EXECUTIVE SUMMARY

The Third United States Schizophrenia Advisory Panel Meeting

December 10, 1995

San Juan, Puerto Rico

The third meeting of the U.S. Schizophrenia Advisory Panel convened on December 10, 1995, in San Juan, Puerto Rico to discuss olanzapine, the Eli Lilly and Company antipsychotic in development. Ten of the 11 schizophrenia specialists who serve on the panel were present along with medical, research, and marketing executives from Eli Lilly and Company.

The meeting began with first-time presentation of efficacy and safety results from HGAJ, the pivotal phase 3 trial by Charles Beasley, Jr, MD, and a review of the developmental history and update of the integrated olanzapine data base by Gary Tollefson, MD, PhD. The second half of the meeting was devoted to a presentation of previously unreleased long-term efficacy data by Pierre Tran, MD, and a review by Jim Lancaster of the olanzapine label. The presentations were followed by group discussions.

Advisor reactions to the HGAJ data and the overall integrated database were overwhelmingly positive. Most commented that many of their patients could benefit significantly from olanzapine; advisors, patients, and patient caregivers anxiously await its approval.

HGAJ: AN INTERNATIONAL, MULTICENTER COMPARATOR TRIAL

HGAJ, a phase 3 international, multicenter, randomized, double-blind, parallel trial, was conducted from June 1993 through February 1995. There were 174 investigators involved in 17 countries. Of the 2223 subjects entered into the study, 1996 were randomized. Of the 227 patients who were not randomized, 68.7% were not randomized because they failed to meet study criteria; only 3.1% were not randomized because they experienced an adverse event. All subjects were ≥ 18 years old, and:

- met DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder;
- had a BPRS total initial score ≥18 *or* were patients who could no longer tolerate their neuroleptic (excluding haloperidol) treatment, or who recently had an adverse event likely attributable to that treatment

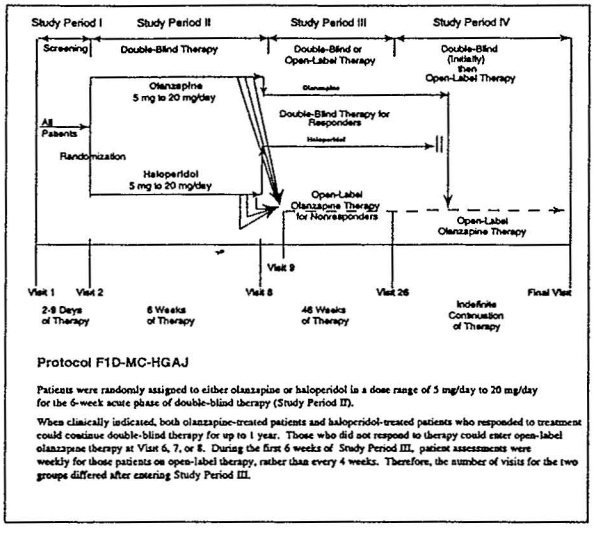
The trial was designed to study the safety and efficacy of olanzapine as compared with haloperidol through 1 year or more of treatment. Assessments were made of the following:

- incidence of treatment emergent adverse events, changes in vital signs, and laboratory analytes;
- incidence and severity of extrapyramidal symptoms (Simpson-Angus Scale, Barnes Akathisia Scale, and the AIMS);
- efficacy of olanzapine in alleviating positive and negative psychotic symptoms as well as overall psychopathology (BPRS extracted from the PANSS, subscale scores on the PANSS and BPRS);

- changes in severity of depressive symptoms during olanzapine treatment (MADRS)
- and the effects of olanzapine on suicidality (specific items and/or subscales of BPRS, PANSS, MADRS)

Study design

The study design is shown in graphic form in figure 1.



After a 2 to 9 day screening period, patients were randomized to treatment groups at a 2:1 ratio. Approximately 2/3 of randomized patients received olanzapine and 1/3 received haloperidol. Olanzapine was administered once daily in doses of 5, 10, 15, or 20 mg/day; haloperidol was administered once daily in doses of 5, 10, 15, or 20 mg/day. The starting dose for both drugs was 5 mg/day, and each could be titrated upwards in 5 mg increments to 20 mg/day as needed. Patients who responded to double-blind treatment entered into the acute therapy phase of treatment which lasted 6 weeks. Following completion of acute therapy, patients were then allowed to continue their double-blind treatment for a total of 1 year. Patients who did not respond to double-blind treatment at three weeks could enter open-

label treatment and receive olanzapine for 46 weeks. Some patients potentially crossed from double-blind therapy with olanzapine to open-label therapy with olanzapine.

