

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-520

MEDICAL REVIEW

Review and Evaluation of Clinical Data
Safety Team Leader Review of Selected Safety Issues in the
Response to Approvable Letter

NDA: 21-520

Drug: olanzapine/fluoxetine combination (SYMBYAX)

Route: oral

Indication: bipolar depression

Sponsor: Lilly

Action Date: 12/25/03

1 Background

Dr. Hammad has provided a thorough review of Lilly's response to the OFC approvable letter. In this memo, I will address only selected safety issues that need additional discussion.

2 Selected safety issues

2.1 Treatment-emergent mania

The review of the original NDA safety database with regard to treatment-emergent mania (TEM) in the bipolar depression studies (HGGY 1 and 2) showed there was no excess of discontinuations due to induction of mania in the OFC group compared to the placebo and olanzapine arms. Additionally, the total AE (serious + non-serious), Y-MRS, and CGI results didn't demonstrate any difference in the frequency of the TEM across treatment groups. The only signal of concern with regard to TEM was a small excess in serious AEs due to "manic reaction" and "manic depressive reaction"; however, the excess was based on a very small number of cases (0, 1, or 2 in each treatment group). Although there did not appear to be important differences in the frequency of TEM between the treatment arms in the original NDA, we requested two pieces of information to further evaluate the potential association. We asked the sponsor to report the frequency of TEM-related adverse events (manic reaction, manic depressive reaction) by study, since the NDA presented the data from the studies pooled. Additionally, the submission did not include time-to-event analyses. Because TEM-related events could have been qualitatively different in OFC-treated patients compared to olanzapine and placebo patients (despite the fact that it did not appear to be quantitatively different), we requested information on time to event.

The incidence of TEM-related AEs in the OFC group was slightly lower than the olanzapine and placebo groups in HGGY-1 and slightly higher in HGGY-2 (FDA Tables 1-3 in Dr. Hammad's review of the response to the AE letter). When pooled, the frequencies were nearly identical across the treatment groups. Although there was some

inconsistency between HGGY-1 and -2 on TEM-related AEs, it is hard to interpret the finding since it is based on 1-3 events in the OFC group.

The time to event analysis showed a shorter time to TEM for the OFC compared to olanzapine in HGGY-2, but not HGGY-1 or the combined data.

Proposed labeling

2.2 Effect of OFC on the QTc interval

In the original NDA, the sponsor used the Fridericia correction method ($QTc=QT/RR^{0.33}$) and the regression-based correction method ($QTc=QT/RR^{0.41}$) for calculating the QTc interval, as planned a priori. The regression-based correction factor for QT interval (0.41) was based on 13,039 drug-free ECG recordings collected in the sponsor's clinical trials across a range of drug products and indications). In the approvable letter, we asked Lilly to calculate the regression-based correction factor based on the baseline ECGs in the OFC development program alone. The correction factor they calculated was 0.39. Dr. Hammad asserts that this result is close enough to the one used in the original analysis (0.41) to allow us to rely on the data provided in the original NDA submission, and I agree.

Reviewer Table 1. Mean change from baseline for QTc in the pooled OFC database

Mean change from baseline	OFC (N=352)	FLX (N=129)	OLZ (N=394)	PLA (N=305)
Regression based (0.41)	+4.9	+3.7	+0.6	-0.9
Fridericia (0.33)	+5.9	+6.0	-0.7	-1.7

* source: submission 12/16/02, sponsor's table 21

Since 0.39 is between the two correction factors used to calculate the mean changes above, one can extrapolate that the mean change from baseline for the corrected QT interval in each treatment group will fall between the values in the table above. Hence, the placebo-subtracted mean change from baseline for OFC is between 6-8 msec. Most

of this change is accounted for by fluoxetine which had a placebo-subtracted mean change from baseline between 5-8 msec.

The values in the table above combine the three dose levels that were tested in the OFC controlled trials: 6/25, 6/50, and 12/50. Breaking out the mean change from baseline by dose may help to further define a potential effect of OFC on cardiac repolarization.

The sponsor explored the potential dose-response relationship for QT prolongation in the data from study HGIE, the only fixed dose study in the OFC development program (conducted in treatment resistant depression). Although the data from a fixed dose study would usually be useful for studying the potential dose-response effect, the data from this study are limited in value for another reason. HGIE began with a seven week treatment period with venlafaxine (to ascertain treatment resistance). The baseline ECG used to calculate the mean change from baseline for the double blind period was the one performed at the end of the venlafaxine treatment period. Although the venlafaxine was tapered over a week long period, there was no drug free period between the end of the taper and the randomization to the double-blind treatment. Since the effect of venlafaxine alone on ventricular repolarization was not characterized, it is difficult to interpret the QTc change from baseline data, given that the baseline likely reflects at least some exposure to venlafaxine. However, the data may be helpful in a comparative sense, because the effect of the venlafaxine, if any, should be similar across the randomized treatment groups.

Reviewer Table 2. Mean change from baseline for QTc in OFC-treated patients by dose, Study HGIE

Mean change from baseline	OFC 6/25 (N=54)	OFC 6/50 (N=55)	OFC 12/25 (N=54)	OFC 12/50 (N=50)
Regression based (0.41)	7.6 ± 18.3	8.4 ± 14.7	1.2 ± 17.9	4.3 ± 21.9

* source: submission 12/12/03, sponsor's table 1

Proposed labeling:

The effect of the individual component drugs on the QTc interval (see table 1 above) suggests that the effect of OFC on the QTc interval is approximately additive, with the primary effect coming from the fluoxetine. When compared to placebo, the mean change from baseline for the pool of OFC doses across controlled trials is about 6 msec. Since the effect appears to be coming primarily from fluoxetine, one might expect the dose-response data from HGIE to show a prolongation when going from the x/25 mg to x/50 mg fluoxetine dose arms. As seen in Table 2 above, such a signal is not consistently observed. In the dose arms with 6 mg of olanzapine, there is a minimal increase in the QTc when going from 25 to 50 mg of fluoxetine. In the dose arms with 12 mg of olanzapine, the increase in QTc from 25 to 50 mg of fluoxetine is more marked, but the absolute value is below 5 msec (the threshold below which changes in QTc are not thought to be clinically relevant¹).

¹ CDER preliminary concept paper "The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs", November 15, 2002, p. 22.

Vital signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients. (see WARNINGS, Orthostatic hypotension). The mean heart rate of SYMBYAX-treated patients was reduced by _____

2.3 Orthostatic Hypotension

The incidences of PCS orthostatic hypotension for each of the treatment groups in the OFC pooled database provided in the original NDA ISS were erroneous. The sponsor provided the correct incidences in their response to the AE letter (section 2.6.1 in Dr. Hammad's review). The corrected values are shown in the table below.

Reviewer table 3: Incidence of PCS orthostatic hypotension (fall in SBP supine → standing \geq 30 mmHg) in each of the treatment groups in the pooled controlled OFC database

Event	OFC (N=512)			FLX (N=204)			OLZ (N=644)			PLA (N=445)			
	n	%	Rate*	RR#									
Orthostatic Sys BP Decr	21	4	25	10	5	31	16	2	20	8	2	17	1.46

* Rate is per 100 patient year.

In the bipolar depression trials (HGGY-1 and -2), the excess of PCS orthostatic hypotension in the OFC group was more marked than in the OFC pooled database.

Reviewer Table 4. Incidence of PCS orthostatic hypotension (fall in SBP supine → standing \geq 30 mmHg) in each of the treatment groups in the pooled bipolar depression database

Event	OFC (N=82)			OLZ (N=346)			PLA (N=352)			
	n	%	Rate*	n	%	Rate*	n	%	Rate*	RR#
Orthostatic Sys BP Decr	6	7.3	54	5	1.4	12.8	5	1.4	13.1	4.1

* Rate is per 100 patient year

2.3.1 Orthostatic hypotension and bradycardia

As discussed in section 2.3 of my team leader review of the original OFC NDA submission, several healthy subjects in clinical pharmacology trials of olanzapine (n=3) and OFC (n=3) had episodes of hypotension accompanied by bradycardia. The three patients in the olanzapine studies had sinus pauses associated with their hypotensive episode (the patients in the OFC trials did not have cardiac monitoring so there is no information regarding sinus pauses). The reflex that leads to bradycardia in response to hypotension occurs mainly in healthy young people with high vagal tone.

My concern based on those subjects' experiences, was that patients with bipolar depression who are antipsychotic naïve could be at risk for this bradycardic response to hypotension. Unlike patients with acute bipolar mania, for which olanzapine is already approved, patients with bipolar depression would not be expected to have a high sympathetic tone, perhaps increasing their risk of this bradycardic response. As such, we requested that the sponsor further analyze the bipolar depression population and the OFC pooled database population to characterize this potential risk.

The sponsor's original response to this analysis request focused solely on OFC-treated patients and did not provide comparison to the other treatment groups. In their 12/2/03 response to a Division request, Lilly provided the comparator data.

In an attempt to cast the broadest net for any bradycardia in association with a drop in systolic blood pressure (SBP), the sponsor counted patients who had any drop in heart rate (≥ 1 bpm).

Reviewer table 5: Incidence of patients with a ≥ 1 bpm decrease in orthostatic pulse and a ≥ 20 mm hg decrease in orthostatic systolic blood pressure in the OFC pooled database

Event	OFC (N=549)		FLX (N=241)		OLZ (N=659)		PLA (N=455)	
	n	%	N	%	n	%	n	%
Orthostatic Sys pulse and BP decrease	10	1.8	4	1.7	15	2.3	9	2.0

(Source: sponsor submission 12/2/03)

As is seen in the preceding table, there was no important difference between the treatment groups with regard to the incidence of a ≥ 1 bpm decrease in orthostatic pulse concomitant with a ≥ 20 mm hg decrease in orthostatic SBP.

Reviewer table 6: Incidence of patients with a ≥ 10 bpm or a ≥ 20 bpm decrease in orthostatic pulse and a ≥ 20 mm hg decrease in orthostatic systolic blood pressure in the OFC pooled database

Event	OFC (N=549)		FLX (N=241)		OLZ (N=659)		PLA (N=455)	
	n	%	N	%	n	%	n	%
Orthostatic Sys pulse decrease ≥ 10 bpm	3	0.55	1	0.42	5	0.77	2	0.45
Orthostatic Sys pulse decrease ≥ 20 bpm	2	0.37	0	0.0	5	0.77	1	0.22

As seen in the table above, when a higher threshold is placed on drop in pulse (≥ 10 bpm or ≥ 20 bpm), there was no important difference between the OFC and placebo groups with regard to the incidence of either a ≥ 10 bpm or a ≥ 20 bpm decrease in orthostatic pulse concomitant with a ≥ 20 mm hg decrease in orthostatic SBP. However, olanzapine monotherapy appeared to be associated with an excess of patients who had the most marked bradycardic changes associated with an orthostatic drop in systolic blood pressure.

Of the 2001 OFC-treated patients in the OFC 2-month safety update database with vital signs data, 37 (1.8%) patients met the criteria of a ≥ 1 bpm decrease in orthostatic pulse concomitant with a ≥ 20 mm hg decrease in orthostatic SBP. Lilly checked all OFC-treated patients for any adverse event (whether it be an actual event term or a mapped COSTART term) that included "syncope," "hypotension," or "conscious" (any term with conscious as the root [e.g., unconscious]). Of the 37 patients identified by the orthostatic criteria above, three (0.15%) had associated adverse events of syncope or dizziness. One of these patients had a pulse decrease of 30 (78 \rightarrow 48) in association with a SBP decrease of 23.

Additionally, we had requested that the sponsor characterize the vital sign changes in patients who had suffered AEs potentially related to orthostatic hypotension. As before,

the sponsor's original response to this request focused solely on the OFC group. To put the risk associated with OFC into perspective with the other treatment groups, we requested the comparator data.

Reviewer table 7: Incidence of patients with adverse events possibly related to orthostatic hypotension by treatment group and blood pressure/pulse response in the OFC pooled database.

Event	OFC (N=571)		FLX (N=251)		OLZ (N=685)		PLA (N=477)	
	n	%	N	%	n	%	n	%
Possible syncope [^]	2	0.4	1	0.4	2	0.3	1	0.2
↓BP + ↓P	3	0.5	2	0.8	4	0.6	4	0.8
↓BP + ↔P	2	0.4	0	0	3	0.4	1	0.2
Both*	5	0.9	2	0.8	7	1.0	5	1.0

[^] event specifically suggestive of syncope, without regard to change in vital signs

* includes patients with syncope and (↓BP + ↓P) OR (↓BP + ↔P).

The preceding table shows that there was a slight excess of events suggestive of syncope in the OFC group compared with the placebo group, although this is based on a small number of events. There was no excess of events associated with decreased SBP and pulse in the OFC group compared with the placebo group.

Finally, we had requested that the sponsor provide the incidence of injury and/or fall among patients who met criteria for bradycardia in the OFC pooled database. In each treatment arm 1-3% of patients met the criteria for having bradycardia².

Reviewer table 8: Incidence of patients with an adverse event possibly associated with an injury and/or fall among patients who met criteria for bradycardia in the OFC pooled database.

Event	OFC (N=11)		FLX (N=6)		OLZ (N=6)		PLA (N=13)	
	n	%	n	%	n	%	n	%
Injury and/or fall	2	18	0	0	0	0	0	0

Although there is an excess of injury/fall in the OFC group compared to the other treatment arms, this is based on a very small number of cases.

2.3.2 Antipsychotic naïve patients

In the AE letter, we requested that the sponsor stratify the OFC bipolar depression database and the OFC pooled database based on previous exposure to antipsychotics to determine whether new exposure to OFC was associated with an excess risk of orthostatic hypotension (see Dr. Hammad's review, section 2.8).

The comparative conclusions from this analysis are limited by the fact that most patients in the OFC trials were antipsychotic naïve (91% of participants in the bipolar depression database and 94% of the participants in the OFC pooled database); however, these analyses provide useful information regarding the experience of PCS orthostatic blood pressure in the antipsychotic naïve population.

² The criteria for bradycardia included the following: 1) reported an adverse event of "bradycardia" or "sinus bradycardia"; 2) had a pulse ≤50 bpm (per vital signs); or 3) had a heart rate ≤50 bpm (per ECG)

Reviewer table 9. Rates of antipsychotic naïve patients with PCS decrease in orthostatic blood pressure (>30 mm hg) at any time within the OFC pooled database and the subset of acute bipolar-depression trials

	OFC pooled database				Bipolar depression database [^]			
	N	n	%	Rate*	N	n	%	Rate*
FLX	204	8	4	25	-	-	-	-
OFC	497	13	3	16	75	4	5	42
OLZ	597	9	2	12	320	2	1	6
PLA	394	3	1	7	316	1	0.3	3
RR#	--			2.22	--			13.9

[^] There was no FLX arm in the bipolar depression trials

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

As can be seen in the preceding table, the percentage and rate of PCS orthostatic hypotension in antipsychotic naïve patients in the OFC group was about two times that in the placebo group. The excess risk in the OFC group in the bipolar depression trials was substantially higher than in the OFC pooled database; however, these rates are based on a small number of events.

2.3.3 Accidental Injury/Falls

Orthostatic hypotension may not be reliably detected at routine visits; however, if patients are having episodes of orthostatic hypotension in the course of their daily lives, they may sustain injuries secondary to syncope/pre-syncope.

We asked the sponsor to calculate the incidence of a combined definition of “accidental injury/falls” to capture adverse events potentially related to injuries that would not be coded to “accidental injury”. The sponsor used the following terms to search the adverse event database: abrasion, accidental injury, black, bleed, blood, break, broke, bruise, bump, contusion, crack, cut, discoloration, fall, fracture, gash, graze, hemorrhage, laceration, lesion, rupture, scrape, scratch, shatter, and tear. They then reviewed the terms obtained by the search, and excluded events not related to injury/fall (e.g., tearfulness, falls asleep easily, etc.).

The sponsor provided the list of events that they included and those that they excluded from the incidence calculation. I reviewed these lists and found that there were some inconsistencies in the lists, including events that were inappropriately counted (“breakthrough bleeding”, “bruise...secondary to phlebotomy”), as well as those that were inappropriately excluded (“car accident”, “accidental fall”). I manually recounted the events after reclassifying them (I was not blinded to treatment assignment). My calculations are in the following table along with the sponsor’s. Although the incidences based on my classification are slightly higher than the sponsor’s, the relative differences between treatment arms are similar.

Reviewer table 10. Incidence of Adverse events related to injury/fall in the OFC controlled database

Event	OFC (N=571)			FLX (N=251)			OLZ (N=685)			PLA (N=477)			RR#
	n	%	Rate*										
Injury/Fall-sponsor	30	5.2	35	17	6.8	47	37	5.4	45	14	2.9	29	1.2
Injury/Fall-reviewer	34	6.0	39	16	6.4	44	39	5.7	48	15	3.1	32	1.2

* Rate is per 100 patient year.

Although the incidence of injury/fall was numerically greater in the active drug groups compared to the placebo group, the difference between OFC and placebo was not substantial.

Proposed labeling:

The excess risk of orthostatic hypotension in the OFC arm of the bipolar depression database is more marked than that observed in the OFC pooled database. Given the small controlled treatment experience of OFC in bipolar depression (n=86), it is hard to determine whether the larger excess occurred by chance, or whether patients with bipolar depression are potentially more sensitive to the hemodynamic effects of OFC compared to patients with treatment resistant depression or depression with psychotic features. We will propose to include data from both pools of patients in labeling.

To put into perspective the experience of healthy subjects in OFC/olanzapine clinical pharmacology trials having episodes of severe hypotension and bradycardia, we will include the incidence of a substantial decrease in SBP (≥ 20 mmHg) associated with a substantial decrease in pulse (≥ 20 bpm) from the OFC pooled database.

There is no need to include the data from the injury/falls analysis because there were no important differences between treatment groups.

We will remove the purported mechanism for the orthostatic hypotension (attributed to olanzapine) because it is clear from the data that patients treated with fluoxetine alone also were at risk for orthostatic hypotension.

Orthostatic hypotension

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2.4 *[Note to sponsor: In reviewing the frequencies of PCS orthostatic hypotension in antipsychotic naïve patients, we noted an inconsistency in the number of patients with PCS orthostatic hypotension. Refer to Table 9, p. 370, RESPONSE_6-7.pdf, 7/31/03 submission. The "n's" in that table, adding naïve to previously exposed patients, do not match the total number of patients with "orthostatic Sys BP decr", as presented in Table 1, p. 11, RESPONSE_6-7.pdf, 6/24/03 submission. We would like to see the inconsistency explained, and the corrected data prior to determining if "antipsychotic naïve patients" should be added to the list of patients in the preceding paragraph in whom. — (should be used with caution.)]*

2.4 Diabetes/Hyperglycemia

In September 2003, the Division sent out class labeling for the atypical antipsychotics regarding the occurrence of hyperglycemia related adverse events in association with the use of these drugs. Lilly has already adopted this labeling for olanzapine. The same labeling language will be inserted into the Warnings section of the OFC labeling.

Hyperglycemia and Diabetes Mellitus

2.5 Cerebrovascular Adverse Events

Following the identification of an elevated risk of cerebrovascular adverse events (CVAE, including stroke and transient ischemic attacks) in patients with dementia-related psychosis (DRP) with risperidone, the Division requested that each of the sponsors of the other atypical antipsychotic drugs review its safety database for such a signal. Dr. Hammad has reviewed Lilly's submissions (dated 12/17/02, 1/29/03, 11/18/03) and concluded that there is evidence of a greater than 4x increased risk of CVAE in patients with DRP taking olanzapine compared with those taking placebo.

Based on their analyses, Lilly placed a statement in Precautions describing the higher incidence of CVAEs in the patients with DRP who took olanzapine compared to those who took placebo. Additionally, they added a statement emphasizing that all the patients who experienced CVAE had risk factors for them.

The size of the increased risk for CVAE with olanzapine is statistically significant and similar to that observed in the risperidone DRP trials. We will recommend that similar language be used to describe the increased risk of CVAE with olanzapine that was used in the risperidone labeling; the statement will be placed in the Warnings section, as was done for risperidone.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

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Judith Racoosin
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MEDICAL OFFICER

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MEMORANDUM

DATE: December 23, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-520

SUBJECT: Action Memo for NDA 21-520, for the use of Symbyax (olanzapine/fluoxetine hydrochloride) in the treatment of depressive episodes associated with bipolar disorder

NDA 21-520, for the use of Symbyax (olanzapine/fluoxetine hydrochloride) in the treatment of depressive episodes associated with bipolar disorder, was submitted by Eli Lilly and Co., Inc., on 11/24/02. The application was the subject of an Approvable letter issued 5/5/03. The letter contained a number of requests and, of course, included draft labeling. The sponsor submitted a complete response to our letter on 6/24/03.

The response has been reviewed by Dr. Paul Andreason, medical officer and team leader (review dated 12/18/03), Dr. Tarek Hammad, medical officer, safety team (review dated 12/12/03), Dr. Judy Racoosin, safety team leader (memo dated 12/19/03), Dr. Sally Yasuda, Office of Clinical Pharmacology and Biopharmaceutics (reviews dated 11/7/03 and 12/22/03), Dr. Sonia Tabacova, pharmacologist (review dated 12/18/03), Dr. Michael Skelly, Division of Scientific Investigations (reviews dated 7/7/03 and 8/29/03), Ms. Linda Kim, Division of Medication Errors and Technical Support (review dated 7/25/03), Mr. Scott Dallas, Division of Medication Errors and Technical Support (review dated 12/15/03), Ms. Jeanine Best, Division of Surveillance, Research, and Communication Support (review dated 7/22/03), Dr. Katherine Bonson, Controlled Substances Staff (review dated 7/28/03), and Dr. Li-Shan Hsieh, chemist (review dated 9/10/03). The clinical team recommends that the application be approved. I will briefly describe the responses to the questions in the Approvable letter, and offer the rationale for the division's action.

The Approvable letter asked questions in numerous disciplines:

- 1) CMC issues, including inspectional issues
- 2) Requests for two Phase 4 commitments for additional pre-clinical studies
- 3) Dissolution specifications and a request for a Phase 4 commitment to perform a drug interaction study
- 4) Notification that an acceptable inspection of the biopharmaceutics studies was necessary
- 5) Multiple clinical questions and issues
- 6) Draft labeling, including requests related to the container label

1) CMC issues

All chemistry issues have been resolved, including an acceptable recommendation from compliance (issued on 7/28/03; a problematic site has been withdrawn by the sponsor).

2) Pre-clinical phase 4 commitments

We had asked the sponsor to perform a peri-natal study. The sponsor had argued that the peri-natal study should not be required, [] The pharmacology team still requires that the peri-natal study be done []

3) Dissolution specifications and request for a Phase 4 interaction study

The Agency has agreed to the sponsor's proposed dissolution specifications, and agreed with the sponsor's justification for not requiring the previously requested Phase 4 interaction study.

4) Inspection of the biopharmaceutics studies

The 8/29/03 memo from Dr. Michael Skelly of the Division of Scientific Investigations recommends that, "...the clinical portions of Study H6P-FW-HDAK [a bioequivalence study comparing the commercial formulation and the clinical trial formulation] be accepted for review.". However, in an earlier memo of 7/7/03, Dr. Skelly re-iterated DSI's objection to the analytic results of this study. These objections relate to the fact that the "[redacted]"

[redacted]

[redacted]

[redacted]

5) Clinical questions/issues

The sponsor has responded to the Agency's requests and all issues have been resolved. In particular, we had been particularly concerned about the

absence of a fluoxetine-only arm in the controlled trials (the absence of this arm complicated the ability of the trial to document the contribution of each component of the combination, as is required by regulation). The sponsor has submitted a literature review, letters from experts, and professional practice guidelines, all of which attest to the inappropriateness of treating these patients with an anti-depressant alone. Dr. Andreason finds this argument very persuasive.

6) Labeling, including container labeling

We have reached agreement with the sponsor on the language for the package insert and Patient Package Insert (PPI). In addition, the Division of Medication Errors and Technical Support has concluded that the sponsor has adequately addressed the container labeling concerns we had raised.

