Efficacy and Safety of Iloperidone in Bipolar Mania:

A Double-Blind, Placebo-Controlled Study

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Abstract

Objective: To determine if iloperidone, a second-generation antipsychotic, reduces symptoms of bipolar mania.

Methods: This phase 3, randomized, double-blind, placebo-controlled study was conducted in adults with bipolar mania at 27 US and international sites between April 2021 and September 2022. Participants were randomized 1:1 to iloperidone (up to 24 mg/d given twice daily) or placebo for 4 weeks. The primary efficacy endpoint was change from baseline to week 4 in Young Mania Rating Scale (YMRS) total score versus placebo. Secondary efficacy endpoints included change from baseline in the Clinical Global Impressions-Severity and Clinical Global Impression of Change scales.

Results: Altogether, 414 participants were randomized and administered at least 1 dose of study medication (iloperidone, n = 206; placebo, n = 208). Overall, 139 (67.1%) iloperidone patients and 153 (72.9%) placebo patients completed the study. Iloperidone demonstrated significant improvement versus placebo at week 4 for the primary and secondary endpoints. Differences in the least-squares mean (95% CI; *P* value) of change from baseline for YMRS total scores were −4.0 (−5.70 to −2.25; adjusted *P* = .000008). The most encountered adverse events with iloperidone were tachycardia, dizziness, dry mouth, alanine aminotransferase increased, nasal congestion, increased weight, and somnolence. The incidence of akathisia and extrapyramidal symptom–related treatment-emergent adverse events was low.

Conclusions: Iloperidone is effective in treating patients with bipolar mania. The tolerability and safety profile of iloperidone in bipolar mania is consistent with previous clinical studies of patients with schizophrenia, and no new safety concerns were identified.

Trial Registration: ClinicalTrials.gov identifier: NCT04819776; EudraCT: 2020–000405-83

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Bipolar I disorder is a mood disorder characterized by at least 1 manic episode, presenting as increased energy, decreased need for sleep, increased psychomotor agitation, and racing thoughts or distractibility.[1–3] Bipolar disorder is heritable,[4–6] with an estimated lifetime prevalence for bipolar I disorder of 0.6%–1% in the general population,[7–9] and has one of the highest rates of serious impairment among mood disorders.[10,11] Patients can suffer from a plethora of associated comorbidities, including increased propensity for suicide and self-harm,[12] substance abuse,[13] obesity, and cardiovascular and metabolic disease,[14] and have a severely decreased lifespan compared to the general population.[15]

Pharmacologic interventions for patients with bipolar disorder include second-generation antipsychotics (SGAs) and mood stabilizers as first-line treatment options,[16,17] but tolerability and effectiveness can vary greatly from patient to patient. In 2011, a meta-analysis concluded that SGAs were more effective for treating bipolar mania than mood stabilizers (eg, lithium, divalproex, carbamazepine, and lamotrigine).[18] This finding was later supported by a 2022 meta-analysis suggesting that most SGAs improve symptoms faster than mood stabilizers.[17] This work also supported that SGAs improve psychotic symptoms in patients with bipolar mania, whereas all mood stabilizers analyzed did not.[17] SGAs differ in their pharmacodynamic profiles, resulting in unique clinical profiles, especially on aspects of their safety and tolerability.[19]

Iloperidone is a second-generation antipsychotic approved by the US Food and Drug Administration (FDA) in 2009 for the treatment of schizophrenia in adults.[20–24] Iloperidone and its primary metabolite, P88, possess high (nM) binding affinity for serotonin 5-HT_{2A} and dopamine D_2 and D_3 receptors,[25] and inhibition at

Clinical Points

- Numerous agents are available for bipolar mania, although many patients cannot find a suitable treatment option.
- Iloperidone can provide a new option to treat bipolar mania with a favorable side effect profile for the categories of akathisia/extrapyramidal side effects, weight gain, and sedation.

these monoaminergic receptors is thought to contribute to the antimanic effects of iloperidone and other atypical antipsychotics, whether the bipolar mania is psychotic or nonpsychotic.[25–27] Iloperidone and P88 are also potent norepinephrine NEα receptor antagonists, which has been proposed to account for the unique tolerability profile of iloperidone, including its reduced propensity for akathisia and extrapyramidal side effects (EPS) in comparison to other second-generation antipsychotics.[28–31]

Here, we report results from a phase 3, randomized, placebo-controlled study designed to assess the efficacy and safety of iloperidone for the acute treatment of manic or mixed episodes associated with bipolar I disorder (bipolar mania).