Acute Phase Results

Patient characteristics

Patients were primarily in their late thirties, 35% were female, 65% were male. Patients were predominantly Caucasian. The age of onset of illness was approximately 24 years. The majority of patients had a diagnosis of paranoid schizophrenia, approximately 2% had a diagnosis of schizophreniform disorder, and 15% had a diagnosis of schizoaffective disorder. Approximately 70% of patients were being treated with a dopaminergic antipsychotic at the time of study entry. Patients in the olanzapine treatment group and haloperidol treatment group were similar in age and origin distribution. There were no statistically significant differences between patients in the two treatment groups in length of current episode, distribution of number of previous episodes, or in having a previous exposure to haloperidol. The mean baseline severity of illness as measured by the BPRS Total was approximately 33.

Medication use

Mean daily dose: The mean daily dose of olanzapine for patients completing ≥3 weeks of treatment was 13.2; the median was 15.0. The mean daily dose of haloperidol for patients completing ≥3 weeks of treatment was 11.8; the median was 10.0.

Anticholinergic use: Markedly more haloperidol-treated patients used anticholinergics than olanzapine-treated patients (47.7% haloperidol vs 17.1% olanzapine; $p<.001$) The mean mg/day/patient was .33 for olanzapine and 1.29 for haloperidol.

Benzodiazepine use: There was only a slight difference in benzodiazepine usage between the two treatment groups (60.5% olanzapine vs 66.2% haloperidol).

Completion rates

HGAJ showed the highest completion rates of olanzapine clinical trials to date: 66% of the patients completed olanzapine, and 47% completed haloperidol ($p <.001$). Statistically significantly more patients discontinued haloperidol than olanzapine for lack of efficacy (olanzapine 20.7% vs. haloperidol 32.1%; p<.001) and patient decision (olanzapine 3.6% vs. haloperidol 7.4%; p<.001).

Efficacy

Endpoint analyses: The primary efficacy analysis was the analysis of mean change from baseline to endpoint in BPRS total score. The improvement in the olanzapine treatment group was significantly greater than in the haloperidol treatment group in the BPRS total score, PANSS negative score, CGI Severity score, and MADRS total score (p=.015, p=.032, p=.029, p=.001, respectively). The PANSS Total missed achieving statistical significance by .001 (p=.051).

Response rate analyses: Substantially more olanzapine-treated patients responded to treatment than haloperidol treated patients (olanzapine 51.6% vs haloperidol 34.2%, p<.001). Patients with a decrease of 40% or more in BPRS total score from baseline and who remained in the study for more than three weeks were classified as responders. Only those patients who remained in the study for more than 3 weeks *and* who had a baseline BPRS greater than 18 were included in the analysis of response rates.

Adverse events

Three adverse events were reported at a greater rate with olanzapine as compared with haloperidol: dry mouth, weight gain, and increased appetite. Adverse events that occurred at a greater rate in the haloperidol group included nervous system events (akathisia, dyskinesia, dystonia, extrapyramidal syndrome, hypertonia, hypokinesia, movement disorder, nervousness, oculogyric crisis, and tremor) and other events such as insomnia, vomiting, anorexia, and increased salivation.

Extrapyramidal symptoms: Extrapyramidal treatment-emergent adverse events were reported statistically significantly less often in the olanzapine treatment group as compared with the haloperidol treatment group for dystonic, parkinsonism, akathisia, dyskinetic and residual events.

Vital signs, ECG: There was no change in resting vital signs or orthostatic blood pressure decreases. There were no changes in ECG.

Seizure: Incidence of seizure in the HGAJ trial has not been formally analyzed; data pooled from other clinical trials suggest that seizure is rare.

Weight: Weight gain with olanzapine over the six week acute phase averaged about 1.88 kg. Weight gain appears to be the most consistent nontherapeutic physical finding across olanzapine clinical trials. Treatment-emergent type II diabetes was rare. The mechanism behind the weight gain is unknown, but a decrease in satiety may be involved. [Note: For all patients treated with olanzapine for any amount of time, forty percent gained ≥7% body weight. Patients who remained on olanzapine for 12 months gained an average of 24 lbs at the end of the 12 months. The data on factors associated with weight gain is currently being analyzed.]

