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(Report) F1D-MC-HGAJ: Olanzapine Versus Haloperidol in the Treatment of Schizophrenia and Other Psychotic Disorders
(Continued)

Zyprexa MDL Plaintiffs' Exhibit No.01507

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8. Summary and Conclusions

The overall objective of the trial was to study the acute and long-term safety and efficacy of olanzapine in doses of 5, 10, 15, or 20 mg compared with haloperidol in doses of 5, 10, 15, or 20 mg. Clinical studies support the dose range of 5 to 20 mg/day of haloperidol as optimal (Van Putten et al, 1990, 1992). The randomization ratio in the study was 2:1 Olz to Hal. The number of patients randomized to the Olz treatment group was 1336, and the number of patients randomized to the Hal treatment group was 660. The primary efficacy analysis for both acute and extension therapy was the LOCF comparison of mean change from baseline to endpoint in BPRS total score. In addition, survival analyses of time to relapse were performed in the extension phase. For safety, the study compared the incidence of treatment-emergent adverse events, change in vital signs, change in extrapyramidal symptoms rating scales, and change in laboratory analytes between the Olz and the Hal treatment groups.

8.1. Acute Phase

8.1.1. Efficacy

For the primary efficacy analysis, the improvement in BPRS total score for the Olz treatment group was significantly greater than for the Hal treatment group (p=.015). There was no statistically significant geographic region-by-treatment interaction. The percentage of patients who discontinued from the acute phase of the study for any reason statistically significantly favored the Olz treatment group (33.5%) over the Hal treatment group (53.2%). The patients in the Olz treatment group who discontinued prior to completion of the acute phase generally exhibited less efficacy than the patients in the Hal treatment group who discontinued prior to the completion of the acute phase; therefore, the LOCF analysis of BPRS total score is not biased by patients who discontinued early. In this study olanzapine, at the dose range of 5, 10, 15, or 20 mg/day, produced significantly greater antipsychotic efficacy as measured by the BPRS total score than the preferred dose range of haloperidol cited in the literature.

Treatment response was defined as a minimum decrease in BPRS total score of 40% from baseline to endpoint and a baseline BPRS total score >18 among patients completing at least 3 weeks of double-blind therapy. Given this definition, patients in the Olz treatment group had a significantly higher response rate (51.6%) compared with the Hal treatment group (34.2%, p<.001). The within-treatment group change from baseline to endpoint in BPRS total score was -10.89 from a baseline mean of +33.05 (items scored 0 to 6) for the Olz treatment group. This large effect size

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and the large difference in percentage of patients classified as responders indicate that the improvement in the Olz treatment group was clinically significant.

Secondary analyses of overall psychopathology (CGI severity and PGI improvement scores) also showed efficacy in favor of Olz over Hal. The Olz treatment group experienced significantly greater mean improvement in the CGI severity score than the Hal treatment group (p=.029). The Olz treatment group also experienced significantly greater mean improvement in the PGI Improvement score than the Hal treatment group (p<.001).

Olz showed greater efficacy than Hal in the improvement of negative symptoms and in secondary mood/anxiety features of psychotic disorders. The Olz treatment group demonstrated superior improvement of negative symptomatology on both the BPRS negative score (p=.002) and PANSS negative score (p=.032) in mean change from baseline to endpoint compared with the Hal treatment group. The Olz treatment group experienced significantly greater mean improvement in the MADRS total score (p=.001) than the Hal treatment group.

Protocol violations appeared to be randomly distributed between the two treatment groups. Eighty-five patients were discontinued from the acute phase of the study due to a protocol violation. Protocol variations experienced by those patients who did not discontinue from the study that could potentially affect the efficacy results were very small compared with the large sample of patients studied. It is believed that the nature and incidence of these protocol variations did not affect the overall conclusions and statistical inferences of the efficacy results of the study.

8.1.2. Safety

During the double-blind acute phase of the study, safety data were collected through the use of open-ended questions for treatment-emergent adverse events, a standardized questionnaire to solicit a group of predefined adverse experiences (AMDP-5), vital signs, clinical laboratory tests, ECGs, chest X-rays, and ophthalmological assessments. The ophthalmology assessments and the chest X-rays are reported in the extension phase.