I agree that all issues raised in the Approvable letter have been satisfactorily addressed. For this reason, then, I will issue the attached Approval letter.

Russell Katz, M.D.

**APPEARS THIS WAY
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this page is the manifestation of the electronic signature.**

/s/

Russell Katz
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MEDICAL OFFICER

APPEARS TO BE
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Review and Evaluation of Clinical Efficacy Data

NDA #21,520

NDA #: 21-520
Sponsor: Eli Lilly and Company
Material Reviewed: Response to Approvable Action Letter
Submission Date: June 24, 2003
Drug: combination olanzapine/fluoxetine
(SYMBYAX®)
Proposed Indication: Bipolar Depression
Dosage Forms, Strengths, and Route of Administration: 6/25, 6/50, and 12/50-mg tablets

Background

This review addresses the responses to efficacy issues from the Sponsor's Response-to-Approvable-Action-Letter and serves as the Clinical Psychopharmacology Team Leader memo for this action. Safety issues are addressed by the Division of Neuropharmacological Drug Products Safety Team in the review by Dr. Hammad and Safety Team Leader memo by Dr. Racoosin.

I concur with Dr. Racoosin's conclusions and labeling recommendations found in her memo.

Data Reviewed

The sponsor did not present any new efficacy data in this submission and none was requested by the Agency. The Agency requested that the sponsor discuss their decision to exclude a fluoxetine alone arm from the study design. I note that the original study design of this combination drug did not include a fluoxetine alone treatment arm. I also note that there was some discussion and debate at the Office level as to the appropriateness of a less than full factorial design in the development program for this drug. The Approvable Action Letter stated:

Justify the absence of a fluoxetine-only treatment arm. Submit a comprehensive discussion, including a discussion of any data available, documenting that treatment with fluoxetine does indeed increase the risk of serious manic episodes in this population.

The Sponsor included a review of the literature, statements from the American Psychiatric Association Practice Guidelines, and letters of experts in the field. This review is adequately complete and convincing that a fluoxetine alone arm would be inappropriate for the Agency to require in a pivotal study design for testing the efficacy SYMBIAX.

I remain convinced that, the omission of the fluoxetine alone arm from the design was appropriate, and I note that it was discussed with the Sponsor, and agreed upon by the Division in advance of the studies' commencement. The Division allowed the study to proceed as a pivotal study without the fluoxetine alone arm since it is widely accepted in

the clinical and academic community that treating bipolar depressed patients with antidepressants alone in general, and fluoxetine alone specifically, presents an unacceptable risk of inducing mania in patients. It is currently considered inappropriate and perhaps negligent in the practice of clinical psychopharmacology to knowingly treat a bipolar depressed patient with antidepressant monotherapy (i.e. in the absence of some kind of mood stabilizing or anti-manic agent). Therefore the study design for HGGY appropriately excluded a fluoxetine alone arm.

Labeling

The Sponsor proposed adding a table to the clinical trial section to summarize the results of studies HGGY 1 and 2. The table accurately reflects the results of the study and seems clearer than the text that was originally proposed. I propose the following changes to the clinical trials section based on the use of the table:

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. The results of the studies are summarized below (Table 1).

**Table 1: MADRS Total Score
Mean Change from Baseline to Endpoint**

	<u>Treatment Group</u>	<u>Baseline Mean</u>	<u>Change to Endpoint Mean¹</u>
<u>Study 1</u>	<u>SYMBYAX</u> <u>(N=40)</u>	<u>30</u>	<u>-16^a</u>
	<u>Olanzapine</u> <u>(N=182)</u>	<u>32</u>	<u>-12</u>

	<u>Placebo</u> <u>(N=181)</u>	<u>31</u>	<u>-10</u>
<u>Study 2</u>	<u>SYMBYAX</u> <u>(N=42)</u>	<u>32</u>	<u>-18^a</u>
	<u>Olanzapine</u> <u>(N=169)</u>	<u>33</u>	<u>-14</u>
	<u>Placebo</u> <u>(N=174)</u>	<u>31</u>	<u>-9</u>

¹ Negative number denotes improvement from baseline.

² Statistically significant compared to both olanzapine and placebo.

III. Conclusions and Recommendations

The Division has been unable to agree on final labeling with the Sponsor at the writing of this review; however, we do not require any further data in order to take an action.

 12/18/03
Paul J. Andreason, M.D.

cc: NDA#21-520
HFD-120
HFD-120/
P Andreason
D Bates
T Laughren
J Racoosin

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/s/

Paul Andreason
12/18/03 12:30:19 PM
MEDICAL OFFICER

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

**REVIEW OF NDA RE-SUBMISSION IN RESPONSE TO
APPROVABLE LETTER**

Brand Name: Symbiax

Generic Name: Olanzapine/fluoxetine hydrochloride

Sponsor: Eli Lilly and Company

Indication: Depressive episodes associated with
bipolar disorder

NDA Number: 21-520

Submission Date: 6/24/2003, 7/31/2003, and 12/2/2003

Safety Reviewer: Tarek A Hammad, MD, PhD, MSc, MS

Review completed: 12/12/2003

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Glossary

This section provides an explanation of some of the terminology used in this review.

OFC: Olanzapine and fluoxetine combination.

The sponsor: the term refers to Eli Lilly and Company.

FDA table: the term refers to tables generated by this FDA reviewer.

Sponsor's table: the term refers to tables generated by the sponsor.

**APPEARS THIS WAY
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1 Background

On November 4, 2002, the sponsor submitted a new drug application (NDA 21-520) for the use of olanzapine/fluoxetine combination for the treatment of depressive episodes associated with Bipolar disorder. The Division of Neuropharmacological Drug Products subsequently deemed the application approvable in a letter dated May 5, 2003. Ten requests for further clarification and additional analyses of the safety data were included in the approvable letter.

In this document I specify the FDA requests then I summarize and discuss the sponsor's response.

2 Sponsor's response to FDA requests

2.1 FDA request 1

The safety update indicates that there had only been one additional death since the submission of the ISS; however, review of selected serious adverse events identified a second patient who died during the safety update reporting period (HGIE-617-6552). Please explain the discrepancy. Also, please review the serious adverse events for any additional deaths and provide us with your findings.

2.1.1 Sponsor's response to request 1

Patient HGIE-617-6552 died (C J) due to complications associated with heart surgery after the patient had discontinued the study on (C J) Because the patient did not die during the FID-MC-HGIE study and the death was not believed by the investigator to be related to the drug or the protocol procedures, the sponsor did not put it in the OFC clinical database as a death. Alternatively, the sponsor discussed the case as a follow-up note in a narrative that was presented in the HGIE open-label phase abbreviated clinical study report (Appendix 5.2, page 1102 of the report, submission dated 11/4/2002, table ISS.4.1 page 61).

A systematic review done by the sponsor of serious adverse events revealed no additional deaths.

2.1.2 Reviewer comment

The sponsor is citing section 3.9.3.2.2 (page 119) of the HGIE protocol, as the reason that this death was not included in the database. I reviewed the section, which states "Serious adverse events occurring after a subject is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol

procedure." I found that the same is true for other studies e.g. HGGY (section 3.9.3.2.2 of HGGY protocol, p 1787, appendix 6.1.1).

I examined the FDA draft guidance entitled "Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" and it was silent on this issue.

I also examined the ICH E3 "structure and content of clinical study reports" (dated July, 1996). It states under section 12.3.1.1: "All deaths during the study, including the post-treatment followup period, and deaths that resulted from a process that began during the study, should be listed". However, under section 12.3.2, the guidance adds, "Events that were clearly unrelated to the test drug/investigational product may be omitted".

In the case under consideration, a patient was admitted to the hospital for pulmonary edema and required a replacement of her mechanical mitral valve. The patient had continued on open-label OFC but then was discontinued from the study about one month after the surgery. She had an additional heart surgery a week later and then died of complications of the surgery and sepsis. While it seems probable that the death was related to post-cardiac surgery complications, for completeness, it would have been preferable for the sponsor to include this death in the safety update. It would be prudent to make certain that in future protocols, all SAEs occurring within a specified period of time after discontinuation (perhaps 30 days) are required to be included in the study report.

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2.2 FDA request 2

With regard to treatment-emergent mania, there did not appear to be a difference in incidence across the treatment groups in HGGY-1 and -2. However, no information was provided on the time to event for the emergence of mania. Please provide an analysis that compares the time to emergence of mania across the three treatment groups.

2.2.1 Sponsor's response to request 2

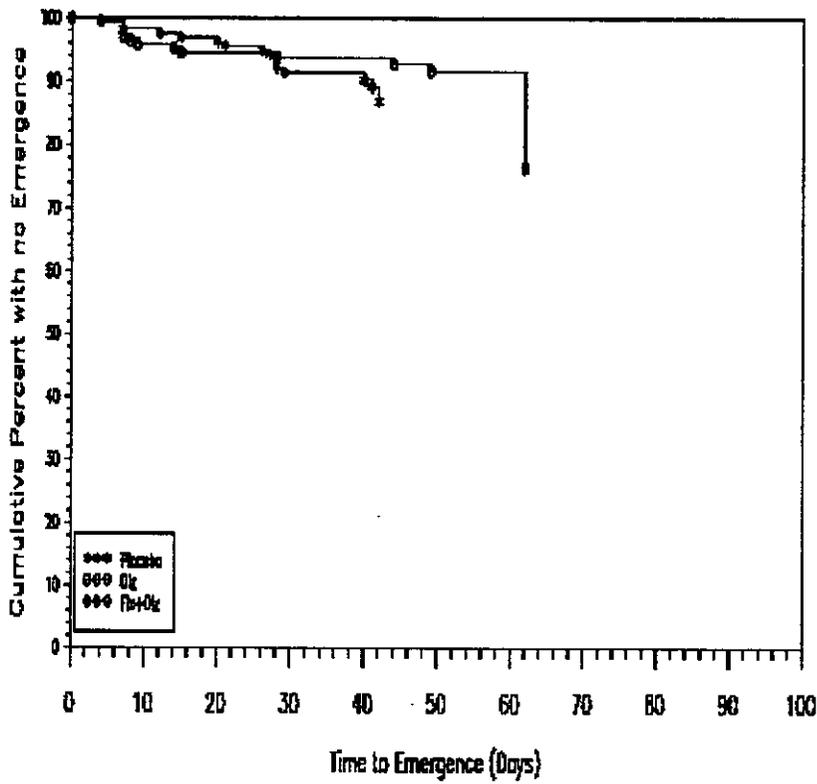
The sponsor provided graphical display of time to symptomatic emergence of mania with Kaplan-Meier estimated time-to-response curves and the results of the log-rank test.

The sponsor defined symptomatic emergence of mania as a Young Mania Rating Scale (YMRS) total score of <15 at baseline and a ≥ 15 total score postbaseline. The sponsor did not provide the raw data for the individual studies (HGGY1 and 2), but in the original data submitted 11/1/402 (sponsor's table HGGYc.11.85, p 285 of HGGYc study report), the proportion of patients meeting that criterion at any time during the study was similar across the three study groups (OFC 6.4% [5/78], olanzapine 5.7% [19/355], and placebo 6.7% [23/345]) in the combined HGGY1 and 2 data.

The sponsor provided the analysis for studies HGGY1 and 2 separately and combined, which I am presenting next in my review.

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Time to Symptomatic Emergence of Mania
Placebo-Control Olanzapine Monotherapy for Bipolar I Depression
F10-MC-HCGY Study 1, Acute Phase

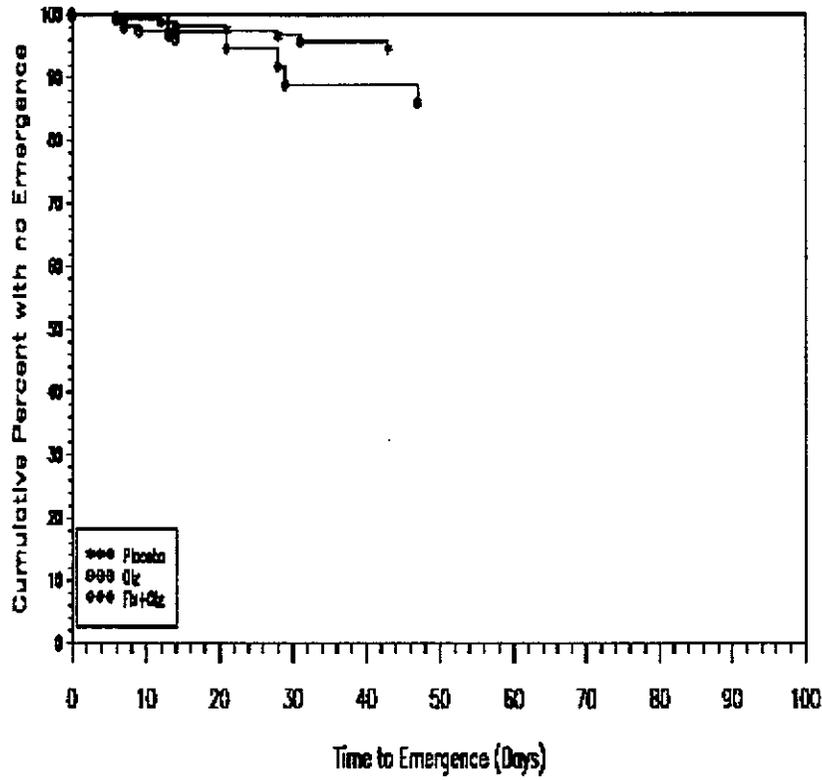


P.S. There were no OFC treated patients with emergence of mania, which explains why there is no OFC line.

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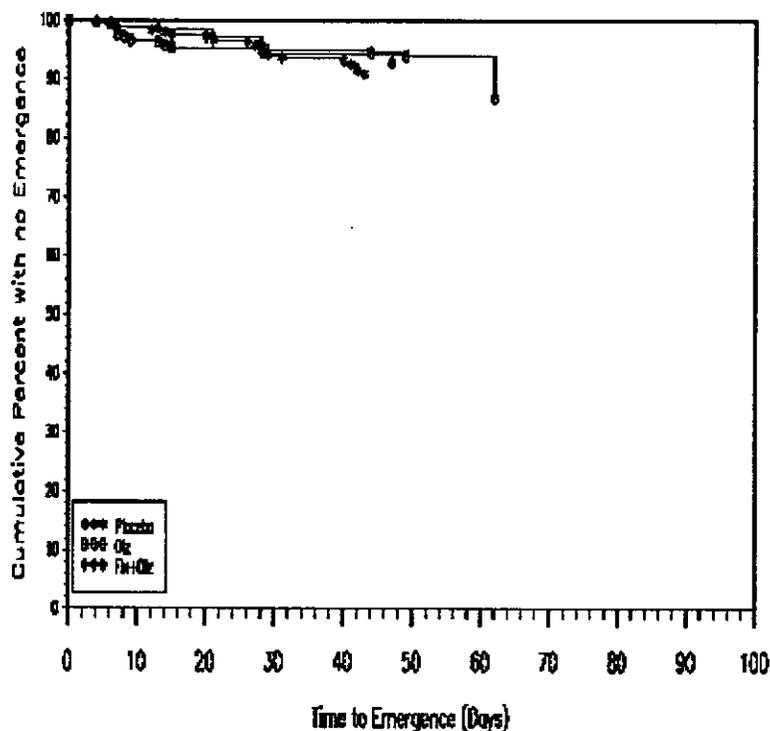
Time to Symptomatic Emergence of Mania
Placebo-Control Ginzapine Monotherapy for Bipolar I Depression
FID-MC-HCY Study 2, Acute Phase



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Time to Symptomatic Emergence of Mania
Placebo-Control Olanzapine Monotherapy for Bipolar I Depression
F1D-MC-HGGY Studies 1 and 2, Acute Phase



2.2.2 Reviewer's comment

- ✚ The data show no difference in the time-to-event between various treatment groups in the combined data. However, there was a statistically significant p-value for OFC versus olanzapine in the study HGGY-2 with the OFC group slightly worse.
- ✚ The sponsor provided a time-to-event analysis for emergent mania as defined by the YMRS and not for the treatment-emergent adverse events of manic reaction and manic depressive reaction, perhaps because the number of treatment-emergent adverse events was too small to interpret (see response to next request).

2.3 FDA request 3

Please provide table ISS.10.47 broken out by individual study (i.e., one table for HGGY-1 and one table for HGGY-2).

2.3.1 Sponsor's response to request 3

The sponsor provided the requested tables, which I am presenting in this review.

FDA table 1: Incidence of treatment-emergent manic reaction or manic depressive reaction in F1D-MC-HGGY study 1 acute phase (sponsor's table 4, re-submission response1-5.pdf).

Adverse Event	OFC N=43 n(%)	Olz N=191 n(%)	Pla N=193 n(%)	p-value
Patients with ≥1 event	1 (2)	10 (5)	15 (8)	.382
Manic reaction	1 (2)	10 (5)	13 (7)	.585
Manic depressive reaction	0 (0)	0 (0)	2 (1)	-

FDA table 2: Incidence of treatment-emergent manic reaction or manic depressive reaction in F1D-MC-HGGY study 2 acute phase (sponsor's table 5, re-submission response1-5.pdf)

Adverse Event	OFC N=43 n(%)	Olz N=179 n(%)	Pla N=184 n(%)	p-value
Patients with ≥1 event	3 (7)	7 (4)	5 (3)	.353
Manic reaction	3 (7)	5 (3)	5 (3)	.316
Manic depressive reaction	0 (0)	2 (1)	0 (0)	-

FDA table 3: Incidence of Treatment-emergent manic reaction or manic depressive reaction in F1D-MC-HGGY study 1 and study 2 combined acute phase (sponsor's table 6, re-submission response1-5.pdf)

Adverse Event	OFC N=86 n(%)	Olz N=370 n(%)	Pla N=377 n(%)	p-value
Patients with ≥1 event	4 (5)	17 (5)	20 (5)	.945
Manic reaction	4 (5)	15 (4)	18 (5)	.856
Manic depressive reaction	0 (0)	2 (1)	2 (1)	1.000

2.3.2 Reviewer's comments

- ✦ Note that treatment-emergent manic reaction and manic depressive reaction is numerically lower in the OFC group as compared to placebo in the HGGY-1 study, but the reverse is true in HGGY-2. However, none of the differences is statistically significant, and the number of events is too small to interpret.

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2.4 FDA request 4

Please provide Table HGGYc.12.8 broken out by individual study (i.e., one table for HGGY- 1 and one table for HGGY-2).

2.4.1 Sponsor's response to request 4

The sponsor provided the requested tables. I summarized in the following tables adverse events with at least one event in the OFC group.

FDA table 4: Serious treatment-emergent adverse events by decreasing incidence F1D-MC-HGGY Study 1, acute phase.

AE term	Placebo (N=193)		Olanzapine (N=191)		OFC (N=43)	
	N	%	n	%	n	%
Depression	5	2.6	3	1.6	1	2.3
Anxiety	1	0.5	0	0	1	2.3
Chest pain	0	0	0	0	1	2.3
Dyspnea	0	0	0	0	1	2.3

FDA table 5: Serious treatment-emergent adverse events by decreasing incidence F1D-MC-HGGY Study 2, acute phase.

AE term	Placebo (N=184)		Olanzapine (N=179)		OFC (N=43)	
	N	%	n	%	n	%
Depression	7	3.8	6	3.4	1	2.3
Manic reaction	0	0	1	0.6	1	2.3
Psychosis	0	0	1	0.6	1	2.3

2.4.2 Reviewer's comment

- ✚ There is no discernable difference between the pattern of serious adverse events in HGGY-1 and HGGY-2, as the numbers of patients and events are small in the OFC groups.

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2.5 FDA request 5

Please recalculate the regression-based correction factor based on the baseline ECGs collected in the olanzapine/fluoxetine hydrochloride development program. Depending on the factor that is calculated, we may request that you re-correct the QT values included in the analyses in the NDA submission.

2.5.1 Sponsor's response to request 5

The sponsor re-calculated the regression-based QT Interval correction factor using baseline ECG data (3,857 observations) collected during the OFC development program, resulting in a factor of 0.39 ($QT_c = QT/RR^{0.39}$).

2.5.1.1 Reviewer comment

- ✦ The value of 0.39 is very close to the regression factor that was used by the sponsor in the original submission, which is 0.41. Therefore, I do not believe re-calculation of the QT_c values is warranted.

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2.6 FDA request 6

Please explain the inconsistency in number of patients in each treatment group as displayed in Table 11 of the 12/16/02 response for the "Orthostatic Sys BP Decr" and the "Orthostatic Sys BP Low". For these events, the "N" for each treatment group is substantially different (lower) than the "N" for the other PCS vital sign and weight changes. Please provide a corrected table.

2.6.1 Sponsor's response to request 6

The sponsor states that "Orthostatic Sys BP Low" has been removed from this table "because there were no potentially clinically significant criteria set for these measures". I checked the original ISS (table ISS.5.6, page 83) and it was true.

As for the "Orthostatic Sys BP Decr", the original table had 0 of 45 (0%) patients who met the potentially clinically significant (PCS) criteria for orthostatic blood pressure, which was > 30 mm Hg decrease in systolic BP (supine to standing). The sponsor acknowledged that these values were erroneous. The corrected values are 21 of 512 (4%) patients. The data are summarized in the following table.

FDA table 6: Incidence of orthostatic hypotension (fall in SBP supine → standing ≥ 30 mmHg) in various treatment groups in the pooled controlled OFC database.

Event	OFC (N=512)			FLX (N=204)			OLZ (N=644)			PLA (N=445)			
	n	%	Rate*	RR#									
Orthostatic Sys BP Decr	21	4	25	10	5	31	16	2	20	8	2	17	1.46

* Rate is per 100 patient year.

2.6.2 Reviewer's comment

- ✚ Note that there is a slight numerical excess of this adverse event in the OFC than the placebo group.

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2.7 FDA request 7.A.

Please provide the following information in regard to the occurrence of hypotension and bradycardia in the bipolar depression trials:

- Please provide a narrative for any patient who had a fall in heart rate from baseline associated with a decrease in orthostatic systolic blood pressure of >20 mmHg; what adverse events were associated with these changes in vital signs? What was each patient's outcome?
- For patients who reported adverse events related to orthostatic hypotension (including, but not limited to, postural hypotension, syncope, hypotension), please provide the details of the associated vital sign changes and each patient's outcome.
- For patients who reported adverse events related to bradycardia, please describe the associated changes in blood pressure, any associated adverse events, and each patient's outcome.

2.7.1 Sponsor's response to request 7.A. (bullet 1)

FDA request: Please provide a narrative for any patient who had a fall in heart rate from baseline associated with a decrease in orthostatic systolic blood pressure of >20 mmHg; what adverse events were associated with these changes in vital signs? What was each patient's outcome?

Of the 82 OFC-treated patients in the acute bipolar-depressed database who had vital sign measurements for the analysis, 3 (3.7%, RR=1.7) met the criteria of having a decrease in orthostatic pulse (supine to standing) of ≥ 1 bpm and a decrease in orthostatic systolic blood pressure of >20 mm Hg. None of these patients had associated adverse events. In comparison, 1.7% (6 of 351) of olanzapine-treated patients and 2.2% (8 of 357) placebo treated patients met these criteria during the acute phase of the bipolar-depression trials.

One of 82 patients (1.2%, RR=4) treated with OFC in the acute bipolar-depressed database met the criteria of having a decrease in orthostatic pulse of ≥ 1 bpm and a decrease in orthostatic systolic blood pressure of >30 mm Hg. In comparison, 0.6% (2 of 349) of olanzapine-treated patients and 0.3% (1 of 357) placebo-treated patients met these criteria during the acute phase of the bipolar depression trials.

Of 2001 OFC-treated patients in the OFC 2-month safety update database included in the analysis, which includes the bipolar-depressed patients (in addition to patients with treatment-resistant depression and major depressive disorder with or without psychotic features), 37 (1.8%) met the criteria of having a decrease in orthostatic pulse of ≥ 1 bpm and a decrease in orthostatic systolic blood pressure of >20 mm Hg. Three of the 37 patients had associated adverse events (HGFR- 01-1005, HGHZ-20-1956, and HGIP-609-6402). Six of 2001 (0.3%) OFC-treated patients met the criteria of having a decrease in orthostatic pulse (supine to standing) of ≥ 1 bpm and a decrease in orthostatic systolic blood pressure of >30 mm Hg; none had associated adverse events.

