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ICI 204,636, an Atypical Antipsychotic: Efficacy and Safety in a Multicenter, Placebo-Controlled Trial in Patients With Schizophrenia [Article]

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Abstract TOP

ICI 204,636 is a new, potentially atypical antipsychotic.In early phase II trials, the antipsychotic was well tolerated and results suggested efficacy in the treatment of the positive and negative symptoms of schizophrenia. The efficacy and safety of ICI 204,636 were evaluated on a larger scale in a 6-week, multicenter, double-blind trial. Hospitalized patients who met DSM-III-R criteria for chronic or subchronic schizophrenia with acute exacerbation, as well as other criteria, were randomized to ICI 204,636 (75 to 750 mg daily) (N = 54) or placebo (N = 55). Patients were assessed weekly by use of the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and Clinical Global Impression Scale (CGI) for efficacy and the Simpson Scale and Abnormal Involuntary Movement Scale for extrapyramidal side effects (EPS). Significant differences (p less or equal to 0.05) between treatment groups, which favored ICI 204,636, were identified throughout the trial. Endpoint differences were significant (by analysis of covariance) for BPRS factor IV (activation) and SANS scores and were marginally significant for total BPRS, BPRS factor III (thought disturbance), BPRS positive-symptom cluster, and CGI Severity of Illness item scores (p = 0.07, 0.09, 0.06, and 0.09, respectively). ICI 204,636 was well tolerated, although it was associated with mild transient increases in alanine aminotransferase and a higher incidence of somnolence and anticholinergic effects compared with

Article Outline

Figures/Tables

placebo. In the dose range studied, treatment with ICI 204,636 did not induce EPS as determined by analysis of Simpson Scale total scores and lack of treatment-emergent acute dystonic reactions. Furthermore, ICI 204,636 did not produce sustained levels of prolactin; the mean change from baseline at endpoint (-7.2 micro gram/L) was comparable ($p = 0.44$) to that for placebo (-8.2 micro gram/L). These findings distinguish ICI 204,636 from standard antipsychotics and confirm preclinical predictions that ICI 204,636 is an atypical antipsychotic. (J Clin Psychopharmacol 1996;16:158-169).

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Clozapine was one of the first antipsychotic agents to have few of the extrapyramidal side effects (EPS) routinely associated with standard antipsychotic use. As such, clozapine's efficacy in the treatment of schizophrenia sparked much clinical interest. Evidence of clozapine's superiority in the treatment of the positive symptoms of schizophrenia is well recognized for patients with treatment-refractory conditions, [1] although it remains suggestive [2-4] for patients with nonrefractory schizophrenia. Had it not been for treatment-related agranulocytosis [5,6] and other adverse events, including seizures, sedation, hypotension, and hypersalivation, [7] a more general use of clozapine may have resulted.

By altering the structure of clozapine, a dibenzodiazepine, researchers sought to create a compound with superior efficacy and a better side effect profile. Whereas early efforts met with limited success, [8-10] recent efforts have resulted in the development of ICI 204,636 (Seroquel; ZENECA Pharmaceuticals, Wilmington, DE), a dibenzothiazepine with affinity for multiple brain receptors, including serotonergic type 2 ($5HT_2$) and dopaminergic type 2 (D_2) receptors (IC_{50} = 148 and 329 nM, respectively). Receptor-binding assays also show that ICI 204,636 has affinity for histamine type 1 and $alpha_1$ - and $alpha_2$ -adrenergic receptors (inhibitory concentration [IC_{50}] = 30, 90, and 270 nM, respectively) and minimal affinity for D_1 receptors (IC_{50} = 1,243 nM). Unlike clozapine, ICI 204,636 is essentially inactive (IC_{50} > 10,000 nM) at muscarinic-cholinergic and benzodiazepine receptors. [11]

Differences in receptor affinities also distinguish ICI 204,636 from risperidone, a recently marketed antipsychotic. Although both have greater affinity for $5HT_2$ receptors than for D_2 receptors, absolute affinities at D_2 receptors differ; ICI 204,636 has weak D ($_2$) receptor affinity, like clozapine, whereas risperidone has very high affinity, like haloperidol. [12]

Researchers predicted that ICI 204,636 would show antipsychotic activity in humans on the basis of activity in preclinical behavioral and electrophysiologic tests considered predictive of antipsychotic activity. [13,14] In behavioral tests, ICI 204,636 effectively blocks conditioned-avoidance responses in squirrel monkeys (median effective dose = 8.4 mg/kg) and reverses the behavioral effects induced by the dopamine agonists apomorphine and amphetamine, namely, errant swimming, climbing, and hyperactivity in rats; gaze shifting in cats; and blinking in monkeys. In electrophysiologic tests, ICI 204,636 reverses the inhibitory actions of amphetamine on mesolimbic (A10) and nigrostriatal (A9) dopamine-containing cells.