Two deaths were reported during the acute phase of the study. One patient died of lung carcinoma with peritoneal metastases without ever having received study drug. One patient died 20 days after being discontinued from Olz; based on the autopsy report, the cause of death was determined to be myocardial infarction with stenoses of the coronary vessels.

Overall, the percentage of patients who experienced any serious adverse event was slightly lower in the Olz treatment group than in the Hal treatment group. One hundred fourteen patients in the Olz

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treatment group (8.5%) versus 65 patients in Hal treatment group (9.8%) experienced a serious adverse event. Hospitalization was the primary reason for events being recorded as serious, with schizophrenic reaction being the most prevalent event requiring hospitalization.

Review of the patient disposition showed that the percentage of patients who discontinued due to adverse events in the Olz treatment group (4.5%) was very low and significantly lower than that of the Hal treatment group (7.3%, p=.010). This observation together with the fact that a significantly greater percentage of patients from the Olz treatment group (66.4%) than from the Hal treatment group (46.8%) completed the acute phase of the study (p<.001) indicated that olanzapine at the dose range of 5, 10, 15, or 20 mg/day is extremely well tolerated. Overall, patients tolerated Olz better than Hal.

Detailed assessments of the reasons for discontinuation showed that 16 patients in the Olz treatment group had schizophrenic reaction (eg, worsening of underlying schizophrenic symptoms); 3 had increase of CPK (without neuroleptic malignant syndrome); 1 had a grand mal convulsion; 1 had viral hepatitis (hepatitis C); and 1 had an asymptomatic mild leukopenia. No patient treated with Olz was discontinued due to abnormality of liver functions. Akathisia, anxiety, extrapyramidal syndrome, suicide attempt, and vomiting were events reported as the reason for discontinuation that were statistically significantly different in incidence between treatment groups. Only patients in the Hal treatment group reported these events as the reason for discontinuation.

With respect to treatment-emergent adverse events, significantly more patients in the Olz treatment group (21.4%) reported no treatment-emergent adverse events than patients in the Hal treatment group (13.9%, p<.001). Patients in the Olz treatment group reported incidences of only six events that were statistically significantly greater than those occurring with patients in the Hal treatment group. Patients in the Hal treatment group reported incidences of 24 events that were statistically significantly greater than those occurring with patients in the Olz treatment group. Dry mouth, weight gain, increased appetite, cough increased, liver function tests abnormal, and peripheral edema were reported statistically significantly more often by patients in the Olz treatment group than by patients in the Hal treatment group.

Patients in the Hal treatment group reported statistically significantly more extrapyramidal symptoms (akathisia, dyskinesia, dystonia, extrapyramidal syndrome, hypertonia, hypokinesia, oculogyric crisis, tremor), gastrointestinal symptoms (anorexia, increased salivation, vomiting), psychological events (insomnia, nervousness), joint disorder; amblyopia; chills; and weight loss. All the treatment-emergent adverse events cited above had an incidence of more than 1%.

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With respect to anticholinergic events, only dry mouth was reported by statistically significantly more patients in the Olz treatment group than in the Hal treatment group. There were no statistically significant differences with regard to constipation, thirst, dry eyes, and urinary retention. This observation suggests that Olz and Hal share similar potential for clinically mild anticholinergic adverse events.

Similar analysis of the AMDP-5 also confirmed that Olz caused fewer adverse events than Hal. In the Olz treatment group, only two solicited events from the AMDP-5 occurred statistically significantly more frequently than in the Hal treatment group; these events were excessive appetite and dry mouth. In contrast, in the Hal treatment group, 25 solicited events occurred statistically significantly more frequently than in the Olz treatment group. These events included difficulty falling asleep, interrupted sleep, shortened sleep, early waking, drowsiness, decreased appetite, hypersalivation, nausea, vomiting, palpitations, blurred vision, increased perspiration, micturition difficulties, heaviness in legs, hot flashes, chills, conversion symptoms, hypertonia, hypotonia, tremor, acute dsykinesia, hypokinesia, akathisia, ataxia, and increased dreams/nightmares.

When extrapyramidal treatment emergent events were organized into 4 clinical categories and 1 residual category (dystonic events, parkinsonian events, akathisia events, dyskinetic events, and residual events), patients in the Hal treatment group reported statistically significantly greater incidences in 4 of the 5 categories (dystonic events, parkinsonian events, akathisia events, and residual events) than patients in the Olz treatment group. Both categorical and mean change analyses of the Simpson-Angus Scale and the Barnes Akathisia Scale further support the conclusion that Olz has a significantly lower propensity to induce extrapyramidal symptoms than Hal. Categorical analyses indicated statistically significantly less treatment-emergent parkinsonism and akathisia in the Olz treatment group compared with the Hal treatment group.