FDA table 7: Incidence of patients with a ≥ 1 bpm decrease in orthostatic pulse and a >20 mm hg decrease in orthostatic systolic blood pressure in the OFC pooled database

Event	OFC (N=549)		FLX (N=241)		OLZ (N=659)		PLA (N=455)	
	n	%	N	%	n	%	n	%
Orthostatic Sys pulse and BP decrease	10	1.8	4	1.7	15	2.3	9	2.0

FDA table 8: Incidence of patients with a ≥ 1 bpm decrease in orthostatic pulse and a >30 mm hg decrease in orthostatic systolic blood pressure in the OFC pooled database

Event	OFC (N=549)		FLX (N=241)		OLZ (N=659)		PLA (N=455)	
	n	%	N	%	n	%	n	%
Orthostatic Sys pulse and BP decrease	1	0.2	0	0	3	0.5	1	0.2

2.7.1.1 Summary of selected patients

In the sponsor's data, orthostatic pulse and orthostatic systolic blood pressure are presented, with orthostatic equal to the supine measurement minus the standing measurement. Thus, a **positive** orthostatic measurement represents a **decrease** in that blood pressure or pulse measurement for a patient going from a supine to standing position.

In the following tables I summarized selected patients that met my selection criteria. Those were patients with a drop in orthostatic systolic blood pressure of ≥ 20 mmHg plus related adverse events or ≥ 30 mmHg after the administration of OFC.

FDA table 9: Summary of vital sign data for patients exhibiting a drop in orthostatic systolic blood pressure of ≥ 20 mmHg plus related adverse events or ≥ 30 mmHg.

Patient ID	Maximum decrease in BP	Decrease in pulse	Time on OFC in days	Adverse events	Outcome
HGGY-007-1631	33	9	7	---	Recovered by next visit
HGGY-264-2789	30	10	23	---	Recovered by next visit
HGFR-01-1005	23	30 (pulse was 48)	24	Syncope*	Recovered by next visit
HGHZ-020-1956	24	4	84	Syncope#	Recovered by next visit
HGIP-609-6402	22	8	5	Dizziness\$	Recovered by next visit
HGGA-012-130	30	2	287	---	Recovered by next visit
HGGA-011-1119	30	2	226	---	Recovered by next visit
HGHZ-20-1983	30	4	3	---	Recovered by next visit
HGHZ-48-3379	30	2	10	---	Recovered by next visit
HGIE-006-1267	40	23	113	---	Recovered by next visit
HGIE-303-3104	31	13	195	---	Recovered by next visit
HGIE-28-4352	32	4	140	---	Recovered by next visit

Patient ID	Maximum decrease in BP	Decrease in pulse	Time on OFC in days	Adverse events	Outcome
HGIE-504-5158	43	1	229	---	Recovered by next visit
HGIP-013-1619	30	3	66	---	Recovered by next visit
HGIP-203-2106	33	2	13	---	Recovered by next visit
HGIP-422-5059	30	12	287	---	Recovered by next visit

* This patient was discussed in Section 10.4.2.1.1 (pg 736), Syncope, of the ISS submitted 11/4/2002 and is summarized below.

This patient was discussed in Section 10.4.2.1.1 (pg 734), Syncope, of the ISS submitted 11/4/2002 and is summarized below.

\$ The patient is summarized below.

I also summarized in more details the three symptomatic patients in the following section:

Patient HGFR-001-1005, a 39-year old female reported a fall and subsequent loss of consciousness between Visits 6 (12 days of OFC therapy) and 7 (24 days of OFC therapy). At Visit 1, this patient had a supine blood pressure of 129/85 with a pulse of 65 that changed to 129/97 and 83 upon standing. At Visit 7, this patient had an episode of concomitant decrease in systolic blood pressure (from 128 to 105 mm Hg) and heart rate (from 78 to 48 bpm) upon standing. No dose adjustment was made after this event. Vital signs after this visit were normal. She remained in the study through Visit 303.

Patient HGHZ-020-1956, a 35-year old female had a baseline blood pressure of 104/64 sitting and 102/56 standing. She experienced a decrease in systolic blood pressure (24 mm Hg) and pulse (4 bpm) at Visit 305, 84 days after starting treatment with OFC. She "fainted" while at a fair between Visits 306 (112 days of therapy) and 307 (140 days of therapy). She was taken to the emergency room and was found to be dehydrated. Her vital signs at Visit 306 were: supine blood pressure 94/62 (pulse 72), standing blood pressure 104/68 (pulse 72). At Visit 307, her vital signs were: supine blood pressure 122/84 (pulse 64), standing blood pressure 102/68 (pulse 76). It is worthy to note that this patient had undergone gastric bypass surgery \sphericalangle \downarrow two years before enrolling in the OFC trial.

Patient HGIP-609-6402, a 51-year-old female who experienced a decrease in systolic blood pressure (22 mm Hg) and pulse (8 bpm) at Visit 3, five days after starting treatment with OFC. The supine blood pressure and pulse at that visit were 145/81 and 83, respectively, with subsequent standing blood pressure and pulse 123/82 and 75, respectively. There were no prior or subsequent visits where event criteria were met. She reported "dizziness" at Visit 3. The investigator recorded no comments regarding this event. Concomitant medications included Synthroid and Ativan. The patient remained in the study through Visit 6 and discontinued because of an adverse event, hostility.

2.7.1.2 Sponsor's comment

The sponsor is arguing (in the original ISS, submitted 11/4/02, page 736) that the concomitant hypotension and bradycardia may be due to a "neurally mediated reflex mechanism with symptomatic bradycardia (NMRB)", which, based on the sponsor submission, can occur in up to 10% of the normal population in association with

decreased venous return (Kosinski et al. 1995, Morillo et al. 1997). In these patients, the typical compensatory tachycardia in response to orthostatic hypotension does not occur. Rather, the patient experiences concomitant bradycardia. The sponsor is asserting that NMRB is widely recognized as a benign, ordinarily self-limited, phenomenon.

2.7.1.3 Current olanzapine label (source: original NDA submission dated 11/4/02)

2.7.1.4 Response to FDA request dated 11/13/03

After reviewing the individual patient narratives identified by the sponsor as being “possibly related to the orthostatic hypotension”, it appeared that they used a narrow definition of “possibly related” adverse events (e.g., hypotension, syncope, orthostatic hypotension). Since several patients did sustain injuries that could have been related to falls due to hypotension, it was important to request an investigation of potentially related AEs that had a broader scope. As such, this information was requested from the sponsor (see below).

FDA request: “Provide the incidence of AEs consisting of injuries (eg, lacerations, bruises, fractures) and/or falls for each of the study arms in the OFC Pooled Database (i.e., OFC, olanzapine, fluoxetine, placebo) among patients with a ≥ 1 bpm decrease in orthostatic pulse and a concomitant >20 mmHg or >30 mmHg decrease in orthostatic systolic blood pressure. Please search verbatim terms to identify such AEs because they may be coded to a variety of preferred terms beyond “accidental injury”.”

For any analyses involving “injury and/or fall” the sponsor used the following terms to search the AEs database: abrasion, accidental injury, black, bleed, blood, break, broke, bruise, bump, contusion, crack, cut, discoloration, fall, fracture, gash, graze, hemorrhage, laceration, lesion, rupture, scrape, scratch, shatter, and tear. The use of these terms is reasonable *in this reviewer’s* opinion.

FDA table 10: Incidence of patients with an adverse event possibly associated with an injury and/or fall among patients with a ≥ 1 bpm decrease in orthostatic pulse and a >20 mm hg decrease in orthostatic systolic blood pressure in the OFC pooled database.

Event	OFC (N=10)		FLX (N=4)		OLZ (N=15)		PLA (N=9)	
	n	%	N	%	n	%	n	%
Injury and/or fall	1	10	0	0	0	0	1	10

None of the AEs were serious and none had an associated >30 mm hg decrease in orthostatic systolic blood pressure

2.7.1.5 Reviewer's comment

- ✚ The sponsor is reporting 6 out of 2001 (0.3%) OFC-treated patients as having met the criterion of a decrease in orthostatic systolic blood pressure of >30 mm Hg. However, upon reviewing the narratives I found 13 (0.6%) patients met this criterion.
- ✚ In the acute bipolar-depressed database I found the incidence of decrease in orthostatic systolic blood pressure of >30 mm Hg (regardless of changes in pulse) in the OFC group to be four times that in the placebo group, although this is based on one case in each group.
- ✚ I reviewed the provided references for NMRB and found that they refer to patients with recurrent unexplained syncope that might have a vasodepressor (vasovagal or neurocardiogenic) response responsible for the phenomenon in up to 50% of the cases. Such vasodepressor responses can only be detected through specialized autonomic testing. Otherwise, the pathophysiological mechanisms involved still remain either unknown or incompletely understood. This explanation should not be considered the sole reason for the observed phenomenon of concurrent drop in blood pressure and pulse.
- ✚ Bradycardia must be added to the description of orthostatic hypotension in the OFC label.

- ✦ Other than the bradycardia, the adverse events reported in association with the episodes of hypotension were consistent with what is known about the hypotensive syndrome that occurs with olanzapine as described in its labeling.
- ✦ Although, there were no reported cases of sinus pause (defined as sinoatrial node based irregular pause in heart rate noted on ECG) associated with decreases in blood pressure in OFC-treated patients, we had no ambulatory heart rhythm monitoring to rule out such an event.

2.7.2 Sponsor's response to request 7.A. (bullet 2)

FDA request: For patients who reported adverse events related to orthostatic hypotension (including, but not limited to, postural hypotension, syncope, hypotension), please provide the details of the associated vital sign changes and each patient's outcome.

The sponsor reviewed data for OFC-treated patients who had adverse events possibly related to orthostatic hypotension. In addition to bipolar-depressed patients (F1D-MC-HGGY Studies 1 and 2), all patients in the 2-month safety update database were analyzed. All OFC-treated patients were checked for having had any event, whether it is an actual event term or a mapped COSTART term, that included "syncope", "hypotension", or "conscious" (any term with conscious as the root [e.g., unconscious]).

Of the 82 OFC-treated patients from the acute bipolar-depressed database with measurements available for analysis, none met the criteria. Of the 440 OFC-treated patients from the overall bipolar-depressed database (controlled and open-label data), 9 (2%) met the criteria.

Of the 2001 OFC-treated patients from the 2-month safety update included in the analysis, 74 (3.7%) met the criteria. The sponsor categorized these 74 patients, which include the nine bipolar-depressed patients, into six groups.

The first group was based upon selection of treatment-emergent adverse events occurring at any time (i.e., not necessarily associated with a change in vital signs) specifically suggestive of syncope (20 patients, 1 from HGGY). The other five groups (which include all patients in the first group) were based on specific vital sign measurements at any index episode of a new event (e.g. first occurrence of event suggestive of possible syncope), as follows:

1. Patients with a decrease in blood pressure and a decrease in pulse (11 patients, 2 from HGGY),

2. Patients with a decrease in blood pressure and no change in pulse (10 patients, 2 from HGGY),
3. Patients with a decrease in blood pressure and an increase in pulse (36 patients, 3 from HGGY),
4. Patients with an increase in blood pressure (13 patients, 2 from HGGY), and
5. Patients with no change in blood pressure and an increase in pulse or patients without vitals at the visit in question (4 patients, 0 from HGGY).

The sponsor listed vital signs for each of the patients within each of the six groups. It also provided a brief narrative only for patients with possible syncope, patients with a decrease in blood pressure and a decrease in pulse, and patients with a decrease in blood pressure and no change in pulse. For the purpose of addressing our concern about an OFC-associated decreased blood pressure occurring without a reflex increase in pulse, I reviewed only these three groups.

ECGs were not taken in HGGA and HGFR as part of the study, and thus ECG data is not available for some narratives. A **positive** orthostatic measurement represents a **decrease** in that measurement (blood pressure or pulse) for a patient going from a supine to standing position.

2.7.2.1 Selected patients

2.7.2.1.1 Patients with possible syncope (20 patients, 1 from HGGY)

I reviewed the narratives provided by the sponsor and summarized the ones that met my selection criteria. Those were patients that did not have symptoms before starting OFC and had sustained symptoms for two or more consecutive visits or the reported symptom was in the patient's last visit. Four patients met these criteria, which are summarized below.

Patient HGIP-017-1805:

Patient HGIP-017-1805 is a 33-year-old female who "fainted" after an emotional argument with her husband between Visit 11 and Visit 12. She had reported orthostatic dizziness at Visits 3 (3 days of therapy) and 10 (108 days of therapy). At Visit 11, the patient reported a twisted ankle. At Visit 12, the patient reported fainting. The patient was reported to have syncope at Visit 13. An ECG done at Visit 14 showed bradycardia but was otherwise normal. She reported a bruised elbow and shoulder pain at Visit 15. She remained in the study through Visit 19.

Visit	Visit Date	Therapy	Dias Std BP	Dias Sup BP	Syst Std BP	Syst Sup BP	Pulse Stand-ing	Pulse Sup	Ortho Static Pulse	Ortho- static Systolic	Adverse Event Actual/CoStart
1	2000-04-24		75	80	119	115	79	73	-6	-4	
2	2000-05-09		70	65	140	120	75	72	-3	-20	
3	2000-05-12	OFC	82	83	106	115	91	76	-15	9	ORTHOSTATIC DIZZINESS
4	2000-06-01	OFC	75	70	110	110	78	72	-6	0	
5	2000-06-19	OFC	81	82	113	104	89	82	-7	-9	
6	2000-06-26	OFC	86	93	96	114	118	97	-21	18	
7	2000-07-10	OFC	83	78	115	124	63	69	6	9	
8	2000-07-25	OFC	90	84	106	108	85	75	-10	2	
9	2000-08-11	OFC	87	83	104	106	98	99	1	2	

10	2000-08-25	OFC	65	60	105	110	92	95	3	5	ORTHOSTATIC DIZZINESS, POSTURAL HYPOTENSION
11	2000-09-12	OFC	94	90	119	117	102	95	-7	-2	
12	2000-10-17	OFC	94	89	115	139	108	92	-16	24	FAINING, SYNCOPE
13	2000-11-16	OFC	97	85	121	121	108	86	-22	0	SYNCOPE
14	2000-12-14	OFC	80	76	114	113	83	68	-15	-1	
15	2001-01-30	OFC	91	88	113	115	108	94	-14	2	FAINING, SYNCOPE
16	2001-03-05	OFC	92	76	124	116	105	77	-28	-8	
17	2001-04-09	OFC	85	77	131	117	97	90	-7	-14	
18	2001-05-08	OFC	97	88	116	113	101	88	-13	-3	
19	2001-05-29	OFC	86	82	104	105	92	79	-13	1	

Patient HGIP-001-1046:

Patient HGIP-001-1046 is a 25-year-old female who reported an episode of “syncope” at Visit 23, which was her last recorded visit (18 months into OFC therapy). Investigator comments read: “Patient had an episode of syncope after having her blood drawn this Visit. Patient stated she was feeling woozy, we laid her down and she briefly lost consciousness. We applied a wet compress to her forehead and after about 2 minutes, the patient was awake and feeling her normal self.” The sponsor states that there were no other adverse events reported that were deemed to have been possibly related to orthostatic hypotension. ECG’s were collected at Visits 1, 14, 20, and 23 and were all read as normal. Blood pressure measurements were collected in every visit and did not show orthostatic changes.

Patient HGIP-203-2107:

Patient HGIP-203-2107 is a 36-year-old female with a reported adverse event of “unconscious” at Visit 20, which is the last reported visit (11 months into OFC therapy). This event resulted from an “impulsive overdose” of her study medication; the amount of OFC consumed in the overdose was not available. The only other adverse event deemed possibly related to orthostatic hypotension was “black spots reported in the field of vision” reported at Visit 4 and Visit 5. ECG’s were collected at Visits 1, 14, and 20. Her baseline ECG was read as “abnormal” with a heart rate of 54. Her heart rate was then 56 and 63 at subsequent visits, and there were no significant ECG changes throughout the course of the study. Blood pressure measurements were collected in every visit and did not show orthostatic changes. This patient was discontinued (patient decision) from the study at Visit 20 after the overdose.

Patient HGHZ-020-1956: is summarized in the previous section [use hyperlink to get to the section.

It is worth noting that other patients within this group reported injuries, which are most likely, *in this reviewer’s opinion*, secondary to fall subsequent to loss of consciousness. Patient HGIE-001-1011 reported “bruised cheeks” and “eyebrow laceration”, patient HGFR-01-1005 reported “facial laceration” and “bruises (knee and shoulder)”, patient HGIP-017-1805 reported twisted ankle, bruised elbow and shoulder pain, and patient HGIE-303-3109 reported “sprained right wrist”.

2.7.2.1.2 Patients with a decrease in blood pressure and a decrease in pulse (11 patients, 2 from HGGY)

Eleven patients (2 bipolar-depressed patients) with an adverse event possibly suggestive of orthostatic hypotension were identified as having had a decrease in blood pressure and a decrease in pulse. Three out of these eleven patients had syncope (patients HGFR-001-1005, HGIE-001-1011, and HGIP-017-1805). The decrease in pulse and BP was temporally associated with the clinical adverse event for patient 1005, but not for patient 1805. Patient 1011 had a history of bradycardia at baseline.

I reviewed the narratives provided by the sponsor and summarized the ones that met my selection criteria. Those were patients that did not have symptoms before starting OFC and had sustained symptoms for two or more consecutive visits (associated with low blood pressure measured during the visits) or the reported symptom was in the patient's last visit. Two patients (HGIE-010-1481 summarized below, and HGIP-017-1805 summarized in the previous section [use hyperlink to get to the section]) met the criteria.

Patient HGIE-010-1481:

Patient HGIE-010-1481 is a 68-year-old male. The investigator reported that this patient had sinus bradycardia at baseline. No other comments were made regarding this event. No details are provided in the narrative so I am presenting his actual measurements. I looked for the CRF in the original ISS to try to get more details, but did not find any. Although the patient had borderline sinus bradycardia at baseline, I included this case in my review because of the persistent nature of his low blood pressure.

Visit	Visit Date	Therapy	Dias Std BP	Dias Sup BP	Syst Std BP	Syst Sup BP	Pulse Stand-ing	Pulse Sup	Ortho static Pulse	Ortho- static Systolic	Adverse Event Actual/CoStart
1	2001-03-27		70	70	96	100	60	60	0	4	
2	2001-04-03		64	72	92	120	68	64	-4	28	
3	2001-04-10	VNL	76	78	92	106	68	64	-4	14	
4	2001-04-17	VNL	76	82	98	110	80	66	-14	12	
5	2001-04-23	VNL	76	80	102	108	68	68	0	6	
6	2001-05-09	VNL	62	68	92	96	64	66	2	4	
7	2001-05-23	VNL	78	74	106	110	68	66	-2	4	
8	2001-05-31	VNL	80	78	106	110	62	58	-4	4	
9	2001-06-05	OFC	72	70	108	106	72	64	-8	-2	
10	2001-06-08	OFC	68	70	102	100	58	60	2	-2	
11	2001-06-13	OFC	70	80	120	120	60	62	2	0	
12	2001-06-22	OFC	80	76	106	104	76	64	-12	-2	
13	2001-06-27	OFC	70	70	100	98	72	64	-8	-2	
14	2001-07-03	OFC	60	64	102	108	65	71	6	6	
15	2001-07-10	OFC	70	70	100	100	61	54	-7	0	
16	2001-07-17	OFC	60	70	90	98	66	53	-13	8	
17	2001-07-26	OFC	70	70	92	94	60	56	-4	2	
18	2001-08-01	OFC	62	70	90	94	58	60	2	4	
19	2001-08-08	OFC	70	68	92	98	68	64	-4	6	
20	2001-08-15	OFC	68	68	100	98	68	58	-10	-2	
21	2001-08-21	OFC	60	58	90	90	61	59	-2	0	
301	2001-08-29	OFC	68	80	92	92	60	66	6	0	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
302	2001-09-07	OFC	70	60	94	92	60	58	-2	-2	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
303	2001-09-21	OFC	60	62	92	94	64	66	2	2	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
304	2001-10-17	OFC	78	62	98	98	60	58	-2	0	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION

305	2001-11-14	OFC	62	60	98	99	62	58	-4	1	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
306	2001-12-12	OFC	72	72	96	100	62	58	-4	4	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
307	2002-01-09	OFC	72	64	98	92	59	60	1	-6	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
308	2002-03-06	OFC	70	62	92	90	68	62	-6	-2	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
309	2002-05-02	OFC	68	70	92	104	72	64	-8	12	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION
310	2002-06-26	OFC	50	60	90	98	68	60	-8	8	ORTHOSTATIC HYPOTENSION POSTURAL HYPOTENSION

2.7.2.1.3 Patients with a decrease in blood pressure and no change in pulse (10 patients, 2 from HGGY)

I reviewed the narratives of patients in this section and found no symptoms reported with the episodes of hypotension that is beyond what is known about the hypotensive syndrome that occurs with olanzapine as described in its labeling.

2.7.2.2 Reviewers comments

- ✚ One patients reported "black spots in the field of vision". This is more likely due to postural hypotension, than to a primary visual adverse event. Nonetheless, I discussed the finding with the pharmtox reviewer for possible ocular findings in animals and there were no abnormal ophthalmoscopic or histopathologic findings in sub-chronic studies in rats (study # R03500) and dogs (study # D01700). Additionally, I did not identify any excess of visual events associated with OFC in my original review of the NDA safety database.
- ✚ Otherwise, no symptoms reported with the episodes of hypotension that is beyond what is known about the hypotensive syndrome that occurs with olanzapine as described in its label.
- ✚ Although here were no cases of sinus pause (defined as sinoatrial node based irregular pause in heart rate noted on ECG) associated with decreases in blood pressure in OFC-treated patients, we had no ambulatory heart rhythm monitoring to rule out such an event.
- ✚ Based on individual patient narratives, there is more evidence that information should be added to the label to draw the attention of patients that OFC-related orthostatic hypotension might lead to falls and injuries.
- ✚ Upon reviewing the individual patients' data, I noted that some patients have adverse events that are ongoing at many subsequent visits. The sponsor is arguing that this is probably due to the principal investigators not adding a stop date to the event. This argument seems to hold because the reported blood pressure measurements do

not show sustained orthostatic hypotension in these patients. However, the sponsor's contention may not be true if patients are experiencing intermittent orthostatic hypotension that is not picked up on routine visits.

2.7.2.3 Response to FDA request dated 11/13/03

After reviewing the individual patient narratives, it seemed important to compare the frequency of these events occurring in association with OFC with the frequency in the comparator groups. As such, this information was requested from the sponsor (see below).

FDA request: “For each of the six subgroups (e.g., possible syncope, decreased BP + decreased pulse, etc) described in this section, please provide the incidence among each of the study arms in the OFC Pooled Database (i.e., OFC, olanzapine, fluoxetine, placebo). The incidence of SAEs should also be reported.”

FDA table 11: Incidence of patients with adverse events possibly related to orthostatic hypotension by treatment group and blood pressure/pulse response in the OFC pooled database.

Event	OFC (N=571)		FLX (N=251)		OLZ (N=685)		PLA (N=477)	
	n	%	N	%	n	%	n	%
↓BP + ↓P	3	0.5	2	0.8	4	0.6	4	0.8
↓BP + ↔P	2	0.4	0	0	3	0.4	1	0.2
Both*	5	0.9	2	0.8	7	1.0	5	1.0
Possible syncope	2	0.4	1	0.4	2	0.3	1	0.2

* includes patients with syncope, ↓BP + ↓P, and ↓BP + ↔P.

None of the events were serious.

Additionally, the review of the individual patient narratives identified by the sponsor as being “possibly related to the orthostatic hypotension” showed that they used a narrow definition of “possibly related” adverse events (e.g., hypotension, syncope, orthostatic hypotension). Since several patients did sustain injuries that could have been related to falls due to hypotension, it was important to request an investigation of potentially related AEs that had a broader scope. As such, this information was requested from the sponsor (see below).

