

**HGAJ Data Presentation**

Charles Beasley, Jr., MD

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**DR. BEASLEY:** We actually as of about 3 o'clock yesterday thought this would be a satellite symposium presented from the Hilton at O'Hare. Fortunately, several of us were able to find a plane working that had a windshield and we got here late last night, but four of us were sitting there wondering.

What I'm going to do, as Gary said, is present the results of our international multicenter olanzapine/haloperidol comparator trial conducted in 17 countries. It's certainly exciting that just two years ago we were in Honolulu talking about the results of one trial with 335 total patients. Here we stand today, being able to talk about a database of over 3000 patients. This is a very prophetic number, we hope: It was 1996 patients entered into the trial.

A little bit about the methodology. As I said, 1996 patients. Patients could be inpatients or outpatients during the entirety of the trial, move from one status to the other. The majority began as inpatients. DSM-III diagnoses included schizophrenia, schizophreniform disorder, or schizoaffective disorder. Requirements were, in addition to diagnosis, a BPRS score of 0 to 6, a score of 18 or greater, or no minimum BPRS score and intolerant of current antipsychotic medication. In point of fact, only two percent of patients in both treatment arms made it in as intolerance with lack of a BPRS of 18.

There were 174 investigators in 17 countries. There was an acute phase, and this is what I'll be talking about today, a six-week trial with a double-blind continuation phase for responders and an open-label extension for non-responders. I'll show you a bit more about the complexity of the patient flow in a moment. Olanzapine dose, 5-20 mg with patients

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beginning at 5 mg, dosed potentially up to 20, haloperidol comparably 5 to 20 mg. The randomization was two olanzapine to one haloperidol. We used PANSS, BPRs extracted from the PANSS, Barnes and Simpson-Angus, AIMS. Benzodiazepines and anticholinergics were allowed.

This was the patient flow: a lead-in period, nonplacebo randomization to the two arms. This period was six weeks in length. Patients who completed three weeks and were not doing well on either haloperidol or olanzapine could cross blindly to open-label olanzapine. Some patients potentially crossed from olanzapine to olanzapine.

Patients completing the six weeks and doing well continued double-blind for something up to slightly in excess of a year. The timing of the completion of this protocol was really driven by numbers of patients randomized and continued for over a year across several studies.

Patient characteristics—this is very comparable to what we've seen in our other three trials. Mean age—late 30s, gender distribution about 65/35, predominantly Caucasian.

With regards to diagnosis, the majority of patients, in fact, had a schizophrenic diagnosis with the majority of those being paranoid. Subtype—only approximately two percent schizophreniform and approximately 15 percent across both groups schizoaffective.

With regard to course—chronic with acute exacerbation predominant. We'll get into a bit more about acute episodes for those patients who had them.

Age of onset of psychosis of these patients—approximately 24 years of age, so clearly patients into the middle phases of their illness. For those patients classified as having an acute exacerbation, substantially fewer

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episodes obviously with a whopping standard deviation, but the picture here is one of chronicity and stable exacerbation with previous episodes, and this defines the patients who entered with substantial symptomatology versus those who were entering with minimal symptomatology but intolerant of current therapy.

We're trying to look a little bit more at details of longitudinal response to medication. This was actually an issue that we had intended to do, but we have taken a bit more prospective look at this, primarily because of some comments on the manuscript that came out of the data that we showed you last year on study HGAP. We have basically 70 percent of patients being treated at the time they entered this protocol with a dopaminergic antipsychotic. Seventy percent of patients were receiving treatment.

The proportion of patients whose last antipsychotic treatment, now this would include these patients, but some who were in fact off, were discontinued from their antipsychotic either to enter the trial or otherwise judged unresponsive to the last antipsychotic. We're talking about slightly over 75 percent of patients.

A proportion of patients treated with clozapine, 10 percent, and this was restricted to the last two years prior to entering this trial. Almost 11 percent of the olanzapine patients, that was the fifth most common drug out of 53. For the haloperidol patients, 10 percent, sixth most common out of 47. The database that we showed you last year, HGAP—clozapine was number 2 and number 3 most commonly-used drug and was used in 25 percent of the patients entered in the trial. Patients weren't supposed to be refractory.

We stated exclusion, but we made a very robust definition of refractory. Any patients who had ever budged on basically anything by 1

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CGI point was considered to be nonrefractory, if they had ever budged by 1 CGI point retrospectively assessed on anything. They had to be pretty refractory to clearly meet our definition.

Baseline severity of illness—BPRS of 33. This is slightly lower than seen in our other trials, which required a mandatory BPRS of 24, but certainly substantially above the 18 in reflecting the very small number of patients entering because of intolerance, PANSS, CGI severity, and we included a MADRS to look at depressive symptomatology in this patient population.

The study drug is very interesting. The mean dose of olanzapine was 13.2, median 15; haloperidol 11.8 with a median 10. This is restricted to patients who were in the trial at least three weeks in terms of defining these. We take patients who were in the trial at least three weeks. We take the dose that they were on for the most days during their trials. We then averaged those to take a median across that subset of patients. And what's very interesting in looking at weekly changes in dose, the olanzapine patients drifted up, drifted up, drifted up, and stabilized. The data would suggest that the haloperidol patients were actually taken up above these figures and then brought back down. The whys of that I can't comment on. Steve.

