37 ILOPERIDONE: PLACEBO- AND RISPERIDONE-CONTROLLED STUDY IN PATIENTS WITH SCHIZOPHRENIA

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Abstract

Background: Iloperidone, a novel atypical antipsychotic, is being developed for the treatment of schizophrenia. An international randomized, double-blind, placebo-controlled 6-week study with risperidone as an active comparator assessed the efficacy and safety/tolerability of 2 nonoverlapping dose ranges of iloperidone in patients with schizophrenia.

Methods: After fixed-dose titration to iloperidone 6 mg/d or 12 mg/d, risperidone 6 mg/d, or placebo (PLA) (Days 1–7), patients received flexible dosing with iloperidone 4–8 mg/d (2–4 mg bid; ILO-Low) or 10–16 mg/d (5–8 mg bid; ILO-High), risperidone 4–8 mg/d (2–4 mg bid; RIS), or PLA (Days 8–42). Primary efficacy variable was baseline to end point change on a Brief Psychiatric Rating Scale (BPRS) derived from the Positive and Negative Syndrome Scale (PANSS). Safety and tolerability assessments included adverse events (AEs), extrapyramidal symptoms (EPS), and akathisia using the Extrapyramidal Symptom Rating Scale and Barnes Akathisia Scale, vital signs, and laboratory value changes.

Results: Of the 616 patients randomized, 48% of ILO-Low, 56% of ILO-High, 58% of RIS, and 40% of PLA patients completed the study. Significant improvements in efficacy (score reductions) for BPRS from baseline to end point vs PLA were observed for ILO-Low (−6.2, P=.012), ILO-High (−7.2, P=.001), and RIS (−10.3, P<.001). ILO-Low group had significant improvements from baseline to end point vs PLA in PANSS total (PANSS-T: −9.5, P<.05), PANSS positive syndrome (PANSS-P: −3.5, P<.05), and PANSS general psychopathology (PANSS-GP: −4.2, P<.05). From baseline to end point, ILO-High group had significant improvements in PANSS-T (−11.1, P<.05), PANSS-P (−4.1, P<.05), PANSS negative syndrome (PANSS-N: −2.4, P<.05), and PANSS-GP (−4.8, P<.05) compared with PLA. For RIS, significant improvements in efficacy from baseline to end point vs PLA were observed (PANSS-T: −16.6, P<.05; PANSS-P: −6.0, P<.05; PANSS-N: −3.0, P<.05; PANSS-GP: −7.8, P<.05). The longer titration schedule of ILO (steady state in 7 days) relative to RIS (steady state in 3 days) might have contributed to the smaller clinical effect size for ILO. Treatments were generally well tolerated. AE and tolerability profiles of ILO were recognizably different from those of RIS. The RIS group had a higher incidence of akathisia, dystonia, muscle rigidity, somnolence, and sedation than did the PLA group; small improvements in dyskinesia and akathisia were observed in the ILO groups. Mean changes in prolactin (ng/mL) from baseline to end point were decreased for ILO-Low (−9.5), ILO-High (−8.0), and PLA (−13.6) and increased for RIS (+34.5). Mean weight changes (kg) from baseline to end point in ILO-Low, ILO-High, RIS, and PLA groups, respectively, were +1.6, +2.2, +1.9, and −0.3. Mean changes (mg/dL) from baseline to end point were ILO-Low, +3.0; ILO-High, +7.8; RIS, +0.5; and PLA, −0.7 for glucose and ILO-Low, +2.9; ILO-High, +2.9; RIS, +1.1; and PLA, −2.0 for total cholesterol. From baseline to end point, mean changes in triglycerides (mg/dL) decreased for all groups: ILO-Low (−25.8); ILO-High (−24.2); RIS (−27.6); and PLA (−35.6). In future clinical studies, an active comparator with a titration schedule and safety/tolerability profile (eg, EPS) similar to ILO should be considered to avoid potential bias in efficacy estimates.

Conclusion: Iloperidone, administered at either of 2 nonoverlapping dose ranges, was effective, safe, and well tolerated for schizophrenia with some potential safety advantages on existing atypical antipsychotics.