Endpoint mean changes on both the Simpson-Angus Scale and the Barnes Akathisia Scale reflected improvement for patients in the Olz treatment group, compared with worsening endpoint mean change for those in the Hal treatment group. For the AIMS total score, the within-treatment group reduction in mean change from baseline to endpoint was significant in the Olz treatment group (p<.001), and the change from baseline to endpoint was significantly decreased in the Olz treatment group compared with the Hal treatment group (p=.007). This observation may suggest that Olz can improve dyskinetic symptoms during the acute phase.

With respect to vital signs, comparisons of mean change from baseline to endpoint and of weight gain ≥7% from baseline showed that patients in the Olz treatment group had a significant weight increase compared with those in the Hal treatment group (p<.001). Within-treatment mean weight

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change in the Olz treatment group was also statistically significant; patients treated with Olz gained on average 1.88 kg from baseline to endpoint.

Although the mean supine and standing heart rate increase from baseline to endpoint was statistically significant within the Olz treatment group, no statistically significant difference was noted in either the mean supine or standing heart rate between the two treatment groups. The increase in heart rate in patients in the Olz treatment group was comparable to those patients in the Hal treatment group and was not clinically significant. Patients in both treatment groups experienced treatment-emergent adverse events of dizziness, postural hypotension, hypotension, and tachycardia. The incidence of these events was not statistically significant between the two treatment groups. There were no statistically significant between-treatment group differences with respect to diastolic, systolic, or orthostatic changes as measured by mean change in supine to standing heart rate or blood pressure change. Further categorical analyses of orthostatic blood pressure change failed to reveal any differences between the two treatment groups. Olz and Hal had comparable effects on blood pressure in this patient population.

Given the large number of patients per treatment group, the laboratory analytes assayed, the frequency of assay, and the large number of statistical analyses (baseline to endpoint, minimum, and maximum for both raw and rank-transformed data; incidence of treatment-emergent high or low laboratory values at any time during the acute phase and at endpoint) without correction for multiple comparisons, it was not surprising that statistically significant differences were observed between the two treatment groups. However, the magnitude of the mean changes are not believed to be clinically significant. The categorical analyses are more sensitive to relatively rare but potentially important treatment-emergent extreme values than are analyses of change in central tendency. Therefore, the categorical analyses enhance detection of potentially important laboratory findings.

Patients in the Olz treatment group had statistically significantly higher incidence of elevated hepatocellular enzyme values than patients in the Hal treatment group. When comparing categorical treatment-emergent abnormal, high, or low laboratory values at endpoint, patients in the Olz treatment group had a statistically significantly higher incidence of elevated ALT/SGPT. Elevated ALT/SGPT and AST/SGOT were reported statistically significantly more frequently at any time for patients in the Olz treatment group. The incidence rates in the Olz-treated patients for high laboratory values at any time of ALT/SGPT and AST/SGOT were 7.9% and 4.4%, respectively, compared with the Hal-treated patients, who demonstrated incidence rates for ALT/SGPT and AST/SGOT of 1.1% and 1.4%, respectively. There were no clinically symptomatic individuals with either reported treatment-emergent events of jaundice or

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bilirubinemia among these patients. At endpoint both analyte values fell to 2.6% for ALT/SGPT and 1.4% for AST/SGOT for patients in the Olz-treated group and to 0.8% for ALT/SGPT and 0.6% for AST/SGOT for patients in the Hal-treated group.

GGT high laboratory values at any time did not demonstrate a statistically significant difference between the two treatment groups. The incidence of high laboratory values for GGT in the Olz treatment group at any time (1.2%) decreased at endpoint (0.5%).

No patients in the Olz treatment group were discontinued from the study due to the adverse event liver function test abnormal. Elevated liver function laboratory values were typically transient, with or without continuation of Olz treatment. No statistically significant increases of incidence rates associated with the Olz treatment group were found for other events potentially associated with the hepatic system (nausea, vomiting, nausea and vomiting, hepatitis, bilirubinemia, and jaundice).