Several advisors commented on the association of olanzapine with weight gain and encouraged Lilly to subject the data to a full analysis. Clinically significant weight gain is a risk factor for other conditions such as increased blood pressure, increased cholesterol, and type II diabetes. The advisors also noted that Lilly has an opportunity to develop strategies to help manage the weight gain.

Laboratory analytes: There was a transient increase in hepatic transaminases with olanzapine treatment, but there were no clinical symptoms and no discontinuations as a result of the increases. The olanzapine treatment group showed no evidence of hematotoxicity. There was a mild, transient increase in prolactin in the olanzapine treatment group, but this was statistically significantly lower in magnitude and less frequent than in the haloperidol treatment group.

Of interest to the advisors was the unexpected finding that many study subjects were found to be positive for hepatitis C. The study protocol did not call for a screen for hepatitis C, it was only discovered to be a significant problem when a study subject treated with olanzapine had large fluctuations in transaminase levels, and was subsequently found to be infected with hepatitis C.

Summary of Acute Phase Results

Efficacy

Olanzapine treatment shows:

- Superior overall and negative symptom efficacy compared to haloperidol
- Excellent positive symptom efficacy
- Superior efficacy with respect to depressive symptoms compared to haloperidol

Safety

Olanzapine treatment shows:

- Mild sedation
- Mild anticholinergic effects
- Minimal subjective dizziness without orthostasis
- Some transient, asymptomatic hepatic transaminase elevations
- Minimal parkinsonism and akathisia with rare dystonias

Atypical Profile

Olanzapine has the following characteristics associated with atypicality:

- Greater efficacy against negative symptoms than haloperidol (overall efficacy also greater)

- Rare dystonic reactions and less parkinsonism and akathisia than with haloperidol
- Substantially less prolactin elevation than with haloperidol

OVERVIEW OF THE INTEGRATED OLANZAPINE DATABASE

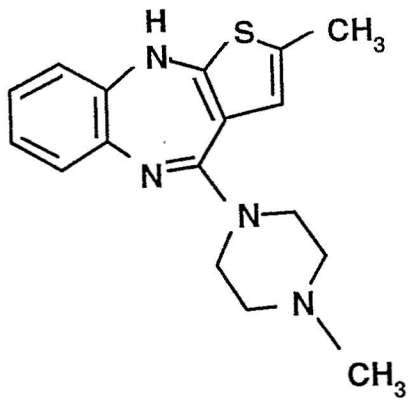
BACKGROUND

Olanzapine was first synthesized in April, 1982. An IND was filed in July, 1986, and the first human dose was given in September of that year. The first open-label clinical dose was given about two years later, in December 1988, and the first double-blind, placebo-controlled efficacy trial began three years later in November 1991. After 1991, the development course accelerated. The core studies were completed in February 1995, and world-wide regulatory submissions were filed by September 1995.

Human exposure to olanzapine as of February 14, 1995 is as follows:

≥ 1 dose:	3,139 subjects
> 1 month:	>1,962
> 6 months:	> 876
> 1 year:	> 301

The structural moiety of olanzapine is shown below. The two clear differences between olanzapine and clozapine is that olanzapine lacks the halogenated side chain of clozapine and olanzapine has the thiol ring.



PRECLINICAL PHARMACOLOGY

Preclinical studies reveal that olanzapine is a more potent 5-HT_2 than D_2 antagonist. Olanzapine has a favorable side-effect profile with respect to prolactin changes and extrapyramidal syndrome. The compound appears to have an atypical activity profile similar to that of clozapine.

Although most of the preclinical data on olanzapine has been published, some studies have recently been completed that further elucidate the binding profile, electrophysiology, and behavioral pharmacology of the compound. Findings of these in vitro and ex vivo studies provide additional support for the in vivo data.

Receptor binding affinity

- Greater affinity for $5HT_2$ receptors than D_2 receptors
  - A PET study by Lars Farde at the Karolinska Institute revealed that olanzapine has greater affinity for the $5HT_2$ receptors than D_2 receptors. This study involved 3 normal volunteers who

received 10 mg of olanzapine (the recommended starting dose). PET scans showed 84% occupancy at $5HT_2$ and 61% occupancy at D_2. This is very similar to the profile exhibited by clozapine in similar studies.