ICI 204,636 also meets several other pharmacologic criteria that comprise current putative predictors of atypicality (clozapine-like activity). Specifically, ICI 204,636 has a greater affinity for $5HT_2$ receptors than for D_2 receptors; limbic system selectivity as evidenced by depolarization inactivation of A10 but not A9 dopamine-containing cells after long-term administration; [13] a tendency to produce nonsustained elevations in prolactin levels in plasma after short-term administration in rats; [11] and a decreased EPS liability as shown by tests considered predictive of EPS, including minimal dystonic reactions, in haloperidol-sensitized and drug-naive cebus monkeys. [14] Recent primate studies have shown that even at doses fivefold higher than the projected antipsychotic dose range for humans, ICI 204,636 maintains minimal dystonic liability. In contrast, risperidone produces dose-related dystonic reactions in sensitized monkeys at doses that are within the predicted therapeutic dose range for humans. [15]

The results of two early phase II clinical trials suggest that ICI 204,636 is effective in the treatment of the positive and negative symptoms of schizophrenia. In each of the trials-a 12-patient, single-center, double-blind, placebo-controlled U.S. trial [16] and a multicenter, open-label international trial [17] -ICI 204,636 was well tolerated and did not induce EPS. These results were encouraging and merited further investigation on a larger scale. Therefore, in a phase II, multicenter, placebo-controlled trial, we evaluated the efficacy, safety, and tolerability of ICI 204,636 in patients with chronic or subchronic schizophrenia.

Methods TOP

The efficacy and safety of ICI 204,636 in hospitalized schizophrenic patients were evaluated in a 6-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group trial. Institutional review board approval was granted for each of the 12 participating centers, and patients gave written informed consent before entry.

Patients TOP

Men and women, 18 through 60 years of age, were eligible for trial entry if they met the criteria for chronic or subchronic schizophrenia with acute exacerbation, according to DSM-III-R. Patients met additional entry criteria if they obtained a total score of at least 45 on the Brief Psychiatric Rating Scale (BPRS), based on 18 items scored 1 (absent) through 7 (severe), and scores of 4 (moderate) or greater for at least two of the four items that constitute the positive-symptom cluster: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. A Clinical Global Impression Scale (CGI) Severity of Illness item score of at least 4 (moderately ill) was also required for trial entry.

Patients who met DSM-III-R diagnostic criteria for any other psychiatric disorder coded on axis I were excluded. Suicidal ideation within a year of trial entry, mental retardation, convulsive disorders, history of severe head trauma or suspected organic brain disease, and risk of pregnancy were major exclusion criteria. Conditions likely to interfere with safety and efficacy evaluations, such as clinically significant laboratory findings or abnormal electrocardiograms (ECGs), were also reasons for exclusion. Patients could not enter the trial within 4 weeks of receiving antipsychotic agents in long-acting injectable formulations.

Procedures TOP

Patients entered a minimum 2-day (maximum, 10 day), single-blind, placebo phase, and all psychotropic medications were discontinued. During this period, each patient took one placebo tablet three times a day. On day 0, (the last day of the single-blind, placebo phase [baseline]), patients who still met entry criteria were randomized to treatment with ICI 204,636 or placebo.

Patients randomized to treatment with ICI 204,636 initially received 25 mg three times a day for 1 to 2 days. Thereafter, the dose was titrated upward, using a combination of 25-, 50-, 100-, and 200-mg tablets, until an adequate therapeutic effect was achieved. An optional dose at bedtime and dose adjustments in response to side effects, such as sedation and postural hypotension, were also permitted. The maximum daily dose was 750 mg, but daily doses greater than 500 mg were limited to 14 days. (Limits were set on the basis of toxicology and clinical data available at the time of the trial.) Patients randomized to placebo treatment received matching placebo tablets in the same manner as patients treated with ICI 204,636.