**DR. MARDER:** What were the dosing instructions?

**DR. BEASLEY:** The dosing instructions were you began at 5 mg a day. You can then go up by 5 mg a visit. You can come down at any time by any amount. The minimum time between visits was 5 days.

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**DR. MARDER:** And the maximum dose was 20?

**DR. BEASLEY:** And the maximum dose was held at 20 for both compounds.

**DR. MARDER:** And if somebody couldn't tolerate 5?

**DR. BEASLEY:** If they couldn't tolerate 5, they were out. Benzodiazepine use: statistically slightly numeric difference. Marked difference in the use of anticholinergics: 17 percent in olanzapine patients, 47 haloperidol patients. In our placebo controlled trials with placebo, this has usually varied from 14 to 16 percent, and mean mg per day for patients, .33 versus 1.29.

The completion information is very interesting, I think to some extent driven by the fact that we ran half of this in Europe, half in the U.S., with a lot of enthusiasm around the compound. We saw certainly our highest completion rates to date: two thirds of the patients completed olanzapine, almost 50 percent on haloperidol but, again, a substantial difference. Adverse events leading to discontinuation: four months haloperidol patients, lack of efficacy greater among haloperidol and patient decision as well. Twice as many among haloperidol as olanzapine-treated patients.

Here is a numeric summary of the efficacy findings. We'll look at these in bar chart form: extracted BPRS, statistically significant. PANSS total just missed. That's .0506, approximately. PANSS positive is relatively comparable. PANSS negative, statistically significant, CGI significantly different, and MADRS, significantly different change.

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That's the BPRS total. Endpoint last observation period: forward analysis looks very interesting, observed case analyses in these studies. Something that we had really not expected to see—again, this is observed case, this is the patient flow per week, patients contributing to the analysis—is statistically significant differences in the observed case sample. What we've usually seen is a pattern where you get a little bit and then patients are discontinued. Then at the endpoint—this is a completers analysis—that tends to be not a statistically significant difference. So we're very happy with seeing this.

Here we have PANSS total, and on PANSS total observed case, completers statistically significant superiority for olanzapine. Positive symptoms and weight gain, slight numeric difference. Negative symptoms, negative symptoms observed case weeks 4, 5 and 6, completers.

MADRS—this is actually the largest difference that we see in terms of ratio of change in terms of symptomatology, that duration carried forward and for the CGI comparable.

Now let's go to a categorical analysis. What we're looking at here are response rates. Only among the subset of patients who made it at least three weeks in therapy, so we're not prejudicing against early dropouts, discontinuations, if there is a difference in adverse event profile, which obviously there was. We're now down to 1099 patients treated with olanzapine who made it at least three weeks and who also began with a BPRS greater than or equal to 18, and 514 haloperidol patients.

Our definition of response was a decrease of 40 percent or greater in BPRS, and here we're talking about 0 to 6. So this would be roughly comparable to a 22 percent percentage decrease. You're talking about a

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BPRS with either a score of 1 to 7. We're getting 51.6 percent of olanzapine patients, 34.2 percent of haloperidol patients, obviously substantially significantly different.

The adverse event profile is rather interesting. What we have represented here are all the adverse events reported. Again, this is a spontaneous report. Part of the patients were reported by the physicians. All events statistically significantly different between the two compounds at a rate of two percent or greater for either compound. What we see is that there are three events reported at a greater rate among olanzapine: dry mouth, weight gain (statistical weight gain), increased appetite. Now, I would point out to you that this does not reflect change on scales. This reflects an assessment on the part of investigators that weight gain should be described as an adverse event. What we see is a whole laundry list then of events overrepresented statistically significantly among haloperidol-treated patients—EPS, psychomotor activation including insomnia, nervousness, some GI, complaint of vomiting, anorexia. Joint disorder has tended to be used interestingly enough as a nonspecific form of EPS. We have tremor, hypertonia. These are manifestations of parkinsonism. Extrapyrimalidal syndrome is the COSTART dictionary term intended to be used for parkinsonism. We see increased salivation, joint disorder, and then dystonias as well.

Looking formally at EPS, what we have are endpoint last observation carried forward analysis of changes on the formal scales. These are potentially influenced by the use of anticholinergic medication. Remember that there was substantially conditional use among the haloperidol-treated patients. So here we have Simpson-Angus, statistically significantly

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different. Barnes is the same pattern, decrease from baseline to endpoint among olanzapine-treated patients, increase among haloperidol, statistically significantly different.

Here we have AIMS, decrease, decrease, but the difference is statistically significant. Now as Gary pointed out, Dr. Street is going to be presenting a poster dealing in greater detail with our TD experiences in our long-term double-blind trials, but I'm going to preview that with a couple of slides.

**DR. CASEY:** All that last information was a filtered change?

**DR. BEASLEY:** Those were change scores from baseline.

**DR. CASEY:** You still have positive scores overall, but these were change scores.

**DR. BEASLEY:** Those were change scores from baseline to endpoint. We've got the analyses for max case and categorical analysis. I would be happy to cite those off for you if you would like.

