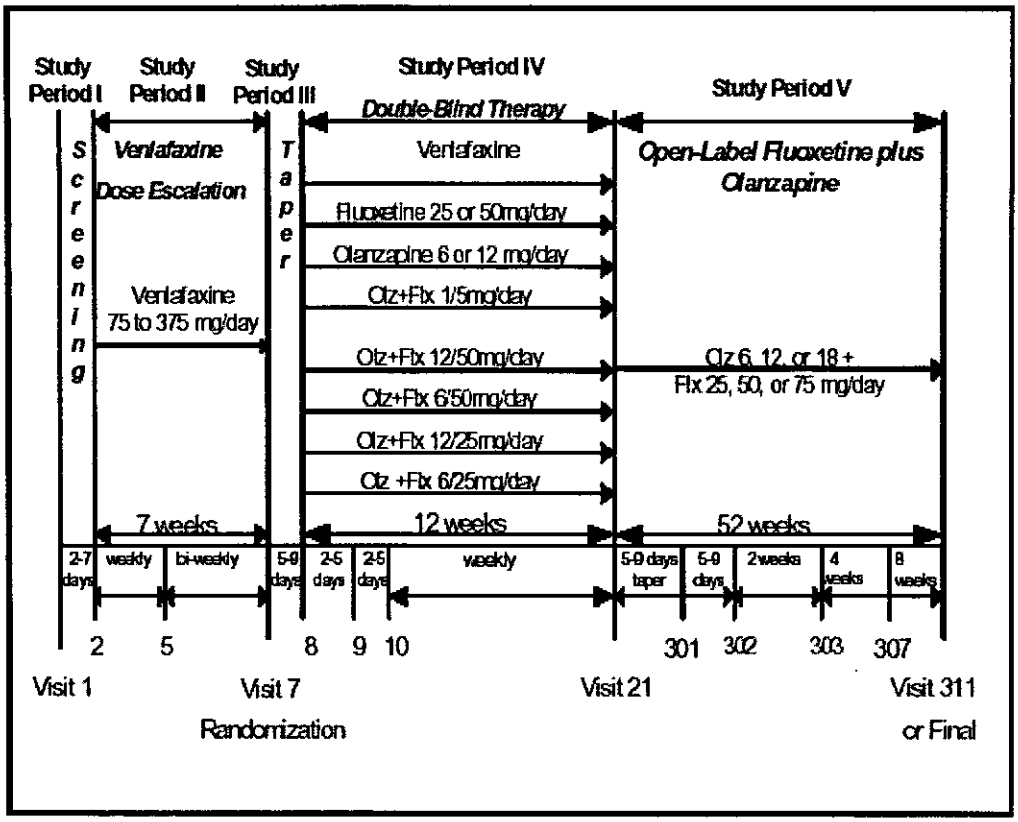


Figure 2. Illustration of Study Design for Protocol F1D-MC-HGIE

Study F1D-MC-HGGY

The primary objective of Study 1 and Study 2 was to assess: acute olanzapine therapy compared with placebo in patients with Bipolar I Disorder – Depressed, according to the DSM-IV, in improving overall symptomatology as measured by the mean change in the MADRS total score from baseline to the end of eight weeks of therapy.

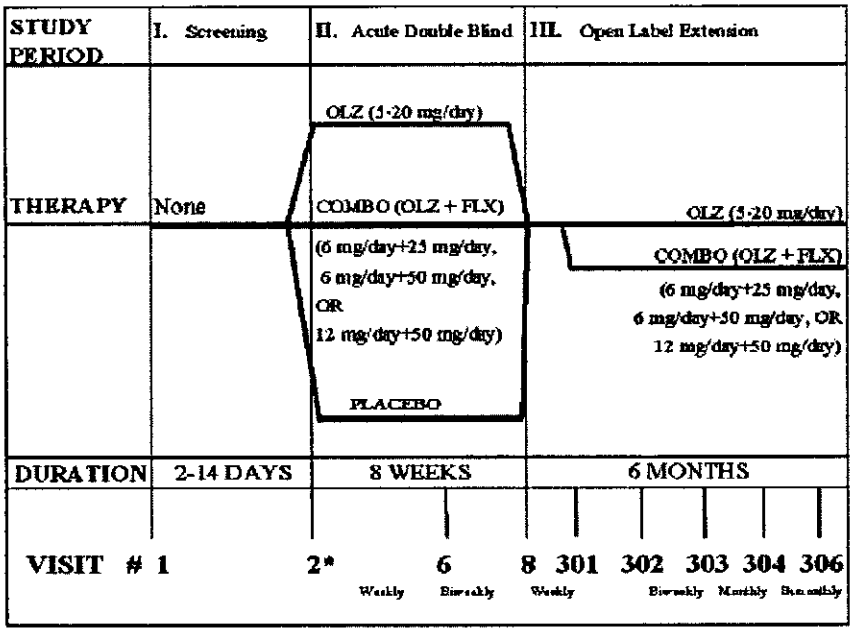
This study was designed as two randomized, double-blind, parallel clinical studies of approximately 792 patients (396 inpatients or outpatients per study) meeting diagnostic criteria for Bipolar I Disorder – Depressed, according to the DSM-IV and confirmed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version (SCID-P).

Prior to any patient enrollment, investigative sites were divided into two separate studies at random. Acute phase efficacy data were analyzed separately for Studies 1 and 2. Acute phase efficacy subgroup and acute phase safety data were combined prior to analyses. No blood samples were taken.

Study Period II (Visits 2 through 8) was an 8-week, double-blind (acute phase) therapy period of the study. Patients were randomized at a ratio of 4:4:1 to receive either

olanzapine (5 to 20 mg/day), placebo, or olanzapine plus fluoxetine in combination (6 plus 25 mg/day [OFC 6/25], 6 plus 50 mg/day [OFC 6/50], or 12 plus 50 mg/day [OFC 12/50]). Therapy was initiated with the lowest dosage (olanzapine 5 mg or OFC 6/25 or placebo). Patients who were unable to tolerate the lowest dosage of study medication were to be discontinued. Patients were assessed weekly from Visit 2 to Visit 6 and biweekly from Visit 6 to
Visit 8.

Study Period III (Visits 8 through 306) was a 6-month, open-label extension phase. Patients who completed the acute phase were eligible to continue into the open-label phase. Those patients who demonstrated no clinical improvement (same or higher CGIBP-Severity Overall score compared to Visit 2 score) at Visit 6 or beyond, were also eligible to enter the open-label phase, as were any patients demonstrating manic symptoms at Visit 6 or beyond. Patients received olanzapine 5 or 10 mg/day at Visit 8. Thereafter, the dose could have ranged from 5 to 20 mg/day. For those patients who exhibited a major depressive episode, based on clinical judgment, at visits subsequent to Visit 8 were offered OFC 6/25 at the next visit. Thereafter, the dose could have been OFC 6/25, OFC 6/50, or OFC 12/50. Based on the clinical judgment of the investigator, patients could have switched between olanzapine and OFC during the 6-month, open-label phase, as long as the change occurred at scheduled visits. Patients had two weekly visits, one biweekly visit, one monthly visit, and two bimonthly visits for a total period of 6 months.



Abbreviations: Olz=olanzapine; FLX=fluoxetine.

*Randomization occurs at Visit 2.

Note that patients eligible (Section 9.1.2) may move into open-label therapy from Visit 6 and beyond.