With a few exceptions, the only nonpsychotropic drug allowed was acetaminophen. Chloral hydrate was permitted orally, throughout the trial, for acute agitation (500 mg) or insomnia (500-1,000 mg), up to 2,000 mg in 24 hours. Lorazepam, 1 to 2 mg orally or intramuscularly, was reserved for agitation or insomnia unresponsive to chloral hydrate, on a single-dose basis, up to 8 mg in 24 hours. The use of lorazepam was permitted only through the first 7 days of randomized treatment. Neither chloral hydrate nor lorazepam was permitted within 6 or 12 hours, respectively, of efficacy assessments. EPS rated moderate according to the Simpson Scale, [18] and present for at least 24 hours, were treated with benztropine mesylate (up to 4 mg orally or 2 mg parenterally) for no more than 3 days per episode; akathisia was treated with 50 mg of oral diphenhydramine hydrochloride. Either drug could be used without restriction for the treatment of acute dystonic reactions.

Assessments TOP

Efficacy. Psychiatric symptomatology was assessed by use of the BPRS, the CGI, and the Modified Scale for the Assessment of Negative Symptoms (SANS) [19] before trial entry, on the last day of the single-blind, placebo phase (day 0), and weekly thereafter for 6 weeks (on days 7, 14, 21, 28, 35, and 42). If treatment was discontinued before day 42, all efficacy assessments were completed at the time of withdrawal.

Safety. Adverse events were assessed by the investigator throughout the trial for severity and relationship to treatment. EPS and abnormal involuntary movements were assessed at day 0 and weekly by use of the Simpson Scale, modified to include an akathisia item, and the Abnormal Involuntary Movement Scale (AIMS), [20] respectively. Additional methods to assess safety, used at entry and throughout the trial (as indicated), included routine clinical laboratory testing and urinalysis (weekly) and weight and vital signs measurements (weekly and daily, respectively); ECG and determination of prolactin levels in plasma (days 21 and 42); and physical examinations (day 42). Blood samples for the analysis of prolactin levels in plasma were taken at random, and results were not reflective of trough concentrations. If treatment was discontinued before day 42, patients underwent all safety assessments at the time of withdrawal.

Statistical methods TOP

Power calculations were based on the ability to detect a minimum difference of 8 units between mean changes from baseline in BPRS total scores. A variance estimator from a previous study (mean square error of 123.9; data on file, ZENECA Pharmaceuticals) was used to determine that 50 patients per treatment group would allow detection of this difference with a power of at least 0.90 and a two-sided alpha = 0.05 level test.

Efficacy. The primary efficacy variables were the BPRS total score and the CGI Severity of Illness item score. Secondary efficacy variables included five BPRS factor scores, the BPRS positive-symptom cluster score, the CGI Global Improvement score, and the SANS summary score (sum of the SANS global ratings for affective blunting, alogia, avolition-apathy, anhedonia-asociality, and attention). BPRS factor scores were derived by calculating the mean score of the following component items: somatic concern, anxiety, guilt feelings, and depressive mood for factor I (anxiety/depression); emotional withdrawal, motor retardation, blunted affect, and disorientation for factor II (anergia); conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content for factor III (thought disturbance); tension, mannerisms and posturing, and excitement for factor IV (activation); and hostility, suspiciousness, and uncooperativeness for factor V (hostile/suspiciousness).

The population for the analysis of efficacy included all patients who entered the randomized phase of the trial and had efficacy data for at least one time after day 0. The primary time for the analysis of efficacy was day 42, the last day of randomized treatment. For patients who withdrew before day 42, data from their final evaluations were carried forward and included in the endpoint analysis. Additional analyses evaluated data corresponding to each designated time before day 42, with last observations carried forward for patients who withdrew.

Proportions of patients who withdrew from the trial, along with reasons for withdrawal, were tabulated. Baseline characteristics were compared between treatment groups by the use of analysis of variance (ANOVA) for continuous variables and the Cochran-Mantel-Haenszel chi squared test for categorical measures. Efficacy data were analyzed by the use of analysis of covariance (ANCOVA) (PROC GLM procedure; SAS, SAS Institute, Cary, NC) for change from baseline in BPRS total and factor scores, CGI Severity of Illness item score, and SANS summary score. The model included baseline score (covariate), center, and treatment. Least squares means from ANCOVA were compared; the difference was calculated, and a 95% confidence interval was constructed for the difference.