Three of our trials had double-blind, long-term extensions. HGAD the very first trial we presented, this is the North American trial, E003, European, sister to that HGAJ, the trial that we're looking at now. We had multiple doses of olanzapine in this along with placebo, haloperidol. That was the 5 plus or minus 2.5 which translated into 7.5 plus or minus 2.5, 12.5, and the higher dose arm, which was 15 plus or minus 2.5, which was a 17.5-

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mg arm in essence. E003 was comparable. This just had a 1-mg arm, but we excluded that arm from the analysis.

The mean exposure to olanzapine, 237 days; for haloperidol, 203 days. This analysis is restricted to only those patients who made it into the long-term extension. So every patient had at least six weeks of treatment, and in some cases, treatment here ranged up over three years. Two olanzapine patients were on over three years when these analyses were done.

Our definition of a treatment-emergent dyskinesia we based on cross sectional RDC criteria as assessed by items 1 through 7 of the AIMS. Definition of a dyskinesia was one or more items with a 3 or greater or two or more items with a 2 or greater. John, do you want to comment on whether you think that's reasonably appropriate?

**DR. KANE:** Yes.

**DR. BEASLEY:** Thank you, I appreciate it. I was a little afraid of what you might say since we didn't call you about that. Then we were restricting this, although Jaime is going to have more detail on multiple populations, the figures I'm going to show you are for no historical or secondary condition recorded in the patient's chart of tardive dyskinesia, and also failure to meet this definition at their baseline. So we're not talking about patients with no past neuroleptic exposure, but we're talking about patients who, as best as we can determine from the data as recorded by investigators, had no tardive dyskinesia at baseline and had no history of it. John, do you care to speculate on the outcome?

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**DR. BEASLEY:** Actually, we're concerned that the data looks confabulated because of the data on haloperidol. It's amazing.

We took three longitudinal cuts. Anybody who had any visit had a postbaseline assessment, positive for treatment-emergent dyskinesia, a final AIMS assessment, and then final two AIMS assessments. In general, these would have been at least one month apart. So this would be any place from that visit after six weeks going away to a single or multiple visits any place after three years. This would be at the final AIMS assessment and, again, final two AIMS assessments. So present at two time points, one following the other, and a month apart. I can't guarantee you what they were like between that.

Again, we have patients who made it to the long-term study with no history of tardive dyskinesia and failure to meet our operational definition at baseline, 700 olanzapine patients, 197 haloperidol-treated patients. You can see that as you begin to move down the scale of presumed persistence or, again, you've got point persistence, point persistence, but this requires the final visit. You're having transient changes. You're getting down to the final two visits. You're seeing 4.6 percent among haloperidol. That's very close to five percent versus one percent for olanzapine.

Comments, thoughts?

**DR. CASEY:** Seven percent of the people had AIMS scores when they began and one percent when...

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**DR. BEASLEY:** No, this is saying when these patients began, none of these 707 had it at baseline. At one visit, at one visit during the past six weeks, 7 percent of this 707 had an AIMS score by definition.

**MALE QUESTIONER:** Theoretically, they could have had that elevation at their first visit in the extension?

**DR. BEASLEY:** They could have had that at the first visit in the extension and it was transient. So this is single point any time in extension. This is single point at their last visit in extension. So this would have been for a patient with three years. They would have had approximately 36 opportunities to have this and then have it resolve. These patients would have had only one point potential to have it, and these patients obviously had to have it at two specific points in their course of therapy.

**DR. MARDER:** What was the average pre/post interval?

**DR. BEASLEY:** I gave it to you for medians because of the skewing. It was the 237 versus 203. Actually that should be plus one month. Otherwise they wouldn't have scores. Bill.

**DR. GLAZER:** Have you performed a life-table-type analysis for dropouts?

**DR. BEASLEY:** No, we haven't. When we saw the raw data without doing this by life table, this was one of many things we were going to do to get to the agency, but when we saw this without adjusting, looking at time to first

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onset, we have a lot to do. That's one of the things that we're going to go back and do for publication purposes.

**DR. CASEY:** Do you have any idea if these are the same patients from assessment to assessment? Are they the same patients meeting the criteria from assessment to assessment? You've got 50 in the first group. Are they the 7 that ended up in the final group?

**DR. BEASLEY:** They would have to be a subset of those. So this is a subset of this, which is a subset of this.

**DR. CASEY:** It doesn't seem that way by your definition.

**DR. BEASLEY:** If you had it at your last two visits, you had it at your last visit. If you had it at your last visit, you had it at some visit.

**DR. TAMMINGA:** Charles, isn't this a Haldol rate about twice what John would find?

**DR. KANE:** That's what we find.

**DR. TAMMINGA:** But this is a half year.

**DR. KANE:** It's about 8 months.

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**DR. BEASLEY:** And, again, the mean is pushed farther. We thought that this was. And Bill, I think that's pretty consistent with yours. That's why I don't want to be accused of making this up.

**DR. GLAZER:** If this is true, you're showing one fifth of the risk, which would be tremendous. The definitions here are not the way John and I did it. We made a diagnosis, and I'm sure you'll go back and do that.