Figure 3. Illustration of Study Design for Study 1 and Study 2

Table 4 Baseline Physical Characteristics All Randomized Patients, Acute Phase, Study 1

Variable	Placebo (N=184)	Olz (N=179)	Flx+Olz (N=43)	Total (N=406)	p-Value
Sex: No. (%)					
No. Patients	184	179	43	406	.443*
Male	71 (38.6)	68 (38.0)	12 (27.9)	151 (37.2)	
Female	113 (61.4)	111 (62.0)	31 (72.1)	255 (62.8)	
Origin: No. (%)					
No. Patients	184	179	43	406	.988*
Caucasian	149 (81.0)	149 (83.2)	35 (81.4)	333 (82.0)	
African Descent	11 (6.0)	9 (5.0)	3 (7.0)	23 (5.7)	
Western Asian	2 (1.1)	3 (1.7)	0	5 (1.2)	
Hispanic	21 (11.4)	17 (9.5)	5 (11.6)	43 (10.6)	
Other Origin	1 (0.5)	1 (0.6)	0	2 (0.5)	
Age:yrs.					
No. Patients	184	179	43	406	.504**
Mean	42.36	43.55	42.25	42.97	
Median	43.51	44.16	42.61	43.76	
Standard Dev.	12.10	11.34	11.92	11.74	
Minimum	18.67	18.02	20.97	18.02	
Maximum	72.67	71.45	68.11	72.67	

Note: The following countries have been pooled by GEOCODE:BG ES LB MX AU TR RO HU
Note: GEOCODE is substituted for inv. in this analysis
RMP.F1DP.JCLLIB(GYAP022B)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model-investigator, treatment, and interaction.
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Table 5 Baseline Physical Characteristics All Randomized Patients, Acute Phase, Study 2

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Variable	Placebo (N=193)	Olz (N=191)	Flx+Olz (N=43)	Total (N=427)	p-Value
Sex: No. (%)					
No. Patients	193	191	43	427	.989*
Male	70 (36.3)	71 (37.2)	16 (37.2)	157 (36.8)	
Female	123 (63.7)	120 (62.8)	27 (62.8)	270 (63.2)	
Origin: No. (%)					
No. Patients	193	191	43	427	.090*
Caucasian	161 (83.4)	162 (84.8)	32 (74.4)	355 (83.1)	
African Descent	10 (5.2)	8 (4.2)	5 (11.6)	23 (5.4)	
East/SE Asian	0	1 (0.5)	0	1 (0.2)	
Western Asian	0	0	1 (2.3)	1 (0.2)	
Hispanic	18 (9.3)	20 (10.5)	5 (11.6)	43 (10.1)	
Other Origin	4 (2.1)	0	0	4 (0.9)	
Age:yrs.					
No. Patients	193	191	43	427	1.00**
Mean	41.04	40.87	38.41	40.70	
Median	40.23	39.98	34.69	39.21	
Standard Dev.	12.67	13.47	13.88	13.15	
Minimum	19.05	18.25	18.48	18.25	
Maximum	76.34	78.50	65.81	78.50	

Note: The following countries have been pooled by GEOCODE:ES GR HR MX PT RU
Note: GEOCODE is substituted for inv. in this analysis
RMP.F1DP.JCLLIB(GYAP022A)
RMP.F1DP.SASMACRO(SBASEA)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator, treatment, and interaction.
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Table 6. Allowed and Suggested Visit Intervals Study 1 and Study 2

Period – Phase	Visits	Allowed Intervals	Suggested Intervals
Period I – Screening	Visits 1 and 2	2 to 14 days	2 days
Period II – Acute			
	Visits 2 to 6	5 to 9 days	7 days
	Visits 6 to 8	12 to 16 days	14 days
Period III - Open-label	Visits 8 to 301	5 to 9 days	7 days
	Visits 301 to 302	5 to 9 days	7 days
	Visits 302 to 303	12 to 16 days	14 days
	Visits 303 to 304	24 to 32 days	28 days
	Visits 304 to 306	48 to 64 days	56 days

Study results

Study F1D-MC-HGFR

The sponsor compared the dose and bodyweight normalized steady state concentrations between treatments and between visits for each of the analytes: fluoxetine, norfluoxetine, and olanzapine. In their report, the sponsor concluded that

fluoxetine, norfluoxetine and olanzapine blood concentrations were not affected by the chronic administration of fluoxetine and olanzapine together in this patient population. Norfluoxetine plasma concentrations did not appear to reach steady-state levels after 8 weeks of treatment with a fixed fluoxetine dose. Finally, despite a common elimination pathway, no interaction was detected in treatment resistant MDD patients following multiple-dose administration of fluoxetine and olanzapine.

Study F1D-MC-HGIE

The final population pharmacokinetic model (Run 028) of olanzapine was a one-compartment mixture model with first-order absorption (Ka) and first-order elimination, and with different clearance (CL) for each of two populations in the mixture. Clearance of the first population and volume of distribution of both populations depended on gender. In addition, clearance of the first population depended on concomitant dose of fluoxetine: clearance was 14% lower for fluoxetine doses of 25 mg or higher. The value of the rate constant for
olanzapine was fixed to 0.543 hr-1. A separate exponential inter-subject variability term described variability in clearance of each of two populations, and a proportional error term described the residual variability.

The final population pharmacokinetic model of fluoxetine (Run 291) was a one-compartment model with first-order absorption (Ka) and first-order elimination. Volume depended on weight. Clearance depended on concomitant olanzapine: CL was the same for fluoxetine monotherapy and for all therapeutic doses of concomitant olanzapine (6 mg/day to 18 mg/day), and it was 3 times higher for patients in 1 mg olanzapine/5 mg fluoxetine combination treatment arm. An exponential inter-subject variability term described variability in CL, and a proportional error term described the residual variability.

In addition, the model with different clearance for each fluoxetine dose was run (Run 301). As in the final population model, clearance of 5 mg dose (this was a combination treatment of 1 mg of olanzapine and 5 mg fluoxetine) was more than 3 times higher than for other doses. For all other fluoxetine doses, clearance ranged from 8.11 L/h to 11.3 L/h. Clearance was the same for 50 mg and 75 mg of fluoxetine (6.8 L/h to 9.5 L/h), and was slightly higher (10.2 L/h to 12.4 L/h) for the 25 mg dose.

Study F1D-MC-HGGY

The focus of this review is to explore whether the dose-response relationship in efficacy endpoint can be established with this study, and not the evaluation of efficacy and safety of the combination of olanzapine and fluoxetine.

Sponsor's results and conclusions

Study HGFR

The sponsor concluded that fluoxetine, norfluoxetine and olanzapine blood concentrations were not affected by the chronic use of fluoxetine and olanzapine administered together in this patient population. Norfluoxetine plasma concentrations

did not appear to reach steady-state levels after 8 weeks of treatment with a fixed fluoxetine dose. Variability in patient metabolite elimination rates may explain this observation. Finally, despite a common elimination pathway and despite previous results in a controlled study, no interaction was detected in treatment resistant MDD patients following multiple-dose administration of fluoxetine and olanzapine.

Study HGIE

Tables 7 and 8 list the parameter estimates of the final population models for olanzapine and fluoxetine. Figures 6 and 7 show the association between the population predicted versus observed values for olanzapine and fluoxetine.
The sponsor had developed a population pharmacokinetic model for olanzapine in an earlier study HGAJ. The structural model in this population pharmacokinetic model included two distributions for clearance (amixture model). Population 1 was a "low" clearance group where the typical value of the clearance was 13.4 L/hr. Population 2 was a "high" clearance group where the typical value of clearance was 26.4 L/hr.

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Table 7 Olanzapine Pharmacokinetic Parameters in Final Population Model (Study HGIE)

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Parameter Description	Population Estimate[a] (%SEE)	Inter-Subject Variability (%SEE)
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.543 (Fixed)	---
Clearance		
Parameter for CL for males, population 1 (L/hr)	24.2 (8.18)	33.3% (13.5)
Fraction of CL for females, population 1	0.802 (6.06)	---
Parameter for CL, population 2 (L/hr)	11.2 (8.38)	24.6% (28.5)
Effect of concomitant fluoxetine on CL [a]	0.136 (32.4)	
Fraction of population 1		
Parameter for fraction	0.765 (13.5)	---
Volume of Distribution		
Parameter for V in males (L)	1360 (Fixed)	---
Fraction of V for females	0.707 (Fixed)	---
Residual Error (proportional)	23.7% (10.5)	

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution; GEND = gender index (1 for males, 0 for females); IFLU = index for concomitant fluoxetine (1, when > 25 mg ; 0 otherwise)

a Equation used to evaluate the covariate influence on clearance of Population 1:
CL = 24.2*(GEND + 0.802*(1-GEND))*(1-IFLU*0.136)

Table 8 Fluoxetine Pharmacokinetic Parameters in Final Population Model (Study HGIE)

Parameter Description	Population Estimate [a] (%SEE)	Inter-Subject Variability (%SEE)
Rate of Absorption (hr^{-1})		
Parameter for Ka	1.10 (27.0)	---
Clearance (L/hr)		
Parameter for CL	9.35 (4.11)	58.3% (15.0)
Parameter for CL in OFC1/5 combination dose	30.6 (7.61)	---
Volume of Distribution		
Parameter for V (L)	2790 (5.95)	---
Parameter for weight effect in V [a]	0.340 (13.9)	---
Residual Error (proportional)	27.6% (11.8)	

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL = clearance; V = volume of distribution

a Equation used to evaluate the weight influence on V: V = 2790*EXP(0.34*(WT-75)/22)

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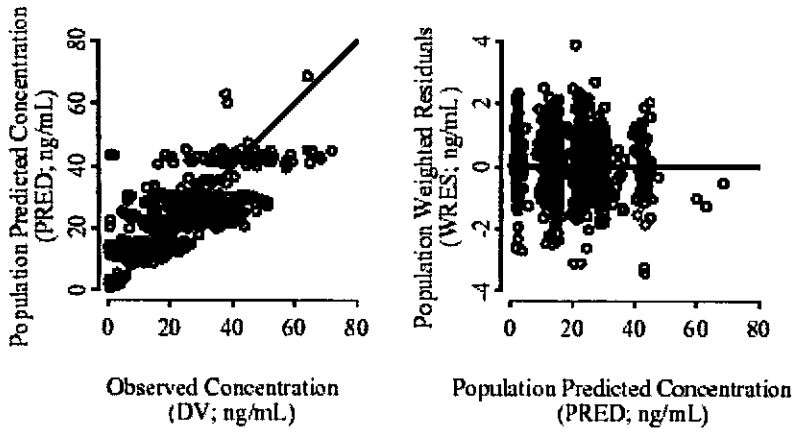


Figure 6 Population predicted olanzapine concentrations and weighted residuals for final olanzapine model for a dose ranging study: olanzapine plus fluoxetine combination therapy in treatment-resistant depression (Study HGIE).