CGI Global Improvement scores were analyzed by use of the Cochran-Mantel-Haenszel chi squared tests (controlling for center). Responses were grouped to form three categories of patients: those much or very much improved, those with minimal change (either direction) or no change, and those much or very much worse.

Residuals from all final ANCOVA models were evaluated for deviation from normality by use of the Shapiro-Wilk test. The assumption of homoscedasticity was evaluated by comparing variances in the treatment groups by use of the F-test for equality of variances. The assumption of parallelism (i.e., no significant baseline-by-treatment interaction) and possible treatment-by-center interactions were investigated by including these interaction terms in the final model. A stratified Wilcoxon Rank Sum test was used to corroborate the findings when assumptions of ANCOVA were untenable.

Two of the 12 centers did not recruit adequate numbers of patients to allow for the estimation of treatment effects; therefore, data from those centers were pooled for all efficacy analyses. All statistical tests were conducted with two-sided alpha = 0.05, with marginal significance indicated by $0.05 < p < 0.1$. Unless otherwise indicated, all mean changes refer to least squares mean changes.

Safety. All randomized patients were included in the analyses of safety. Adverse events were classified by the preferred terms from the COSTART system of nomenclature. Crude incidence rates and numbers of events and their severity were tabulated by body system and preferred term for each treatment group. Vital signs and weight were summarized by the use of descriptive statistics for actual values as well as for changes from baseline.

The distributions of Simpson Scale total scores and AIMS total scores at baseline were extremely skewed, with the majority of patients having minimum total scores for each scale (e.g., Simpson Scale total scores of 10, 11, or 12 and AIMS total scores of 0, 1, or 2). The use of parametric methods such as ANOVA or ANCOVA was inappropriate for these data. Therefore, frequency distributions of grouped total scores and grouped change from baseline scores were calculated. The analyses of the change from baseline for both Simpson Scale and AIMS total scores were based on chi squared tests, with Cochran-Mantel-Haenszel methods to control for center effect. Change scores were grouped into categories of improved (change of -1 or less), no change (change of 0), or worsened (change of +1 or more).

Changes in laboratory data from baseline to final observation were analyzed by the use of ANCOVA, with baseline values as covariates. The model did not include center because a central laboratory was used. To explore laboratory data for trends over time, a slope analysis was also conducted. For each laboratory test, a least squares regression line was fit to all available baseline and postbaseline data for each patient. Mean slopes were then compared between treatment groups by the use of ANOVA.

ANCOVA was used to compare changes from baseline in ECG parameters, with baseline, center, and treatment included in the model. Additionally, a slope analysis, similar to that used for laboratory data, was conducted in an attempt to detect changes over time.

Results TOP

Patients TOP

One hundred forty-six patients entered the single-blind, placebo phase, and 109 were randomized to treatment. Of those patients, 54 received ICI 204,636 and 55 received placebo. None of the 12 centers recruited more than 16% of all randomized patients.

The majority (91%) of patients were men (Table 1), partly because women of childbearing potential were initially excluded and partly because of the population demographics at a number of centers. The average age was 36 years (range, 18-58). Generally, the treatment groups were well balanced with regard to demographics, age when patients were first treated for schizophrenia, and DSM-III-R diagnosis. Most patients had acute exacerbation of either chronic undifferentiated schizophrenia (N = 52) or chronic paranoid schizophrenia (N = 39). Although formal data regarding history of response to previous antipyschotics were not collected, history of previous hospitalizations (53% of patients with more than eight), along with mean age at first treatment (22 years), in general, suggests the chronic nature of the patients' psychiatric illnesses.