Background

- Atypical antipsychotics are viewed as a significant advancement over older drugs, but they still have limited efficacy in many patients.[1]
- It has been estimated that 20% to 40% of patients with schizophrenia are resistant to antipsychotic therapy,[2] and more than half enrolled in controlled trials discontinue treatment within 6 months, most often due to lack of efficacy.[3]
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed that 74% of 1432 patients with schizophrenia who received at least one dose of olanzapine, perphenazine, quetiapine, ziprasidone, or risperidone (RIS) discontinued treatment within 18 months.[4]
- Iloperidone (ILO) is a novel antipsychotic and mixed D_2/5-HT_2 antagonist.[5-7]
  - Low affinity for histamine H1 receptors may lower risk for weight gain and somnolence.[6,7]
- Summarized here are efficacy results for ILO obtained in 3 similar 6-week clinical trials conducted between October 1998 and June 2002.

Methods

Patients

- For all 3 trials, men and women aged 18 to 65 years with acute or subacute exacerbation of schizophrenia and a Positive and Negative Syndrome Scale total (PANSS-T) score ≥60 at screening and baseline were included.

Study Design and Treatment

- All 3 trials were randomized, double-blind, placebo (PLA)- and active-controlled, parallel-group designs.
- Following prerandomization screening, eligible patients entered a single-blind, 3-day PLA run-in period. Patients meeting entry criteria at the end of this period were randomized to active treatment, consisting of a 7-day fixed titration period followed by maintenance dosing on days 8–42. The maintenance doses were:
  - Study 3000: ILO 4, 8, and 12 mg/d and haloperidol (HAL) 15 mg/d
  - Study 3004: ILO 4–8 and 10–16 mg/d and RIS 4–8 mg/d
  - Study 3005: ILO 12–16 and 20–24 mg/d and RIS 6–8 mg/d
- Titration to maintenance levels of ILO ≥10 mg/d and HAL utilized the full 7 days; titration to ILO 4–8 mg/d maintenance levels was scheduled over 3 to 5 days. RIS titration was more rapid, occurring in 3 days.

Assessments

Primary Efficacy Variables

- Study 3000: change from baseline to end point in PANSS-T scores
- Studies 3004 and 3005: change from baseline to end point on the 18-item BPRS (Brief Psychiatric Rating Scale derived from PANSS)

Secondary Efficacy Variables

- All 3 studies: changes from baseline to each postbaseline assessment on PANSS positive syndrome (–P), negative syndrome (–N), and general psychopathology (–GP) scores and BPRS score
- Studies 3004 and 3005: Clinical Global Impression of Severity (CGI-S) score

Safety

- Safety evaluations included physical examination, electrocardiograms, and laboratory values. Adverse events (AEs) were recorded.

Statistical Analysis

- Efficacy analyses were based on the intent-to-treat population, comprising all patients receiving ≥1 dose of study medication with ≥1 complete PANSS assessment using last observation carried forward (LOCF) method.

Time-Based Analyses

- Because of the 7-day titration schedule of most ILO treatment arms and the resulting time to reach steady-state therapeutic doses, an additional analysis evaluated change for all patients who remained on treatment for ≥2 weeks. This analysis pooled results for patients receiving ILO 4–8 mg/d (2–4 mg bid), ILO 10–16 mg/d (5–8 mg bid), ILO 20–24 mg/d, RIS 4–8 mg/d (2–4 mg bid), HAL 15 mg/d, or PLA.

Results

Patients

- In total, 1943 patients were randomized.

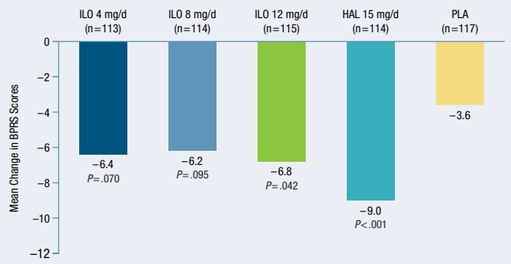
Table 1. Baseline Demographic and Clinical Characteristics