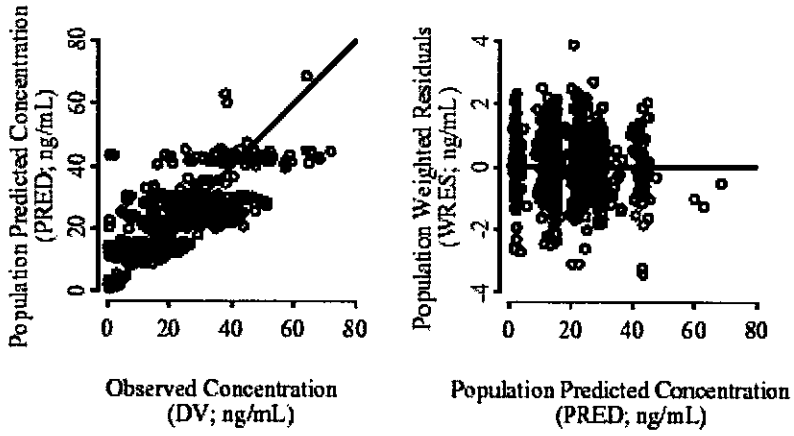


Figure 7 Population predicted fluoxetine concentrations and weighted residuals for final fluoxetine model for a dose ranging study: olanzapine plus fluoxetine combination therapy in treatment-resistant depression (Study HGIE).

The sponsor's main conclusions are listed as following:

- Steady-state concentrations and pharmacokinetic parameters of olanzapine were similar following administration of olanzapine given as monotherapy versus in combination with fluoxetine.

- Concomitant administration of fluoxetine was not found to be a clinically significant factor in the pharmacokinetics of olanzapine.

- Olanzapine clearance was 24.2 L/hr and 19.4 L/hr for males and females, respectively, for the majority of the study population (sponsor's population 1) (77%), and 11.2 L/h for the rest of the patients.

- Steady-state concentrations and pharmacokinetic parameters of fluoxetine were similar following administration of fluoxetine given as monotherapy versus in combination with olanzapine.

- Concomitant administration of olanzapine did not produce clinically significant changes in the pharmacokinetics of fluoxetine in the therapeutic range of doses.

- Clearance and volume of distribution of fluoxetine were 9.35 L/hr and 2790 L, respectively. Fluoxetine clearance was slightly higher for the 25 mg/day dose of fluoxetine (10.2 L/h to 12.4 L/h) than for the 50 mg/day and the 75 mg/day dose (6.8 L/h to 9.5 L/h) indicating possible nonlinearity of fluoxetine pharmacokinetics.

- Steady-state concentrations of norfluoxetine following administration of fluoxetine given as monotherapy were similar to those following combination therapy.

- Ratios of norfluoxetine to fluoxetine concentrations were similar in all treatment groups in the therapeutic range of doses (25 mg/day to 75 mg/day of fluoxetine).

Reviewer comments

Study HGFR

1. Study HGFR's sample size as shown in Table 9 is small. Overall the sample size of each group was smaller than 10. Especially, when mean dose-weight-normalized olanzapine concentrations at visit 12 between the olanzapine and the olanzapine plus fluoxetine groups were compared, the sample size of the olanzapine group was 4 and the sample size of the olanzapine plus fluoxetine was 9. There is little power to demonstrate whether there is, or is not, a difference in mean dose-weight-normalized olanzapine or fluoxetine concentrations between the monotherapy and the combination therapy.

Table 9 Sample size at each visit and treatment arm

	Fluoxetine	Olanzapine	Fluoxetine+Olanzapine
Visit 4	10	7	9
Visit 8	10	8	10
Visit 12	6	4	9

2. The sponsor conducted statistical analyses via a linear mixed-effects model based on a crossed-nested design. In their statistical model, treatment and visits formed fixed factors and subjects within treatment a random factor. Here, the

main interest was the treatment effect shown in the last visit. A linear mixed-effects model may be not necessary.

3. Table 10 lists the 95% confidence intervals of the difference in mean plasma concentration between the monotherapy and the combination treatment. These intervals are wide. The lack of significant olanzapine or fluoxetine concentration differences between the monotherapy and the combination of olanzapine and fluoxetine does not mean that no olanzapine-fluoxetine interaction exists.

Table 10 The 95% confidence interval of the difference in plasma concentrations between the monotherapy and combination therapy at visit 12

	95% confidence interval	Monotherapy concentration range ug/mL
Olanzapine concentration: monotherapy vs. combination treatment of olanzapine and fluoxetine	(-55.36, +38.8)	4.67-115.22
Fluoxetine concentration: monotherapy vs. combination treatment of olanzapine and fluoxetine	(-283.25, +119.03)	61-486.59

4. Since the fluoxetine displays nonlinear kinetics over the clinical dosing range, the sponsor may need to address the extent of nonlinearity and to show robustness of the assumption of linear pharmacokinetics.

Study HGIE

1. The fundamental flaw in the evaluation of the influence of fluoxetine on olanzapine PK was the assumption that fluoxetine affects the systemic clearance of olanzapine. As clearly evident from the intense sampling study F1D-MS-HGCI, the area under the curve (AUC) of olanzapine was about 18% higher with fluoxetine, but not the terminal half-life (t1/2). If CL has been affected then both AUC and t1/2 would have been different by about the same magnitude. Since olanzapine undergoes substantial first-pass metabolism, it can be rationalized that fluoxetine, by blocking CYP2D6, permits more drug to escape the pre-systemic metabolism. Hence the sponsor should have tested if the relative bioavailability was different in the two study periods (with and without fluoxetine). By forcing the comparison via CL, the estimation of any difference is hindered by the natural tendency of the curve fitting to satisfy the terminal portion of the curves on both study periods equally well. The reviewer performed re-analysis to find that the relative bioavailability of olanzapine is significantly affected (about 10% increase) by 25 mg or higher doses of fluoxetine ($p \leq 0.05$). The reviewer estimated the parameters using the first-order conditional estimation method. It

is not clear why the model which treats all doses of fluoxetine (including 5 mg) together did not result in a statistically significant finding.

2. HGIE was a pharmacokinetic interaction study with sparse sampling. Note that Study HGCI (*Pharmacokinetic Interaction Study of Fluoxetine on Olanzapine after Single and Repeated Administration of Fluoxetine in Healthy Volunteer, N21520*) was a pharmacokinetic interaction study of fluoxetine with olanzapine after single and repeated administration of fluoxetine in healthy volunteers, which showed a reduction in clearance (16%) on coadministration of fluoxetine. Study HGCI showed statistically significant lowering of clearance. However, the Guidance for industry: In Vivo drug metabolism/drug interaction studies—study design, data analysis, and recommendations for dosing and labeling, November 1999, states that "it is unlikely that population analysis can be used to prove the absence of an interaction that is strong suggested by information arising from in vitro or in vivo studies specifically designed to assess a drug-drug interaction since the power of a sparse sampling strategy to detect drug-drug interactions is not well established".

3. The base model for the olanzapine population pharmacokinetics was initially developed by the first-order estimation (FO) method before Study HGIE was conducted. In general, FO method is a crude method, the sponsor should have used the first-order conditional estimation method to develop the base model.

4. Since no plasma data were collected in study HGIE from the non-steady state phase for olanzapine and fluoxetine and both olanzapine and since fluoxetine have a long half-life, it is not possible to have good estimate for volume of distribution. In addition, it is not possible to estimate absorption rate.

5. The sponsor's previous analysis of the combined factors of smoking and gender suggested that olanzapine clearance for a nonsmoking female is about 2.5 fold lower than that for a smoking male. Based on these apparent facts, the reason why the sponsor did not collect smoking status in Study HGIE is not obvious. Data on the drug-drug interaction for the nonsmoking female population should be presented.