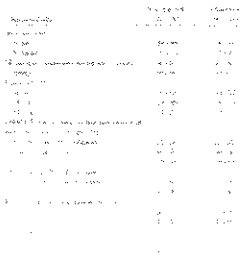


Table 1. Demographics, psychiatric history, and reasons for withdrawal

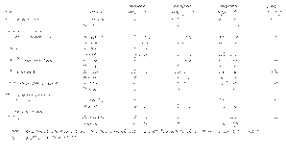
Twenty-six patients treated with ICI 204,636 and 33 placebo-treated patients withdrew before completing 6 weeks of treatment for reasons shown in Table 1. The majority of withdrawals (16 in the ICI 204,636 group; 27 in the placebo group) were attributed to treatment failure.

Clinical efficacy TOP

Three of 109 randomized patients (1 in the ICI 204,636 group; 2 in the placebo group) were excluded from efficacy analyses because postbaseline efficacy data were not available. Therefore, 53 patients per treatment group were included in the analyses of efficacy.

Mean BPRS total scores were comparable between groups at baseline (Table 2). Mean changes showed that ICI 204,636-treated patients improved steadily through 6 weeks of treatment, whereas placebo-treated patients remained essentially unchanged (Figure 1). On days 14, 28, and 35, when statistically significant differences between treatment groups were detected, mean changes in BPRS total scores were -5.6, -8.4, and -8.7, respectively, for ICI 204,636-treated patients compared with 0.5, -1.8, and -1.3 for placebo-treated patients. At endpoint, the difference in changes from baseline (-8.1 for ICI 204,636 and -2.1 for placebo) was marginally significant ($p = 0.07$) (Table 2) and favored ICI 204,636. Smaller changes noted on day 21 also resulted in a marginally significant difference ($p = 0.09$) favoring ICI 204,636.

Table 2. Comparisons of efficacy assessments[a]



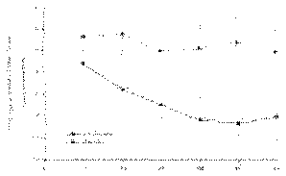


Figure 1. Least squares mean changes from baseline (and standard errors) in the Brief Psychiatric Rating Scale (BPRS) total score for each treatment group by day. Asterisk indicates p less or equal to 0.05.

Significant differences between treatment groups were identified for factor III (thought disturbance) on days 28 and 35 (Figure 2(A)), for the positive-symptom cluster on days 14, 28, and 35 (Figure 2(B)), and for factor IV (activation) on days 7 through 42. Mean changes in thought-disturbance scores were -0.78 and -0.77 (compared with -0.19 and -0.17 for placebo-treated patients) on days 28 and 35, respectively, and mean changes in positive-symptoms cluster scores were -0.65, -0.96, and -0.99 (compared with -0.21, -0.22, and -0.19 for placebo) on days 14, 28, and 35, respectively. Endpoint differences favoring ICI 204,636 were marginally significant for both thought disturbance ($p = 0.09$) and the positive-symptom cluster ($p = 0.06$). Mean changes in activation scores ranged from -0.19 (day 7) to -0.35 (day 42) for patients treated with ICI 204,636 (compared with 0.24 to 0.41 for placebo-treated patients), and endpoint differences were significant ($p = 0.002$). Marginally significant differences were also noted on days 7 ($p = 0.09$) and 21 ($p = 0.06$) for thought disturbance, day 21 ($p = 0.07$) for the positive-symptom cluster, and on days 28 ($p = 0.07$) and 35 ($p = 0.06$) for factor V (hostile/suspiciousness).

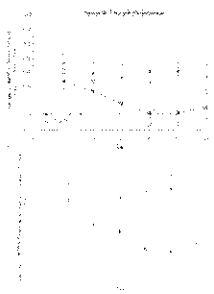
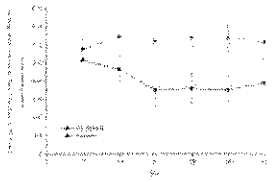


Figure 2. Least squares mean changes from baseline (and standard errors) in Brief Psychiatric Rating Scale (BPRS) factor III thought disturbance (a) and positive-symptom cluster (b) scores for each treatment group by day. Asterisk indicates p less or equal to 0.05.

For patients treated with ICI 204,636, improvement in factor III (thought disturbance) was attributed, on the basis of descriptive statistics, to improvement in all of the component items. Improvement in factor IV (activation) was attributed to improvement in the component items of mannerisms and posturing and tension (the excitement item was unchanged).