	Study 3000					Study 3004				Study 3005			
	ILO 4 mg/d (n=121)	ILO 8 mg/d (n=125)	ILO 12 mg/d (n=124)	HAL 15 mg/d (n=124)	PLA (n=127)	ILO 4–8 mg/d (n=153)	ILO 10–16 mg/d (n=154)	RIS 4–8 mg/d (n=153)	PLA (n=156)	ILO 12–16 mg/d (n=244)	ILO 20–24 mg/d (n=145)	RIS 6–8 mg/d (n=157)	PLA (n=160)
Age, y (mean)	38.4	37.0	40.1	39.1	39.3	38.4	39.3	37.5	38.8	38.9	37.3	39.8	39.0
Gender (%)													
Male	68	75	73	69	71	69	71	75	67	60	68	61	59
Female	32	25	27	31	29	31	29	25	33	40	32	39	41
Race (%)													
White	47	39	54	47	50	60	59	60	57	67	70	76	69
Black	43	46	35	44	43	35	31	33	34	28	23	17	24
Asian	2	1	2	2	0	3	5	1	1	1	2	1	1
Other	8	14	9	7	6	2	5	7	8	5	5	5	6
DSM-IV criteria (%)													
Schizophrenia	74	69	72	63	66	80	81	75	76	77	79	80	75
Schizoaffective	26	30	28	37	34	20	19	25	24	23	21	20	25
Efficacy scores													
PANSS-T	95.2	96.0	95.8	95.7	94.6	95.4	93.4	94.5	94.1	93.7	94.8	95.8	94.9
BPRS	55.3	56.6	55.9	56.0	55.3	55.1	54.1	54.9	54.3	54.4	55.0	55.2	55.3

Efficacy

- In Study 3000, there was a significant improvement from baseline in BPRS scores with ILO 12 mg/d and with HAL.

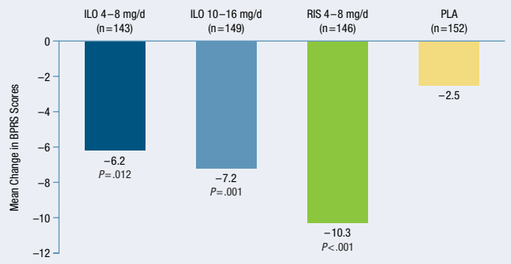
Figure 1. Mean Change From Baseline to End Point in Study 3000 BPRS Scores



All P values vs placebo. Negative change indicates improvement.

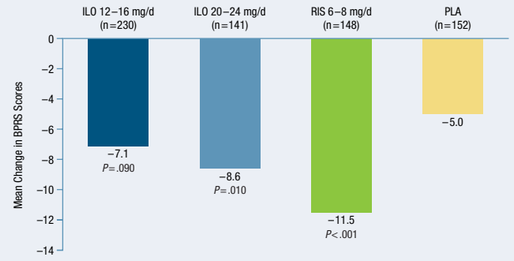
- In Studies 3004 and 3005, BPRS scores improved from baseline with all ILO doses and with RIS.

Figure 2. Mean Change From Baseline to End Point in Study 3004 BPRS Scores



All P values vs placebo. Negative change indicates improvement.

Figure 3. Mean Change From Baseline to End Point in Study 3005 BPRS Scores



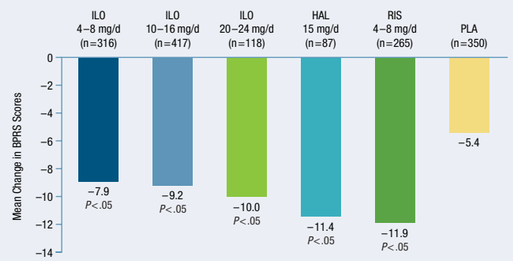
All P values vs placebo. Negative change indicates improvement.

- The discontinuation rates during the first 2 weeks across the 3 studies were 14.6% with ILO 4–8 mg/d, 15.6% with ILO 10–16 mg/d, 16.3% with ILO 20–24 mg/d, 23.7% with HAL, 9.9% with RIS, and 16.9% with PLA.

Time-Based Analyses

- Because of the 7-day titration schedule of most ILO treatment arms and the resulting time to reach steady-state therapeutic doses, an exploratory analysis of BPRS results from all 3 studies included all patients receiving double-blind treatment in these trials for ≥2 weeks. Results from this analysis demonstrated:
  - Greater decreases from baseline vs PLA for all treatments.
  - The greatest reductions in BPRS scores at 6 weeks were observed with ILO 20–24 mg/d, RIS, and HAL.