**DR. BEASLEY:** These were the frequencies that we had of visits. This was, from our perspective, the most objective way to look at the issue, as opposed to recording of adverse events. We still see a numeric difference. The rates are lower, but this is the most objective, concrete, hard-core data that we've got on TD.

**DR. MELTZER:** Within each drug group, did you see a relationship to dose?

**DR. BEASLEY:** We have not looked at these data with regard to dose. We have clearly two studies where we could do that. I don't think that's one we thought about doing. The issue is that the majority of these data, the reason we're putting them in here, in fact come from this J study, and that was a dose-titration study.

**DR. MELTZER:** But for that reason it would be interesting. You could find an inverse relationship here. The lower the dose, the more likely they are to express the symptom.

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**DR. GLAZER:** The other thing is if the AIMS isn't done correctly and they were rated EPS instead of actual AIMS TD movements, you could be seeing EPS here and not tardive dyskinesia.

**DR. BEASLEY:** That's absolutely correct. I can't guarantee you that the 174 people plus that were performing these ratings were extremely well trained.

**DR. KANE:** What you could do is look at the items. That might help reassure you that it is more likely to be a dyskinesia.

**DR. BORISON:** These are data too, though that would be beyond six weeks of therapy, not that you wouldn't have an EPS episode beyond six weeks, but hopefully you've filtered out some of the high incidents by not looking in the first six weeks of treatment.

**DR. BEASLEY:** The anti-post baseline assessment does include acute-phase visits.

**DR. MELTZER:** I think looking at the items is very important.

**DR. DAVIS:** Charles, have you thought through all the issues that will be thrown at you about ascertained bias, even though I think they're unlikely? Do you have explanations that will suffice?

**DR. BEASLEY:** Can you give me some questions?

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**DR. DAVIS:** You obviously have lost your 2:1 randomization, and those are haloperidol patients who are leaving the study for a lack of efficacy.

**DR. BEASLEY:** Don't forget, when you're looking at this data, this is pooled over three studies. So two of the studies that are contributing here, their ratio was, in fact, 3:1.

**DR. TAMMINGA:** You have your worst patients leaving. You have the patients leaving the Haldol group who would be the highest risk. So you would skew your results in the opposite direction. I mean, you have all your high EPS presumably patients leaving.

**MALE PARTICIPANT:** Acute EPS.

**DR. DAVIS:** That's one explanation. That's the positive one, but you could also say things like the people who left the Haldol trial are people who have some other disturbance that suggests other brain damage or less responsive people. And those are people who are more likely to get tardive dyskinesia. I don't know. You don't know who you leave behind. You really can't be sure who you leave behind.

**DR. TAMMINGA:** But you're not thinking that this is a primary analysis. This isn't a study like John usually suggests for instance. This is really a secondary analysis of other data.

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**DR. BEASLEY:** We have retained, and I think from a historical perspective in terms of other long-term trials, our retention in this thing has been, particularly this trial among our set of trials, has been incredible. We were very surprised.

**DR. DAVIS:** Charles, I think the answer to the questions that are going to come up, which will be simple to obtain, is to show that the patients who dropped out of the Haldol study on what we think may be risk factors for tardive dyskinesia don't differ. There is no age differential. Perhaps, your initial EPS exposure is not differential.

**DR. POTKIN:** The other question then, once we get through all of that, and this may be real, is it a masking effect like you see with risperidone and clozapine, because all these people have been exposed to typical antipsychotic medications. So what is it about? If it's true, it's really interesting. This is the best I've seen.

**DR. BEASLEY:** Again, this is classic of what we've seen in our other studies. There is a drop with Haldol. There is a bigger drop acutely with higher doses of olanzapine.

**DR. POTKIN:** Is the assessment of these groups of patients continuing?

**DR. BEASLEY:** Yes.

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**DR. POTKIN:** That would be very important to see if this is just a pattern and that we see the same trend at twice the interval and so on.

**DR. BEASLEY:** Carol had a question.

**DR. POTKIN:** Charles, could you say where we are now? How much further out we are than the 203 and 260 whatever?

**DR. BEASLEY:** In this study we had about 800 patients exposed for six months in this database. We now have approximately close to 800 or 900 exposed here. I can't quote you the medians for these two comparative groups.

**DR. MELTZER:** You're getting closer to even a few months at twice the interval.

**DR. BEASLEY:** That's my speculation given the relevant data.

**DR. KANE:** What portion of the patients had RCD criteria at baseline and were therefore excluded?

**DR. BEASLEY:** Todd, what percentage of patients met the TD at baseline? Could you pull up the data that shows any patient and we'll take the difference in the numbers. Jaime will have the data.

**DR. STREET:** And Charles will answer your questions today.

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**DR. TOLLEFSON:** This subset is AIMS representative of the entire subset.

**DR. BEASLEY:** We have not assessed whether or not there are substantial differences in this group versus H. I would bet you that these are going to be, again since this is restricted to no patients with any history, I would bet you that these patients tend to be a little bit younger than the mean age of the total sample, but that is speculation on my part.