FDA request: “Among the patients in the three categories of possible syncope, decreased BP + decreased pulse, and decreased BP + no change in pulse, provide the incidence of AEs consisting of injuries (eg, lacerations, bruises, fractures) and/or falls for each of the study arms in the OFC Pooled Database (i.e., OFC, olanzapine, fluoxetine, placebo). Please search verbatim terms to identify such AEs because they

may be coded to a variety of preferred terms beyond “accidental injury”. The incidence of SAEs should also be reported.”

FDA table 12: Incidence of patients with an adverse event possibly associated with an injury and/or fall among patients with possible syncope, decreased blood pressure and decreased pulse, or decrease blood pressure and no change in pulse in the OFC pooled database.

Event	OFC (N=5)		FLX (N=2)		OLZ (N=7)		PLA (N=5)	
	n	%	N	%	n	%	n	%
Injury and/or fall	2	40	1	50	1	14	0	0

2.7.2.4 Reviewer comment

The frequency of patients with adverse events possibly related to orthostatic hypotension was similar across the treatment arms in the OFC pooled database. There were too few injuries/falls among patients with decreased blood pressure and pulse to comment on the differences between the treatment arms.

2.7.3 Sponsor’s response to request 7.A. (bullet 3)

FDA request: For patients who reported adverse events related to bradycardia, please describe the associated changes in blood pressure, any associated adverse events, and each patient’s outcome.

The sponsor reviewed the data for all OFC-treated patients in the OFC 2-month safety update database who met one of the following criteria: reported an adverse event of “bradycardia” or “sinus bradycardia”, had a pulse <50 bpm (per vital signs), or had a heart rate <50 bpm (per ECG). The vital signs, other adverse events, and outcomes associated with the bradycardia were reviewed. Five (none were bipolar-depressed patients) of the 55 patients who met one of these three criteria had a possibly related adverse event. I summarized those patients below. Of the 55 patients, none were patients from the acute bipolar-depressed controlled database, and seven (open-label patients) were from the overall bipolar-depressed database.

Patient [HGFR-01-1005](#): reviewed in a previous section [use hyperlink to get to the section].

Patient HGGA-026-2608: is a 34-year-old female who had “bradycardia” reported at Visits 2 through 303 (study days -7 through 70). Her baseline (about two months before starting OFC) ECG revealed an “irregular sinus bradycardia” (reported pulse is 66 and 64 bpm standing and supine, respectively) which was deemed not clinically significant by the investigator. At Visit 301 (she started OFC at this visit) the patient reported “dizziness”, and at Visit 303 (15 days after starting OFC), she complained of intermittent

“yellow spots before eyes”, lasting a few minutes. ECGs taken prior to treatment and while the patient was on blinded placebo were read as “abnormal”. No further information regarding the ECG findings is available. This patient was lost to follow-up after Visit 303, and no further information is available.

Patient HGIE-001-1011 is a 38-year-old male who had a history of sinus bradycardia documented on ECG at Visit 1 (heart rate = 46 bpm, about two months before starting OFC) and a history of passing out when experiencing pain. The patient was reported to have had syncope between Visit 13 (28 days of therapy) and Visit 14 (35 days of therapy). The patient reported some sequelae of the syncope, including “bruised cheeks,” and “eyebrow laceration.” A review of all of the patient’s adverse events revealed the following: the patient had “dizziness” at Visit 4, prior to starting OFC. Subsequently to starting OFC, the patient reported mild “dizziness” at Visit 11 (10 days on OFC therapy) and mild “dizziness upon standing” and mild “fatigue” at Visit 305 (7 months on OFC). ECGs were collected at Visits 1, 8, 17, 21, and 305. All were read as “abnormal”, based on bradycardia (46, 52, 44, 55, and 32, respectively). There were no significant ECG changes during the course of the trial. He remained in the study through Visit 305 (7 months on OFC). The patient discontinued from the trial for clinically significant laboratory tests that are not specified.

Patient HGIP-011-1504 is a 72-year-old female who had a baseline pulse of 48 at Visit 3 (she started OFC at this visit) and 45 at Visit 11 (about three months after starting OFC). This patient reported mild “disequilibrium” at Visit 7, which lasted through Visit 17, and “hip injury” (not recorded as an SAE) at Visit 8, although no comments were made by the investigator regarding either of these events. ECGs were collected at Visits 1, 14, 20, and 23 with “myocardial infarct” from baseline on, and heart rates of 61, 54, 57, and 62, respectively. Sinus bradycardia was noted at Visit 14 (pulse 64 and 61, standing and supine, respectively) and Visit 20 (pulse 72 and 64, standing and supine, respectively). There were no significant ECG changes during the course of the trial. The patient remained in the study through the completion of the protocol, Visit 23.

Patient HGIP-607-6302 is a 32-year-old female who had a pulse of 47 at Visit 11 (1/3/2001) about three months after starting OFC). Her baseline pulse was 88 standing and 68 supine, respectively). This patient reportedly “tripped and fell” during the Visit 8 interval, resulting in a bruise under her eyes (left) and right buttocks. No comments were made by the investigator regarding the bradycardia or the tripping. The patient had chest pain from Visit 13 through Visit 15. The patient also broke her left shoulder (Visit 14, associated with an “accidental injury”). ECGs were collected at Visit 1 and Visit 14 and were both read as normal. There were no significant ECGs during the course of the study. This patient remained in the study through Visit 18 and discontinued secondary to inability to keep appointments.

2.7.3.1 Response to FDA request dated 11/13/03

The review of the individual patient narratives identified by the sponsor as being “possibly related to the orthostatic hypotension” showed that they used a narrow

definition of “possibly related” adverse events (e.g., hypotension, syncope, orthostatic hypotension). Since several patients did sustain injuries that could have been related to falls due to hypotension, it was important to request an investigation of potentially related AEs that had a broader scope. As such, this information was requested from the sponsor (see below).

FDA request: “Among the patients who met one or more of the criteria for bradycardia, provide the incidence of AEs consisting of injuries (eg, lacerations, bruises, fractures) and/or falls for each of the study arms in the OFC Pooled Database (i.e., OFC, olanzapine, fluoxetine, placebo). Please search verbatim terms to identify such AEs because they may be coded to a variety of preferred terms beyond “accidental injury”. The incidence of SAEs should also be reported.”

FDA table 13: Incidence of patients who met criteria for bradycardia in the OFC pooled database

Event	OFC (N=571)		FLX (N=251)		OLZ (N=685)		PLA (N=477)	
	n	%	n	%	n	%	n	%
Possible bradycardia	11	1.9	6	2.4	6	0.9	13	2.7

FDA table 14: Incidence of patients with an adverse event possibly associated with an injury and/or fall among patients who met criteria for bradycardia in the OFC pooled database.

Event	OFC (N=11)		FLX (N=6)		OLZ (N=6)		PLA (N=13)	
	n	%	n	%	n	%	n	%
Injury and/or fall	2	18	0	0	0	0	0	0

None of the events were serious.

2.7.3.2 Reviewers comments

- ↓ One patient reported “intermittent yellow spots before eyes, lasting a few minutes” 15 days after starting OFC. As I mentioned earlier, this visual change is more likely due to postural hypotension than a primary visual effect related to the OFC. However, the recorded blood pressure measurement during the patient’s visit did not suggest this as the change was 2 mmHg from supine to standing. Nonetheless, these blood pressure measurements were not likely taken at the same time as the patient’s complaint.
- ↓ It seems, from FDA table 14, that there is some trend towards higher rate of injury and/or falls in the OFC group among those with possible bradycardia. However, the numbers are too small to support a strong conclusion from the data.

2.8 FDA request 7.B.

In the controlled pooled OFC population, compare the subset of patients who were antipsychotic naïve to those who had been previously exposed to antipsychotics and provide the following analyses:

- Calculate mean change in orthostatic systolic and diastolic blood pressures across the treatment groups.
- Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at any time.
- Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at endpoint.
- Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at any time.
- Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at endpoint.

2.8.1 Sponsor's response to request 7.B. (bullet 1)

The sponsor reviewed the data to determine whether or not a difference exists between patients who have previously been treated with antipsychotics and those who have not with regard to the risk of developing orthostatic hypotension during treatment with OFC. The sponsor is noting that 94% of all of the patients treated in the acute phases of the OFC trials were antipsychotic naïve. The percentage of antipsychotic naïve patients in the acute bipolar depressed database was 91%.

FDA table 15: Mean change in orthostatic systolic blood pressure comparing antipsychotic naïve versus previously exposed to anti-psychotics (AP) within OFC pooled database (source: table 7, submission dated 6/24/03, page 364).

	FLX			OFC			OLZ			PLA		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
No previous AP use	201	0.79	9.06	494	-0.43	8.61	594	-0.32	8.69	391	-0.12	9.06
Previous AP use	0	--	--	15	-0.27	10.45	46	1.39	9.28	54	-0.54	10.07
P-value	-			0.94			0.20			0.75		

FDA table 16: Mean change in orthostatic systolic blood pressure comparing antipsychotic naïve versus previously exposed to anti-psychotics (AP) within acute bipolar-depressed database (source: table 19, submission dated 6/24/03, page 384).

	OFC			OLZ			PLA		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
No previous AP use	75	-0.05	7.27	318	-0.10	8.32	313	-0.33	9.03
Previous AP use	7	-3.14	11.26	30	0.63	9.55	41	-1.59	7.04
P-value	0.3			0.7			0.4		

2.8.2 Sponsor's response to request 7.B. (bullets 2 and 3)

FDA table 17: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>30 mm hg) at any time comparing antipsychotic naïve versus previously exposed to antipsychotics within OFC pooled database (source: tables 10 and 11, submission dated 7/31/03, page 27).

	No previous AP use				Previous AP use				
	N	n	%	Rate*	N	n	%	Rate*	
FLX	204	8	4	25	0	0	0	UN	
OFC	497	13	3	16	15	0	0	0	
OLZ	597	9	2	12	47	1	2	62	
PLA	394	3	1	7	54	0	0	0	
RR#	-				2.22	-			UN

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

UN=undefined

FDA table 18: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>30 mm hg) at endpoint comparing antipsychotic naïve versus previously exposed to antipsychotics within OFC pooled database (source: tables 12 and 13, submission dated 7/31/03, page 29).

	No previous AP use				Previous AP use				
	N	n	%	Rate*	N	n	%	Rate*	
FLX	204	1	0.5	3	0	0	0	UN	
OFC	497	1	0.2	1	15	0	0	0	
OLZ	597	2	0.3	3	47	0	0	0	
PLA	394	1	0.3	2	54	0	0	0	
RR#	--				0.5	-			UN

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

UN=undefined

FDA table 19: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>30 mm hg) at any time comparing antipsychotic naïve versus previously exposed to antipsychotics within acute bipolar-depressed database (source: tables 18 and 19, submission dated 7/31/03, page 35).

	No previous AP use				Previous AP use				
	N	n	%	Rate*	N	n	%	Rate*	
OFC	75	4	5	42	7	0	0	0	
OLZ	320	2	1	6	31	1	3	29	
PLA	316	1	0.3	3	41	0	0	0	
RR#	-				13.9	-			UN

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

UN=undefined

FDA table 20: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>30 mm hg) at endpoint comparing antipsychotic naïve versus previously exposed to antipsychotics within acute bipolar-depressed database (source: tables 20 and 21, submission dated 7/31/03, page 37).

	No previous AP use				Previous AP use			
	N	n	%	Rate*	N	n	%	Rate*
OFC	75	0	0	0	7	0	0	0
OLZ	320	0	0	0	31	0	0	0
PLA	316	1	0.3	3	41	0	0	0

RR#	--	UN	--	UN
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* Rate is per 100 patient years.
 # Rate ratio is calculated as OFC rate/PLA rate.
 UN=undefined

2.8.3 Sponsor's response to request 7.B. (bullets 4 and 5)

FDA table 21: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>20 mm hg) at any time comparing antipsychotic naïve versus previously exposed to antipsychotics within OFC pooled database (source: tables 14 and 15, submission dated 7/31/03, page 31).

	No previous AP use				Previous AP use			
	N	N	%	Rate*	N	n	%	Rate*
FLX	204	27	13	84	0	0	0	UN
OFC	497	44	9	54	15	2	13	120
OLZ	597	44	7	58	47	4	9	77
PLA	394	26	7	62	54	5	9	103
RR#	--			0.87	--			1.17

* Rate is per 100 patient years.
 # Rate ratio is calculated as OFC rate/PLA rate.
 UN=undefined

FDA table 22: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>20 mm hg) at endpoint comparing antipsychotic naïve versus previously exposed to antipsychotics within OFC pooled database (source: tables 16 and 17, submission dated 7/31/03, page 33).

	No previous AP use				Previous AP use			
	N	N	%	Rate*	N	n	%	Rate*
FLX	204	3	1	9	0	0	0	UN
OFC	497	6	1	7	15	0	0	0
OLZ	597	9	2	12	47	0	0	0
PLA	394	8	2	19	54	0	0	0
RR#	--			0.39	--			UN

* Rate is per 100 patient years.
 # Rate ratio is calculated as OFC rate/PLA rate.
 UN=undefined

FDA table 23: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>20 mm hg) at any time comparing antipsychotic naïve versus previously exposed to antipsychotics within acute bipolar-depressed database (source: tables 22 and 23, submission dated 7/31/03, page 39).

	No previous AP use				Previous AP use			
	N	n	%	Rate*	N	n	%	Rate*
OFC	75	7	9	73	7	1	14	121
OLZ	320	10	3	29	31	3	10	86
PLA	316	18	6	54	41	4	10	103
RR#	--			1.35	--			1.17

* Rate is per 100 patient years.
 # Rate ratio is calculated as OFC rate/PLA rate.
 UN=undefined

FDA table 24: Rates of patients with potentially clinically significant decrease in orthostatic blood pressure (>20 mm hg) at endpoint comparing antipsychotic naïve versus previously exposed to antipsychotics within acute bipolar-depressed database (source: tables 24 and 25, submission dated 7/31/03, page 41).

	No previous AP use				Previous AP use			
	N	n	%	Rate*	N	n	%	Rate*
OFC	75	0	0	0	7	0	0	UN
OLZ	320	3	1	9	31	0	0	0
PLA	316	5	2	15	41	0	0	0
RR#	--				0			

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

UN=undefined

2.8.4 Reviewer's comments

- In general, there is an apparent pattern, although not consistent, in some analyses (FDA-tables 10 and 12) to support the notion that patients that "AP naive" might be more susceptible to orthostatic blood pressure changes. However, note that the number of patients in the groups with "previous AP use" is too small to support any strong conclusion from the data.
- The difference between the rates of orthostatic changes as measured at "end point" and at "any time", with the former usually lower than the latter, might reflect the patients' accommodation to the hypotensive effects of OFC.

2.8.5 Sponsor's conclusions in response to request 7

"The data presented in the response to Statement 7 demonstrate that some OFC patients had generally transient changes in vital signs that is consistent with both historical olanzapine data and olanzapine data contained within this submission. The potential change in vital signs does not appear to differ between antipsychotic naïve patients and those with a history of treatment with antipsychotics, nor does it appear to significantly differ between patients with bipolar depression and those with other diagnoses included in the OFC 2-month update safety database. Moreover, for patients with a possibly clinically significant change in vital signs, the change typically occurred at a single visit."

2.9 FDA request 8

Please provide a new Table 7 from the 12/16/02 submission "Incidence of Diabetes Mellitus and hyperglycemia in the olanzapine/fluoxetine hydrochloride pooled data" excluding the patients who had pre-existing diabetes mellitus at baseline.

To clarify the difference in findings I included here a table with the original data:

FDA table 25: Incidence of Diabetes Mellitus and hyperglycemia[®] in the OFC pooled data (source: submission 12/16/2002, sponsor's table 7).

Event	OFC (N=571)			FLX (N=251)			OLZ (N=685)			PLA (N=477)			
	n	%	Rate*	N	%	Rate*	n	%	Rate*	N	%	Rate*	RR#
Diabetes Mellitus	5	1	6	0	0	0	1	0.15	1	1	0.21	2	2.74
Hyperglycemia	6	1	7	0	0	0	8	1	10	0	0	0	undefi ned

@ Analysis includes patients with preexisting diabetes.

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

2.9.1 Sponsor's response to request 8

The sponsor presented the requested information, which I summarized in the next table:

FDA table 26: Incidence of Diabetes Mellitus and hyperglycemia[@] in the OFC pooled data (source: submission 6/24/2003, response_8-10.pdf, sponsor's table 1).

Event	OFC (N=541)			FLX (N=243)			OLZ (N=659)			PLA (N=445)			
	n	%	Rate*	RR#									
Diabetes Mellitus	3	1	4	0	0	0	0	0	0	0	0	0	undefi ned
Hyperglycemia	3	1	4	0	0	0	4	1	5	0	0	0	undefi ned

@ Analysis excludes patients with preexisting diabetes or hyperglycemia.

* Rate is per 100 patient years.

Rate ratio is calculated as OFC rate/PLA rate.

2.9.2 Reviewer's comments

- ✚ The reanalysis still show that both the cases of diabetes mellitus and hyperglycemia are numerically higher in the OFC group and in the olanzapine group than placebo.

2.10 FDA request 9

The fluoxetine labeling and proposed olanzapine/fluoxetine hydrochloride labeling includes a statement in the Warnings section about allergic reactions that says, "Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis have been reported rarely. These events have occurred with dyspnea as the only preceding symptom."

At least two patients treated with olanzapine/fluoxetine hydrochloride have had serious AEs that might qualify as such a pulmonary event.

- Patient HGIE-025-4206 developed pneumonitis after about 10 weeks on olanzapine/fluoxetine hydrochloride therapy. She was discontinued due to persistent dyspnea. Please provide any additional follow-up that describes her response to dechallenge. Also, was any additional work-up performed to investigate the elevated sedimentation rate (e.g., a work-up for connective tissue disease)?

- Patient HGIP-608-6354 developed lung “crackles”, dyspnea on exertion, and a chest x-ray finding that led to hospitalization for work-up of these abnormalities. What was the finding on the chest x-ray that led to the hospitalization? Following the hospitalization, the patient remained on olanzapine/fluoxetine hydrochloride. Did the dyspnea on exertion resolve? Did she require additional work-up? Was any diagnosis made with regard to her pulmonary abnormality?
- Did any other patients in the olanzapine/fluoxetine hydrochloride development program develop a pulmonary syndrome or symptoms consistent with the Warnings statement in labeling?

2.10.1 Sponsor’s response to request 9

The sponsor provided the requested details on the two cases.

Patient HGIE-025-4206:

This patient is a 48-year-old female smoker with a long history of hypertension, allergies, and sinus surgeries who experienced “pneumonitis” first reported 32 days (Visit 13, 27 _____) after starting treatment with OFC. The pneumonitis continued through patient’s discontinuation from the study at Visit 301 (_____) Her last dose of study medication was 24 September 2001. The patient was hospitalized for 4 days at Visit 15 (_____) for pneumonitis and a second time on (_____) at Visit 20 for shortness of breath with “hypoxia secondary to acute interstitial pneumonitis.” The latter admission record noted the following: The patient was being followed by a pulmonologist for chronic interstitial lung disease and had a CT scan showing the “presence of ground glass appearance of the lungs.” A thoracoscopy had been done on (_____) and a biopsy (_____) showed “mild interstitial fibrosis.” Previous chest x-rays had identified interstitial infiltrates. Labs done approximately 1 month prior to the second hospitalization revealed a sedimentation rate of 130, positive c-reactive protein, and negative ANA and rheumatoid factors. The sedimentation rate at time of hospitalization was 104. It was also stated in the admission note that “The patient works in a very dusty atmosphere.” The patient was discharged on a tapering dose of prednisone. There was no available follow-up data on the patient until (_____) at which time it was revealed that the patient is stable and occasionally has had crackles in her lungs related to seasonal allergies.

Patient HGIP 608-6354:

This patient is a 60-year-old obese female with history of hypertension who reported “shortness of breath” (actual term was ‘breathing heavy’) starting at Visit 4 and had reported “crackles in lungs” starting at Visit 5. The comments from the investigator stated that the patient “was admitted to hospital for investigation of crackles in lungs.” Work up included a chest X-ray that was read as normal and a “Gated Blood Pool Scan” that was also normal. These findings ruled out congestive heart failure or previous myocardial infarction. No positive diagnosis was attributed to the patient’s condition, and additional

follow-up was not needed. She remained in the trial through Visit 14 and discontinued due to weight gain.

The sponsor further reviewed the database of OFC-treated patients in order to identify any other patients who might have had pulmonary syndrome or symptoms consistent with the warnings statement in proposed labeling. While no additional patients were identified as having a pulmonary syndrome consistent with the label, the sponsor provided narratives for all patients who had respiratory adverse events that appeared possibly suggestive of clinical concern in the sponsor's research physician's opinion. I summarized these narratives in the following table:

FDA table 27: Summary of narratives for patients who had respiratory adverse events that appeared possibly suggestive of clinical concern in the sponsor's opinion

Patient ID *	Adverse events	Time on OFC in days	Investigations	Medical history	Outcome
HGGA-022-2201	Acute pancreatitis, MI, possible pneumonia	8, onset might have been prior to OFC	Urine culture +ve for e-coli, CXR +ve rt lobe infiltrate, elevated cardiac enzymes, +ve dobutamine thallium test, +ve echocardiogram, high amylase (235) and lipase (200)	GERD, lupus, hypothyroidism, COPD, alcohol abuse, and hypertension.	All events resolved in three weeks, patient continued on drug for 93 days
HGGY-052-1655	chest pain and shortness of breath	12	Patient discharged 2 days later. No investigations reported.	Exercise-induced asthma, hypercholesterolemia, hypertension, MI and quadruple cardiac bypass surgery.	Chest pain resolved next day, patient discharged and discontinued 2 days later
HGIE-016-1752	Pneumonia	221	No investigations reported for pneumonia	Insulin-dependent diabetes mellitus and hypertension.	Discharged in "stable condition" after 5 days
HGIE-017-1807	shortness of breath upon exertion, productive cough, difficulty breathing supine, and peripheral edema	16	Normal cardiac enzymes, CBC, and CXR, sinus tach in ECG, +ve echocardiogram, Doppler scan -ve for DVT	obesity, hypertension, irritable bowel syndrome, recent bouts of diarrhea, chronic osteoarthritis, hyperlipidemia, and hypothyroidism.	Discharged in 2 days without diagnosis, edema persisted until end of study, other events resolved. Patient continued on drug for 353 days
HGIE-017-1815	chest discomfort and dyspnea on exertion	21	Normal CXR, ECG, troponin test, lung ventilation and perfusion scan,	Obesity, hypertension, and bronchitis.	Symptoms resolved next day without diagnosis

Patient ID *	Adverse events	Time on OFC in days	Investigations	Medical history	Outcome
			venous duplex, adenosine scan. Grade 2/6 murmur of mitral regurgitation was heard at the apex.		

* [HGHZ-027-2305](#) is summarized under response for request 10 [use hyperlink to get to the section].

2.10.2 Reviewer Comment

- For patient HGIE-025-4206 the pneumonitis was temporally related to OFC and the information provided does not clear OFC from having a potential role in the development of the AE.
- For patient HGIP 608-6354, although no formal diagnosis was conferred, the workup does not clear OFC from having a potential role.
- The additional cases described by the sponsor do not raise concerns related to the current labeling on pulmonary events.

2.11 FDA request 10

Follow-up was requested on specific cases; see subsections below for details of requests.

2.11.1 Sponsor's response to request 10

The sponsor provided the requested details on the cases.

2.11.1.1 Patient HGHZ-027-2305:

FDA request: Please provide any additional details available regarding this patient's complicated hospital course. A skin biopsy and the report of a dermatological consultant regarding the diagnosis and etiology of the toxic epidermal necrolysis would be particularly helpful. Also, if an autopsy was conducted, please submit the autopsy report.