Mean CGI Severity of Illness item scores were comparable between treatment groups at baseline (Table 2). From day 7 onward, mean changes indicated improvement in patients treated with ICI 204,636 but not in placebo-treated patients. Differences between treatment groups reached significance on days 21, 28, and 35 (Figure 3), with mean changes from baseline of -0.30, -0.28, and -0.30, respectively, for the ICI 204,636 group and 0.24, 0.28, and 0.28, respectively, for the placebo group. At endpoint, the difference between treatment groups was marginally significant ($p = 0.07$) and favored ICI 204,636 (Table 2).

Figure 3. Least squares mean changes from baseline (and standard errors) in the Clinincal Global Impression (CGI) Severity of Illness item score for each treatment group by day. Asterisk indicates p less or equal to 0.05.



The distributions of patients in the grouped categories for the CGI Global Improvement item at endpoint were significantly different (p = 0.02) between treatment groups; 28% of ICI 204,636-treated patients compared with 25% of placebo-treated patients were rated as improved, and 17% of ICI 204,636-treated patients compared with 42% of placebo-treated patients were rated as worsened (**Figure 4**). The frequency distributions of response were significantly different for the two treatment groups from day 21 onward (p less or equal to 0.05). At each of these days, a greater proportion of placebo-treated patients were considered worsened.

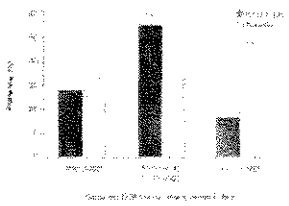
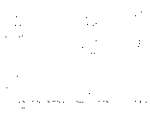


Figure 4. Comparisons of Clinical Global Impression (CGI) Global Improvement (grouped responses) at endpoint. Between treatment groups, the distributions of patients among the grouped categories were significantly different at endpoint (p = 0.02) and from day 21 onward (p less or equal to 0.05).

Mean SANS summary scores for ICI 204,636-treated patients showed evidence of steady improvement from day 7 through day 35, as well as sustained improvement at day 42. In contrast, mean scores for the placebo group deteriorated from baseline for all days. Differences between treatment groups from day 21 onward were significant (p less or equal to 0.05) (**Figure 5**), with mean change at endpoint reaching -1.04 for the ICI 204,636 group and 0.56 for the placebo group (**Table 3**). Patients treated with ICI 204,636 showed improvement in all five of the subscale global areas, with greatest improvement in avolition-apathy, anhedonia-asociality, and alogia, whereas scores for placebo-treated patients either worsened or did not change (**Table 3**).

Figure 5. Least squares mean changes from baseline (and standard errors) in the Scale for the Assessment of Negative Symptoms (SANS) summary score for each treatment group by day. Asterisk indicates p less or equal to 0.05.

Table 3. SANS summary and descriptive global ratings



Safety TOP

The mean daily dose of ICI 204,636 was 307 mg (range, 58-526 mg). On average, patients in the ICI 204,636 group were treated for 30 days (median, 41 days) and patients in the placebo group were treated for 27 days (median, 25 days). More than half of the patients in each treatment group, 70% (38 of 54) treated with ICI 204,636 and 80% (44 of 55) treated with placebo, received at least one dose of chloral hydrate during the randomized treatment phase; duration of use averaged 15 days (range, 1-42 days) and 14 days (range, 1-44 days), respectively, per treatment group. Seventeen patients in the ICI 204,636 group and 15 in the placebo group (30% per group) received at least one dose of lorazepam, with patients in the ICI 204,636 group treated for an average of 7 days (median, 2 days) and patients in the placebo group treated for an average of 5 days (median, 3 days) (cumulative doses, 13 and 12 mg, respectively).

There were no deaths during the trial, and most adverse events were rated as mild. Those events that occurred in more than 5% of patients in either group appear in Table 4, by descending frequency for patients treated with ICI 204,636. Somnolence, commonly associated with antipsychotic use, was the most frequently occurring event in the ICI 204,636 group. Agitation and insomnia, which were attributed to the underlying illness, occurred in 28 and 15% of ICI 204,636-treated patients, respectively, and in 20 and 15% of placebo-treated patients, respectively. Motor system adverse events (akathisia, tremor) occurred infrequently, with similar incidences (< 0.1%) in both treatment groups.