6. For the olanzapine and fluoxetine models, Figures 6 and 7 indicate that there may be a large portion of variability not explained by the compartmental model and measured covariates. The inclusion of other covariates may help, such as smoking in the olanzapine model.

7. The sponsor found out that CL in the fluoxetine model for all other increasing doses of olanzapine is lower than that in that the fluoxetine model for 1 mg dose of olanzapine.

8. The sponsor found that there was possible nonlinearity of fluoxetine pharmacokinetics in study HGIE. The clearance confidence intervals of fluoxetine 50 and 75 mg/day are 6.8-9.5 L/h. The clearance confidence intervals of

fluoxetine at 25 mg/day was 10.2-12.4 L/h. Hence when the sponsor compared the mean dose-weight normalized concentration in Study HGFR, they may need to consider this factor.

9. Concomitant administration of fluoxetine of 25 mg or more increased the 13.6% of olanzapine exposure compared to the olanzapine monotherapy, from other studies. However the sponsor concluded that the influence of fluoxetine is not clinically significant. The negative finding from the HGIE should be overruled by: 1) mechanistic plausibility of the interaction and 2) previous evidence from specific studies suggesting the presence of an interaction between olanzapine and fluoxetine.

10. The current labeling states, on lines 48-50, "In another study, a similar decrease in olanzapine clearance of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more." Appropriate language indicating: 1) area under the curve increases by 14% and 2) the terminal half-life is not affected, hence the time to reach steady-state should not be altered by fluoxetine.

Reviewer's analysis

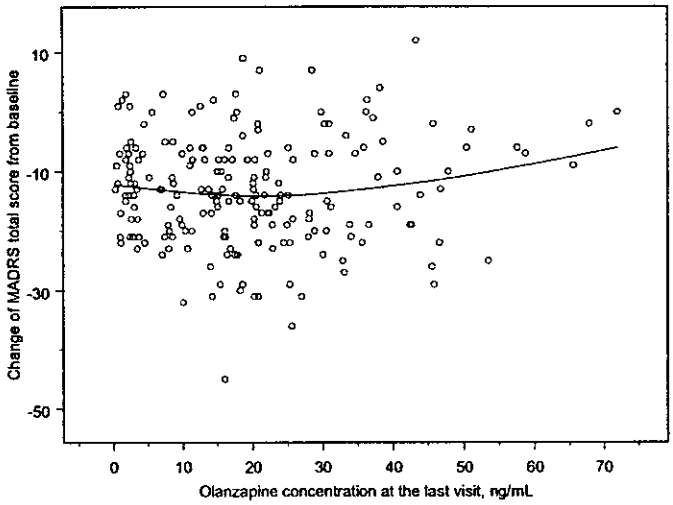
Concentration-response in study HGIE

The MADRS score changes from the baseline versus the olanzapine concentration at last visit is shown in the Figure 8. From the loess curve, the change of MADRS score from the baseline does not change much as the concentration increases from 0 to 70 ng/mL. There is a little up-trend in the tail and also there are fewer points at high concentration than at the lower concentration. Similar trends between the change of MADRS score from the baseline and fluoxetine concentration or the norfluoxetine concentration at last visit are observed as shown in Figures 9 and 10.

The MADRS change from baseline was modeled with general linear modeling. In this statistical model, olanzapine concentration or fluoxetine concentration or norfluoxetine concentration formed fixed factors. The estimated parameters are summarized in Table 11. We see no evidence of linear trend with concentration.

Table 11 Parameter estimates for Concentration-response at last visit in study HGIE

	Olanzapine concentration model			Fluoxetine concentration model			Norfluoxetine concentration model		
	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.5006	2.7019	0.5793	3.5407	2.7327	0.1966	3.3245	2.7845	0.23339
Concentration	0.0823	0.0421	0.0519	0.0014	0.0041	0.7318	0.0016	0.0057	0.7803
MADRS baseline score	-0.5605	0.0914	<0.0001	-0.6153	0.0893	<0.0001	-0.6094	0.0899	<0.0001



. Figure 8 Change of MADRS total score from baseline against the olanzapine concentration at last visit

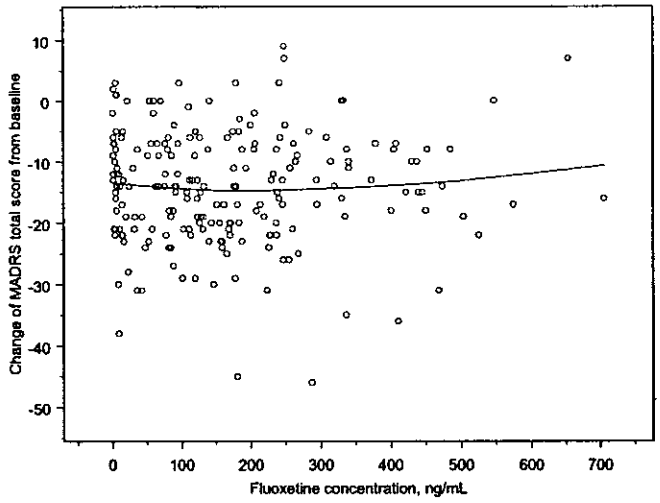


Figure 9 Change of MADRS total score from baseline against the fluoxetine concentration at last visit

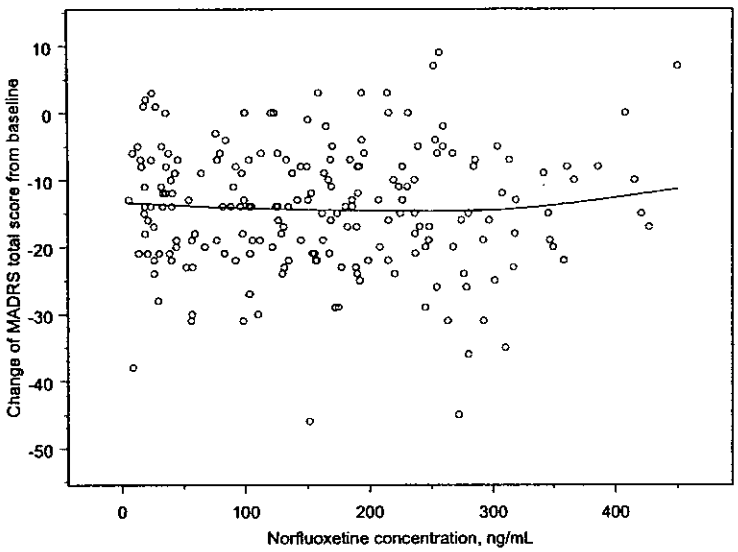


Figure 10 Change of MADRS total score from baseline against the Norfluoxetine concentrations at last visit

The MADRS score changes from the baseline versus the olanzapine concentrations for all visits are shown in the figure 11. Overall, the change of MADRS score from baseline does not change much as the concentration increases from 0 to 70 ng/mL. There is a little up-trend in the tail and also there are fewer points at high concentration than at the lower concentration. Similar trends between the change of MADRS score from the baseline and fluoxetine concentrations or the norfluoxetine concentrations at all visits are observed as shown in Figures 12 and 13.

The MADRS change from baseline was modeled with a linear mixed-effects strategy because we want to estimate the inter-subject variability. In this statistical model, olanzapine concentration or fluoxetine concentration or norfluoxetine concentration formed fixed factors and subject formed a random factor. The estimated parameters are summarized in Table 12. Again, there is no evidence of trend with concentrations.