This 60-year-old male patient's first dose of OFC was 18 May 2000 and his last dose was on 26 July 2000. On [redacted] he complained of left-sided back pain to his primary care physician and was diagnosed with nephrolithiasis. On [redacted] the diagnosis was confirmed, and a questionable right pelvic mass was identified by ultrasound. The patient also noticed increased pain and swelling of his small joints as well as generalized body edema. According to his hospital discharge summary, he was admitted to the

hospital on [redacted], with a diagnosis of septicemia NOS. The patient had an extremely complicated hospital course, which included diagnoses of staph aureus septicemia with shock, respiratory insufficiency, hypotension, atrial fibrillation, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, hypokalemia, hypomagnesemia, diabetes mellitus, drug rash (toxic epidermal necrolysis, believed to be secondary to nafcillin), and anasarca. The patient had a history of diabetes, hypercholesterolemia, nephrolithiasis, and osteoarthritis.

On [redacted] the patient was first noted to have a macular, erythematous rash on his torso and extremities, sparing his face. At the time, sotalol was discontinued, as it was the only recently added medication. The rash continued to get worse, however, and the patient developed a mucositis, so the nafcillin and rifampin, as well as the morphine, were discontinued on [redacted] per dermatology recommendations. At this time the dermatologist diagnosed the patient with toxic epidermal necrolysis. He was then seen by the burn team who recommended BID body washes with hibiclens and bacitracin and exu-dry dressing on affected areas.

There was no apparent skin biopsy or additional dermatological report. The discharge summary noted that the toxic epidermal necrolysis appeared to be a drug reaction, probably due to nafcillin.

The patient's final diagnosis and cause of death on [redacted] was staph aureus septic shock with renal involvement, leading to respiratory insufficiency, rhabdomyolysis, and disseminated intravascular coagulation. No autopsy was performed. According to a Lilly analysis statement created on [redacted] there was an inability to exclude causality on the basis of available information. Nephrolithiasis probably contributed to the development of urosepsis, septic shock, and death. Toxic epidermal necrolysis probably contributed to death, and this was probably secondary to antibiotic treatment.

2.11.1.1 Reviewer comment:

The patient was diagnosed with TEN about a month after he stopped OFC. The clinical course suggests that other drugs might be responsible.

2.11.1.2 Patient HGIP-007-1334:

FDA request: Please provide any details that might be available of the "allergic reaction" that led the patient to discontinue from the trial.

This patient was a 33-year-old female who discontinued the study via communication over the telephone citing an allergic reaction. The site did not observe the patient and no assessment was done. The site did enter the following comments on the case report form: "the patient will be discontinued from the study due to an apparent allergic reaction, which included among other symptoms swelling of her throat with labored breathing." According to the patient, all of the symptoms resolved. Although the patient did not

return for a final visit, medications were eventually returned on 22 August 2000. The patient took three days worth of medication (OFC 6 mg/25 mg).

2.11.1.2.1 Reviewer comment:

The clinical course does not clear OFC from having a potential role in the development of the AE. In total, ten OFC-treated patients had an allergic reaction in the controlled dataset, but only patient number 1334 discontinued because of one.

2.11.1.3 Patient HGIE-026-4253:

FDA request: Was there any additional follow-up for this patient after he discontinued for a convulsion?

This patient is a 28-year-old male who was randomized to fluoxetine treatment on 04 June 2001. He entered the open-label OFC treatment phase on 04 September 2001. The patient reported the serious adverse event of convulsion on [redacted] (between Visit 306 and Visit 307), and was hospitalized for seizure. He was not treated with any medications and was discharged on [redacted]. The patient's last dose of open-label study drug was 11 February 2002, and he was discontinued from the trial on 12 February 2002 (Visit 307) due to the previous convulsion event. The patient was not receiving any concomitant medications at the time of the reported seizure, and he did not have a history of previous seizure disorder.

The event was witnessed by friends who reported full body shaking for one minute after he had vomited several times. Physical examination revealed an area of ecchymosis and laceration on the right side of his tongue. There was no loss of urine. The EEG, while awake, was normal. The head CT scan was normal. A toxicology screen was positive for marijuana. The site has not been able to get a hold of the patient for further follow-up. The only information they have been able to obtain is from his roommate, who stated that the patient has not had a further seizure.

2.11.1.3.1 Reviewer comment:

The clinical course does not clear OFC from having a potential role in the development of the AE. Three other OFC-treated patients had seizures and are detailed in my original review.

2.11.1.4 Patient HGIE-303-3108:

FDA request: After the patient was treated for the allergic reaction, how much longer was she maintained on olanzapine/fluoxetine hydrochloride? Did she have to stay on prednisone? If so, for how long?

The patient is a 48-year-old female who was randomized to OFC 12 mg/25 mg on 18 April 2001. On [redacted] she was admitted to the hospital for swelling of lips and tongue, nausea and wheezing, and red welts under the arm pits. She was treated intravenously with saline, phenergan, and hydrocortisone and was started on oral prednisone and valium. She took the prednisone for three days and remained in the study without further symptoms. The event was reported as resolved on [redacted]. The patient remained in the study until 28 August 2001, at which time the patient discontinued due to patient perception of lack of efficacy.

2.11.1.4.1 Reviewer comment:

The clinical course does not clear OFC from having a potential role in the development of the AE, although the negative rechallenge does not support a causative role for OFC in this episode of angioedema.

2.11.1.5 Patient HGIE-013-1602:

FDA request: The patient was admitted to the hospital with dyspnea after nine months on open label olanzapine/fluoxetine hydrochloride and received a diagnosis of congestive heart failure. The narrative did not describe what diagnostic tests were done to make that diagnosis and the treatment for CHF was not specified. Please provide this information. If CHF treatment was added, did the patient have to stay on it chronically?

The patient is a 38-year-old female who was randomized to venlafaxine treatment on 30 May 2000. The patient was exposed to 143 days of venlafaxine treatment including double-blind therapy and the venlafaxine lead-in phase. The patient entered the open-label OFC treatment phase on 01 September 2000. The patient's medical history included morbid obesity, hypertension, poorly controlled Type 2 diabetes mellitus, diabetic neuropathy and nephropathy, gastroparesis, and hyperlipidemia. She complained of shortness of breath to her primary care physician on [redacted] and was sent to the emergency room at which time she was admitted as an inpatient for congestive heart failure. This diagnosis was based upon a chest X-ray. Upon admission she actually denied shortness of breath, but did have dyspnea on exertion. While hospitalized, the patient was treated with a decreased dose of study drugs: 60 mg of fluoxetine and 5 mg of olanzapine. She was also treated with metoclopramide, pioglitazone, insulin, and glyburide.

Work-up revealed the following results: physical exam - an obese female in no acute distress with "good air entry" on lung exam, and bilateral bibasilar crackles; cardiac enzymes negative; a 2-D echo - normal to mild left ventricular dysfunction with an ejection factor of 45% to 50%, with possible lateral wall hypokinesis, mild concentric left ventricular hypertrophy, normal left atrial size, and no effusion or left ventricular thrombus; ECGs done on [redacted] - all normal; venous duplex - negative for DVT. The patient was seen by a cardiologist who recommended an outpatient Persantine thallium test. The patient was

also seen by a pulmonologist who recommended aggressive weight loss and outpatient polysomnography. She was placed on enalapril, spironolactone, and furosemide for congestive heart failure (CHF), and ciprofloxacin for a urinary tract infection. Her condition improved and she was discharged on [redacted] She resumed her previous doses of both study drugs: 75 mg of fluoxetine and 12 mg of olanzapine after discharge from the hospital. The patient completed the trial at Visit 311 on 27 August 2001 and had been exposed to OFC study drug for 352 days.

2.11.1.5.1 Reviewer comment:

Although the clinical course does not clear OFC from having a potential role in the development of the AE, this patient had several other comorbidities that put her at risk for cardiovascular disease. No other OFC patients were diagnosed with treatment-emergent CHF.

2.11.1.6 Patient HGGA-022-2201:

FDA request: Please provide any additional details that are available regarding the patient's hospitalization for acute MI and pancreatitis. These details should include, but are not limited to, the evidence supporting the diagnosis of acute MI (e.g., cardiac enzymes, echocardiogram results), the peak lipase level associated with the pancreatitis, and the CT scan appearance of the pancreatitis.

The patient is a 46-year-old female with a history of GERD, lupus, hypothyroidism, COPD, alcohol abuse, and hypertension. The patient started study drug in the open label phase on 14 July 1998 and last received study drug on 21 July 1998. The patient was admitted to the hospital on [redacted] for severe dehydration after 2 weeks of vomiting and diarrhea (onset predated start of study drug) and was discovered to have metabolic acidosis, believed to be secondary to bicarbonate loss from the diarrhea. Urine culture was positive for e-coli and CXR revealed a possible right lower lobe infiltrate. The patient gave a history of chest pain associated with smoking and exercise on the day of admission. On [redacted] the patient's acidosis worsened with respiratory decompensation and hypotension. The patient's respiratory status became compromised and therefore required intubation. The patient had elevated cardiac enzymes and was found to have a sustained a non-Q wave myocardial infarction. An echocardiogram showed a 40% ejection fraction with severe anterior septal wall abnormalities. A dobutamine thallium test on [redacted] showed small areas of potential ischemic myocardium and a small infarction area in the right coronary artery distribution with an ejection fraction of 66%. Her acidosis resolved on [redacted] On [redacted] the patient developed vomiting and right lower quadrant abdominal pain. Her amylase was 235 U/L (normal, 26-125 U/L). Her lipase was 200 U/L (normal, 7-60 U/L). The patient was felt to have acute pancreatitis and possibly pneumonia. Additionally, a urinary tract infection was noted. All events were resolved on [redacted] and the patient was discharged. At the time of hospitalization, the patient had been in the open-label phase for 8 days.

2.11.1.6.1 Reviewer comment:

The clinical course does not clear OFC from having a potential role in the development of the AE, although the onset of some of the symptoms seemed to predate the treatment with OFC. No other patients had the same AEs.

**APPEARS THIS WAY
ON ORIGINAL**

3 Safety Update

(Submissions dated 6/4/03 and 7/31/03)

The cut-off date for the last safety update was July 31, 2002. The current safety update provides an update for three studies that were ongoing (HGIE and HDAO) or had not yet been initiated (HGLL) at the time of the original NDA submission:

- F1D-MC-HGIE (lock date 09 December 2002);
- H6P-MC-HDAO (lock date 22 May 2003);
- H6U-MC-HGLL (lock date 04 June 2003).

Studies HDAO and HGLL are still ongoing.

3.1 Follow-up on studies submitted as part of the original NDA

Overall, there were no additional patients added to the 2066 OFC-treated patients already included in the 2-month safety update analyses. Among those 2066 patients, there were three additional serious adverse events of depression, one of diabetes mellitus, and one of lung disorder. No deaths were reported (source: safety update, table 1, page 6, submission 6/24/2003). These figures exclude the new patients from the blinded study H6P-MC-HDAO. Narratives for the patients with SAEs were previously submitted to the Division, except one patient. This patient (HGIE-624-6914) is summarized below.

The sponsor is stating that there were no differences between the 2-month safety update and the current approvable letter safety update in the discontinuation due to adverse events. They reported that no difference was observed in the overall patterns of treatment-emergent adverse events (source: safety update, table 2, page 7, submission 6/24/2003).

3.1.1 Study F1D-MC-HGIE

The sponsor states that as of 22 May 2003, any patient who had died, had a serious adverse event, or discontinued due to an adverse event had a narrative previously submitted to the Division, except one patient. This patient (HGIE-624-6914) is summarized below.

Patient HGIE-624-6914

This patient was a 49-year-old male who was randomized to olanzapine plus fluoxetine in combination (OFC) 12 mg/50 mg (on 12 June 2001) and received 85 days of double-blind therapy. He entered the open-label OFC phase on 11 September 2001 and began taking OFC 6 mg/25 mg. On [redacted], the patient was hospitalized for depression. The patient remained in the study through completion at Visit 311 (01 October 2002). The patient's last dose of study drug was 30 September 2002. The patient remained hospitalized through [redacted] and continued on OFC. The symptoms of depression improved during hospitalization. The patient was then followed by his

psychiatrist and remained stable on olanzapine and fluoxetine until January 2003, when he could no longer afford the olanzapine and was switched to trazadone.

3.2 Studies initiated since the original NDA submission

3.2.1 Study H6P-MC-HDAO

3.2.1.1 Description of study design

Study H6P-MC-HDAO is a double-blind, multi-center, parallel, randomized study of OFC in patients with treatment-resistant depression. It has four periods. Study Period-I is a screening phase and consists of a minimum of three days and a maximum of 14 days.

Study Period II is an 8-week, open-label, dose titration lead-in phase during which treatment resistance is assessed based on the response (or lack thereof) to fluoxetine treatment. All patients were prescribed open-label fluoxetine 25 mg/day for at least the first day. Thereafter, patients were titrated up to 50 mg/day at the investigator's discretion. Patients who could not tolerate 50 mg/day were discontinued from the study.

Study Period III is an 8-week, double-blind, treatment phase of therapy designed to demonstrate the efficacy and safety of olanzapine plus fluoxetine in combination (OFC) for treatment of treatment-resistant depression. Patients who did not respond to fluoxetine treatment during the lead-in phase, and who were not ineligible by interim exclusion criteria were randomized to one of three treatment arms for the duration of the treatment phase. A 1:1:1 ratio was used for treatment group randomization: OFC (olanzapine/fluoxetine 6/50, 12/50, or 18/50 mg/day), OLZ (olanzapine 6, 12 or 18 mg/day), or FLX (fluoxetine 50 mg/day). One goal of the treatment phase was to titrate the study drug to the maximum tolerated dose without discontinuing patients because of tolerability issues.

Study Period IV is an 8-week, open-label extension phase. Only OFC was allowed in the open-label extension phase. In order to maintain the treatment phase blind and to avoid tolerability issues with patients entering from the olanzapine arm of the treatment phase, all patients who entered the open-label extension phase at Visit 16 initially received a single dose capsule of OFC 6/25. At Visit 301, patients were titrated to OFC 6/50 or 12/50. At the discretion of the investigator, the allowed doses after Visit 301 were OFC 6/50 (minimum allowed dose), OFC 12/50, and OFC 18/50.

3.2.1.2 Adverse events

The study is still blinded. As of May 22, 2003, 564 patients entered the "lead-in phase" and 234 were randomized for the "treatment phase". No deaths were reported in the study. In this submission, the sponsor presented serious adverse events and adverse events leading to discontinuation before and after randomization. For the purposes of this review, I focused only on the adverse events after randomization, which I summarized in

the following table. Overall, 2/234 patients reported serious adverse events and 13/234 patients discontinued for an adverse event.

Age and gender	Adverse event (AE)	Time on drug (days)	Serious	Discontinued	Follow-up	Comments
31 y/F	Suicidal ideation	32	√		Resolved	
54 y/M	Congestive heart failure	20	√	√	Continued	Not treatment emergent
48 y/M	Increase blood sugar	27		√	NA	
53 y/F	Restlessness	40		√	Resolved	
22 y/F	Weight gain	28		√	Continued	
32 y/M	"Feels Exhausted"	26		√	Resolved	
38 y/M	"pressure in head"	19		√	Improved	Not treatment emergent
38 y/M	Sleepiness	4		√	Resolved	
47 y/M	Disorientation and confusion	3		√	Resolved	
24 y/F	Elevated AST and ALT, > 3x	7		√	Continued	Started prior to randomiz. to OFC. No elevated bilirubin
38 y/F	Weight gain and high blood sugar	41		√	NA	
41 y/M	Drowsiness	28		√	Resolved	
36 y/F	Weight gain	31		√	Resolved	
38 y/F	Weight gain	85		√	NA	Patient discontin. in open extension on OFC

3.2.1.3 Reviewer's comments

- Although the study is still blinded, the types of SAEs and AEs leading to discontinuation are consistent with what was observed in the original NDA.

3.2.2 Study H6U-MC-HGLL

This is a study to assess the safety, tolerability, and plasma profiles of multiple doses of olanzapine alone compared to combination with atomoxetine and with atomoxetine combined with fluoxetine in stable schizophrenic subjects. This study was slated to begin in late May 03. As of 04 June 03, the sponsor is reporting no deaths, serious adverse events, or discontinuations due to adverse events.

3.3 Review of the literature

Julie Birt, Pharm D, an Associate Medical Information Consultant in Global Medical Information at Eli Lilly and Company, completed a worldwide literature search to identify articles regarding the safety of olanzapine plus fluoxetine in combination. The databases searched included Embase (1988 to Week 23 of 2003) and PsycINFO (1872 to Week 1 of June 2003). Search strategy included the search terms of fluoxetine AND olanzapine, specifying literature classified as an adverse drug reaction, drug interaction, pharmacokinetics, or drug toxicity for each agent. This result was then combined with the indexed terms of "drug safety", or "danger, risk, safety and related phenomena", or "safety". To ensure the capture of all relevant articles, the sponsor conducted a broader search for any articles that mentioned olanzapine and fluoxetine, with the two words within two words of each other (search term = olanzapine adj2 fluoxetine).

The search strategy resulted in the identification of 509 articles. Titles and abstracts of all of the retrieved references were reviewed to determine those that specifically discussed the combined use of olanzapine and fluoxetine in combination and those that also at least mentioned safety of the combined use. Nineteen articles met these criteria.

Sara Corya, MD, a clinical research physician in Lilly Medical, completed a detailed review of the full text of these nineteen articles and found the safety profile consistent with that presented in the NDA submission and 2-month safety update.

I reviewed the presented abstracts and papers that are dealing with safety issues. One new adverse event not discussed in the original NDA submission was described in a case report. A 14-year-old African American female developed "esotropia" six months after initiation of treatment with OFC. Upon discontinuation of olanzapine (fluoxetine was continued unchanged), the patient recovered. No re-challenge was done.

3.3.1 Reviewer's comments

- The search criteria for the review of the literature are reasonable.
- Other than one case of esotropia, no unexpected AEs were reported in the presented literature.
- No cases of esotropia are mentioned in the olanzapine label. However, there is a mention of "ocular muscle abnormality".

- There are no differences between the AEs described in the 2-month safety update and the ones in the current safety update (submitted with the response to the approvable letter).

3.4 Safety information from the spontaneously reported adverse events database

The sponsor has a computerized safety database, called "Clintrace", which includes serious and non-serious adverse events reported spontaneously from post-marketing experience (including literature and regulatory reports) and clinical trial events described as "serious". In contrast to the COSTART coding used in the clinical trial database, all adverse events in the Clintrace are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 5.1.

Both olanzapine and fluoxetine have been available for combination use since olanzapine gained regulatory approval in October 1996. The sponsor reviewed all spontaneous adverse event reports temporally associated with the use of olanzapine and fluoxetine in combination (OFC) and received it between 01 October 1996 and 30 April 2003. Combination therapy is defined as the use of the two drugs at the time of the event. In that period, the sponsor received spontaneous adverse event reports for 1233 patients receiving combination therapy, 23931 patients receiving olanzapine without fluoxetine, and 26713 patients receiving fluoxetine without olanzapine. The original NDA submission included data between 01 October 1996 and 31 January 2002 during which the sponsor received spontaneous adverse event reports for 1029 patients receiving concomitant olanzapine and fluoxetine, 18909 patients receiving olanzapine monotherapy, and 24566 patients receiving fluoxetine monotherapy.

To provide context, all spontaneous event reports for olanzapine without fluoxetine and for fluoxetine without olanzapine received during the same time period were also reviewed by the sponsor.

I reviewed the reported adverse events and no unexpected rare events were reported. However, the sponsor did not present the deaths and serious adverse events (AEs) separately. Alternatively, they presented adverse events with reporting rate of at least 1%, which might have excluded the deaths and serious AEs.

In response to the division's request, the sponsor subsequently submitted information about the subset of spontaneous reports describing death and serious adverse events (SAE) (submission dated 12/2/2003).

There were a total of 204 spontaneous AEs reported in the time period from 01 February 2002 to 30 April 2003, 46 (22.5%) of these reports were considered serious (regulatory) reports. Within these 46 reports, there were 73 SAEs and a total of 135 AEs (serious and

nonserious) noted. Death as an outcome was reported in 11 (5.4%) of the spontaneous reports.

A total of two maternal exposures were reported, and five newborn reports were identified in the SAE reports for OFC. One of the newborn reports was the outcome of a mother report (US_021089349, US_020484031). Five of the reports were prospectively reported, and two were retrospectively reported. In three pregnancies the baby was born prematurely, but two of the three did not suffer any serious sequelae (no outcome provided for third baby).

3.4.1 Reviewer's comments

Overall, compared to the data reported with the original NDA submission, serious events and events occurring in more than 1% of reports for olanzapine and fluoxetine in combination (and in excess of the sum of both monotherapies) reflect a similar pattern to those submitted in the original NDA submission.

4 Labeling

Specific comments on the proposed label can be found in a separate file by this reviewer.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tarek Hammad
12/12/03 12:25:00 PM
MEDICAL OFFICER

Judith Racoosin
12/12/03 02:59:59 PM
MEDICAL OFFICER
See my review for additional comments on selected safety
issues.

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Clinical Data
Safety Team Leader Review

NDA: 21-520

Drug: Symbiax™ (olanzapine-fluoxetine combination)

Route: oral

Indication: bipolar depression

Sponsor: Lilly

Action Date: 5-4-03

1 Background

Dr. Hammad has provided a thorough review of the safety experience with the olanzapine-fluoxetine combination drug product (OFC). In this memo I will address only selected safety issues that need additional discussion.

2 Selected Safety Issues

2.1 Treatment-emergent Mania

Treatment-emergent mania (TEM) is a concern with the treatment of bipolar depression. The sponsor evaluated the incidence of this adverse event in the bipolar depression trials (HGGY-C, acute and open-label) and the open-label bipolar mania trial (HGEH) using three approaches: 1) evaluation of related adverse events; 2) change in score on the Young Mania Rating Scale (Y-MRS); 3) change in score on CGI- Severity of Mania.

2.1.1 Adverse events

When summarizing the incidence of treatment-emergent adverse events (TEAE) associated with TEM, the sponsor included the preferred terms “manic reaction” and “manic depressive reaction”. I reviewed the verbatim terms for these two preferred terms and they appeared to be inclusive of reactions in the spectrum of hypomania and mania (see Appendix 1). In the acute randomized controlled phase of HGGY-C, there was a two-fold excess in the incidence of SAEs for these preferred terms between the OFC and the OLZ and PBO groups¹. However, there was no difference across the groups for discontinuations due to these AEs, or total occurrence (serious + non-serious) of these AEs (regardless of whether one considers risks or rates).

¹ Comparison of TEM-SAE rates for OFC, OLZ, and placebo (9/100 patient-yrs vs. 5/100 patient-yrs vs. 5/100 patient-yrs) shows a similar, but slightly less marked excess.

Table HGGYc.12.8. Serious Treatment-Emergent Adverse Events by Decreasing Incidence All Randomized Patients, Acute Phase, Studies 1 and 2

SERIOUS ADVERSE EVENTS	Placebo			Olz			Plx+Olz			Fisher's Exact P-Value
	N	n	%	N	n	%	N	n	%	
	MANIC REACTION	377	2	0.5%	370	2	0.5%	86	1	
MANIC DEPRESSIVE REACTION	377	1	0.3%	370	1	0.3%	86	0	0.0%	1.000

Table ISS.10.47. Treatment-Emergent Adverse Events Incidence of Manic Reaction or Manic Depressive Reaction F1D-MC-HGGY-C Acute Phase

Adverse Event	OFC	OLZ	PLA	p-value
	N=86 n (%)	N=370 n (%)	N=377 n (%)	
Patients with ≥1 event	4 (5)	17 (5)	20 (5)	.945
Manic reaction	4 (5)	15 (4)	18 (5)	.856
Manic depressive reaction	0 (0)	2 (1)	2 (1)	1.000

Abbreviations: N = total number of patients; n = number patients with event; OFC = olanzapine + fluoxetine; OLZ = olanzapine; PLA = placebo.

Source: RMP.H6PSISSB.SASPGM (STMANGY2).

2.1.2 Y-MRS

The criterion for TEM as measured by the Y-MRS (11 items with a total score ranging from 0-60; a score below 15 is considered to be in the normal range) was a post-baseline total score > 15 in a patient who had a baseline score < 15. The sponsor presented the proportion of outliers using many different cutpoints in the Y-MRS total score; but the protocol specified definition of symptomatic induction of mania was a Y-MRS total score of 15 or more.