Categorical analyses showed that, at endpoint, patients in the Olz treatment group had a statistically significantly higher incidence of elevated eosinophils and elevated non-fasting glucose than the Hal treatment group. Twenty-three patients treated with Olz had individual high marked laboratory abnormalities for eosinophils, with most of the values returning to normal during either the acute phase or during the extension phase. Seventeen patients had high marked abnormalities for non-fasting glucose, with 6 of these patients being diabetic and the remainder of the patients being clinically asymptomatic.

The proportion of patients with high-marked CPK elevation was similar in both treatment groups. Thirty-four patients treated with Olz had high marked CPK elevation versus 15 patients treated with Hal. Three Olz-treated patients discontinued due to CPK elevation. In 2 Olz-treated patients with elevated CPK, appropriate assessments for the evaluation of possible NMS were conducted, with neither patient receiving a confirmed diagnosis of NMS.

Patients in the Hal treatment group had a statistically significantly higher incidence of elevated prolactin than patients in the Olz treatment group.

ECGs were reviewed by the Krannert Institute of Cardiology, Indianapolis, IN, for interpretation and technical errors for tracings with ventricular tachyarrhythmias and conduction defects. The changes identified across both treatment groups were not associated with other ECG findings and the possibility of increased cardiac risk. Treatment with Olz did not induce any clinically significant ECG findings in either the type of change or frequency of change.

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Subgroup analyses for gender, age, and racial origin did not identify any specific safety concerns.

8.1.3. Conclusion

In conclusion, results from the acute phase of this study indicate that Olz is statistically significantly superior to Hal in the treatment of overall psychotic symptomatology. The dose range of haloperidol was representative of the most commonly prescribed dose range by clinicians worldwide. Results also indicate that Olz is safe and well tolerated. Statistically significantly fewer patients in the Olz treatment group discontinued from the study due to adverse events than patients in the Hal treatment group. Overall, treatment with Olz was associated with mild clinical anticholinergic activity, weight gain, increased appetite, transient elevation of several analytes, including liver enzymes (ALT/SGPT, AST/SGOT and GGT), eosinophils, CPK, and prolactin. Therefore, olanzapine in the dose range of 5, 10, 15, or 20 mg/day is both safe and effective in the treatment of psychotic symptomatology.

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8.2. Double-Blind Extension Phase

8.2.1. Efficacy

The relatively long-term (≥ 1 year of double-blind therapy for many patients) effectiveness of the 2 treatment groups, after achieving an operationally defined acceptable degree of symptom reduction after 6 weeks of double-blind therapy, was compared in the double-blind extension analyses. This comparison of long-term efficacy is of obvious clinical importance because it addresses the relative utility of the treatments as they are used in real-world clinical practice for sustaining early patterns of response.

The clinician typically uses one or more treatments (where each treatment may be mono- or polytherapy) sequentially until an acceptable degree of symptom reduction is achieved and almost invariably continues that "acutely effective" treatment with the hope of maintaining or further improving symptom reduction. Moreover, it is not common practice to switch from the "acutely effective" treatment to an alternative treatment for the purpose of maintenance. Further, in the treatment of psychosis, premature drug discontinuation (eg, immediately following the initial resolution of symptoms) would violate routine guidelines in treating psychotic disorders (Kane JM 1995). Thus, the questions most relevant to clinical practice in the treatment of psychotic disorders are 1) if a given treatment appears to be effective for reducing symptoms to an acceptable level in the short-term, will it continue to maintain the reduction of symptoms in the long-term and 2) what is the risk/benefit profile of that treatment compared with other treatments that also appear to have short-term efficacy?

These questions are different from the question of the relative maintenance efficacy of multiple treatments following acute response to one active treatment, which is addressed by the classic two-phase rerandomization design routinely employed in maintenance studies as discussed and criticized by Greenhouse (Greenhouse and Meyer 1991, Greenhouse et al. 1991). The clinical questions of interest are also distinct from the question of the relative maintenance efficacy of treatment strategies involving treatment crossovers proposed by Greenhouse (Greenhouse and Meyer 1991, Greenhouse et al. 1991) for the study of maintenance therapy in mood disorders. The study design employed here addresses the question of maintaining long-term efficacy relevant to antipsychotic treatments and also avoids the potential design problems inherent in the two-phase rerandomization design discussed by Greenhouse (Greenhouse and Meyer 1991, Greenhouse et al. 1991). These problems include potential withdrawal effects (only patients in 1 maintenance treatment group being discontinued from the effective acute treatment) and selection bias (only

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patients in 1 maintenance treatment group being continued on the treatment to which they initially responded).