  - A SPECT study by Robert Cohen in the United Kingdom showed olanzapine responsive patients to have lower striatal D_2 occupancy than typical antipsychotic and risperidone responsive patients and occupancy comparable to clozapine responsive patients.

- Greater affinity for D_4 receptors than D_2 receptors
  - Several in vitro assays have shown consistently that D_4 occupancy is greater than D_2. The range of the D_4 to D_2 ratio across the studies was 1.7 to 4.6 fold.
- Slightly greater affinity for olfactory tubercle D_2 receptors than striatal D_2 receptors

- Broad receptor profile.
  - Preclinical studies show olanzapine has significant affinity for $5HT_{2C}$, $5HT_3$, $5HT_6$, D_3, D_1, muscarinic (m_1 through m_5, but especially m_1), alpha1 and H_1 receptors. Unlike clozapine, olanzapine does not have significant alpha2 affinity.

Electrophysiologic studies

- Acute administration of olanzapine does not increases A9 firing rates, but does increase A10 firing

- Chronic administration of olanzapine increase A9 firing at higher doses, and decreases A10 firing

- Olanzapine reverses d-amphetamine inhibition of A9 firing at a dose 6 times higher than the dose which reverses inhibition of A10 firing

Behavioral pharmacology

- Olanzapine blocks both apomorphine-induced climbing behavior and 5HTP-induced head twitch in a dose-dependent manner, indicating 5HT and dopamine antagonism in vivo.

- Olanzapine blocks oxotremorine-induced tremor in a dose-dependent manner, indicating cholinergic antagonism in vivo.

- The ratio of the olanzapine dose required to interfere with conditioned avoidance to the dose required to induce catalepsy suggests antipsychotic activity with relatively low potential for extrapyramidal symptoms. This is supported by studies which compare the dose that influences hind leg retraction versus the dose that influences frontal leg retraction. Similar to clozapine, olanzapine has been shown to increase hind leg retraction at a dose lower than that needed to increase frontal leg retraction.

- Unlike typical antipsychotics, olanzapine increases punished responding in a conflict model similar to clozapine. This suggests olanzapine may have some anxiolytic properties. However, olanzapine does not substitute in animals trained to discriminate for the benzodiazepine, chlordiazepoxide.

- Olanzapine selectively antagonizes NMDA antagonist induced activities similar to clozapine. Olanzapine has been shown to antagonize the following 3 effects:
  1) MK-801 induced locomotion in mice
  2) PCP induced locomotion in rats (relative to amphetamine induced locomotion) without impairing motor activity
  3) PCP induced social isolation in rats (this may be a facsimile of negative symptoms in animals)

- Olanzapine antagonizes PCP- and MK-801-induced decreases in prepulse inhibition of the startle reflex without affecting baseline reactivity.

- Similar to clozapine, olanzapine selectively antagonizes:
  –cocaine induced hyperactivity compared to d-amphetamine induced hyperactivity in rats; and
  –low dose versus high dose d-amphetamine induced hyperactivity.
  –olfactory tubercle dopamine induced hyperactivity relative to nucleus accumbens ergometrine induced hyperactivity

- Olanzapine substitutes in animals trained to discriminate clozapine, suggesting similarities in pharmacologic profile
- Olanzapine antagonizes grooming induced by selective D1 agonist, similar to clozapine, but facilitates vacuous chewing at higher doses which is unaffected by clozapine
- Olanzapine decreases the reinforcing effects of cocaine, an effect which, to date, has not been shown with clozapine
- Unpublished data from Daniel Casey's rhesus monkey model study suggests that there is a 10 to 20 fold difference between the expected clinically efficacious dose of olanzapine and the predicted threshold dose needed to induce EPS.

HUMAN PHARMACOKINETICS

The time to peak plasma concentration is approximately 5 hours. The half-life of the parent compound is approximately 24 hours, which is consistent with a once-a-day dosing schedule. The half-life for total radiocarbon excretion is 59 hours. Single-dose studies suggest a linear dose proportionality in plasma concentration. Finally, food has no effect on absorption or peak plasma levels.