Using the criterion of baseline <15 and post-baseline > 15, the proportion of patients meeting that criterion at ANY time during the study was similar across the three study groups (OFC 6.4% [5/78]; OLZ 5.7% [19/355]; PBO 6.7% [23/345]). Using a criterion that examines a change from a much lower baseline (<5) to the post-baseline >15, the proportions shifted somewhat, such that there is a small increase in the number of OFC patients meeting that criterion, associated with a slight fall in the other groups (OFC 8.2% [4/49]; OLZ 4.5% [9/199]; PBO 5.4% [11/205]). Finally, if one uses the same original criterion for baseline (<15), but requires a more marked increase in Y-MRS score (>20), there are fewer OFC and OLZ, and more PBO patients that meet that criterion (OFC 2.6% [2/78]; OLZ 2.4% [8/355]; PBO 4.6% [16/345]). The analyses that examined change from baseline to endpoint, rather than to ANY time during the study, showed similar results.

For the group of patients in each treatment group meeting the criterion [baseline <15/post-baseline >15], the mean maximum increase from baseline was slightly smaller in the OFC group (n=5) compared to the OLZ (n=19) and PBO (n=23) groups (13.6 OFC, 16.3 OLZ, 16.6 PBO) resulting in mean maximum total scores of 18.2 OFC, 22.7 OLZ, and 22.39 PBO. Only two of five OFC patients who met the criterion [baseline <15/post-baseline >15] had a post-baseline score exceeding 20 (the highest being 22 on a 60 point scale).

The only other analysis that specifically addressed the subset of patients who qualified for TEM by YRMS score examined scores on individual questions within the rating scale. In the acute phase of HGGY-C, there was no important difference between treatment groups in mean change in individual item scores from baseline to TEM diagnosis.

2.1.3 CGI

The sponsor examined one other measure of TEM, the change in the “clinical global impression” or CGI (score ranges from 1 [normal] to 7 [among the most extremely ill]). The criterion examined was a baseline <2 with a change to >4 at any time. There was no difference between treatment groups in the proportions of patients meeting this criterion (OFC 1.8% [1/57]; OLZ 2.0% [5/248]; PBO 3.2% [8/251]). Other cutpoints analyzed did not reveal important differences between treatment groups.

Reviewer comment: The sponsor’s analysis of TEM did not include a discussion of discontinuations due to “induction of mania” in the bipolar depression trials. These frequencies by treatment group are shown in the table below and do not differ importantly across treatment groups.

Reviewer Table 1.

	OFC (n=86)	Olanzapine n=370)	Placebo (n=377)
Discontinuation for induction of mania	4 (4.6)	15 (4.1)	24 (6.4)

Although there was a small excess in SAEs due to “manic reaction” and “manic depressive reaction”, there was no excess of discontinuations due to induction of mania in the OFC group. The total AE (serious + non-serious), Y-MRS, and CGI results don’t demonstrate any difference in the frequency of the TEM across treatment groups. However, the sponsor did not present analyses regarding time to event; thus we have no information regarding potential differences in the time course of TEM by treatment group. We’ll ask the sponsor to look at this.

I focused my description of the incidence of TEM on the data from the acute randomized, placebo-controlled portion of HGGY-C. Since the background incidence of mania is common in the population of patients with bipolar depression, the incidence of TEM in open-label, uncontrolled trials is difficult to interpret.

2.2 QT/QTc prolongation

For calculating QTc interval, as planned a priori, the sponsor used the Fridericia correction method ($QTc=QT/RR^{0.33}$) and the regression-based correction method ($QTc=QT/RR^{0.41}$). The regression-based correction factor for QT interval (0.41) was based on 13,039 drug-free ECG recordings collected in the sponsor clinical trials. The correction factor was determined using linear regression of the log QT versus the log RR. The sponsor's research has shown that the regression-based formula more accurately minimizes the correlation between QT and RR intervals than Fridericia's correction method. This 0.41 correction factor falls between the 0.50 correction factor used with Bazett's method and the 0.33 correction factor used with Fridericia's method.

Using the regression-based correction factor and the Fridericia correction factor, the following mean changes from baseline were identified:

Reviewer Table 2.

Mean change from baseline	OFC (N=352)	FLX (N=129)	OLZ (N=394)	PLA (N=305)
Regression based (0.41)	+4.9	+3.7	+0.6	-0.9
Fridericia (0.33)	+5.9	+6.0	-0.7	-1.7

* source: submission 12/16/02, sponsor's table 21

The results shown in the preceding table show that OFC was associated with a mean change from baseline in QTc of about 5 msec using the regression-based correction, and slightly higher using the Fridericia correction. The majority of the prolongation appears to come from the fluoxetine component. The impression held by CDER as it is explained in the draft guidance for evaluating QTc prolongation in non-antiarrhythmic drugs² is that a QTc prolongation less than five msec is not associated with an important increase in risk of ventricular arrhythmia. The risk associated with prolongation in the range of 5-10 msec is not well understood. In at least one case, a mean change from baseline in QTc of 6 msec has led to the placement of a Warnings statement (e.g., moxifloxacin, a fluoroquinolone antibiotic).

Before we can interpret the mean change from baseline calculated for OFC, however, we need to address the correction method used by the sponsor. Generally, when sponsors have utilized the regression-based correction method, they have used baseline ECG measurements from the clinical trial population being studied. In another recent development program (atomoxetine), Lilly, the OFC sponsor, used baseline measurements to generate the QT correction factor. It is unclear why here they have chosen to use a correction factor based on a large number of ECGs drawn from many development programs. I am not convinced that this approach is reasonable, given that the population of patients with bipolar disease may differ from the populations included in correction factor calculation. As such, we will request that the sponsor calculate the regression-based correction factor from the baseline ECGs in the OFC development program. Depending on the factor that is calculated, we may request that the sponsor recorrect the QT values included in the analyses in the NDA submission.

² "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs"; <http://cdernet/qtwg/QT%20Workshop/qt4jam.pdf>

2.3 Orthostatic Hypotension

Orthostatic hypotension is a recognized side effect of olanzapine. In the bipolar depression trials, significantly more OFC patients had a PCS decrease in orthostatic systolic BP (>30 mmHg) as compared to olanzapine and placebo patients.

Reviewer Table 3.

Proportion of patients with PCS decrease in orthostatic systolic blood pressure	OFC	OLZ	PLA
Bipolar depression	7.3% (6/82)	1.4% (5/346)	1.4% (5/352)

Inconsistent with the data presented above, the sponsor's Table 11 of the "Regulatory Response 11-25-02" (submitted 12/16/02) presented the following frequencies for PCS decrease in orthostatic systolic blood pressure for the controlled pooled OFC database:

	OFC (N=45)	FLX (N=0)	OLZ (N=85)	PLA (N=88)
Proportion of patients with PCS decrease in orthostatic systolic blood pressure	0 (0)	0 (0)	1 (1)	3 (3)

* source: submission 12/16/02, sponsor's table 11

Based on the bipolar depression data presented above in Reviewer Table 3, there is no possibility that the numbers submitted by the sponsor in Table 11 of the 12/16/02 response could be correct. We will ask the sponsor to explain these findings.

In a clinical pharmacology study of OFC, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2-9 hours following OFC dosing. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular). This phenomenon of an abnormal reflex of bradycardia, sometimes associated with sinus pause, in response to hypotension was discussed at the Psychopharmacological Drug Products Advisory Committee for intramuscular olanzapine in February 2001. The perception by the cardiologist consultant to the advisory committee was that this phenomenon is generally limited to young healthy subjects who have a high vagal tone. This phenomenon of severe hypotension with bradycardia has not been observed in patients with schizophrenia treated with olanzapine. The fact that patients with schizophrenia do not show this response to hypotension with olanzapine is probably related to the fact that they don't have high vagal tone and they have been exposed to antipsychotic drugs previously.

My concern is that patients with bipolar depression who are antipsychotic naïve could be at risk for this bradycardic response to hypotension. Unlike patients with acute bipolar mania, for which olanzapine is already approved, patients with bipolar depression would not be expected to have a high sympathetic tone, thus perhaps increasing their risk of this abnormal response.

In order to address this concern, we will request the following information:

- ? For the patients in the combined bipolar depression trials HGGY-1 and -2, provide a narrative for any patient who had a fall in heart rate from baseline associated with a decrease in orthostatic systolic blood pressure of >20 mmHg; what adverse events were associated with these changes in vital signs? What was each patient's outcome?
- ? For patients who reported adverse events related to orthostatic hypotension (including, but not limited to, postural hypotension, syncope, hypotension), please provide the details of the associated vital sign changes and each patient's outcome.
- ? For patients who reported adverse events related to bradycardia, please describe the associated changes in blood pressure and any associated adverse events and each patient's outcome.

In the combined bipolar depression trials HGGY-1 and -2, compare the subset of patients who were antipsychotic naïve to those who had been previously exposed to antipsychotics and provide the following analyses:

- ? Calculate mean change in orthostatic systolic and diastolic blood pressures across the treatment groups.
- ? Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at any time.
- ? Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at endpoint.
- ? Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at any time.
- ? Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at endpoint.

2.4 Diabetes mellitus/hyperglycemia

The Division of Neuropharmacological Drug Products has been evaluating the association between the atypical antipsychotics and the development of diabetes mellitus/hyperglycemia (DM/HG) for the last few years. A review of clinical trial data from the olanzapine development program revealed inconclusive evidence of a causal relationship with DM/HG; however, spontaneous reports submitted to FDA following the marketing of olanzapine revealed cases of severe hyperglycemia, sometimes leading to ketoacidosis, hyperosmolar coma, and/or death in patients with no prior history of hyperglycemia. Additionally, glucose levels normalized in some patients after discontinuation of olanzapine, and some patients had a recurrence of hyperglycemia following a rechallenge. Subsequent epidemiological studies have demonstrated an increased risk of DM/HG in users of atypical antipsychotics compared to the general population; however, the Division is awaiting additional epidemiological data to clarify the causal relationship between the atypical antipsychotics and DM/HG.

In the OFC development program there was some evidence of an association between OFC and development of DM/HG. Regarding serious adverse events (SAEs), there were six cases of hyperglycemia, two in the controlled phase (HGHZ-051-3503-prior diagnosis of DM, HGIE-613-6358), and four in the open-label phase (HGIE-503-5101- prior

diagnosis of DM, HGIP-015-1716, HGIE-631-7181, and HGHZ-016-1761). No SAEs for hyperglycemia were reported for other arms of treatment.

The following table shows the incidence of DM/HG adverse events. The analysis is limited by the fact that it included patients with pre-existing DM. Patients with DM have exacerbations related to any number of factors (e.g., intercurrent illness, noncompliance with medications, changes in diet or exercise habits), thus mixing these patients in with those who did not have a prior history of diabetes makes interpretations of the incidence of the AEs DM/HG difficult. We will ask the sponsor to repeat this analysis with only patients who did not have diabetes at baseline.

FDA Table 1: Incidence of Diabetes Mellitus and hyperglycemia[@] in the OFC pooled data (source: submission 12/16/2002, sponsor's table 7).

Event	OFC (N=571)			FLX (N=251)			OLZ (N=685)			PLA (N=477)			
	n	%	Rate*	N	%	Rate*	n	%	Rate*	N	%	Rate*	RR#
Diabetes Mellitus	5	1	6	0	0	0	1	0.15	1	1	0.21	2	2.74
Hyperglycemia	6	1	7	0	0	0	8	1	10	0	0	0	undefined

[@] Analysis includes patients with preexisting diabetes.

* Rate is per 100 patient year.

Rate ratio is calculated as OFC rate/PLA rate.

Furthermore, while going through some patient narratives for other events, I noted that patients were not always referred for evaluation of hyperglycemia at the time it was first noted in during the clinical trials. Patients may have had abnormal glucose measurements at multiple visits before they were referred for evaluation. Thus the number of DM/HG AEs shown in the preceding table likely underestimates the number that occurred.

One way to detect the emergence of hyperglycemia is to look at the laboratory values. The best way would be to look at fasting glucose measurements; however, fasting values are not available. The following table shows the incidence of treatment-emergent hyperglycemia based on non-fasting glucose measurements.

FDA Table 2: Summary of abnormalities in nonfasting glucose in the OFC pooled data (source: submission 12/16/02, sponsor's tables 33-35).

Event	OFC (N=487)			FLX (N=230)			OLZ (N=559)			PLA (N=374)			
	n	%	Rate*	RR#									
Any time ¹	22	5	27	6	3	17	15	3	21	2	1	5	5.40
At endpoint ²	14	3	17	4	2	11	10	2	14	2	1	5	3.44

* Rate is per 100 patient year.

Rate ratio is calculated as OFC rate/PLA rate.

1 patients with baseline nonfasting glucose <200 mg/dL and a subsequent nonfasting glucose ≥200 mg/dL at any time.

2 nonfasting glucose ≥200 mg/dL at endpoint among patients with a baseline nonfasting glucose <200 mg/dL.

The data associating OFC with DM/HG is consistent with the belief that olanzapine is associated with DM/HG. The co-administration of fluoxetine with olanzapine does not

appear to lessen the association with DM/HG. When the Division finalizes the olanzapine labeling with regard to DM/HG, the OFC labeling will need to be updated.

2.5 Adverse events associated with the concomitant use of fluoxetine and olanzapine during post-marketing

In an effort to glean any pertinent information about OFC from the postmarketing experience with olanzapine and fluoxetine, the sponsor searched for adverse events in the postmarketing databases of both component drugs, looking for concomitant treatment with the two drugs. For several events, the proportion of concomitant olanzapine and fluoxetine reports containing that event exceeded twice that for both olanzapine monotherapy reports and fluoxetine monotherapy reports. These events included cardiac failure congestive, suicidal ideation, vomiting NOS, depression NOS, ECG QT prolonged, syncope, body temperature increased, depressed level of consciousness, dysarthria, dyskinesia, pneumonia aspiration, choking, intentional self-injury, pancreatitis, respiratory arrest, and sweating increased (see Dr. Hammad's review, section 2.6.6.3.2 for frequencies).

The interpretation of these frequencies is fraught with difficulty. To begin with, the frequencies are not incidences, but rather proportions of the total reports for the combined use of the products. Since there are many fewer total reports for the combined use of the products than the individual products, the point estimates for the combined use are more unstable than the point estimates for the individual components. Second, the population using these drugs concomitantly is different than the populations using the individual therapies, so the background rate of the adverse events are likely different.

Most reasonably, we will use this list of events as a starting place for monitoring the safety of the combination product at the time of marketing.

3 Additional requests

1. The safety update indicates that there had only been one additional death since the submission of the ISS; however, review of selected serious adverse events identified a second patient who died during the safety update reporting period (HGIE-617-6552). Please explain the discrepancy. Also, please review the serious adverse events for any additional deaths and provide us with your findings.
2. With regard to treatment-emergent mania, there did not appear to be a difference in incidence across the treatment groups in HGGY-1 and 2. However, no information was provided on the time to event for the emergence of mania. Please provide an analysis that compares the time to emergence of mania across the three treatment groups.
3. Please recalculate the regression-based correction factor based on the baseline ECGs collected in the OFC development program. Depending on the factor that is

calculated, we may request that you recorrect the QT values included in the analyses in the NDA submission.

4. Please explain the inconsistency in number of patients in each treatment group as displayed in Table 11 of the 12/16/02 response for the “Orthostatic Sys BP Decr” and the “Orthostatic Sys BP Low”. For these events, the “N” for each treatment group is substantially different (lower) than the “N” for the other PCS vital sign and weight changes. Please provide a corrected table.
5. Please provide the following information in regard to the occurrence of hypotension and bradycardia in the bipolar depression trials:
 - ? For the patients in the combined bipolar depression trials HGGY-1 and –2, provide a narrative for any patient who had a fall in heart rate from baseline associated with a decrease in orthostatic systolic blood pressure of >20 mmHg; what adverse events were associated with these changes in vital signs? What was each patient’s outcome?
 - ? For patients who reported adverse events related to orthostatic hypotension (including, but not limited to, postural hypotension, syncope, hypotension), please provide the details of the associated vital sign changes and each patient’s outcome.
 - ? For patients who reported adverse events related to bradycardia, please describe the associated changes in blood pressure and any associated adverse events and each patient’s outcome.

In the combined bipolar depression trials HGGY-1 and –2, compare the subset of patients who were antipsychotic naïve to those who had been previously exposed to antipsychotics and provide the following analyses:

- ? Calculate mean change in orthostatic systolic and diastolic blood pressures across the treatment groups.
 - ? Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at any time.
 - ? Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at endpoint.
 - ? Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at any time.
 - ? Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at endpoint.
6. Please provide a new Table 7 from the 12/16/02 submission “Incidence of Diabetes Mellitus and hyperglycemia in the OFC pooled data” excluding the patients who had pre-existing DM at baseline.
 7. The fluoxetine labeling and proposed OFC labeling includes a statement in the Warnings section about allergic reactions that says, “Pulmonary events, including

inflammatory processes of varying histopathology and/or fibrosis have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.”

At least two patients treated with OFC have had serious AEs that might qualify as such a pulmonary event:

- ? Patient HGIE-025-4206 developed pneumonitis after about 10 weeks on OFC therapy. She was discontinued due to persistent dyspnea. Please provide any additional follow-up that describes her response to dechallenge. Also, was any additional work-up performed to investigate the elevated sedimentation rate (e.g., a work-up for connective tissue disease)?
- ? Patient HGIP-608-6354 developed lung “crackles”, dyspnea on exertion, and a chest x-ray finding after ten days on OFC that led to hospitalization for work-up of these abnormalities. What was the finding on the chest x-ray that led to the hospitalization? Following the hospitalization, the patient remained on OFC. Did the dyspnea on exertion resolve? Did she require additional work-up? Was any diagnosis made with regard to her pulmonary abnormality?

Did any other patients in the OFC development program develop a pulmonary syndrome or symptoms consistent with the Warnings statement in labeling?

8. Please provide follow-up on the following patients:
 - ? HGIP-007-1334: Please provide any details that might be available of the “allergic reaction” that led the patient to discontinue from the trial.
 - ? HGIE-026-4253: Was there any additional follow-up for this patient after he discontinued for a convulsion?
 - ? HGIE-303-3108: After the patient was treated for the allergic reaction, how much longer was she maintained on OFC? Did she have to stay on prednisone? If so, for how long?
 - ? HGIE-013-1602: The patient was admitted to the hospital with dyspnea after nine months on open label OFC and received a diagnosis of congestive heart failure. The narrative did not describe what diagnostic tests were done to make that diagnosis and the treatment for CHF was not specified. Please provide this information. If CHF treatment was added, did the patient have to stay on it chronically?
 - ? HGG-022-2201: Please provide any additional details that are available regarding the patient’s hospitalization for acute MI and pancreatitis. These details should include, but are not limited to, the evidence supporting the diagnosis of acute MI (e.g., cardiac enzymes, echocardiogram results), the peak lipase level associated with the pancreatitis, and the CT scan appearance of the pancreas.

4 Labeling Comments

For simplicity, Dr. Hammad and I have combined our comments in the labeling section in his safety review.

Appendix 1 Coding of verbatim terms to mania-related preferred terms

MANIC DEPRESSIVE REACTION (preferred term)

BIPOLAR I DISORDER
BIPOLAR MIXED
DYSPHORIC MANIC EPISODE WITH PSYCHOTIC FEATURES
EXACERBATION OF MDD
EXACERBATION OF SOME MDD
MIXED EPISODE
MIXED EPISODE (MANIC DEPRESSIVE)

MANIC REACTION (preferred term)

ACUTE MANIA
DESIRE TO START NEW PROJECTS
HYPOMANIA
HYPOMANIC EPISODE
HYPOMANIC EPISODES
HYPOMANIC STATE
HYPOMANIC SYMPTOMS (HYPOMANIA)
INDUCTION OF MANIA
MANIA
MANIA ACUTE
MANIC
MANIC EPISODE
MANIC REACTION
MILD HYPOMANIA
SLIGHTLY HYPOMANIC

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/s/

Judith Racoosin
4/22/03 04:55:41 PM
MEDICAL OFFICER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 21, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Symbiax® (olanzapine/fluoxetine combination) for the treatment of bipolar depression

TO: File, NDA 21-520
[Note: This memo should be filed with the November 4, 2002 original submission of this NDA.]

1.0 BACKGROUND

Symbiax® is a fixed dose combination formulation of two currently marketed Eli Lilly drug products, olanzapine and fluoxetine. This combination is not currently approved for use in any disease. The sponsor seeks a claim for SYMBIAX® in the treatment of adult patients with bipolar depression in dose combinations of olanzapine/fluoxetine of 6/25, 6/50 and 12/50-mg/day. This NDA was granted a priority 6-month review since there were no approved treatments for the acute treatment of bipolar depression.

Even though there are no approved drugs for this indication, the American Psychiatric Association Practice Guidelines on the treatment of depressed patients with Bipolar Disorder, recommends the use of lithium or lamotrigine as first line treatments with more serious patients being treated with lithium and an antidepressant simultaneously¹. Several popular, but off-label treatments combine lithium or valproate with one of any of the antidepressants from various drug groups. No one combination is widely believed to be preferable over another with regard to efficacy in the treatment community.

Olanzapine is the third drug approved of the class of atypical antipsychotic drugs. Olanzapine is marketed as ZYPREXA® and was first marketed in September of 1996 for the treatment of psychosis associated with schizophrenia. It has since been approved for the treatment of mania. Effective doses for the treatment of both schizophrenia and mania range from 10-20-mg/day. Olanzapine is not approved for use in children.

Fluoxetine was the first approved of the SSRI drugs. Fluoxetine, now available in generic form, was developed originally as an antidepressant, but has also proven efficacious in the treatment of Obsessive

¹ American Psychiatric Association. 2002. Practice guidelines for the treatment of bipolar disorder (revision). Am J Psy 159:1-50.

Compulsive Disorder (OCD), Panic Disorder, Bulimia, and Premenstrual Dysphoric Disorder (PMDD) in doses ranging from 20-80-mg/day. Eli Lilly markets fluoxetine as SARAFEM® for the treatment of PMDD. Fluoxetine is approved for use in children and adolescents (ages 6-18 years) for the treatment of depression and OCD in doses up to 60-mg/day.

Two studies are submitted in support of the efficacy of OFC for the acute treatment of Bipolar Depression. These are Studies HGGY 1 and HGGY 2 (referred to as studies 1 & 2 in this review). These studies ran from one protocol and were considered different as they represent data from a priori randomized different sites.

The confirmation of the safety and effectiveness of OFC in the treatment of bipolar depression was not originally the primary objective of protocol HGGY. The primary objective of Protocol HGGY was to assess the efficacy of acute olanzapine therapy compared with placebo in treating Bipolar I Disorder Depression as measured by mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to the end of 8 weeks of therapy, in two parallel studies (HGGY 1 and 2). The OFC treatment arm was exploratory in nature and the original plan was to combine the OFC arms for HGGY 1 and 2 for the purposes of analysis. The sponsor originally expected the OFC arms to be under powered; however, results from these studies were so compelling that discussions with the Division lead to the conclusion that these studies should be submitted and reviewed since there were no approved safe and effective treatments for Bipolar Depression and off label treatments left much to be therapeutically desired.

2.0 CHEMISTRY

Symbiax has shown adequate stability with regard to its appearance, identity, assay, impurities and dissolution. This NDA is **approvable** from a Chemistry viewpoint. The approval is contingent upon an acceptable recommendation from the Office of Compliance. The Eli Lilly site ☐

☑ The site was submitted to the NDA

as a drug product labeler, packager and other tester.

3.0 PHARMACOLOGY

Pharmacology Team reviews were not available at this point in the review cycle.

4.0 BIOPHARMACEUTICS

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) found NDA-21-520 for SYMBIAX acceptable, pending the outcome of the DSI inspection report of the pivotal bioequivalence study (HDAK). OCPB recommended that the specification be changed to $Q = \frac{1}{2}$ at 15 minutes and they stated that the sponsor's dissolution method was acceptable. Sally Usdin Yasuda was the primary OCPB reviewer.