Table 12 Parameter estimates for concentration-response for all visits in Study HGIE

		Olanzapine concentration model			Fluoxetine concentration model			Norfluoxetine concentration model		
		Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value
Covariance parameter	Subject	41.65			45.18			45.19		
	Residual	25.26			28.39			28.46		
Fixed effect	Intercept	2.2576	1.9983	.2596	1.1389	2.0503	.5791	1.4244	2.0767	.4933
	Concentration	0.0051	0.0271	.8521	0.0013	0.0023	.5786	-0.0015	0.0034	.6707
	MADRS baseline	-0.4873	0.0647	<.0001	-0.4590	0.0661	<.0001	-0.4544	0.0663	<.0001

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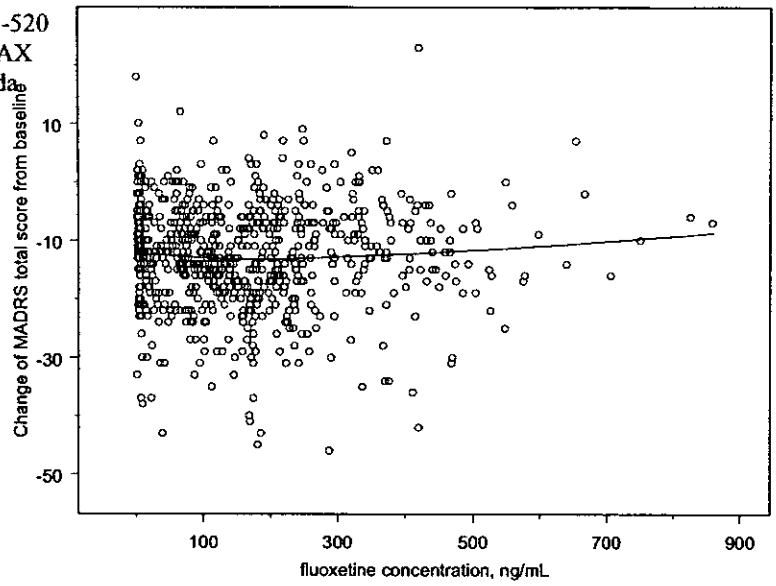
NDA 21-520
SYMBIAX
S. Yasuda



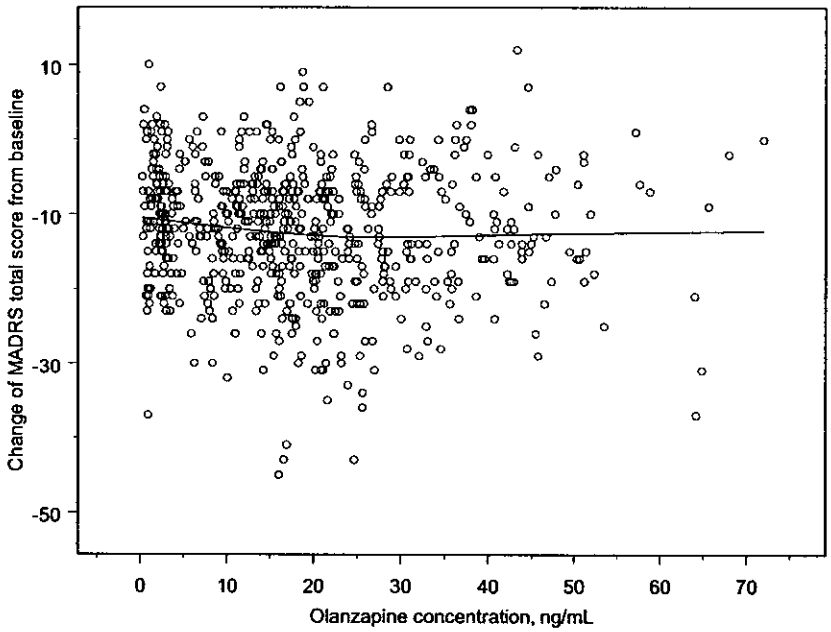


Figure 11 Change of MADRS total score from baseline against the olanzapine concentration for all visits

Figure 12 Change of MADRS total score from baseline against Fluoxetine concentration for all visits

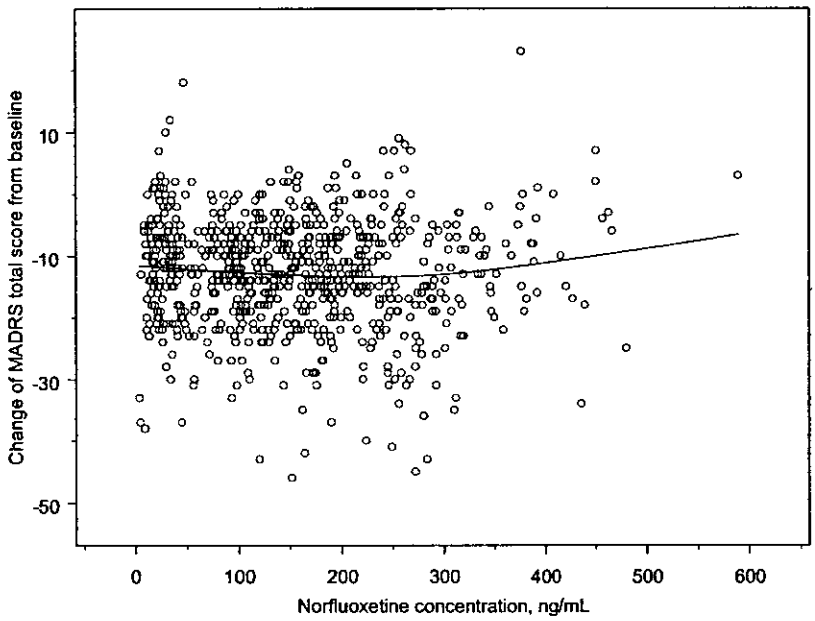


Figure 13 Change of MADRS total score from baseline against Norfluoxetine concentration for all visits

Dose-response in study HGIE

The MADRS score changes from the baseline versus the fluoxetine dose for all visits are shown in the figure 14. Overall, there is a small decrease in the change of MADRS score from the baseline as the fluoxetine dose increases. However, there is no placebo group in the study. Hence it is difficult to evaluate the dose-response relationship. As shown in Figure 15, there is a small decrease in the change of MADRS score from the baseline as the olanzapine dose increases.

Table 13 Parameter estimates for dose-response in Study HGIE

		Olanzapine dose model			Fluoxetine dose model		
		Estimate	SE	P-value	Estimate	SE	P-value
Covariance parameter	Subject	39.65			41.74		
	Residual	25.42			25.18		
Fixed effect	Intercept	4.084	2.03	0.0453	1.741	2.055	0.3975
	Dose	-0.057	0.021	0.0062	0.096	0.098	0.3311
	MADRS baseline	-0.4541	0.063	<0.0001	-0.491	0.065	<0.0001

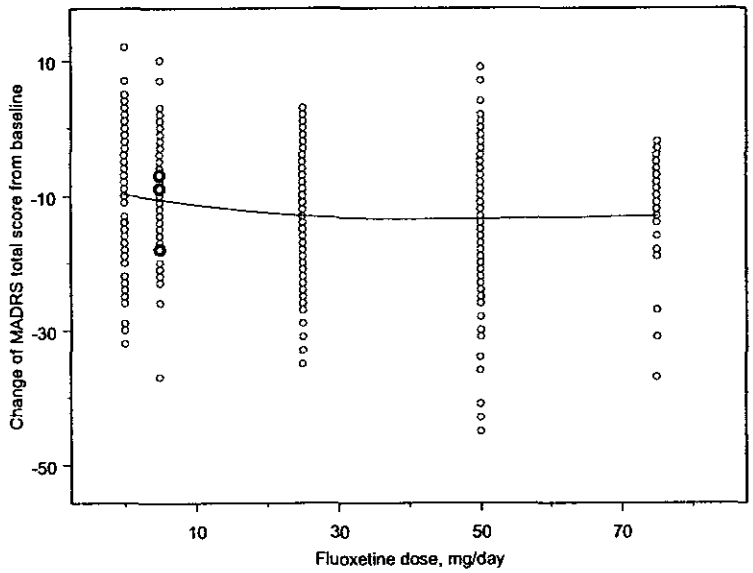


Figure 14 Change of MADRS total score from baseline against the fluoxetine dose for all visits

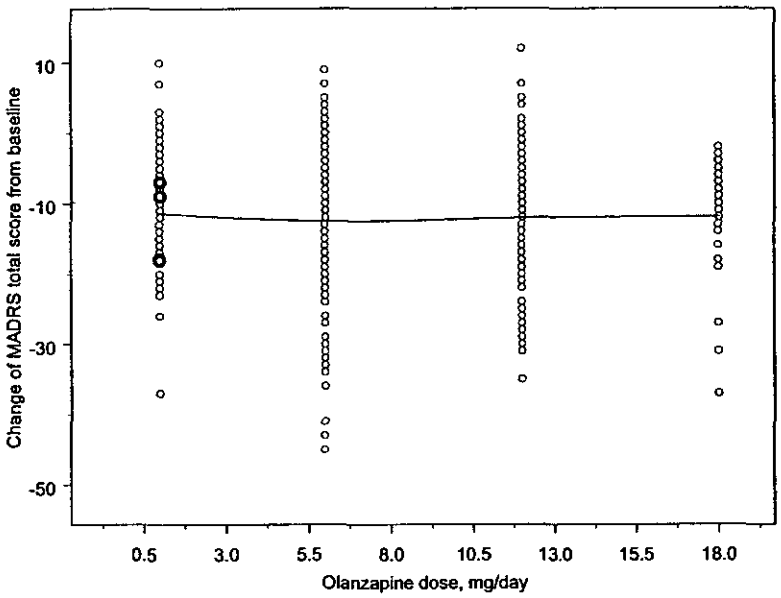
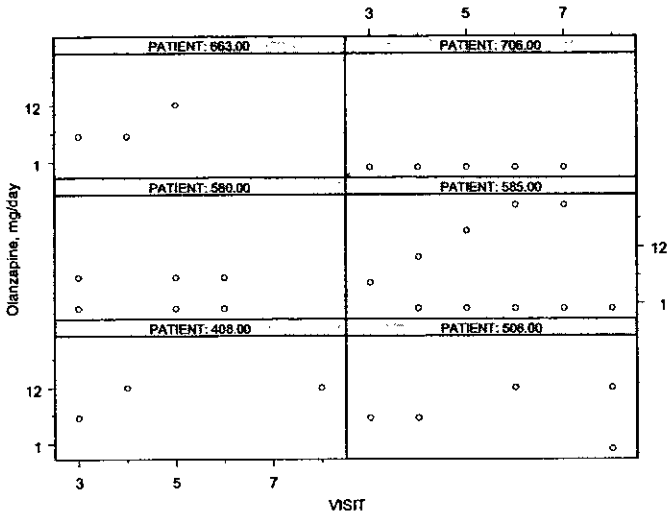