As discussed by Greenhouse et al, a group of patients discontinued from acutely effective therapy, in order to initiate a maintenance treatment, can be reasonably expected to respond less well to that maintenance treatment compared with another group of patients continued on an acutely effective therapy as a maintenance treatment. The latter group of patients benefits from the lack of discontinuation and benefits from selection bias in that the patients were known to have acute response to their maintenance treatment. The study design described in this report involved no discontinuation of acute phase treatment prior to initiating the maintenance treatment, thereby avoiding the potential for withdrawal effects. The problem of selection bias was avoided for the evaluation of maintenance treatment in that all patients were assigned to the treatment to which they had acutely responded.

The three analyses--1) survival analysis of time to relapse, 2) LOCF analysis of mean change from baseline to endpoint in efficacy rating scale scores, and 3) visitwise OC analysis of mean change in efficacy rating scale scores--provide complementary views of the longitudinal long-term effects of the treatments. The survival analysis of time to relapse provides the most important comparison in that it assesses the relative benefit of long-term continuation of olanzapine versus haloperidol. Two definitions of relapse were assessed. The analysis of relapse by primary definition presented was based on both rehospitalization for psychotic symptoms and a clinical assessment of significant worsening in the CGI Severity score. The analysis of relapse by secondary definition was based only on rehospitalization for psychotic symptoms. The LOCF analysis of mean change from baseline in efficacy rating scale scores provides comparisons of long-term efficacy at endpoint. The visitwise OC analysis of mean change in efficacy rating scale scores provides an assessment of efficacy at any point in time for patients who showed improvement during the acute phase, continued into the double-blind extension, and remained in the study. Patients relapsing, necessitating discontinuation, might be expected to contribute markedly to decreases in their treatment group's mean improvement at the visit at which they are discontinued. The visitwise OC analysis shows the degree of efficacy that could be expected among patients who are able to continue to a given visit.

The survival analysis of relapse by primary definition indicated that there were no statistically significant differences in survival curves with respect to time to relapse between the Olz and Hal treatment groups. Survival analysis of relapse by secondary definition showed that the estimated percentage of patients not relapsing at 1 year was 80.9% for the Olz treatment group and 72.2%

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for the Hal treatment group. There was a statistically significant difference in survival curves with respect to time to relapse by secondary definition between the 2 treatment groups.

The LOCF analyses of mean change in BPRS total, PANSS total, PANSS positive, and PANSS negative revealed clinically comparable improvement for patients treated with both Olz and Hal.

The visitwise OC analyses of mean change in BPRS total and PANSS total scores detected no statistically significant differences between the 2 treatment groups. A similar conclusion can be drawn with regard to PANSS positive and PANSS negative scores. Except for an isolated visit where the Olz treatment was statistically significantly superior to the Hal treatment group (Visit 23 for PANSS positive and Visit 9 for PANSS negative), no other statistically significant differences were detected at other visits.

Overall, the Olz treatment group had a significantly greater percentage of patients completing the extension phase than the Hal treatment group (p=.010). The percentages of patients at each visit during the extension phase who remained in the Hal treatment group were lower than those of the Olz treatment group. At Visit 26 (Week 52), improvement in BPRS total score was numerically comparable for both treatment groups. At that visit, the Hal treatment group contained only 39 patients compared with 183 patients remaining in the Olz treatment group. These results indicate that patients who are able to remain on Hal are very much improved, but few patients remain on Hal for long periods of time and discontinue for a variety of reasons.

In summary, both olanzapine and haloperidol were equally effective in continuation therapy following an initial period of acute stabilization, but olanzapine was significantly superior to haloperidol in the prevention of hospitalization secondary to exacerbation of psychotic symptoms. These data indicate that olanzapine in the dose range of 5, 10, 15, or 20 mg/day is an effective antipsychotic agent against overall psychopathology and core positive symptoms in continuation therapy.