OCPB recommended that the sponsor agree to a phase IV study 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 fluoxetine a CYP2D6 inhibitor) 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.

5.0 CLINICAL

The clinical review was divided into efficacy and safety reviews. Tarek Hammad of the DNDP Safety Team performed the primary safety review. I performed the primary efficacy review.

Efficacy

Unlike studies of unipolar depression, one cannot assume that short-term relief of depressive symptoms is proof of the principle of efficacy. There must also be evidence that the drug is safe from a disproportionately increased risk of induction of mania. There was no controlled data to evaluate the question of longer-term risk of mania induction; however, the safety review addressed the open label extension data.

This formulation is a combination drug and was reviewed with the Agency's combination drug policy in mind. Studies 1 & 2 did not however employ a full factorial design. The psychiatric community's sentiment is strong that antidepressant monotherapy for depressed patients with Bipolar Depression carries unacceptable risk. It is strong enough that it is thought to be unethical to treat these patients in a control group with antidepressants alone. This is the reason that no fluoxetine alone treatment arm was included in this study. The Division concurred with this design decision in our review of the original study protocol.

Studies 1 and 2 were submitted in support of the efficacy of OFC for the acute treatment of Bipolar Depression. These studies ran from one protocol (HGGY) and were considered different as they represent data from a priori randomized different sites. This protocol was designed as two randomized, double-blind, parallel studies of approximately 792 patients (396 inpatients or outpatients per study). Patients were randomized into the three treatment groups of olanzapine monotherapy, placebo or OFC at a ratio of 4:4:1. Patients randomized to the OFC treatment group received olanzapine 6 mg plus fluoxetine 25 mg (OFC 6/25), olanzapine 6 mg plus fluoxetine 50 mg (OFC 6/50), or olanzapine 12 mg plus fluoxetine 50 mg (OFC 12/50) daily. Treatment was initiated at the lowest dose (olanzapine 5 mg, placebo, or OFC 6/25) and was titrated up based on the investigator's judgement of clinical need. Patients who could not tolerate the lowest dose were discontinued.

The following table displays the results of the LOCF analysis of the ITT population of studies 1 and 2 along with the results of the pooled patients from the combined HGGY studies.

Results of Pivotal Studies LOCF Analysis of ITT Population MADRS Mean Change from Baseline

Study	Treatment Group	n	Baseline		Change to Endpoint		p-Values	
			Mean	SD	Mean	SD	Pairwise vs. PBO	Pairwise vs. OFC
HGGY-1	OFC	40	29.9	5.0	-16.2	11.2	0.002	
	OLZ	182	32.3	6.3	-11.9	11.8	0.06	.023
	Placebo	181	31.2	5.7	-9.6	12.0		<.001
HGGY-2	OFC	42	31.7	6.8	-17.8	9.2	<.001	
	OLZ	169	32.8	6.1	-13.7	11.3	<.001	.039
	Placebo	174	31.4	6.6	-9.2	11.4		<.001
HGGY-1 and 2 Pooled Efficacy Data	OFC	82	30.8	6.1	-17.0	10.2	<.001	
	OLZ	351	32.6	6.2	-12.7	11.6	<.001	.002
	Placebo	355	31.3	6.1	-9.4	11.7		<.001

Comparison of the treatment groups with respect to induction of mania follows. From a safety standpoint, pooling the two studies is much more appropriate than looking at them separately. In doing this it is fairly clear that in the short term, OFC is less of a risk than placebo for the induction of mania.

Dropouts Due to induction of Mania in the Pooled Trials HGGY 1 & 2						
	Placebo N=377		Olanzapine N=370		OFC N=86	
	n	%	n	%	n	%
Induction of Mania	24	6.4	15	4.1	4	4.6

Generally speaking, the Division of Biometrics review and analysis of the raw data agreed with the sponsor's analysis. The Division of Biometrics however calculated a p-value of 0.041 as opposed to the sponsor-calculated value of 0.039 for the OFC vs. olanzapine comparison in study 2. This is a minor difference that is of no regulatory consequence.

Efficacy Conclusion

Studies 1 & 2 represent two well controlled adequately designed positive clinical trials that provide convincing evidence that OFC is effective in the acute treatment of Bipolar Depression. OFC was more effective than placebo and olanzapine alone in the treatment of Bipolar Depression as measured by the LOCF mean change from baseline of the MADRS scale.

The induction of mania was less, on a numerical basis, in the OFC group of the pooled data compared to placebo but not olanzapine alone. Therefore it does not appear that there is an acute risk of induction of mania in the short-term use of OFC in the acute treatment of Bipolar Depression.

Safety

A relatively small proportion of the total exposure was in patients with bipolar depression (n=86, about 15% of the controlled OFC database). The sponsor fulfilled the ICH guidelines for long-term exposure data to OFC (300 individuals exposed to an effective dose for 6 months and 100 individuals exposed to an effective dose for 1 year).

Dr. Hammad concluded that the OFC combination safety profile reflected the safety profile of the individual drugs added together. He stated that there did not appear to be any instances where a negative synergistic effect occurred with respect to incidence or severity of adverse event occurrence.

The Safety Team was concerned about the increased risk of orthostatic hypotension in antipsychotic naïve patients. They have suggested labeling to convey this concern.

The Safety Team has also taken the opportunity to add warnings of reports of cerebrovascular adverse events and stroke in older patients treated with olanzapine in trials of dementia-related psychosis. They suggested that the Division add a warning regarding the risk of these CVAEs.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related

psychosis. In placebo-controlled trials, there was a higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine

The Safety Team also has several outstanding review questions that the sponsor needs to address. Some of these are extracted from Dr Racoosin's memo and follow:

1. The safety update indicates that there had only been one additional death since the submission of the ISS; however, review of selected serious adverse events identified a second patient who died during the safety update reporting period. Please explain the discrepancy. Also, please review the serious adverse events for any additional deaths and provide us with your findings.
2. Please recalculate the regression-based correction factor based on the baseline ECGs collected in the OFC development program. Depending on the factor that is calculated, we may request that you recorrect the QT values included in the analyses in the NDA submission.
3. Please provide the following information in regard to the occurrence of hypotension and bradycardia in the bipolar depression trials:
 - For the patients in the combined bipolar depression trials HGGY-1 and -2, provide a narrative for any patient who had a fall in heart rate from baseline associated with a decrease in orthostatic systolic blood pressure of >20 mmHg; what adverse events were associated with these changes in vital signs?
 - For patients who reported adverse events related to orthostatic hypotension (including, but not limited to, postural hypotension, syncope, hypotension), please provide the details of the associated vital sign changes
 - For patients who reported adverse events related to bradycardia, please describe the associated changes in blood pressure and any associated adverse events

In the combined bipolar depression trials HGGY-1 and -2, compare the subset of patients who were antipsychotic naïve to those who had been previously exposed to antipsychotics and provide the following analyses:

- Calculate mean change in orthostatic systolic and diastolic blood pressures across the treatment groups.
- Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg).
- Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg.

4. Please provide a new Table 7 from the 12/16/02 submission “Incidence of Diabetes Mellitus and hyperglycemia in the OFC pooled data” excluding the patients who had pre-existing DM at baseline.
5. The fluoxetine labeling and proposed OFC labeling includes a statement in the Warnings statement about allergic reactions that says, “Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.”

At least two patients in treated with OFC have had serious AEs that might qualify as such a pulmonary event.

- Patient HGIE-025-4206 developed pneumonitis after about 10 weeks on OFC therapy. She was discontinued due to persistent dyspnea. Please provide any additional follow-up that describes her response to dechallenge. Also, was any additional work-up performed to investigate the elevated sedimentation rate (e.g., a work-up for connective tissue disease)?
- Patient HGIP-608-6354 developed lung “crackles”, dyspnea on exertion, and a chest x-ray finding that led to hospitalization for work-up of these abnormalities. What was the finding on the chest x-ray that led to the hospitalization? Following the hospitalization, the patient remained on OFC. Did the dyspnea on exertion resolve? Did she require additional work-up? Was any diagnosis made with regard to her pulmonary abnormality?

Did any other patients in the OFC development program develop a pulmonary syndrome or symptoms consistent with the Warnings statement in labeling?

6. Please provide follow-up on the following patients:
 - HGIP-203-2109: Was there a change in weight between initiation of OFC and discontinuation for hepatomegaly seven months later? If so, how much weight was gained or lost?
 - HGIP-007-1334: Please provide any details that might be available of the “allergic reaction” that led the patient to discontinue from the trial.
 - HGIE-026-4253: Was there any additional follow-up for this patient after he discontinued for a convulsion?
 - HGIE-303-3108: After the patient was treated for the allergic reaction, how much longer was she maintained on OFC? Did she have to stay on prednisone? If so, for how long?
 - HGIE-013-1602: The patient was admitted to the hospital with dyspnea after nine months on open label OFC and received a diagnosis of congestive heart failure. The narrative did not describe what diagnostic tests were done to make that diagnosis and the treatment for CHF was not specified. Please provide this information. If CHF treatment was added, did the patient have to stay on it for a prolonged period?
 - HGGA-022-2201: Please provide any additional details that are available regarding the patient’s hospitalization for acute MI and pancreatitis. Specifically, what was the peak lipase level associated with the pancreatitis? Was there an CT scan of the pancreas? If so, what were the findings?

Labeling

Draft labeling recommendations are included in the Approvable Package in ~~strikeout~~ and underline format. This draft labeling was generated from the sponsor's original labeling document provided on November 4, 2002. Bracketed comments in the draft labeling explain the rationale behind individual changes by the Division.

DMETS recommended that the sponsor include patient information with this drug product. They stated that the Information for Patients subsection of PRECAUTIONS has a substantial amount of patient information including, use of Symbiax with alcohol, cautions about cognitive and motor impairment, information about the concomitant use of Symbiax with other fluoxetine and olanzapine containing products, information about heat exposure and dehydration, nursing, orthostatic hypotension, pregnancy, and rash. They argue that it is unreasonable to expect a patient to retain this information after discussion with their physician. There is risk to the patient if the information is not heeded .

6.0 WORLD LITERATURE

The sponsor's and my literature search did not reveal any safety concerns that the Division is not aware of.

7.0 FOREIGN REGULATORY ACTIONS

I am not aware of any foreign regulatory actions regarding the use of OFC in patients with bipolar depression or any other disorder.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

DSI inspected three clinical sites. The sites were chosen in concert with the DNNDP review staff. All clinical sites had acceptable data from a DSI viewpoint even though one site had minor deviations from regulations.

DSI was not able to investigate the pivotal biopharm site (Study HDAK) in Singapore due to current Agency travel restrictions.

10.0 APPROVABLE LETTER

An approvable letter acknowledging our decision and draft labeling is included with the approvable package. This letter also requests an additional follow-up information on adverse events from the Safety Team, and a Phase IV drug interaction study from OCPB.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that the Division take an Approvable Action on NDA 21-520. Studies 1 & 2 represent two well controlled adequately designed positive clinical trials that provide convincing evidence that OFC is effective in the acute treatment of Bipolar Depression. OFC was more effective than placebo and olanzapine alone in the treatment of Bipolar Depression as measured by the LOCF mean change from baseline of the MADRS scale.

The induction of mania was less, on a numerical basis, in the OFC group of the pooled data compared to placebo but not olanzapine alone. Therefore it does not appear that there is an acute risk of induction

of mania in the short-term use of OFC in the acute treatment of Bipolar Depression. However, the sponsor did not present analyses regarding time to event; thus we have no information regarding potential differences in the time course of TEM by treatment group. The safety Team will ask the sponsor to perform this analysis.

There is an outstanding trade name dispute. Symbiax will not be allowed as the drug trade name. The sponsor has alternatives under review.

The Eli Lilly site [redacted] is [redacted]. The site was submitted to the NDA as a drug product labeler, packager and other tester. Symbiax may not be approved until this or some other site is qualified as a drug product labeler, packager and other tester.

The sponsor needs to address the Divisions draft labeling changes as well as drafting a Patient Package Insert in their anticipated Response to Approvable Letter.

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/s/

Paul Andreason
4/21/03 01:43:32 PM
MEDICAL OFFICER

NDA 21-520

Clinical Review Cover Sheet

NDA #:	21-520
Sponsor:	Eli Lilly and Company
Material Reviewed	Original New Drug Application
Submission Date:	November 4, 2002
Drug	combination olanzapine/fluoxetine (SYMBIAX®)
Proposed Indication:	Bipolar Depression
Dosage Forms, Strengths, and Route of Administration:	6/25, 6/50, and 12/50-mg tablets

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Clinical Review for NDA 21-520

Executive Summary

I. Recommendations

The clinical review of olanzapine/fluoxetine combination for the acute treatment of bipolar depression was split into efficacy and safety reviews. I recommend that the Division make an approvable action from a clinical efficacy standpoint.

II. Summary of Clinical Findings

A. Brief Overview of Submission

Two studies are submitted in support of the efficacy of OFC for the acute treatment of Bipolar Depression. These are Studies HGGY 1 and HGGY 2 (referred to as studies 1 & 2 in the review). These studies ran from one protocol and were considered different as they represent data from a priori randomized different sites.

The confirmation of the safety and effectiveness of OFC in the treatment of bipolar depression was not originally the primary objective of protocol HGGY. The primary objective of Protocol HGGY was to assess the efficacy of acute olanzapine therapy compared with placebo in treating Bipolar I Disorder Depression as measured by mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to the end of 8 weeks of therapy, in two parallel studies (HGGY 1 and 2). The OFC treatment arm was exploratory in nature and the original plan was to combine the OFC arms for HGGY 1 and 2 for the purposes of analysis. The sponsor originally expected the OFC arms to be under powered; however, results from these studies were so compelling that discussions with the Division lead to the conclusion that these studies should be submitted and reviewed given the lack of safe and effective treatments for Bipolar Depression.

B. Efficacy

Studies 1 & 2 represent two well controlled adequately designed positive clinical trials that provide convincing evidence that OFC is effective in the acute treatment of Bipolar Depression. OFC was more effective than placebo and olanzapine alone in the treatment of Bipolar depression as measured by the LOCF mean change from baseline of the MADRS scale.

The induction of mania was less, on a numerical basis, in the OFC group of the pooled data compared to placebo but not olanzapine alone. Therefore it does not appear that there is an acute risk of induction of mania in the short term use of OFC in the acute treatment of Bipolar Depression..

CLINICAL REVIEW

Executive Summary Section

C. Safety

Safety aspects of OFC are reviewed by the HFD-120 Safety Team and are pending at the time of this review.

D. Dosing

Studies 1 & 2 were flexible dose studies of three fixed dose combinations. The combinations consisted of olanzapine/fluoxetine 6/25, 6/50, and 12/50-mg. Hence one can not comment on what would be considered the least effective dose or most effective combination.

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CLINICAL REVIEW

Clinical Review Section

Clinical Review

I. Introduction and Background-The clinical review of NDA 21-520 is divided into efficacy and safety reviews. The following narrative details the efficacy review.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

SYMBIAX® is the proposed trade name for the combination formulation of olanzapine and fluoxetine. Both of these drugs were originally developed and marketed by Eli Lilly and Company. This combination is not currently approved for use in any disease. The sponsor seeks a claim for SYMBIAX® in the treatment of adult patients with bipolar depression in dose combinations of olanzapine/fluoxetine of 6/25, 6/50 and 12/50-mg/day.

Olanzapine is the third drug approved of the class of atypical antipsychotic drugs. Olanzapine is marketed as ZYPREXA® and was first marketed in September of 1996 for the treatment of psychosis associated with schizophrenia. It has since been approved for the treatment of mania. Effective doses for the treatment of both schizophrenia and depression range from 10-20-mg/day. Olanzapine is not approved for use in children.

Fluoxetine was the first approved of the SSRI drugs. Fluoxetine, now available in generic form, was developed originally as an antidepressant, but has also proven efficacious in the treatment of Obsessive Compulsive Disorder (OCD), Panic Disorder, Bulimia, and Premenstrual Dysphoric Disorder (PMDD) in doses ranging from 20-80-mg/day. Fluoxetine is marketed by Eli Lilly as SARAFEM® for the treatment of PMDD. Fluoxetine is approved for use in children and adolescents (ages 6-18 years) for the treatment of depression and OCD in doses up to 60-mg/day.

B. State of Armamentarium for Indication(s)

There are no approved drugs for the treatment of bipolar depression. The American Psychiatric Association Practice Guidelines on the treatment of depressed patients with Bipolar Disorder, recommends the use of lithium or lamotrigine as first line treatments with more serious patients being treated with lithium and an antidepressant simultaneously¹. Several popular, but off-label treatments combine lithium or valproate with one of any of the antidepressants from various drug groups. No one combination is widely believed to be preferable over another with regard to efficacy in the treatment community.

The psychiatric community's sentiment is strong that antidepressant monotherapy for depressed patients with Bipolar Depression carries unacceptable risk. It is strong enough that it is thought to be unethical to treat these patients in a control group with antidepressants alone. This is the reason that no fluoxetine alone treatment arm was included in this study. The Division concurred with this design decision in our review of the original study protocol.

¹ American Psychiatric Association. 2002. Practice guidelines for the treatment of bipolar disorder (revision). Am J Psy 159:1-50.

CLINICAL REVIEW

Clinical Review Section

When it becomes necessary to treat depressed patients with Bipolar Disorder with an antidepressant and mood stabilizer in combination the treatment community must wrestle with when to discontinue the antidepressant treatment. Even in combination with a mood stabilizer, antidepressant treatment of bipolar patients is considered a risk that must be weighed against potential benefits and specific experience with the individual patient. Therefore, a development program that combines an antidepressant and anti-manic agent needs to address the question of what is the appropriate length of time the combination should be safely and effectively used before returning to a potentially safer mood stabilizer monotherapy.

II. Description of Clinical Data and Sources

A. Overall Efficacy Data

The sponsor presents efficacy data from two identically designed pivotal studies. HGGY-Protocol F1D-MC-HGGY was designed as two identical, randomized, double-blind, parallel studies of 833 patients (427 patients in Study 1 and 406 patients in Study 2). These two studies are hereafter referred to as HGGY-1 and HGGY-2. Patients in both studies met 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).

It is noteworthy that these studies were not originally designed as pivotal studies to demonstrate the efficacy of OFC, but to demonstrate the efficacy of olanzapine monotherapy in the treatment of bipolar depression. Protocol HGGY was submitted to the Division on June 20, 2000 under the title "Olanzapine monotherapy in the treatment of bipolar depression." This study was originally designed as a pair of identically designed Phase III trials to provide support a claim for the treatment of Bipolar Depression with olanzapine alone. The OFC treatment group was exploratory in nature and the unbalanced randomization (4:4:1) of the olanzapine monotherapy, placebo, and OFC treatment arms reflects this. The analysis of the treatment effect of the OFC combination was originally a secondary variable.

III. Clinical Review Methods

A. How the Review was Conducted

The clinical review of NDA 21-520 is divided into efficacy and safety reviews. This represents the efficacy portion of the clinical review. Studies HGGY 1 and 2 were reviewed individually on their own merits.

B. Overview of Materials Consulted in Review

The efficacy review of this submission examined the two placebo and olanzapine controlled studies HGGY 1 and 2 as well as the open label extension studies for these protocols.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Raw data was submitted to the Division of Biometrics via SAS transport files and analyzed according to the methods described in the sponsor's protocol. These results were compared to the analyses in the submission. The submission was also examined for internal consistency.

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D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was performed in accordance with the declaration of Helsinki and its subsequent revisions and the FDA Guideline 21 CFR Parts 50, 56, and 312.

E. Evaluation of Financial Disclosure

A financial disclosure and certification statement was included. This certified that Eli Lilly and Company had not entered into any financial agreement with the clinical investigators whereby the value of the compensation would be effected by the outcome of the study.

IV. Integrated Review of Efficacy

A. Brief Statement of Conclusions

HGGY 1 and 2 are positive studies and support the efficacy of OFC over olanzapine and placebo in the acute treatment of bipolar depression.

B. General Approach to Review of the Efficacy of the Drug

Unlike studies of unipolar depression, one cannot assume that short term relief of depressive symptoms is proof of the principle of efficacy. There must also be evidence that the drug is safe from a disproportionately increased risk of induction of mania. There is no controlled data to evaluate the question of longer-term risk of mania induction; however, the safety review shall address the open label extension data.

C. Detailed Review of Trials by Indication

C-1 Investigators and Sites

A listing of the investigators and sites may be found in Table C-1 in the appendix.

C-2 Objectives

The confirmation of the safety and effectiveness of OFC in the treatment of bipolar depression was not the primary objective of protocol HGGY. The primary objective of Protocol HGGY was to assess the efficacy of acute olanzapine therapy compared with placebo in treating Bipolar I Disorder Depression as measured by mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to the end of 8 weeks of therapy, in two parallel studies (HGGY 1 and 2). The OFC treatment arm was exploratory in nature and the original plan was to combine the OFC arms for HGGY 1 and 2 for the purposes of analysis. The sponsor originally expected the OFC arms to be under powered; however, results from these studies were so compelling that discussions with the Division lead to the conclusion that these studies should be submitted and reviewed given the lack of safe and effective treatments for Bipolar Depression.

C-3 Study Population

The study population consisted of men and non-pregnant/non-breastfeeding women aged 18 years and older with DSM-IV defined Bipolar I Disorder- Depressed (296.50-296.54). The diagnosis was established using clinical assessment and confirmed using the SCID-P. Additionally patients were required to have a MADRS score of ≥ 20 at Visit 1 and 2.

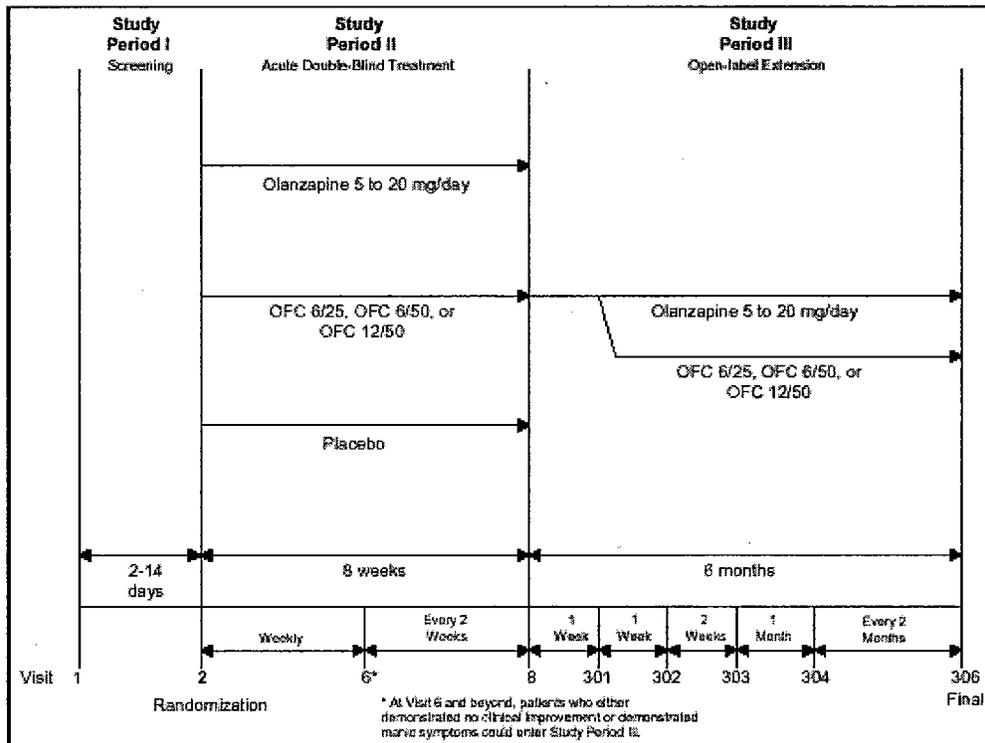
C-4 Design

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This protocol was designed as two randomized, double-blind, parallel studies of approximately 792 patients (396 inpatients or outpatients per study). Patients were randomized into the three treatment groups of olanzapine monotherapy, placebo or OFC at a ratio of 4:4:1. Patients randomized to the OFC treatment group received olanzapine 6 mg plus fluoxetine 25 mg (OFC 6/25), olanzapine 6 mg plus fluoxetine 50 mg (OFC 6/50), or olanzapine 12 mg plus fluoxetine 50 mg (OFC 12/50) daily. Treatment was initiated at the lowest dose (olanzapine 5 mg, placebo, or OFC 6/25) and was titrated up based on the investigator's judgement of clinical need. Patients who could not tolerate the lowest dose were discontinued.