Some differences were found in the pharmacokinetics of olanzapine in subgroups, however, the change that any one of these factors induces is less than the population variability as a whole:

- Olanzapine may possibly have greater oral bioavailability in the Japanese, however, preliminary results from Phase 2 trials in

Japan show the mean modal dose of olanzapine to be consistent with the mean modal dose found in HGAJ.

- Metabolism of olanzapine may be decreased in women and the elderly, however dose adjustments will most likely not be necessary.
- The only two factors which appear to induce metabolism are smoking, probably through induction of the 1A2 cytochrome, and carbamazepine.
- Current in vitro and in vivo data suggest that olanzapine does not have any significant inhibitory effect on any cytochrome system other than 1A2. This suggests that olanzapine is devoid of a significant hepatically-based drug-drug interaction profile.

CORE STUDIES

There are four core olanzapine double-blind clinical trials: HGAP (S1), HGAD (S2), E003 (S3), and HGAJ (S4).[1]

HGAP (S1): It was a 6-week, three-arm fixed dose trial with placebo, olanzapine 1 mg, and olanzapine 10 mg conducted in the US. Subjects (N=152) were schizophrenic inpatients with a BPRS $_{0\text{-}6} \geq 24$. One of the goals of HGAP was to demonstrate that the 1 mg dose was not efficacious.

[1]S1, S2, S3, S4 notation was used in Dr. Tollefson's presentation to simplify discussion of the overall results.

HGAD (S2): This study has been published.[2] It was a 6 week with extension, five-arm, dose-ranging trial with placebo, olanzapine 2.5mg - 7.5 mg/day, olanzapine 7.5mg - 12.5mg/day, olanzapine 12.5mg - 17.5mg/day, and haloperidol 10mg -20mg/day. Subjects (N=335) were schizophrenic inpatients with a BPRS $_{0\text{-}6}\geq 24$. It was conducted in North America.

E003 (S3): This multinational trial was similar in design to HGAD, but with olanzapine 1 mg substituting for placebo. (European ethical review committees do not allow placebo-controlled trials for acute schizophrenia. The olanzapine 1mg dose, which was thought to be an ineffective dose, was inserted to replace placebo. The 1 mg dose, however, showed some unexpected activity, which necessitated initiating HGAP.) This trial was a 6 week with extension, five-arm, dose-ranging trial with olanzapine 1 mg/day, olanzapine 2.5mg - 7.5 mg/day, olanzapine 7.5mg - 12.5mg/day, olanzapine 12.5mg - 17.5mg/day, and haloperidol 10mg -20mg/day. Subjects (N= 431) were schizophrenic inpatients with a BPRS $_{0\text{-}6}\geq 24$. Lack of a placebo has confounded some of the data analysis in this study.

HGAJ (S4). As reviewed above, this was a Phase 3, 6 week with extension, comparator trial with flexible olanzapine (5 - 20 mg/day) and haloperidol (5 - 20 mg/day) dosing. HGAJ had broader diagnostic inclusions than the other three studies. Subjects (N=1996) had schizophrenia, schizophreniform disorder, or schizoaffective disorder, inpatient or outpatient, with a $BPRS_{0\text{-}6} \geq 18$, or were intolerant of current therapy.

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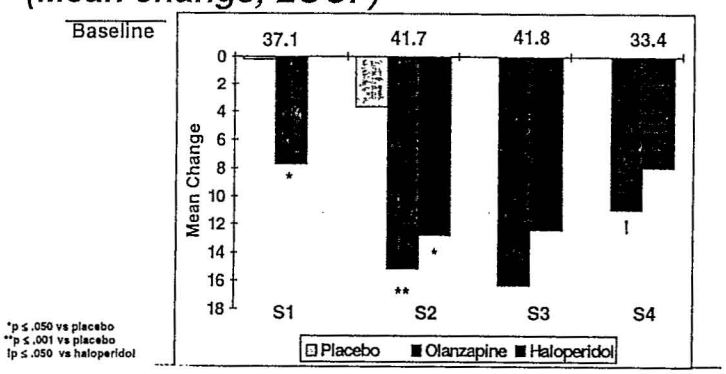
[2] Beasley CM, Jr, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology*. 1996;14:111-123.