**DR. DAVIS:** You also want to check out that they don't have more schizoaffective disease.

**DR. BORISON:** Charles, is it possible that any patients were on antiparkinsonian agents?

**DR. BEASLEY:** Yes. Again, prejudiced more toward haloperidol than olanzapine. What's the total sample size, the unrestricted?

**TODD SANGER:** The unrestricted was 894, and this was 707 and the restricted was 261. That's 197 for Haldol.

**DR. BEASLEY:** So another 250 patients here and another...

**TODD SANGER:** 894 and 261 unrestricted, those two numbers.

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**DR. BEASLEY:** So those are the total number of patients who made it into the extension, analyzable data. It was a month into the extension. Either they had a historical diagnosis recorded or they met the criteria at baseline.

**DR. GLAZER:** It's 21 percent for the olanzapine and 26 percent for the haloperidol.

**DR. BEASLEY:** We've obviously got more work to do with these data, but we were pretty excited about the preliminary.

We'll take an overview of vital signs. Essentially no change in resting vital signs. As far as we have looked, in contrast to normal volunteers, we see no change in orthostatic blood pressure decreases. Weight gain in this study, somewhat less than we've seen. In others, the average gain, last observation carried forward, endpoint analysis, in six weeks is 1.88 kilos, ECG essentially no change areas. Slight decrease in QT intervals. Slight increase in sinus rate, nothing clinically significant.

**DR. GLAZER:** Charles, with that weight gain, what is the ratio to Haldol weight gain in the six-week time? Do you know offhand?

**TODD SANGER:** With J or the overall?

**DR. BEASLEY:** Do you have J?

**TODD SANGER:** I don't have J.

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**DR. BEASLEY:** Let's take overall pool, olanzapine versus haloperidol gain at six weeks.

**TODD SANGER:** Okay, active control. On the active control at six weeks, we had a gain of 2.02 kg in olanzapine and .06 kg on Haldol.

**DR. BEASLEY:** So .6 versus 2.

**TODD SANGER:** .06 versus 2.02, yes.

**DR. BEASLEY:** .06, so basically no gain versus 2.

**TODD SANGER:** That's acute active control.

**DR. CASEY:** What happens if you go on? Do you get 2 kilos after six weeks?

**DR. TAMMINGA:** More at six months? How much?

**DR. BEASLEY:** They should be plateauing, but again we don't have direct comparative clozapine data, but this is looking probably closer to clozapine.

**DR. CASEY:** Does the subset gain weight?

**DR. BEASLEY:** We have yet to cut it out. We're in the process of cutting it out. Not everybody gained weight, but there are some patients who gained a

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substantial amount. In fact, that's the most consistent nontherapeutic physical finding you're talking about.

**DR. CASEY:** Did any develop diabetes?

**DR. BEASLEY:** Very few people have developed type II diabetes during the time of this trial. We have over 400,000 patient days of olanzapine exposure, and the rate for diabetes, a couple of these cases I know are type I who got out of control. Treatment-emergent diabetes, does...

**DR. POTKIN:** Does that happen more often on olanzapine?

**TODD SANGER:** I don't believe it did.

**DR. BEASLEY:** We don't have comparative data long term for haloperidol analyzed at this point. We need six-week data.

**TODD SANGER:** We had 16 cases of treatment-emergent diabetes, which is .6 percent, of all 2500 patients. This is adverse event.

**DR. BEASLEY:** Spontaneous adverse event.

**DR. POTKIN:** You were measuring glucose all along?

**DR. BEASLEY:** And we don't see anything.

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**DR. POTKIN:** Is that pooled?

**TODD SANGER:** That's overall everyone exposed to olanzapine.

**DR. POTKIN:** What was the rate?

**TODD SANGER:** .6 olanzapine. We only had 7 patients discontinue for weight gain out of 2500.

**DR. POTKIN:** Is that acute phase?

**TODD SANGER:** No, any time.

**DR. TAMMINGA:** Charles, do you have any idea of what's the mechanism of the weight gain?

**DR. BEASLEY:** It's probably a decrease in satiety. If you see the adverse event of increased appetite, specifically it's probably decrease in the onset of satiety.

**DR. POTKIN:** Charles, on the weight gain, it's a little bit unclear in the long-term data, we were just talking about the 200-day data, a large number of patients gained weight. What was the degree of weight gain?

**DR. BEASLEY:** There are two controlled data bases. Let's take 7 percent as clinically significant weight gain and let's look at placebo control. Six

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weeks it's 29 percent of olanzapine-treated patients. It's 3.5 percent of placebo-treated patients. If you look at the entire unit database, 2500 patients treated from one day to three years, it's 40 percent of patients gained 7 percent or more body weight. If you're looking at one year, the average weight gain is about 24 lbs.

**DR. POTKIN:** 24? And what about when you compare in this study to Haldol for the patients who stayed on, what was the difference?

**DR. BEASLEY:** Todd, do you recall?

**TODD SANGER:** I think it was like probably any weight gain in Haldol.

**DR. POTKIN:** And 40 percent gained more than 7 percent.

**DR. BEASLEY:** Forty percent gained 7 percent or more, last observation carried forward, 2500 patients, regardless of how many days they stayed on.