Figure 4. Combined Analysis for Patients on Treatment for ≥2 Weeks in Studies 3000, 3004, and 3005 (Change From Baseline to End Point in BPRS)



All P values vs placebo. Negative change indicates improvement.

- ILO was also significantly more effective than PLA in improving secondary end points, including PANSS-P, PANSS-N, PANSS-GP, and CGI-S.

Table 2. Results Based on Primary and Secondary Efficacy Variables (LOCF)

	Study 3000					Study 3004				Study 3005			
Efficacy Measure	ILO 4 mg/d (n=113)	ILO 8 mg/d (n=114)	ILO 12 mg/d (n=115)	HAL 15 mg/d (n=114)	PLA (n=117)	ILO 4–8 mg/d (n=143)	ILO 10–16 mg/d (n=149)	RIS 4–8 mg/d (n=146)	PLA (n=152)	ILO 12–16 mg/d (n=230)	ILO 20–24 mg/d (n=141)	RIS 6–8 mg/d (n=148)	PLA (n=152)
PANSS-T	−9.0	**−7.8**	**−9.9**	−13.9	−4.6	−9.5	−11.1	−16.6	−3.5	−11.0	−14.0	−18.8	−7.6
P value	.097	**.227**	**.047**	<.001	—	.017	.002	<.001	—	.101	.005	<.001	—
PANSS-P	−3.0	−3.3	−3.5	−4.8	−1.9	−3.5	−4.1	−6.0	−1.6	−4.2	−5.1	−7.2	−3.1
P value	.230	.118	.061	<.001	—	.020	.002	<.001	—	.110	.008	<.001	—
PANSS-N	−1.8	−0.9	−1.8	−2.5	−0.9	−1.9	−2.4	−3.0	−1.0	−2.2	−2.8	−3.4	−1.5
P value	.218	.994	.220	.022	—	.133	.021	.001	—	.185	.023	<.001	—
PANSS-GP	−4.5	−3.8	−4.7	−6.7	−1.9	−4.2	−4.8	−7.8	−1.1	−4.7	−5.9	−7.9	−2.8
P value	.057	.172	.038	<.001	—	.017	.003	<.001	—	.070	.007	<.001	—
BPRS	−6.4	−6.2	−6.8	−9.0	−3.6	−6.2	**−7.2**	−10.3	−2.5	**−7.1**	−8.6	−11.5	−5.0
P value	.070	.095	.042	<.001	—	.012	**.001**	<.001	—	**.090**	.010	<.001	—
CGI-S	—	—	—	—	—	−0.6	−0.5	−0.8	−0.2	−0.6	−0.6	−0.9	−0.4
P value	—	—	—	—	—	.003	.006	<.001	—	.028	.037	<.001	—

LOCF=last observation carried forward.
Bold numbers in boxes represent primary efficacy end points.

Table 3. Combined Analysis for Patients on Treatment ≥2 Weeks in Studies 3000, 3004, and 3005 (Change from Baseline to End Point; LOCF)

Efficacy Measure	ILO 4–8 mg/d (n=316)	ILO 10–16 mg/d (n=417)	ILO 20–24 mg/d (n=118)	HAL 15 mg/d (n=87)	RIS 4–8 mg/d (n=265)	PLA (n=350)
PANSS-T	−11.6	−14.1	−16.5	−18.8	−18.9	−7.7
P value	.014	<.001	<.001	<.001	<.001	—
PANSS-P	−4.1	−5.1	−5.8	−6.3	−7.1	−3.0
P value	.031	<.001	<.001	<.001	<.001	—
PANSS-N	−1.9	−2.8	−3.6	−3.7	−3.6	−1.7
P value	.638	.006	.001	.003	<.001	—
PANSS-GP	−5.6	−6.4	−7.3	−8.9	−8.4	−3.1
P value	.002	<.001	<.001	<.001	<.001	—
BPRS	−7.9	−9.2	−10.0	−11.4	−11.9	−5.4
P value	.004	<.001	<.001	<.001	<.001	—
CGI-S	−0.7	−0.7	−0.7	—	−0.9	−0.4
P value	.009	<.001	.007	—	<.001	—

LOCF=last observation carried forward.