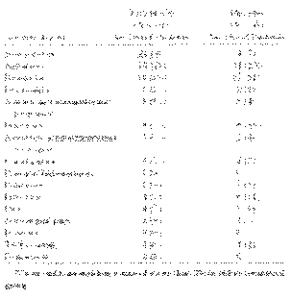


Table 4. Most frequent adverse events[a] by treatment group

Adverse events led to the withdrawal of five patients: three treated with ICI 204,636 and two given placebo. In the ICI 204,636 group, the adverse events included rash; increased levels of alanine transaminase (ALT) and aspartate transaminase (AST); and somnolence, postural hypotension, and psychosis. In the placebo group, adverse events included increased levels of ALT and AST as well as convulsion. The latter event occurred on the first day of randomized treatment and was attributed to the abrupt withdrawal of carbamazepine treatment at trial entry.

In each treatment group, 12 adverse events were rated as severe. Agitation was the most common, in five ICI 204,636-treated patients and seven placebo-treated patients, and was attributed to the underlying disease. In the placebo group, one patient attempted suicide and was withdrawn as a treatment failure. No injuries occurred, and the attempt was attributed to the patient's psychiatric disease.

Patients entered the trial with few or no EPS. At endpoint, the proportions of patients with change scores in the improved, no change, and worsened categories were similar between treatment groups ($p = 0.84$) (Table 5). Fifty-one percent of patients treated with ICI 204,636 were improved compared with 48% of patients treated with placebo. The remaining patients were generally distributed evenly in the no change and worsened categories in each treatment group. The low incidence of treatment-emergent EPS was reflected in the minimal use of benztropine mesylate or diphenhydramine hydrochloride in both treatment groups. Overall, five patients in the ICI 204,636 group and six in the placebo group received benztropine mesylate-in the ICI 204,636 group for 1 to 8 days (mean cumulative dose, 7 mg) and in the placebo group for 1 to 11 days (mean cumulative dose, 10 mg). Fewer patients received diphenhydramine hydrochloride: two in the ICI 204,636 group for 2 to 9 days (mean cumulative dose, 175 mg) and three in the placebo group for 2 to 13 days (mean cumulative dose, 208 mg). No acute dystonic reactions were noted.

Table 5. Comparison of Simpson Scale and AIMS total scores[a]

A large proportion of patients entered the trial with little or no abnormal movements as measured by the AIMS total score; almost half of all patients with baseline and postbaseline values had the minimum total score (0) at baseline (42% of ICI 204,636-treated patients, 50% of placebo-treated patients). Similar results were seen at endpoint, with almost half of all patients having change scores of 0 (43% of ICI 204,636-treated patients, 48% of placebo-treated patients) (Table 5). Analyses of grouped change scores showed no statistically significant differences between treatment groups in the distribution of patients in the three change categories at any day.

Through 6 weeks of treatment, changes in hematologic parameters were neither statistically nor clinically significant and no cases of agranulocytosis, leukopenia, or neutropenia were observed. Treatment with ICI 204,636 was associated with mild, transient, reversible, and clinically asymptomatic increases in ALT concentrations in five patients, with the maximum observed concentration at 10 times the upper limit of normal. Only one patient with ALT elevation had concomitant elevation in AST. Serum transaminase levels generally peaked between days 7 and 21

and usually returned to baseline levels by the end of the trial or shortly thereafter. Concomitant elevations in other hepatic enzymes or total bilirubin were uncommon. Small decreases in mean total thyroxine, which occurred without alterations in mean total triiodothyronine or thyroid-stimulating hormone concentrations, were deemed not clinically significant.

Mean prolactin concentrations were similar between treatment groups at baseline, with values at the upper end of the normal range. Over 6 weeks, concentrations decreased in both treatment groups and no significant differences between treatment groups were identified (Table 6) on either day 21 or day 42.

Table 6. Comparisons of change in prolactin concentrations in serum

ECG findings were not clinically significant. Small increases in atrial and ventricular rates were observed over time in patients treated with ICI 204,636. Mean heart rate increased approximately 9 beats/minute, from 80 at baseline to 89 at endpoint. Although analyses showed significant differences between treatment groups at endpoint for atrial and ventricular rates ($p = 0.0001$), increased heart rates as determined by ECG were not corroborated by the clinical measurement of pulse rates. Differences in QTc intervals were statistically significant between treatment groups, but the small increases in mean QTc intervals for ICI 204,636-treated patients were not considered clinically significant (0.0072 vs. -0.0001 for placebo-treated patients at end point) nor were they associated with cardiovascular adverse events.