**TODD SANGER:** And the average for them was 3.5 kg.

**DR. BEASLEY:** Yes, and the average for them was 3.5 kg. Now if you ask what's the average at 12 months for those patients remaining on 12 months, it was approximately 24 lbs.

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**DR. POTKIN:** About seizures, my recollection was there was a low seizure incidence in this comparison with Haldol. Can you say any more about the relative risk of seizure?

**DR. BEASLEY:** We have not split out this specific. Do you have the J trial data? What we've got is comparisons with placebo that include a geriatric study where we saw more seizures. We have not cut out this study, E003 for comparisons with haloperidol. I think it's going to be roughly comparable.

**TODD SANGER:** Do you want to give the overall incidence figures?

**DR. BEASLEY:** The overall incidence figure is .88 percent. That includes the geriatrics patients where we saw a clustering.

**DR. TOLLEFSON:** Maybe be more specific. These were Alzheimer's.

**DR. BEASLEY:** These were Alzheimer's patients with psychotic features.

**DR. POTKIN:** When you were showing us the design of the study, HGAJ, you talked about how some people were transferred over double-blind and some were switched over to olanzapine. What were the numbers from those that were on olanzapine that were switched over to olanzapine versus haloperidol?

**DR. BEASLEY:** I don't have those specifically. You can go back and take our discontinuation rates. We had 35 percent of patients discontinuing

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olanzapine, 55 percent discontinuing haloperidol. I would say that probably 80-plus percent of those individuals got transferred to open label. That's a rough approximation on my part. Probably higher in the U.S, lower O.U.S.

**DR. POTKIN:** I guess the question I'm asking and couldn't see in the data was how many people failed on each treatment, and then were switched over and survived? I was trying to get a comparison in some way and I couldn't tell from that.

**TODD SANGER:** We haven't done that analysis.

**DR. BEASLEY:** We have not done that analysis. That is clearly something that we want to look at, how many patients didn't do well on haloperidol that subsequently did well on olanzapine versus how many didn't do well on olanzapine or blind and then subsequently did well on olanzapine?

**DR. BORISON:** Was the hypersalivation during the day, or nocturnal like clozapine? Do you have any idea if it was as severe as it is with clozapine?

**DR. BEASLEY:** Let me go back to that adverse event slide. We don't see it, for whatever reasons, with olanzapine. There is hypersalivation statistically significantly more frequently with haloperidol.

**DR. BORISON:** Oh, it was with haloperidol?

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**DR. BEASLEY:** It was just those first three events: dry mouth, weight gain, increased appetite. Those were the only events that were overrepresented in the olanzapine group versus all the rest in the haloperidol group.

**DR. DAVIS:** Charles, can we go back to the weight gain for a second? Associated with that weight gain, do you know for a fact there is no increase in type II diabetes? If you're going to gain 24 lbs in a year, you would expect that would happen.

**DR. BEASLEY:** We need to look at that, but in general the sense has been with these 16 cases that were reported as treatment-emergent, given the amount of exposure we have had, that this is not something we've seen. My greatest familiarity with it comes from the serious adverse event reports that we have, patients getting hospitalized for evaluation.

**DR. DAVIS:** It might be different in an older population. The other question is, what about lipid profiles? Were they changed on the drug?

**DR. BEASLEY:** We looked at total cholesterol, and I don't remember it standing out. Todd, let's take a look.

**DR. DAVIS:** Obviously you want to make sure that you haven't increased cardiac risk factors now that you've got people with 24 more lbs at the end of a year.

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**TODD SANGER:** Overall, we had 3.1 percent who had a high cholesterol one time, but that was based on really a reference range going above the upper limit.

**DR. BEASLEY:** That's for Haldol?

**TODD SANGER:** That was overall.

**DR. DAVIS:** I am really interested in the delta, from the beginning of the study to the end of the year.

**TODD SANGER:** You want the actual mean change? We did not break that out. We had an average increase of .07 mM per liter overall on patients on olanzapine but we didn't break it up.

**DR. BEASLEY:** Todd, let's go to the haloperidol comparative data.

**TODD SANGER:** That's six-week data.

**DR. POTKIN:** You probably haven't done this, but have you looked at the weight gain in terms of whether it was more in low- and normal-weight people?

**DR. BEASLEY:** I made a comment that we're going back now, because we're getting ready for an advisory committee, and looking extensively at weight gain. One of our statisticians who didn't make the trip with us today

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has a major project to look at this, and one of the things that we're going to be looking at is categorizing patients based on their BMI.

**DR. DAVIS:** If you're on the advisory panel, you want to make sure that there aren't any other cardiac risk factors in the change. Weight gain by itself is not a risk factor, but it can be a risk factor for increased blood pressure, for lipid changes, and for diabetes. So you want to show that none of those primary risk factors haven't been affected by a 24-lb weight gain in the average patient.

**DR. TAMMINGA:** Weight gain is an adverse event for marketing, no matter what its other effects are.

**DR. BEASLEY:** We've had, as Todd said, only 7 patients, actually now it's up to 8, discontinued for weight gain.

**DR. POTKIN:** I guess we're just encouraging you to use this statistician to fully characterize this because it's a big issue and not one to be ignored, and global percentages are not going to really address it sufficiently.