Table 4. Treatment-Related Adverse Events Occurring in ≥5% of Patients in Any Active Treatment Group and at Least Twice the Rate of Placebo

Event, n (%)	ILO 4–8 mg/d (n=463)	ILO 10–16 mg/d (n=456)	ILO 20–24 mg/d (n=125)	HAL 15 mg/d (n=118)	RIS 4–8 mg/d (n=306)	PLA (n=440)
Pts with ≥1 AE	375 (81.0)	360 (78.9)	95 (76.0)	112 (94.9)	240 (78.4)	333 (75.7)
Extrapyramidal disorder	25 (5.4)	22 (4.8)	5 (4.0)	24 (20.3)	29 (9.5)	21 (5.8)
Dystonia	4 (0.9)	4 (0.9)	1 (0.8)	14 (11.9)	8 (2.6)	3 (0.7)
Tremor	13 (2.8)	12 (2.6)	6 (4.8)	26 (22.0)	21 (6.9)	8 (1.8)
Akathisia	17 (3.7)	7 (1.5)	6 (4.8)	16 (13.6)	21 (6.9)	16 (3.6)
Dizziness	56 (12.1)	47 (10.3)	29 (23.2)	6 (5.1)	22 (7.2)	30 (6.8)
Dry mouth	24 (5.2)	36 (7.9)	13 (10.4)	3 (2.5)	9 (2.9)	6 (1.4)
Dyspepsia	36 (7.8)	25 (5.5)	6 (4.8)	13 (11.0)	18 (5.9)	24 (5.5)
Nasal congestion	22 (4.8)	23 (5.0)	7 (5.6)	2 (1.7)	8 (2.6)	10 (2.3)
Somnolence	23 (5.0)	26 (5.7)	10 (8.0)	8 (6.8)	18 (5.9)	12 (2.7)
Fatigue	20 (4.3)	21 (4.6)	8 (6.4)	9 (7.6)	5 (1.6)	12 (2.7)

Safety

- ILO was well tolerated in all phase 3 studies. Overall, 79.5% of all patients randomized to ILO experienced treatment-emergent AEs vs 78.4% for RIS, 94.9% for HAL, and 75.7% for PLA.
- The risk for motor-related AEs (eg, akathisia, EPS) was lower with ILO than with RIS or HAL, and generally similar to PLA.
- Extrapyramidal Symptom Rating Scale scores demonstrated significant improvement from baseline to end point with all ILO doses, no significant change with RIS, and significant worsening with HAL.
- None of the patients in these trials experienced QTc prolongations ≥500 ms.
- Treatment with ILO produced only modest changes in body weight. LS mean weight gain from baseline to end point was 1.5 kg (1.9%) with ILO 4–8 mg/d, 2.1 kg (2.7%) with ILO 10–16 mg/d, 1.7 kg (2.4%) with ILO 20–24 mg/d, and 1.5 kg (1.8%) with RIS. No weight change was observed with PLA or HAL.
- LS mean changes in blood glucose were mild: 7.2, 9.0, 16.2, 10.8, and 3.6 mg/dL for ILO 4–8 mg/d, ILO 10–16 mg/d, ILO 20–24 mg/d, HAL, and RIS, respectively. No treatments were associated with changes in total cholesterol. Slight reductions in triglycerides were seen across most treatment groups: −26.5 mg/dL for ILO 4–8 mg/d, ILO 10–16 mg/d, and ILO 20–24 mg/d, 0 mg/dL for HAL, and −26.5 mg/dL for RIS.
- LS mean prolactin levels were generally decreased after treatment with ILO: −38.0 and −23.1 µg/L for ILO 4–8 mg/d and ILO 10–16 mg/d, respectively. HAL and RIS were associated with significant increases of 115.8 and 214.5 µg/L, respectively. Prolactin levels were not recorded for ILO 20–24 mg/d.

Conclusions

- Iloperidone is safe and effective for the treatment of patients with schizophrenia or schizoaffective disorder.
- Treatment with iloperidone results in significant improvements versus placebo in PANSS-T, PANSS-P, PANSS-N, PANSS-GP, and CGI-S scores.
- Analysis of results for all patients who remained on study treatment for ≥2 weeks was performed. The greatest reductions in BPRS scores at 6 weeks were observed with iloperidone 20–24 mg/d, risperidone, and haloperidol.
- Iloperidone demonstrated a favorable safety profile, most notably with regard to EPS and akathisia rates, weight and metabolic parameters, and prolactin levels.

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