Efficacy

The primary efficacy measure in all four studies was the BPRS Total. The figure below shows the mean change in BPRS total score for all four studies.

Overall psychopathology

Efficacy: BPRS - Total Score (Mean change, LOCF)



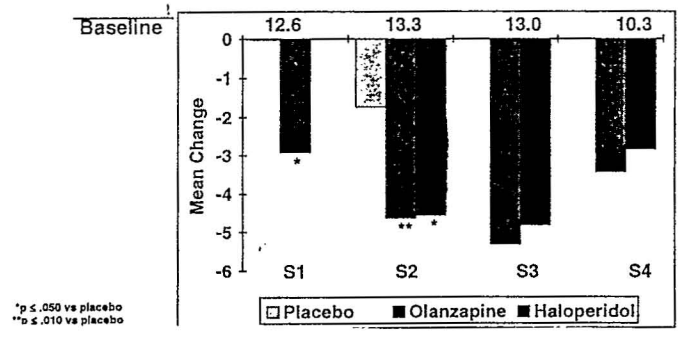
- In S1, or HGAP, the 10 mg olanzapine dose showed significant improvement as compared with placebo. (The 1 mg olanzapine dose from S1 is not displayed on the graphic, however, the data show it is comparable to the placebo arm in S1. Therefore, S1 demonstrates that the 1 mg olanzapine dose is a no-effect dose.)
- Only the higher dose arm from S2, or HGAD, is represented in the graphic, and this shows a clear and significant differentiation from placebo. The data also show a step-wise progression in increasing efficacy from low to medium to high dose. In addition, in contrast to some risperidone data, in the S2 patient population haloperidol was an effective therapy and differentiated significantly from placebo. The efficacy of haloperidol suggests that the patient profile was appropriate, ie, it was not a uniquely refractory population.
- Although S3, or E003, did not show a statistically significant difference between the higher dose olanzapine arm and the 1mg olanzapine arm,

there was a numerical difference. Interpretation of the results from S3 is somewhat complicated because the 1 mg arm showed unexpected efficacy, and there was no placebo arm. (There was, however, evidence of dose linearity, and the higher dose arm did show a significant difference on the secondary efficacy measures, CGI severity scale and PANSS-positive scale, as compared with the 1 mg dose.) Reasons for the unexpected efficacy of the 1 mg dose are currently being explored. Possible reasons include factors involved in patient selection, prior course of therapy, benzodiazepine use, and investigator expectation.

- In S4, or HGAJ, olanzapine produced a statistically significant improvement on the BPRS total as compared with haloperidol. This result is the primary driver of the overall efficacy data for olanzapine. Results from HGAJ are reviewed in greater detail in the previous section, *HGAJ: An International, Multicenter Comparator Trial.*

Positive symptoms

Efficacy: BPRS - Positive Score (Mean change, LOCF)



- The figure shows that in S1 and S2 olanzapine showed significant improvement in positive symptoms as compared with placebo.

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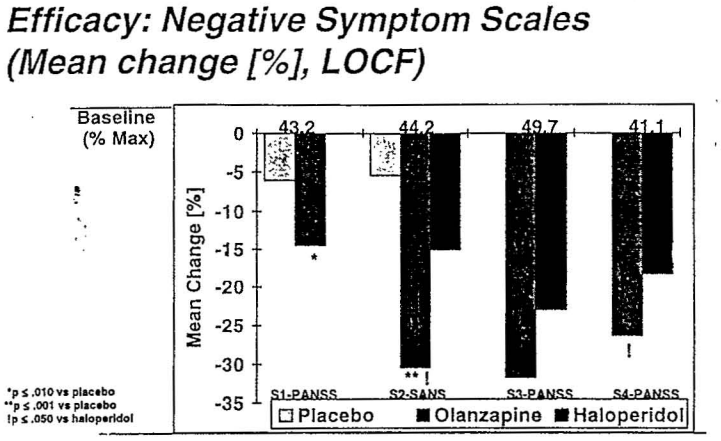
Negative symptoms



- This figure shows that in S1 and S2 olanzapine demonstrates statistically significant superiority to placebo in negative symptom improvement. In addition, the higher dose olanzapine arm in S2 shows statistically significantly superior improvement in negative symptoms as compared with haloperidol. Olanzapine also showed statistically significant superiority in negative symptom improvement as compared with haloperidol in S4. Both S2 and S4 had an acceptable dose range of haloperidol, S2: 10 mg to 20 mg; S4: 5 mg to 20 mg.