Vital signs were similar between treatment groups and were generally within normal limits. Treatment with ICI 204,636 was associated with clinically significant weight gain (an increase of 7% or more from baseline weight) in 25% of patients compared with 4% of placebo-treated patients. Average weights at endpoint represented a change from baseline of +5.5 kg for ICI 204,636-treated patients and +0.5 kg for patients in the placebo group.

Discussion TOP

In this placebo-controlled, multicenter trial, ICI 204,636 was effective in the treatment of the positive and negative symptoms of schizophrenia. Significant differences (p less or equal to 0.05) between treatment groups were identified for the primary efficacy variables, the BPRS total score and CGI Severity of Illness item score, at most times throughout the trial, with marginal significance achieved at endpoint ($p = 0.07$ for both). A combination of methodological issues, including flexible dosing, dose limitations, and patient anticipation of treatment termination, may have been responsible for the lack of statistical significance at endpoint, in view of the significant results seen for other trial days. Results from other phase II trials with ICI 204,636 have not shown an attenuation of effect at endpoint. [21]

Analysis of BPRS factor scores showed that, on various trial days, treatment with ICI 204,636 resulted in selective improvement in the psychosis-related factors of thought disturbance and hostile/suspiciousness, as well as improvement in the mean BPRS positive-symptoms cluster score. The effect of ICI 204,636 on negative symptoms was demonstrated by clinically and statistically significant differences between treatment groups in SANS summary scores from day 21 onward. Because the incidence of EPS was low throughout the trial, with no significant difference between groups at endpoint, the improvement in SANS summary scores in the ICI 204,636 group could suggest an effect on primary negative symptoms. However, this possibility needs to be explored further.

Overall, ICI 204,636 was well tolerated. Most adverse events fell into two categories: those commonly associated with antipsychotic agents, including sedation or somnolence, and those related to the underlying illness, such as agitation and insomnia. The use of concomitant sedating drugs, such as chloral hydrate, was similar between treatment groups; therefore, somnolence in the ICI 204,636 group was considered a treatment effect but was generally rated as mild and not cause for concern.

Treatment with ICI 204,636 did not induce EPS in the dose range studied, as determined by analysis of Simpson Scale total scores and lack of treatment-emergent acute dystonic reactions. These results, along with the limited use of anticholinergic medications and limited incidence of motor system adverse events, indicate that ICI 204,636 has an atypical profile. Because so few patients had abnormal involuntary movements at baseline, the ability of ICI 204,636 to ameliorate such movements was inconclusive.

Mean changes in prolactin levels in the ICI 204,636 group were similar to those in the placebo group. The lack of sustained elevations of prolactin in serum further supports the belief that ICI 204,636 is an atypical antipsychotic.

Patients treated with ICI 204,636 gained, on average, 3.1 kg, and 24% had clinically significant increases in body weight of 7% or more. However, weight gain is not uncommon in schizophrenic patients treated with antipsychotic agents and has been reported in as many as one-third of patients treated with clozapine. [22]

In conclusion, ICI 204,636 showed efficacy in the treatment of the positive and negative symptoms of schizophrenia and was well tolerated. The lack of both treatment-emergent EPS and sustained prolactin elevations in serum distinguishes ICI 204,636 from standard antipsychotic agents and confirms preclinical findings that ICI 204,636 is an atypical antipsychotic.

Additional clinical trials, particularly fixed-dose trials evaluating doses of ICI 204,636 within a given dose range, are ongoing to further demonstrate the efficacy and optimal dose of ICI 204,636 in the treatment of the positive symptoms of schizophrenia These trials will also explore the effects of ICI 204,636 on negative symptoms occurring in the context of an acute exacerbation of schizophrenia. Additional research on ICI 204,636 will be needed to determine whether preclinical findings of atypicality (clozapine-like activity) translate into superior efficacy in the treatment of positive symptoms in treatment-resistant schizophrenic patients, negative symptoms associated with the deficit syndrome, and cognitive dysfunction associated with schizophrenia.

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