8.2.2. Safety

The study design and analyses of results presented here allow double-blind comparison of the relatively long-term safety of olanzapine versus haloperidol based on the absence of an adverse safety outcome of sufficient magnitude to lead to substantial discontinuation during the first 6 weeks of therapy. These analyses would not directly identify relative differences in safety outcomes unique to the long-term phase of therapy (interval safety), but they would identify relative differences in safety outcomes over the entire longitudinal continuum of the study (overall safety). Therefore, the results reported here include safety data collected during the double-blind

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treatment period from randomization to the data cutoff date of 14 February 1995. Interval safety outcomes can be approximated by comparing the safety results of the acute phase of the study to the results of this long-term phase. Any outcome with a substantially greater frequency in this long-term analysis may represent an outcome developing only during later therapy. However, this outcome is an approximation because the patients considered here are only a subset of patients considered in the acute treatment phase, and their frequency of manifesting a particular adverse outcome during acute therapy may differ from the total population studied during the acute therapy phase.

Review of the safety data reported during long-term continuation treatment indicated that olanzapine at doses of 5, 10, 15, or 20 mg/day was well tolerated, as it was in short-term (up to 6 weeks) treatment.

Ten deaths were reported during the double-blind extension phase or following discontinutation from the double-blind extension phase. In the Hal treatment group, one patient reportedly died from natural causes and one from a pulmonary embolus. In the Olz treatment group, one patient with a significant family history of coronary disease died from coronary thrombosis. Seven patients committed suicide, with 2 of these suicides occurring approximately 3 weeks after discontinuation from the double-blind extension phase.

Review of the safety data during the length of the double-blind treatment period, including long-term continuation treatment, indicates that olanzapine at doses of 5, 10, 15, or 20 mg/day is well tolerated. There were 131 discontinuations for adverse events from both treatment groups. The incidence of patients discontinuing because of adverse events is a good measure of how well a drug is tolerated. The incidence of patients discontinuing because of any adverse event was significantly lower in the Olz treatment group than in the Hal treatment group (p=.008). Therefore, patients tolerated Olz better than Hal.

A significantly lower percentage of patients in the Olz treatment group than the Hal treatment group discontinued because of schizophrenic reaction and extrapyramidal syndrome (p=.002 and p<.001), respectively). In the Olz treatment group, 48 out of 718 patients discontinued for schizophrenic reaction and other manifestations of psychopathology compared with 23 out of 215 patients in the Hal treatment group. There was no pattern to the other events causing discontinuation for the Olz-treated patients.

Among 20 treatment-emergent adverse events that had incidence rates that were statistically significantly different between the Olz and the Hal treatment groups, only weight gain and

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increased appetite were reported by significantly more patients in the Olz treatment group compared with the Hal treatment group. As in the acute phase, weight gain and increased appetite continued to be reported with higher frequency by patients treated with Olz compared with those treated with Hal. The incidences of the remaining 18 events were statistically significantly greater in the Hal treatment group. No statistically significant differences were found between the 2 treatment groups for dry mouth, liver function tests abnormal, cough increased, and peripheral edema in the double-blind extension phase.

Furthermore, analysis of the AMDP-5 showed that patients in the Olz treatment group reported a higher incidence for only 2 events (excessive appetite and dry mouth, a potentially anticholinergic event) when compared with patients in the Hal treatment group. In contrast, patients in the Hal treatment group reported a higher incidence for 14 events when compared with those in the Olz treatment group. These 14 events included sleep disturbances (difficulty falling asleep, interrupted sleep, shortened sleep and early morning awakening), extrapyramidal symptoms (hypertonia, tremor, acute dyskinesia, hypokinesia, akathisia and tardive dyskinesia), hypersalivation, decreased appetite, increased perspiration, and nystaganus.

Multiple events reflective of a variety of extrapyramidal syndromes were reported statistically significantly less often in the Olz treatment group compared with the Hal treatment group. There were statistically significantly less events reflective of dystonia, parkinsonism, akathisia, and residual extrapyramidal symptoms in the Olz treatment group compared with the Hal treatment group. Categorical analyses of the Simpson-Angus Scale and the Barnes Akathisia Scale were consistent with the results of treatment-emergent event analyses of extrapyramidal symptomatology. Categorical analyses indicated significantly less treatment-emergent parkinsonism and akathisia in the Olz treatment group compared with the Hal treatment group. Endpoint mean changes on the Simpson-Angus Scale reflected greater improvement for the Olz treatment group compared with the Hal treatment group. With respect to the AIMS, in the Olz treatment group the percentage of patients who developed operationally defined dyskinetic symptoms (Schooler et al. 1982) was significantly less than the Hal treatment group percentage. These findings support the notion that Olz has a lower propensity than Hal in producing extrapyramidal symptoms in long-term treatment.