Safety

Acute EPS

- The data are consistent across all four studies showing that olanzapine produces an improvement in acute EPS from baseline to endpoint on both the Simpson-Angus Scale and the Barnes Akathisia Scale. In addition, S3 and S4 show olanzapine produced statistically significantly greater improvement in acute EPS as compared with haloperidol.

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Adverse events

- Adverse events that occurred at greater than or equal to 2 percent incidence and were significantly different from placebo ($p \leq .05$) in any of the fours studies included: anorexia, delusions, somnolence, dizziness, constipation, pharyngitis, paresthesia, dry mouth, weight gain, increased appetite, akathisia, insomnia, tremor, hypertonia, nervousness, extrapyramidal syndrome, increased salivation, vomiting, joint disorder, amblyopia, dystonia, and weight loss.

- The overall discontinuation rate for olanzapine due to adverse events was approximately 5 percent.

Vital signs, weight, ECG

- Findings were consistent across all four studies for vital signs, weight, and ECG:
  - No change in resting vital signs
  - Slight increase in orthostatic heart rate (not clinically significant)
  - Weight gain dose related
  - ECG: no change or slight increase in sinus rate with a corresponding decrease in QT interval

Laboratory analytes

- Laboratory analytes were also consistent across all four studies.
  - –Transient, possibly dose-related increase in hepatic transaminases, but resulted in:

–no clinical symptoms

–no discontinuations during the acute phase of S4 (HGAJ)

–No evidence of hematotoxicity

–Mild, transient dose-related increase in prolactin but at levels lower than those associated with haloperidol

CONCLUSIONS BASED ON INTEGRATED DATABASE

Efficacy

- Olanzapine demonstrates excellent overall and positive symptom efficacy.
- Olanzapine shows superior negative symptom efficacy as compared with haloperidol. This finding is considered to be the main driver of the efficacy data. Data on the efficacy of olanzapine in improvement of negative symptoms is currently undergoing path analysis to differentiate between primary and secondary negative symptoms. Preliminary results of this analysis suggest that olanzapine has a significant impact on primary negative symptoms.

Safety

Across all four studies olanzapine shows:

- Mild sedation
- Mild anticholinergic effects
- Minimal subjective dizziness without orthostasis
- Some transient, asymptomatic hepatic transaminase elevations
- Minimal parkinsonism and akathisia with rare dystonias

Atypical Profile

- Olanzapine shows three aspects of an atypical agent:
  - –greater efficacy against negative symptoms than haloperidol
  - –rare dystonic reactions and less parkinsonism and akathisia than with haloperidol
  - –substantially less prolactin elevation than with haloperidol
- A study is underway to determine the efficacy of olanzapine in treatment of refractory patients. Positive results from this study would provide the final piece of evidence supporting the atypical profile of olanzapine.

LONG-TERM EFFICACY and EPS DATA

Three of the four major trials, HGAD, E003, and HGAJ had a long-term extension phase. Responders from the acute phase of the trials could continue double-blind therapy, with the same initial study drug at the same dose or dose-range, in the extension phase for at least 12 months. Results of these extension phases of HGAD and E003 are now available. Preliminary results from the HGAJ extension are also available.

Summary

Because the number of patients in each treatment completing the 12 month extension phase in HGAD and E003 studies is small, the data should be interpreted with caution. However, overall, the HGAD and E003 data suggest that maintenance olanzapine treatment may be comparable to haloperidol and more effective than placebo in preventing relapse. In both studies there was a trend for higher dose olanzapine groups to have greater completion rates than lower olanzapine dose groups. In addition, the HGAD and E003 data indicate that maintenance olanzapine treatment produces improvement in parkinsonism (measured by the Simpson-Angus scale) as compared with the haloperidol treatment. Preliminary data from the long-term extension phase of HGAJ, which had a higher retention rate than the two other studies, suggests olanzapine treatment results in a non-relapse rate greater than that reported in either HGAD or E003. In addition, olanzapine treatment significantly reduced rehospitalization as compared with haloperidol.