**DR. BEASLEY:** It is something that we are teasing apart excruciatingly.

**DR. KANE:** Weight gain is a real problem. You have an opportunity to help devise strategies to deal with it.

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**DR. BEASLEY:** We have a major effort, and J.R. or Jim can speak to it, with regard to developing management strategies around it, and clearly one of the things that's going to be attended to is the weight gain issue.

**DR. TAMMINGA:** It's one of the only things to attend to.

**DR. BEASLEY:** Todd, did you get those?

**TODD SANGER:** Do you want the percentage change above?

**DR. BEASLEY:** Let's look first at the mean change.

**TODD SANGER:** Mean change was a decrease of .22 in Haldol and an increase of .1 in the olanzapine. That's mM per liter cholesterol total.

**DR. DAVIS:** Is that for the whole trial or six weeks?

**TODD SANGER:** That's the six-week acute phase. And what it was for the whole period for olanzapine I think was .07 across 2088 patients. You had measurements of .07 mM per liter.

**DR. DAVIS:** From beginning to end?

**TODD SANGER:** Change from baseline to endpoint.

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**DR. BEASLEY:** Clinical chemistries. Reduce any increase in ALT. It's down to the 7.9 percent in this study. This is a study where we were very liberal in not interfering with clinical decision making. No clinical difference, and none of those 1336 patients were discontinued for increased ALTs during this phase of the study.

However, toxicity. You do see mild, transient increases in prolactin. They are statistically significantly lower in magnitude and frequency than seen with haloperidol.

**DR. MARDER:** Could you clarify that? Do you mean only about half of the patients had elevated prolactins?

**DR. BEASLEY:** We see by the most conservative standard assessment—here we used plain numbers—but very standard clinical laboratory units of onefold upper limit of conventional normal. I think in this study we saw only 34 percent of patients with a marginally elevated prolactin. It decreases over time. It seems to be transient.

**DR. MARDER:** And in women versus men?

**DR. BEASLEY:** We did not formally split it out, but in a test that we do for sex differences, it does not come up as a statistically significant different finding across sexes.

**DR. TAMMINGA:** Hematotoxicities in how many patients over how many patient years?

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**DR. BEASLEY:** Do you recall how many patients we had at six months, a year? It's like 800.

**DR. TAMMINGA:** 800 at six months and...

**DR. BEASLEY:** We've got three months and six months. There are some whopping numbers.

**TODD SANGER:** Are you talking about the analysis of hemotoxicity?

**DR. BEASLEY:** This is a further analysis we've done more recently, 1422 patients exposed to olanzapine for at least 12 weeks, and 896 patients exposed for at least six months.

**DR. MARDER:** Regarding that Charles, can you comment on the 45 patients?

**DR. BEASLEY:** 29 patients with prior hematologic abnormalities, some including a documented agranulocytosis on clozapine, exposed to olanzapine, no difficulties. One patient that had a low neutrophil count at endpoint was higher than baseline. There was one patient that was discontinued for a low lymphocyte count. Three or four we had with haloperidol, with past difficulties with clozapine. One of those on exposure to haloperidol brought their neutrophil count some place down to about 100,000. If you take all the data and you put it together, I think what we

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would want to say is that relative to an active comparator which is usually thought of as relatively not hematotoxic, our data would suggest that we are less hematotoxic than that comparator.

**DR. ANDREASEN:** Can you repeat the exposure time?

**DR. TAMMINGA:** I copied them down. Do you want me to read them?  
1422 for 12 weeks, 896 for six months and 301 for a year.

**DR. BEASLEY:** We have done a recent analysis looking at the issue and calculating of confidence intervals around our data. We've looked at a very recent count for three months versus six months. It was 14.2 for three months. For six months, it was 896. And then we've got exposures out past three years. At this point, probably close to four years.

**DR. ANDREASEN:** How many of those, three years?

**DR. BEASLEY:** How many four-year exposures? Three-year exposures, less than 10, probably above five, given that in February it was greater than 2. Those are approximate.

**DR. TAMMINGA:** Charles, you only get transient increases in the transaminase levels, so you're not going to recommend that anybody who has an elevation in liver enzymes stops the drug, but that they just don't last it through?

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**DR. BEASLEY:** What we're currently proposing, and whether the FDA will concur with this, we're currently suggesting that patients with high risk for hepatic disease as clinically defined would get baseline evaluations, and then clinicians do whatever they feel most appropriate with those patients through their course of clinical management. We've had patients with the highest elevations that we've seen in the 400-plus range who have been declined with continued treatment. They are 1336. The majority of these elevations are seen virtually within the second week who were allowed to go up and then it comes back down. Again, no discontinuations. I think there was one olanzapine-treated patient, possibly two, who were discontinued to wait for phases of this study double-blind. The interesting thing, as those of you who have been investigators know, we screen for hepatitis B, both current disease and past exposure. We got a percentage in our screenings inordinately high. Ten percent of the schizophrenics who applied for our study either had prime or past hepatitis B. The worst mistake that we ever made was not screening for hepatitis C. The rate in this population I would bet you is 10 percent-plus prime disease. We only later in studies began testing when patients popped up with elevated transaminases, and we got a whopping number who were positive for C.