The design is outlined in the following figure:



C-5 Assessments and Analysis Plan

Change from baseline to endpoint in the investigator-rated MADRS total score served as the primary efficacy measure. Secondary efficacy variables included the CGI-BP, the HAM-A, and the YMRS. The sponsor's primary analysis model was the MMRM; however, the Division had informed the sponsor that the Division would consider the LOCF analysis of the IIT population as the primary analysis method.

Symptomatic and syndromic characterizations of each patient's response, remission, relapse, and mania induction status were assessed using the MADRS, YMRS, and DSM-IV. The sponsor defined several predefined states of either therapeutic response or failure. The **Symptomatic**

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induction of mania was defined as a ≥ 15 in YMRS total score. The data from this variable shall be summarized in the safety review.

The primary objective of Protocol HGGY was to assess the efficacy of acute olanzapine therapy compared with placebo in treating Bipolar I Disorder Depression as measured by mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to the end of 8 weeks of therapy, in two parallel studies (HGGY 1 and 2). The OFC treatment arm was exploratory in nature and the original plan was to combine the OFC arms for HGGY 1 and 2 as one study for the purposes of analysis. The sponsor originally expected the OFC arms to be under powered; however, results from these studies were so compelling that discussions with the Division lead to the conclusion that these studies should be submitted and reviewed given the lack of safe and effective treatments for Bipolar Depression.

C-6 Patient Disposition

C-6.1 Study HGGY 1

Significant differences in the disposition of patients paralleled the efficacy results of the study. Significantly more patients completed the OFC treatment and fewer dropped out due to lack of efficacy. No patients dropped out due to induction of mania in HGGY 1.

Table C-6.1.1 Patient Disposition for All Randomized Patients in HGGY 1

Reason for Discontinuation	Placebo (N=193)		Olz (N=191)		Flx+Olz (N=43)		p-Value*
	n	(%)	n	(%)	n	(%)	
Reporting Interval Completed	69	(35.8)	85	(44.5)	27	(62.8)	.004
Adverse Event	8	(4.1)	15	(7.9)	1	(2.3)	.254
Lack of Efficacy	59	(30.6)	40	(20.9)	5	(11.6)	.011
Lost to follow-ups	16	(8.3)	13	(6.8)	6	(14.0)	.278
Patient Decision	9	(4.7)	13	(6.8)	0		.189
Criteria not Met/Compliance	7	(3.6)	8	(4.2)	2	(4.7)	.879
Sponsor Decision	1	(0.5)	1	(0.5)	1	(2.3)	.454
Physician Decision	3	(1.6)	3	(1.6)	1	(2.3)	.739
Induction of Mania	17	(8.8)	9	(4.7)	0		.056
Relapse of depression	4	(2.1)	4	(2.1)	0		1.00

*Frequencies are calculated using Fisher's Exact Test

C-6.2 Study HGGY 2

Significant differences in the disposition of patients paralleled the efficacy results of the study. Significantly more patients completed the OFC treatment and fewer dropped out due to lack of efficacy. Greater than 5% and twice the rate in the placebo group dropped out due to the induction of mania in this study. Normally this is considered common and drug related; however, it is most appropriate to pool that patients in the two studies.

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Table C-6.2.1 Patient Disposition for All Randomized Patients in HGGY 2

Reason for Discontinuation	Placebo (N=184)		Olz (N=179)		Flx+Olz (N=43)		p-Value*
	n	(%)	n	(%)	n	(%)	
Reporting Interval Completed	76	(41.3)	94	(52.5)	28	(65.1)	.008
Satisfactory Response	0		1	(0.6)	0		.547
Adverse Event	11	(6.0)	19	(10.6)	1	(2.3)	.123
Lack of Efficacy	62	(33.7)	33	(18.4)	3	(7.0)	<.001
Lost to Follow-Up	10	(5.4)	8	(4.5)	4	(9.3)	.412
Patient Decision	7	(3.8)	10	(5.6)	0		.280
Criteria not Met/Compliance	4	(2.2)	4	(2.2)	1	(2.3)	1.00
Sponsor Decision	0		0		1	(2.3)	.106
Physician Decision	3	(1.6)	3	(1.7)	0		1.00
Induction of Mania	7	(3.8)	6	(3.4)	4	(9.3)	.222
Relapse of depression	4	(2.2)	1	(0.6)	1	(2.3)	.371

Comparison of the treatment groups with respect to induction of mania follows in Table C-6.2.2

	Placebo N=377		Olanzapine N=370		OFC N=86	
	n	%	n	%	n	%
Induction of Mania	24	6.4	15	4.1	4	4.6

From a safety standpoint, pooling the two studies is much more appropriate than looking at them separately. In doing this it is fairly clear that in the short term, OFC is less of a risk than placebo for the induction of mania.

C-7 Baseline Demographics/Severity of Illness

The distribution of age, race, and sex were similar between treatment groups in the pool of HGGY 1 & 2 patients. Treatment response in the pooled subgroups of age, race, and sex were reported as non-significant and no summary tables were provided. The only sub group difference that was reported as significant was that patients who were considered rapid cycling bipolar patients responded less well than non-rapid cycling patients.

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Table C-7.1 Significant sub-group difference in treatment response in Rapid Cycling versus non-Rapid Cycling Bipolar Patients: MADRS Total Score

Subgroup of Interest	Therapy by Subgroup Interaction	Sub-group	Strata	N	Therapy	n	Baseline Mean	Mean Change	p-Value		
									Within PBO	Vs Strata (2)	Vs Strata (3)
RAPID CYCLING	.015	.774	NO	489	(1) Placebo	225	31.82	-8.75	<.001	<.001	<.001
					(2) Olz	216	32.36	-13.97			.022
					(3) Flx+Olz	48	31.38	-18.10			
			YES	293	(1) Placebo	127	30.50	-10.28	.045	.740	.015
					(2) Olz	132	32.89	-10.53			.025
					(3) Flx+Olz	34	30.00	-15.56			

This does not constitute a safety concern and need not be mentioned in labeling.

The mean MADRS score in the OFC group of the pooled patients of studies 1 & 2 was significantly lower at baseline (OFC=30.8; Olanzapine 32.6; PBO 31.3 p=0.009). Mean change from baseline of MADRS was the primary efficacy variable. Since mean change is the comparison and the inter-group difference is small (though significant) this MADRS a difference does not lead to a systematic bias in favor of OFC. Other measures did not show any significant difference.

C-8 Concomitant Medications

Patients taking concomitant medications with primarily CNS activity were excluded from participation in this protocol. Benzodiazepines could be used during the study within certain guidelines; there were no inter-group difference in the frequency or amount of benzodiazepine use during study 1 or 2. There were no significant inter-group differences in the types of drug therapies used at the time of study entry in either study 1 or 2.

C-9 Efficacy Results

The following table displays the results of the LOCF analysis of the ITT population of studies HGGY 1 and 2 along with the results of the pooled patients from the combined HGGY studies. **Results of Pivotal Studies LOCF Analysis of ITT Population MADRS Mean Change from Baseline**

Study	Treatment Group	n	Baseline		Change to Endpoint		p-Values	
			Mean	SD	Mean	SD	Pairwise vs. PBO	Pairwise vs. OFC
HGGY-1	OFC	40	29.9	5.0	-16.2	11.2	0.002	
	OLZ	182	32.3	6.3	-11.9	11.8	0.06	.023
	Placebo	181	31.2	5.7	-9.6	12.0		<.001
HGGY-2	OFC	42	31.7	6.8	-17.8	9.2	<.001	
	OLZ	169	32.8	6.1	-13.7	11.3	<.001	.039
	Placebo	174	31.4	6.6	-9.2	11.4		<.001
HGGY-1 and 2 Pooled Efficacy Data	OFC	82	30.8	6.1	-17.0	10.2	<.001	
	OLZ	351	32.6	6.2	-12.7	11.6	<.001	.002
	Placebo	355	31.3	6.1	-9.4	11.7		<.001

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C. Efficacy Conclusions

Studies 1 & 2 represent two well controlled adequately designed positive clinical trials that provide convincing evidence that OFC is effective in the acute treatment of Bipolar Depression.

The Division asked the sponsor to submit this NDA based on the findings. The Division decided to put aside the original protocol defined requirement that olanzapine alone be more effective than placebo in order to consider a comparison between OFC and olanzapine. This discretion was based on the very narrow margin of failure of olanzapine alone in HGGY 1 ($p=0.06$), the extremely robust results in the combination, and the fact that there are no approved acute treatments for bipolar depression. Given this Divisional discretion, both HGGY 1 and 2 are positive studies and support the efficacy of OFC over olanzapine and placebo in the treatment of bipolar depression.

The induction of mania was the least on a numerical basis in the OFC group of the pooled data.

There are no studies exploring or supporting extended treatment efficacy or prudent length of treatment with OFC. Given the inherent risks of treating bipolar patients with antidepressants, either alone or in combination with anti-manic agents, phase IV development plans need to address these issues.

The safety review is performed by the Safety Team of DNDP (HFD-120).

Overall conclusions shall be summarized in the Team Leader memo.

Paul J. Andreason, MD
Clinical Reviewer, HFD-120

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VI. Appendix

Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
001	1	3	13	28	Lawrence Adler, M.D. Clinical Insights 7310 Ritchie Highway, Suite 512 Glen Burnie, MD 21061
002	1	0	3	5	Richard Naimark, M.D. East Coast Clinical Research 15 Main Street, Suite 204 Salisbury, MA 01952
003	2	0	4	5	Scott Balogh, M.D. SouthEastern NeuroScience, Inc. 1210 Roy Road Augusta, GA 30909
004	2	1	2	6	Jason Denis Baron, M.D. MedLabs Research of Houston, Inc. 6260 Westpark, Suite 110 Houston, TX 77057
005	1	4	12	30	Louise Dabiri Beckett, M.D. IPS Research Co. 1211 N. Shartell, Suite 407 Oklahoma City, OK 73103
006	1	0	2	4	Sajal K. Bose, M.D. Valle Vista Hospital 898 East Main Street Greenwood, IN 46143
007	1	4	16	36	Matthew Brams, M.D. Bayou City Research, Ltd. 550 Westcott, Suite 310 Houston, TX 77007
008	1	1	6	12	Ron Brenner, M.D. Neurobehavioral Research, Inc. 371 Central Avenue Lawrence, NY 11559
010	2	0	0	1	John Carman, M.D. Carman Research

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					4015 South Cobb Drive, Suite 245 Smyrna, GA 30080
011	2	0	2	5	Charles Casat, M.D. Carolinas Medical Center Behavioral Health 1300 Scott Avenue Charlotte, NC 28203
012	1	0	0	1	Franca Centorrino, M.D. McLean Hospital Bipolar & Psychotic Disorders Research 115 Mill Street, NB3 Belmont, MA 02478
013	2	1	4	10	Herman Clements, II, M.D. Pharmacotherapy Research Associates 750 Princeton Avenue, Suite 2 Zanesville, OH 43701
014	1	0	2	5	Anne Gilbert, M.D. Indianapolis Psychiatric Associates 6820 Parkdale Place, Suite 115 Indianapolis, IN 46254
015	1	0	3	4	Robert A. Grillo, Jr., M.D. Middlesex Hospital – Department of Psychiatry 28 Crescent Street Middletown, CT 06457
016	2	1	4	10	G. Michael Dempsey, M.D. Albuquerque Neurosciences, Inc. 715 Dr. Martin Luther King, Jr. Avenue, NE, Suite 203 Albuquerque, NM 87102
018	2	0	2	2	Irl Extein, M.D. Health Sciences America 6100 West Glades Road, Suite 205 Boca Raton, FL 33434
019	1	0	2	4	Louis F. Fabre, M.D., Ph.D. Fabre Research Clinics, Inc.

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					5503 Crawford Street Houston, TX 77004
020	1	1	6	12	Joseph Fanelli, M.D. Midwest Center for Neurobehavioral Medicine 18 W. 100 22 nd Street, Suite 126 Oakbrook Terrace, IL 60181
021	2	0	2	5	Carlos Figueroa, M.D. Advanced Psychiatric Group (Outpatient) 3907 N. Rosemead Blvd., Suite 130 Rosemead, CA 91770
022*	1	0	0	0	William Fuller, M.D. University Physicians, Psychiatry Associates 1400 W. 22 nd Street, Room 308 Sioux Falls, SD 57105
023	2	2	8	18	Robert Gibson, M.D. Piedmont Medical Group 1901 S. Hawthorne Road, Suite 306 Winston-Salem, NC 27103
024	2	1	5	11	Susanna Goldstein, M.D. Medical & Behavioral Health Research 65 Central Park West, 1BR New York, NY 10023
025	2	1	4	8	Paul Gross, M.D. Allentown Associates in Psychiatry 401 N. 17 th Street, Suite 304 Allentown, PA 18104-5014
026	2	2	7	15	James T. Hartford, M.D. Summit Research Network 10550 Montgomery Road, Suite 20 Cincinnati, OH 45242
027	1	2	5	12	Shivkumar Hatti, M.D. Suburban Research Associates 600 N. Jackson Street, 3 rd Floor Media, PA 19063

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
029	2	2	9	20	Robert Lynn Horne, M.D. Lake Mead Hospital 1409 E. Lake Mead Blvd. North Las Vegas, NV 89030
030	2	1	1	6	Keith Isenberg, M.D. Washington University in St. Louis Department of Psychiatry, Suite 15500JJ; Campus Box 8134 4940 Children's Place St. Louis, MO 63110
032	1	2	6	16	Rakesh Jain, M.D., MPH R/D Clinical Research 461 This Way – P.O. Drawer B Lake Jackson, TX 77566
033	1	1	4	8	Alan M. Jonas, M.D. Pharmasite Research, Inc. 1314 Bedford Avenue, Suite 205 Baltimore, MD 21208
034	2	0	0	2	Terence Ketter, M.D. Department of Psychiatry and Behavioral Sciences Stanford University School of Medicine 401 Quarry Road, Room 2124 Stanford, CA 94305-5723
035	2	1	4	7	Mary Ann Knesevich, M.D. St. Paul Professional Bldg. #1 5959 Harry Hines Blvd., Suite 924 Dallas, TX 75235
036	1	2	5	14	H. Edward Logue, M.D. Birmingham Psychiatry Pharmaceutical Studies One Independence Plaza, Suite 900 Birmingham, AL 35209
037	1	0	3	6	Arnold Mech, M.D. Mech Hospital Alternatives 4100 W. 15 th Street, Suite 220

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					Plano, TX 75093
041	1	3	14	29	Hemant Patel, M.D. University of Oklahoma Health Sciences Center 920 Stanton L. Young, WP 3290 – Department of Psychiatry Oklahoma City, OK 73104
042	2	1	5	11	Michael Lambert, M.D. Dallas VA Medical Center Psychiatry Research, 8C 4500 S. Lancaster Road Dallas, TX 75216
044	2	2	10	20	Joachim D. Raese, M.D. Dr. Raese and Associates 5887 Brockton Avenue, Suite 200 Riverside, CA 92506
045	1	0	3	6	Barry Rittberg, M.D. Ambulatory Research Center University of Minnesota, Dept. of Psychiatry Riverside Professional Building 606 24 th Avenue South, Suite 602 Minneapolis, MN 55454
046	2	0	0	1	Leon Rosenberg, M.D. Center for Emotional Fitness 110 Marter Avenue, Suite 304 Moorestown, NJ 08057
047	1	1	4	7	Leon Rubenfaer, M.D. Pioneer Pharmaceutical Research 33497 23 Mile Road, Suite 110 New Baltimore, MI 48047
048	1	2	8	18	John Schmitz, M.D. Horizons in Psychotropic Research 6400 Prospect, Suite 444 Kansas City, MO 64132
050	2	0	2	5	Jeffrey Simon, M.D. Northbrooke Research Center

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					9275 N. 49 th Street, Suite 200 Brown Deer, WI 53223
051	1	1	4	9	Michael Sternberg, M.D. Advanced Research Centers 3166 Golansky Blvd., Suite 201 Woodbridge, VA 22192
052	1	5	17	42	Linda S. Harper, M.D. Clinical Neuroscience Solutions, PA 77 West Underwood Street, 3 rd Floor Orlando, FL 32806
053	1	1	2	6	Sheldon Whitten-Vile, M.D. Bert Nash CMHC 200 Maine, Suite A Lawrence, KS 66044
054	2	1	2	6	Martin Guerrero, M.D. Texas Tech University Health Science Center 4800 Alberta Avenue El Paso, TX 79905-2700
055	2	1	2	4	Andrew Winokur, M.D., Ph.D. University of Connecticut Health Center 10 Talcott Notch, East Lobby Farmington, CT 06030-6415
056	2	2	6	15	Steven Glass, M.D. Comprehensive Clinical Research, PC 130 White Horse Pike Clementon, NJ 08021
057	2	1	6	13	Murray Rosenthal, D.O. Behavioral and Medical Research 3625 Ruffin Road, Suite 100 San Diego, CA 92123
058	2	3	10	24	Nizar El-Khalili, M.D. Alpine Clinic 3660 Rome Drive Lafayette, IN 47905

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
059	2	3	11	24	Janice Miller, M.D. Clinical Neuroscience Solutions, PA 5601 Corporate Way, Bldg. 2, Suite 210 West Palm Beach, FL 33407
060	1	3	10	22	Arifulla Khan, M.D. Northwest Clinical Research Center 1900 116 th Avenue NE, Suite 112 Bellevue, WA 98004
061	2	2	5	14	George Joseph, M.D. CNS of Jacksonville 4063 Salisbury Road N., Suite 108 Jacksonville, FL 32216
101*	1	0	0	0	Professor G. D. Burrows, M.D. Austin & Repatriation Medical Centre Austin Campus Studley Road Heidelberg VIC 3084 Australia
102	2	1	4	9	Russell Franco D'Souza, M.D. Broken Hill Base Hospital Thomas Street Broken Hill NSW 2880 Australia
201	2	1	4	9	José de Jesus Castillo, M.D. Centro Avanzado De Salud Animica Padre Mier 1015 Poniente Esq. Miguel Nieto Col. Centro Monterrey N.L. 64000 Mexico
202	1	0	2	4	Carlos Berlanga Cisneros, M.D. Instituto Mexicano De Psiquiatria Calzada Mexico Xochimilco #101 San Lorenzo Huipulco Mexico City 14370 Mexico
261	1	0	3	6	Dr. Carlos Enrique Parra Clinica Campo Abierto

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					Carrera 63 # 172 - 44 Santafe De Bogota Colombia
262	1	2	10	22	Felicia Daele Ramos, M.D. Hospital Mental De Antioquia – Homo Calle 38 No. 55-310 Bello, Antioquia Colombia
263	2	1	3	8	Carlos A. Lopez, M.D. Clinica Samein Calle 32 F # 63A - 117 Medellin Colombia
264	2	2	7	16	Claudia R. Vanegas, M.D. Clinica Nuestra Señora De La Paz Calle 13 No. 68F-25 Santafe De Bogota Colombia
301	1	1	6	13	Prof. George St. Kaprinis, M.D. Ahepa Hospital Aristotle University of Thessaloniki School of Medicine 3 rd Department of Psychiatry St. Kyriakidi 1 Thessaloniki 546 36 Greece
303	1	0	2	2	Prof. Venetsanos G. Mavreas, M.D. University of Ioannina Department of Psychiatry Medical School 1 Panepistimiou Str. Ioannina Ioannina 451 10 Greece
304	2	2	11	25	Prof. George N. Christodoulou, M.D. Eginition Hospital of Athens 72 Vas. Sophia's Avenue Athens 11528 Greece

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
401	2	1	4	9	Prof. Elsa Lara-Ferreira, M.D., Ph.D. Hospital Ingles De Lisboa R. Saraiva De Carvalho N49 1250 Lisboa Portugal
402	2	1	4	6	Horacio Firmino, M.D. Hospitais Da Universidade De Coimbra Piso 3 – Serviço de Psiquiatria Av. Dr. Bissaya Bareto 3000-075 Coimbra Portugal
403	1	0	0	2	Joaquim Cabeças, M.D. Hospital Sobral Cid Conraria Ceira 3030 Coimbra Portugal
601	1	0	1	1	Ana Gonzalez-Pinto Arrillaga, M.D. Hospital Santiago Apostol Servicio de Psiquiatria Olaguibel, 29 Vitoria Alava 01004 Spain
602	1	0	0	1	Jesus Valle Fernandez, M.D. Hospital de la Princesa Servicio de Psiquiatria, Planta 7 Diego de Leon, 62 Madrid 28006 Spain
603	2	0	0	2	Dr. Alfonso Rodriguez Martinez Hospital I.M.P.U. Germans Desvalls, S/N Barcelona 08035 Spain
605	1	1	2	6	Eduardo Vieta, M.D. Hospital Clinic I Provincial Institut Clinic de Psiquiatria i Psicologia Rosello, 140

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					Barcelona 08036 Spain
606	2	0	3	7	Javier Garcia Campayo, M.D. Hospital Miguel Servet Servicio de Psiquiatria Paseo Isabel La Catolica 1,3 Zaragoza 50009 Spain
701	2	1	2	4	Asst. Prof. Dr. Luchezar G. Hranov University Hospital of Neurology and Psychiatry Tsarigradsko Chausse Boulevard 4 th KM Sofia, 1113 Bulgaria
702	2	0	4	7	Prof. Stephen Todorov, M.D. Medical University Varna 55, Marin Drinov Street Varna, 9002 Bulgaria
726	2	1	2	5	Prof. Nikola Mandic, Ph.D. Klinicka Bolnica Osijek J. Huttlerova 4 Osijek HR-31000 Croatia
727					Vlado Jukic, M.D. Psihijatrijska Bolnica Vrapce Bolnicka Cesta 32 Zagreb HR-10090 Croatia
728	1	0	2	6	Prof. Miro Jakovljevic, M.D. Klinicki Bolnicki Rebro Zagreb Kispaticeva 12 Zagreb HR-10000 Croatia
771	2	0	2	4	Elie Karam, M.D. St. Georges Hospital St. George Street

CLINICAL REVIEW

Clinical Review Section

Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					Beirut 166378 Lebanon
801	1	1	4	8	Virgil Enatescu, M.D., Ph.D. Spitalul Municipal Dr. Luko Bela Piata Eroilor Revolutiei 2-4, CP 19 Satu Mare Romania
802	2	1	4	9	Dr. Iosif Gabos Clinica De Psihiatrie I Strada Gheorghe Marinescu, NR.38 Tg. Mures Romania
803	1	1	4	9	Gavril Cornutiu, M.D., Ph.D. Spitalul Clinic De Psihiatrie Oradea Strada Louis Pasteur, 26 Oradea Bihor 3700 Romania
821	1	0	0	1	Margarita A. Morozova, M.D. National Mental Health Research Centre Kashirskoye Shosse 34 Moscow 115522 Russian Federation
822	1	1	5	10	Prof. Yuri Alexandrovsky, M.D. Serbsky National Research Centre 47 Volokolamskoye Shosse Moscow 123367 Russian Federation
824	2	1	4	9	Prof. Anatoly Smulevich, M.D. Moscow Clinical Psychiatric Hospital #1 – N.A. Alexeyev Zagorodnoye Shosse, 2 Moscow 113152 Russian Federation
871	2	0	3	5	Tayfun Turan, M.D. Erciyes University School of Medicine Kayseri 38039

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Table C-1 Investigators and Sites with Patient Recruitment and Allocation for Studies HGGY 1 and 2.

Site #	Study #	OFC (n=86)	Olanzapine (n=370)	Total (N=833)	Principal Site Investigator
					Turkey

* denotes no randomized patients

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/s/

Paul Andreason
3/31/03 08:16:00 AM
MEDICAL OFFICER