HGAD. In this study, 95 patients completed the acute phase and continued into the double-blind extension phase. Patients on higher dose olanzapine were more likely to enter the long-term extension phase. There was statistically significantly more patients in the OLZ-H treatment group who completed one year of therapy than either the placebo or Hal treatment groups. However, the number of patients in each group was very small. There were only 2 patients each in both the placebo and haloperidol groups who completed the one year extension. Survival analysis of relapse prevention indicated that statistically significantly fewer patients in the Olz-L and Olz-H treatment groups experienced relapse at any given point in time than patients in the placebo treatment group. In addition, olanzapine treatment groups showed greater improvement on the Simpson-Angus scale as compared with the haloperidol treatment groups. Analysis of the extension phase data from HGAJ, which is currently underway, is expected to provide more concrete support for the efficacy of olanzapine in preventing relapse.

A few of the advisors commented that the drop out rate seemed rather high because patients are usually more likely to remain in treatment when they are enrolled in a study. Other advisors did not agree; they felt the drop out rate reflected the natural attrition that occurs in any long-term study. Furthermore, because the sample sizes in each group are so small, the retention or loss of one patient would substantially influence the relapse rate.

E003. In this study, 175 patients completed the acute phase and continued into the double-blind extension phase. Higher dose olanzapine groups were

more likely to complete the one-year extension phase. There were no statistically significant pairwise comparisons in the time to relapse between any of the olanzapine treatment groups and either the Olz1.0 or Hal treatment groups. The low number of patients in the Olz1.0 group who completed one year provides support for the non-efficacy of this dose. In addition, olanzapine treatment groups showed greater improvement on the Simpson-Angus scale as compared with the haloperidol treatment groups.

A few advisors encouraged Lilly to present the long-term data from E003 in another format because the completion rates were so high as to seem an artifact of the study, rather than a true finding. They suggested that all of the data should be presented, including all sample sizes, at each stage of assessment, rather than percentages alone at the start and at endpoint. Furthermore, some argued that detailed survival curves may be helpful in demonstrating the significance of the data, but others disagreed.

HGAJ. Preliminary data from the long-term extension phase of HGAJ suggests retention rates from the acute phase were one and a half to two fold greater than that reported in either HGAD or E003. Analysis of the data is ongoing, but early results suggest that non-relapse rates are significantly higher in the olanzapine treatment group as compared with the haloperidol treatment group. In addition, preliminary results suggest olanzapine treatment significantly reduced rehospitalization as compared with haloperidol.

Advisors commented that the HGAJ data would be important to support the long-term efficacy of olanzapine. Although the data from HGAD and E003

are impressive, the sample sizes are too small to draw any firm conclusions. Advisors also recommended initiating a relapse prevention study with fixed-dose olanzapine to examine the possibility that patients dropped out of the extension phase due to weight gain.

LABELING ISSUES

Jim Lancaster presented the draft indication for olanzapine that was submitted for approval.

Indication

ZYPREX is indicated for the management of the manifestations of psychotic disorders consisting of positive and/or negative psychotic signs and symptoms.

The antipsychotic efficacy of ZYPREX was established in 6-week controlled trials in schizophrenic inpatients and in schizophrenic, schizophreniform, and schizoaffective in- and outpatients. Further, the long-term effectiveness of ZYPREX in maintaining an acute treatment response was demonstrated in 3 double-blind, controlled extension maintenance trials. Consistent with a good standard of practice, the physician who elects to use ZYPREX for extended periods should periodically reevaluate the long-term usefulness of the drug for an individual patient.

Advisors largely agreed that it was both conservative enough to be approved unchanged, and aggressive enough to distinguish olanzapine from other antipsychotics, without overtly suggesting superiority.

Dosage and administration (excerpt)

Usual Dose—The recommended starting dose of ZYPREX is 10 mg administered once daily.

The range of ZYPREX administration is 5 mg to 20 mg/day. When clinically indicated, it is recommended for most patients that an increase to a dose ≥ 15 mg/day be made only after the patient has been treated with a starting dose for at least 4 days.

There was some concern over the recommendation to wait four days before increasing the dose over 10 mg per day. Some advisors felt that some clinicians may interpret this recommendation to mean that olanzapine at 10 mg is not an effective dose, even though it is, and therefore, they might be reticent to start an acutely psychotic patient on olanzapine. Overall,

however, advisors found the draft indication to accurately reflect the findings of the four major clinical trials.