Figure 15 Change of MADRS total score from baseline against the olanzapine dose for all visits

Dose-response in study HGGY

1. Fluoxetine and olanzapine dose change with visit for a random subset of patients

In study HGGY, there was a dose adjustment at each visit. Even in the same visit, the dose was not fixed and maintained for the whole visit period. In order to visualize this situation, the reviewer selected a few subjects here to show the dose changes between visits and during the visits.



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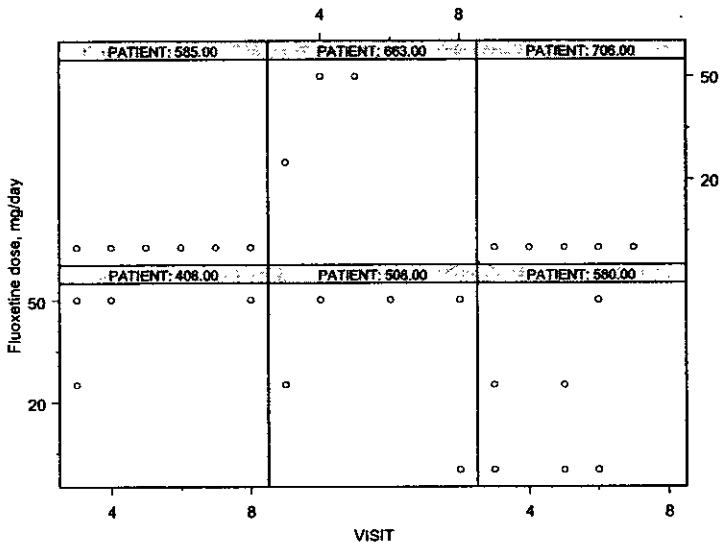
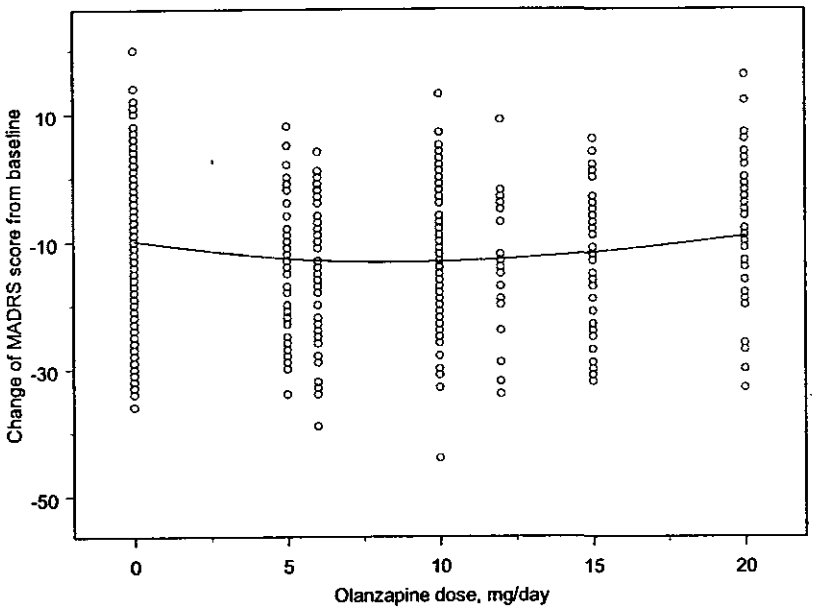


Figure 16 Doses at each visit for a random subset of subjects

2. Dose-response relationship at last visit

Loess line in Figure 17 shows that there is a small decrease as the dose increase in the fluoxetine. Loess line in Figure 17 also shows there is almost no relationship between the olanzapine dose and MADRS score. The reviewer conducted a statistical analysis with the general linear model. In this statistical model, MADRS baseline, fluoxetine dose, olanzapine are factors. The model shows the fluoxetine dose is a significant factor. The mean MADRS score decrease from baseline at 50 mg of fluoxetine is 5.36, which is 50% more than the placebo group. However, it is difficult to interpret the dose-response when the dose at last visit was not maintained for the whole visit period.

Figure 17 Change of MADRS total score from baseline versus the olanzapine dose and versus fluoxetine dose at the last visit



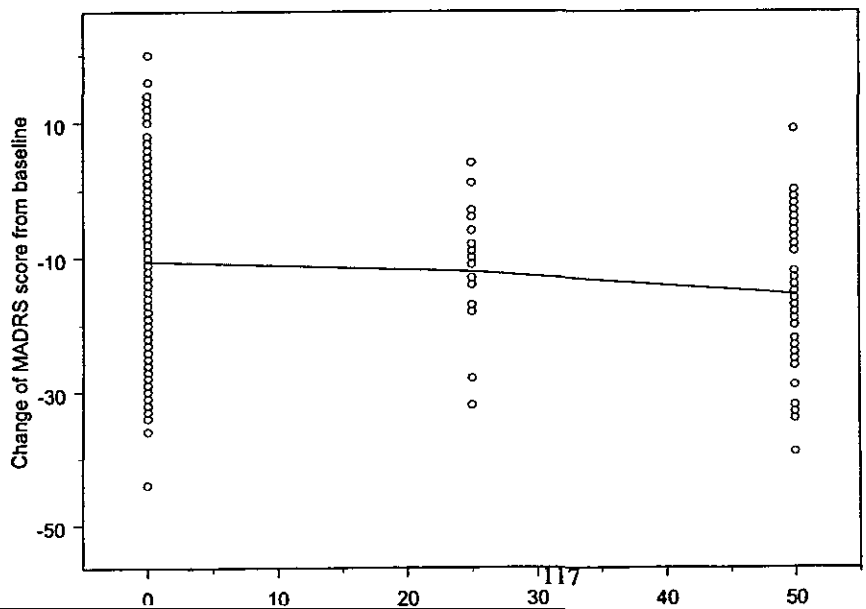


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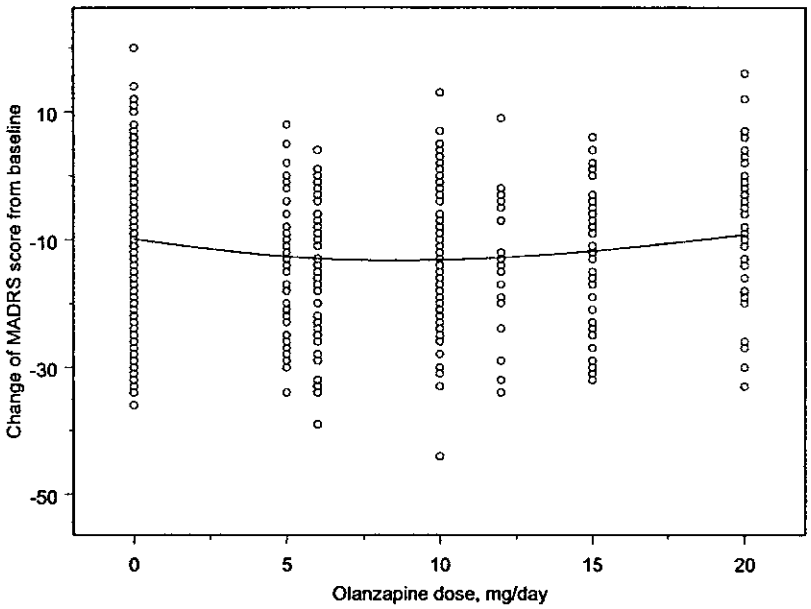
Figure 17 Change of MADRS total score from baseline versus the olanzapine dose and versus fluoxetine dose at the last visit