The patient that got it started was a patient at Cornell who had elevations and on workup turned out to be positive for C. We've got a fabulous patient treated with haloperidol. He comes in for his baseline. ALT is 17. At visit two, at point of randomization, his value is 435. So he's randomized. We don't force the investigator to take him out. It comes down nicely. This patient was treated with olanzapine. One year later, he pops up to a value of over 800. He normalized on drug. It goes over 400 points in

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one week before starting drug, stayed in the teens, the 30s for a year, and then popped to a value of 800. Apparently, this is what you see with chronic hepatitis C.

**DR. MARDER:** That's the problem, and a lot of people have it when you look. I think you'll find more than 30 percent of this population having it, and the trouble is it sometimes doesn't matter because C is a fluctuating illness. So it's really hard to know in a trial what to do. It's a lot of people to eliminate and, in fact, there is nothing special. It just makes it hard to interpret. I think the way to interpret it is to have a placebo group. Then we have an idea of what the change is within the placebo group, because it's not clear.

**DR. MELTZER:** Put a group of these people on placebo for a year. What about the CPK?

**DR. BEASLEY:** You'll be very interested in the CPK data. It's no worse in olanzapine than it is in haloperidol. We'll show you a big data set. It's probably not so much worthy of discussion here, off to the side.

Conclusions: again, given all the constraints around the study, superior in overall negative symptom efficacy compared to haloperidol. Excellent positive symptom efficacy. Superior efficacy with regard to depressive symptoms.

Some safety issues: mild sedation, mild anticholinergic effects.

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**DR. BEASLEY:** And positive also is comparable to haloperidol, not superior. Minimal subjective dizziness without orthostasis, transient. So far asymptomatic transaminase elevations, minimal parkinsonism and akathisia extremely rare.

Atypical profile, greater efficacy against negative symptoms than haloperidol, rare tonic reactions and less parkinsonism, akathisia with the haloperidol and substantially less prolactin elevations than haloperidol.

**DR. TAMMINGA:** Charles, about that first one. As I recall, you said on the PANSS that the difference between olanzapine and haloperidol, that olanzapine was at a  $P=.056$  level, that olanzapine was just about better than haloperidol on positive symptoms. So it might not be fair for you to stress that negative symptoms are helped so much as all symptoms.

**DR. BEASLEY:** Our primary analytic assessment was on BPRS totals defined in the protocol. The other difference was  $P=.015$ . So by our primary methodology for assessing efficacy, our global efficacy also, considering the response rate, the PANSS completer and CGI, clearly statistically significantly superior to haloperidol, and with negative symptoms as well.

**DR. TAMMINGA:** What was the  $P$  value for negative symptoms? Was it .032, and for positive symptoms it was .056. So you can't really say that .056 is not...that's really a very high  $P$  value.

**DR. BEASLEY:** It's close to significant. With that I guess I'll turn it over to Gary, who is going to go through a little preclinical integration.

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**DR. TAMMINGA:** Looks good Charles, very good. I have a question while Gary is gearing up. Given the data that you saw on the treatment-emergent TD, would you still be tempted to do a prospective study? I'm sure the answer must be yes.

**DR. BEASLEY:** Absolutely, yes.

**DR. TOLLEFSON:** To put it another way, is there a convincing need to do such a prospective study?

**DR. KANE:** I think maybe not.

**DR. CASEY:** But from a regulatory view in terms of labeling, you would probably need to do a prospective study. You would be charged with retrospective data analysis, if you tried to get this in your labeling. Certainly you can get it published and everybody in the world will know it.

**DR. MARDER:** But if they want to promote it as a drug with the lower risk of tardive dyskinesia, wouldn't they have to do something like a prospective study?

**DR. TOLLEFSON:** How about a clinical study section?

**DR. CASEY:** Get in the label.

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**DR. BEASLEY:** This was a prospective double-blind comparison. We did intend this and it is so described vaguely but I would argue that it is described in the protocol as one of our interstitial, secondary though it be.

**DR. TOLLEFSON:** Our primary goal was safety analysis.

**DR. GLAZER:** Were the assessments over long term done on a regular basis? It was built on a different AIMS?

**DR. BEASLEY:** Absolutely. That's why our case report form for the study. One patient was 37" high.

**DR. TAMMINGA:** I don't see, then, why your comment that this wasn't a prospectively-designed study that would show a difference in rate would be such a powerful comment.

**DR. CASEY:** I made my comment before I heard that it was stated specifically as one of the outcome measures in the study. If it was stated as one of the outcome measures, even though it may be secondary, I think we are out on solid ground. Then we will need to make the argument that it's not because of selective dropouts.

**DR. TOLLEFSON:** As an advisory committee member, would you require two such studies? I'm just curious.

**DR. CASEY:** Would you?

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**DR. TOLLEFSON:** Would I? My opinion doesn't count. It's somebody with the initials P.L. that I'm concerned about, a friend of yours.

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