Mean weight gain from baseline to endpoint was statistically significantly greater within the Olz treatment group than within the Hal treatment group. Patients in the Olz treatment group had a mean weight gain from baseline to endpoint of 5.09 kg compared with a mean weight gain of 0.26 kg in the Hal treatment group. Overall, weight gain and excessive appetite were consistently reported by more patients in the Olz treatment group.

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With respect to mean change from baseline to endpoint in vital signs, there were no clinically significant changes and few statistically significant changes within treatment groups. There were no clinical or statistically significant differences between treatment groups.

The clinical importance of the analysis of treatment-emergent abnormal, high, or low laboratory values at endpoint has been emphasized previously. The incidence rates for high laboratory values at any time of AST/SGOT, ALT/SGPT, and eosinophils were statistically significantly higher in the Olz treatment group than in the Hal treatment group. No statistical differences were observed for AST/SGOT, ALT/SGPT, or eosinophils between the two treatment groups at endpoint. Only 2 patients in the Olz treatment group (versus 1 patient in the Hal treatment group) were discontinued for abnormal liver function values suggesting that liver function elevations were, for the most part, transient. Patients in the Hal treatment group had a significantly higher incidence of high prolactin concentration than patients in the Olz treatment group.

ECG abnormalities were infrequent, not associated with any one treatment group, and did not manifest any consistent pattern of abnormality within the Olz treatment group. Analysis of patients with normal ECG at baseline and abnormal postbaseline ECG showed no statistically significant difference.

Treatment-emergent abnormal chest X-rays were infrequent. No statistically significant difference in the incidence of treatment-emergent abnormal chest X-rays was observed between the two treatment groups.

Examinations of the eyes, consisting of visual acuity, tonometry, and the physical components of the eyes did not identify any consistent abnormal ophthalmological findings referable to either the Olz or Hal treatment groups that developed over the long-term course of the study.

8.2.3. Conclusion

In conclusion, the results of primary and multiple secondary analyses were consistent with the hypothesis that olanzapine, with a daily dose range of 5, 10, 15, or 20 mg/day, is an effective antipsychotic agent. Furthermore, multiple analyses clearly demonstrated the efficacy of olanzapine against overall psychotic symptomatology and positive psychotic symptoms. In addition, it can be concluded from these analyses that patients who exhibited acceptable reduction in initial symptoms during acute therapy and continued on long-term Olz therapy showed clinically fewer relapses than patients who initially responded to and continued on Hal therapy. LOCF analysis of mean change from baseline to endpoint in efficacy rating scale scores indicated that mean overall efficacy and negative symptom reduction was numerically comparable for both

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treatment groups. The visitwise OC analyses of mean changes in efficacy scale ratings indicated that patients capable of remaining on Hal long-term did well but that few patients were able to continue on Hal for extended periods of time. These results support the hypothesis that olanzapine was effective in maintaining the reduction of psychotic symptoms achieved during acute pharmacology over a long term period.

With respect to safety, results from this study indicate that olanzapine is safe and well-tolerated. With respect to adverse events, the primary findings showed that fewer patients in the Olz treatment group discontinued due to adverse events compared with patients in the Hal treatment group. Long-term treatment-emergent dyskinetic symptoms were less common among Olz-treated patients compared with Hal-treated patients. Olanzapine was associated with weight gain but did not appear to have any clinical effect on other vital signs. Olanzapine was associated with elevations of ALT/SGPT and AST/SGOT which appear to be generally transient. Although olanzapine is associated with some increase in prolactin, the increases were of lesser magnitude than those observed with Hal. The data from the extension phase indicated that olanzapine was safe and well tolerated. The majority of serious adverse events were manifestations of psychopathology, which were not unexpected occurrences in this patient population. Differences between treatment groups with respect to treatment emergent increases in hepatic transaminases at endpoint were lower in the double-blind extension phase than in the acute phase.

Therefore, olanzapine, at doses of 5, 10, 15, or 20 mg, is safe and effective in the treatment of schizophrenia and other psychotic disorders.

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