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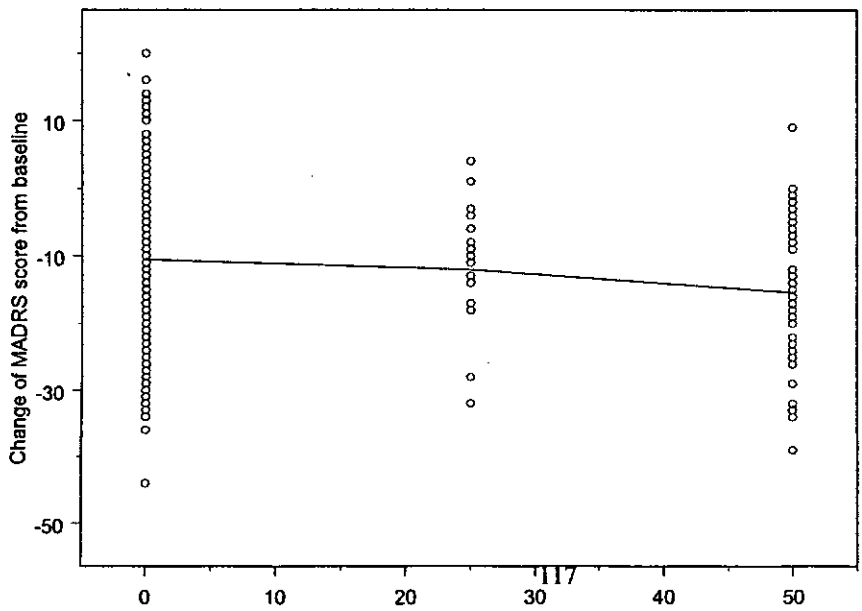

Table 14 Parameter estimates for dose-response at last visit in Study HGGY

	Olanzapine dose model		
	Estimate	SE	P-value
Intercept	2.4625	2.2613	0.2766
MADRS baseline	-0.4075	0.0698	0.0000
Olanzapine Dose	0.0125	0.0625	0.8416
Fluoxetine dose	-0.1071	0.0292	0.0003

3. Dose-response at all visits

Loess line in Figure 18 shows that there is a small decrease in the MADRS score as the dose increases in the olanzapine and fluoxetine. The reviewer conducted a statistical analysis with mixed-effect model. In this statistical model, MADRS baseline, fluoxetine dose, olanzapine dose, and interaction of olanzapine and fluoxetine formed fixed factors and subjects formed a random factor. The model shows that both of olanzapine dose and MADRS baseline are significant factors at 0.05 significance level. The mean MADRS score decrease from baseline at 20 mg of olanzapine is 2.4, which is 24% more than the placebo group. However, it is difficult to evaluate the dose-response because the dose was changed between the visit and during the visit.

Table 15 Parameter estimation for dose-response model at all visits in Study HGGY

		Olanzapine dose model		
		Estimate	SE	P-value
Covariance parameter	Subject	56.99		
	Residual	35.18		
Fixed effect	Intercept	1.888	1.7023	0.2679
	MADRS baseline	-0.3236	0.052	<.0001
	Olanzapine dose	-0.1224	0.0317	0.001
	Fluoxetine dose	-0.02178	0.034	0.524
	Fluoxetine*olanzapine dose	-0.00681	0.035	0.0521

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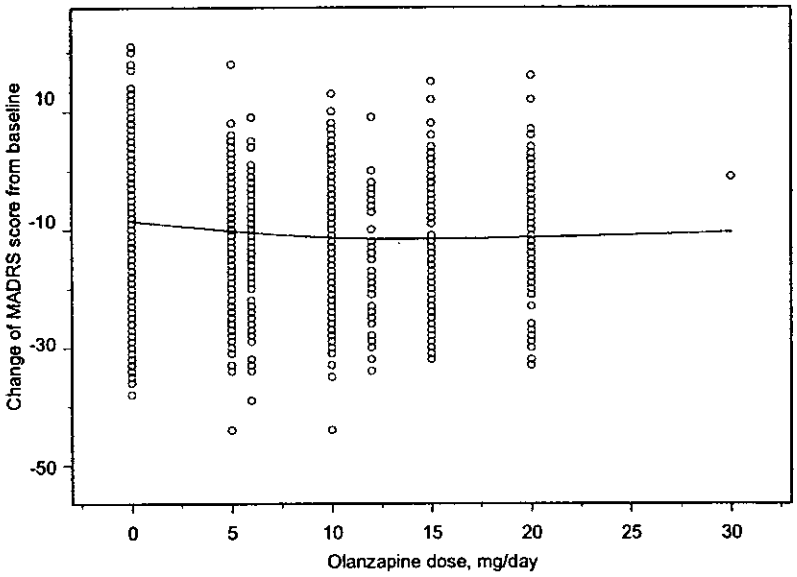

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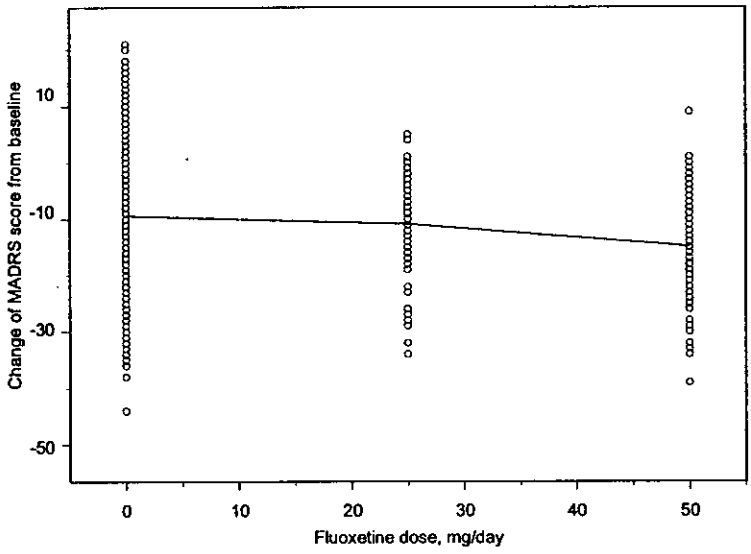
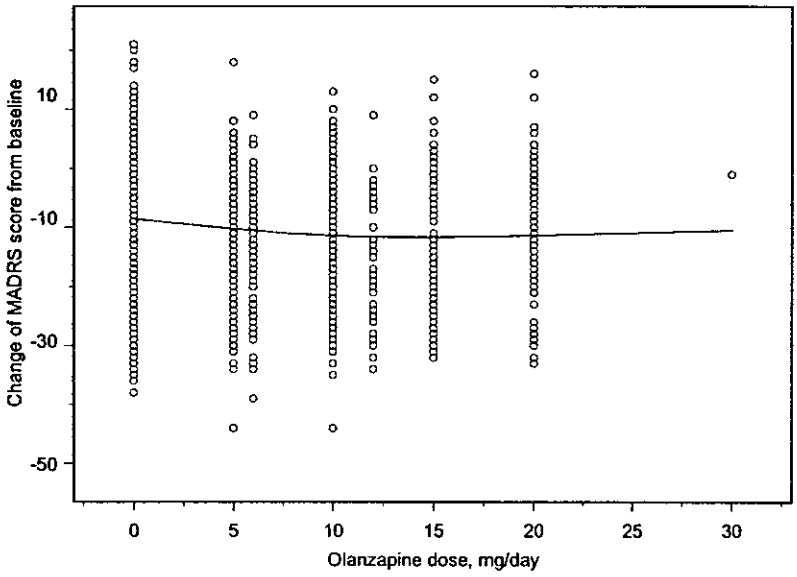


Figure 18 Change of MADRS total score from the baseline against the olanzapine dose or the fluoxetine at all visits



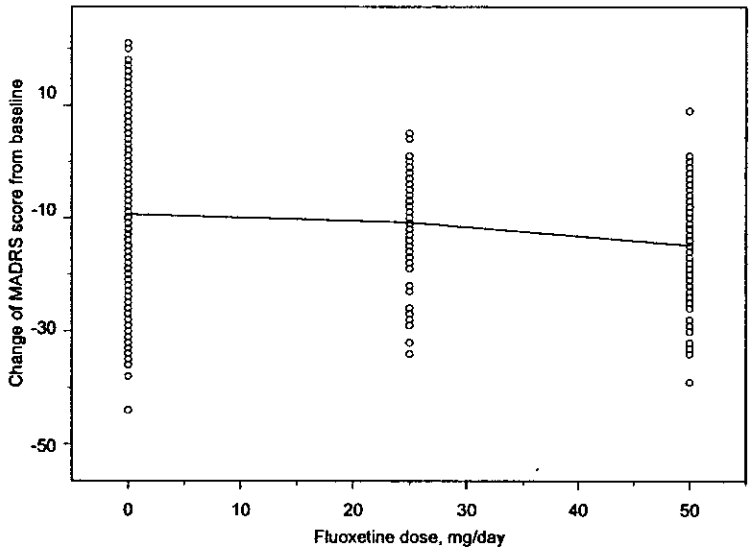


Figure 18 Change of MADRS total score from the baseline against the olanzapine dose or the fluoxetine at all visits

Conclusion

Study HGFY:

1 Since the sample size is small, there is a little power to demonstrate whether there is or not a difference in mean dose-weight-normalized olanzapine or fluoxetine concentrations between the monotherapy and the combination therapy.

2 The 95% confidence intervals between the monotherapy and the combination treatment shown in Table 6 are wide.

Study HGIE :

1 HGIE was a pharmacokinetic interaction study with sparse sampling. Note that HGCI (*Pharmacokinetic Interaction Study of Fluoxetine on Olanzapine after Single and Repeated Administration of Fluoxetine in Healthy Volunteer, N21520*) was a pharmacokinetic interaction study of fluoxetine on olanzapine after single and repeated administration of Fluoxetine in healthy volunteers, which showed a reduction in clearance (16%) on coadministration of fluoxetine. Study HGCI showed statistically significant lowering of clearance. However, the Guidance for industry: In Vivo drug metabolism/drug interaction studies—study design, data analysis, and recommendations for dosing and labeling, November 1999, states that "it is unlikely that population analysis can be used to prove the absence of an interaction that is strong suggested by information arising from in vitro or in vivo studies specifically designed to assess a drug-drug interaction since the power of a sparse sampling strategy to detect drug-drug interactions is not well established".

2 The sponsor's previous analysis of the combined factors of smoking and gender suggested that olanzapine clearance for a nonsmoking female is about 2.5 fold lower than that for a smoking male. Based on these apparent facts, the reason why the sponsor did not collect smoking status in Study HGIE is not obvious. Data on the drug-drug interaction for the nonsmoking female population should be presented.

3 For the olanzapine and fluoxetine models, Figures 6 and 7 indicate that there may be a large portion of variability not explained by the compartmental model and measured covariates. The inclusion of other covariates may help, such as smoking in the olanzapine model.

4 There is no significant concentration-response relationship.

5 Dose-response relationship is not well established.

6 Concomitant administration of fluoxetine of 25 mg or more decreased the 13.6% of olanzapine exposure compared to the olanzapine monotherapy, from other studies. However the sponsor concluded that the influence of fluoxetine is not clinically significant. The negative finding from the HGIE should be overruled by:

1) mechanistic plausibility of the interaction and 2) previous evidence from specific studies suggesting the presence of an interaction between olanzapine and fluoxetine.

7 The current labeling states, on lines 48-50, "In another study, a similar decrease in olanzapine clearance of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more." Appropriate language indicating: 1) area under the curve increases by 14% and 2) the terminal half-life is not affected, hence the time to reach steady-state should not be altered by fluoxetine.

Study HGGY
Dose-response relationship can not be well characterized because the dose was changed between visits and during the visit and concentrations were not measured. Any delay between PK and PD is hard to account for.

Overall, this reviewer can not substantiate the claims of the sponsor that there is not drug-drug interaction between olanzapine and fluoxetine.

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6.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-520**	**Brand Name**	**SYMBIAX**
OCPB Division (I, II, III)	**DPE-I**	**Generic Name**	**Olanzapine-Fluoxetine**
Medical Division	**HFD-120**	**Drug Class**	**Bipolar Depression**
OCPB Reviewer	**Sally Usdin Yasuda, MS, PharmD**	**Indication(s)**	**Depressive Episodes Associated with Bipolar Disorder**
OCPB Team Leader	**Ramana Uppoor, PhD**	**Dosage Form**	**Capsules ——— , 6 mg/25 mg; 6 mg/50 mg; 12 mg/ 25 mg; 12 mg/ 50 mg**
		Dosing Regimen	**6-12 mg olanzapine/25-50 mg fluoxetine once daily in the evening**
Date of Submission	**November 4, 2002**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**3/20/03**	**Sponsor**	**Eli Lilly & Co.**
PDUFA Due Date	**5/5/03**	**Priority Classification**	**4 Priority NDA**
Division Due Date	**4/5/03**		

Clin. Pharm. and Biopharm. Information

Summary: This NDA is for a new drug combination (olanzapine and fluoxetine) for a new indication (depressive episodes associated with bipolar disorder). A bioequivalence study (H6P-FW-HDAK) comparing the highest strength of the combination product with olanzapine and fluoxetine has been included in the submission. The sponsor has requested a waiver of *in vivo* bioequivalence studies for lower strengths of the combination capsule. Three additional pharmacokinetic studies have been submitted evaluating the potential for *in vivo* interaction in healthy volunteers in an acute study (F1D-MS-HGCI) and at steady state in patients with treatment resistant depression (F1D-MC-HGFR and F1D-MC-HGIE). In pivotal clinical trials (F1D-MC-HGGY), individual component dosage forms were used (not the combination product).

	"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			
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:	X	(2) These are also included in "in vivo effects on primary drug")		
In-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	X	(1) (These studies are the drug interaction studies listed above)		
Data sparse:	X	(1) (These studies are the drug interaction studies listed above)		
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	

Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	-	-	-	
Dissolution:	X	1		
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	X	1		Waiver of lower strengths.
BCS class	X			Refer to Guidance for Industry entitled "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" for the following comments: Please provide the raw data supporting high permeability of fluoxetine and of olanzapine from the mass balance study, along with information on study design and methods used. Provide justification for consideration of high permeability for olanzapine and fluoxetine. Please provide information to support high solubility including description of test methods and information on analytical method and composition of the buffer solution, and data for the test results including mean, standard deviation, and coefficient of variation, as well as a graphic representation of mean pH-solubility profile.
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		7		
Filability and QBR comments				

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	"X" if yes	*Comments*
Application filable ?	*X*	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. **Please forward to sponsor :** a) Refer to Guidance for Industry entitled "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" for the following comments: 1) Please provide the raw data supporting high permeability of fluoxetine and of olanzapine from the mass balance study, along with information on study design and methods used. Provide justification for consideration of high permeability for olanzapine and fluoxetine. Please provide information to support high solubility including description of test methods and information on analytical method and composition of the buffer solution, and data for the test results including mean, standard deviation, and coefficient of variation, as well as a graphic representation of mean pH-solubility profile. b) We request an electronic data set for study H6P-FW-HDAK to include subject, sequence, period, treatment, AUC and Cmax for olanzapine and for fluoxetine.
QBR questions (key issues to be considered)	What information is available that contributes to assessment of clinical pharmacology/dose response? Do the drug-interaction studies indicate differences in exposure or response when olanzapine and fluoxetine are given in combination compared to either drug given alone, and does this require a dosage adjustment? What intrinsic factors alter exposure or response following administration of the olanzapine/fluoxetine combination? Do the solubility, permeability, and dissolution data support the BCS I classification? Does the bioequivalence study show similarity of the to-be-marketed combination and the individual drugs when given together? What data support a waiver of in vivo BE data for the lower strength products? Do the dissolution conditions and specifications assure in vivo performance and quality of the product? Are the bioanalytical methods adequate to assess concentrations?	
Other comments or information not included above	We request a consultation from Pharmacometrics for the population PK studies F1D-MC-HGFR and F1D-MC-HGIE (and for PK/PD if feasible) as well as for dose-response if feasible from clinical study F1D-C-HGGY. We will ask chemistry for the expiration dates on the lot numbers used in dissolution and BE studies. PK/PD studies have not been submitted as part of the human pharmacokinetics and bioavailability section. However, we plan to review dose-response relationships in the clinical PD studies in F1D-MC-HGGY. **Comments to the Project Manager:** We request DSI inspection of the pivotal bioequivalence study H6P-FW-HDAK. Please convey this request to DSI.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-520, HFD-850(Electronic Entry or Lee), HFD-120(Bates), HFD-860 (R. Uppoor, C. Sahajwalla, M. Mehta)

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/s/

Sally Yasuda
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MeiYu Shen
3/31/03 10:03:16 AM
BIOMETRICS

Stella Machado
4/1/03 02:25:28 PM
BIOMETRICS

Jogarao Gobburu
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BIOPHARMACEUTICS

Ramana S. Uppoor
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