METHODS

Study Design and Patients

This phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov identifier NCT04819776; EudraCT identifier 2020–000405-83) was composed of 2 phases: a pre-randomization phase including a screening period (up to 7 days) and baseline evaluation period (1 day), and a double-blind, short-term treatment phase (28 days) designed to evaluate the efficacy and safety of iloperidone in the treatment of manic episodes (diagnosed using *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition [*DSM-5*] criteria).[32] The study was conducted from April 4, 2021, through September 7, 2022.

Male and female patients between 18–65 years of age, who had a diagnosis of bipolar I disorder, with or without mixed features, in accordance with *DSM-5* criteria, as confirmed by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition,[33] were included in the study. Patients had at least 1 prior documented manic episode (with or without psychotic symptoms) that required treatment prior to screening and had a Young Mania Rating Scale (YMRS) total score[34] ≥ 20, with ≥ 4 on at least 2 of 4 YMRS items (irritability, speech, content, disruptive/aggressive behavior); Clinical Global Impressions-Severity (CGI-S) score[35] of ≥ 4 at baseline; and a Montgomery-Asberg Depression Rating Scale (MADRS) total score[36] < 18. Patients were excluded if they met criteria for rapid cycling or had a *DSM-5* diagnosis other than bipolar I disorder that was the primary focus of treatment within the previous 6 months. Exclusion criteria included electrocardiogram (ECG) abnormalities, chemical dependency (preceding 6 months), history of treatment-resistant psychotic symptoms based on poor response to 2 antipsychotic treatments over the last 2 years, risk of self-harm or harm to others, mental disability (moderate to severe), or inability to communicate, give informed consent, and/or participate fully in assignments due to these factors. Positive urine screening for drugs other than tetrahydrocannabinol and as-needed benzodiazepines or likely requirement for continuous treatment with any other psychotropic drug, including antidepressants or mood stabilizers, resulted in exclusion. Patients were not excluded due to current diagnosis or history of tardive dyskinesia or drug-induced EPS or ongoing treatment with anticholinergics.

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki.[37] Informed consent was obtained from each patient in writing before any study-specific procedures were performed.

Interventions and Dose Selection

A fixed dose of 24 mg/d (12 mg twice daily) iloperidone (or 12 mg/d [6 mg twice daily] in CYP2D6 poor metabolizers [n = 15/206 for iloperidone], consistent with the current prescribing guidelines[23]) was given. A titration schedule consisting of 1 → 3 → 6 → 9 mg doses twice daily was used to reach target dose over 4 days (2 days for CYP2D6 poor metabolizers). All patients were hospitalized to ensure compliance with dosing and discontinued other antipsychotic treatment prior to their first dose of study medication. Rescue medications allowed on an as-needed basis included zolpidem for insomnia; short acting benzodiazepines (lorazepam unless unavailable) for agitation, anxiety, and severe restlessness; and anticholinergics (benztropine mesylate unless unavailable) for EPS. An optional 52-week long-term, open-label phase followed the randomized portion of the study.

Outcome Measures

Efficacy was evaluated using YMRS total score change from baseline to week 4. YMRS was also evaluated at weeks 1, 2, and 3. Other efficacy parameters included CGI-S score, Clinical Global Impression of Change (CGI-C) (equivalent to the Clinical Global Impressions-Improvement [CGI-I]),[35] YMRS responder analysis, and the MADRS.

Safety was assessed via frequency of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Additional safety metrics included the

frequency and severity of clinically notable or abnormal vital signs, urinalysis, hematology, and chemistry laboratory parameters; 12-lead ECG results; orthostatic response (≥ 20 mm Hg fall systolic blood pressure and/or ≥ 10 mm Hg fall in diastolic blood pressure); physical examination findings during treatment; and EPS as measured by Simpson-Angus Scale (SAS),[38] Abnormal Involuntary Movement Scale (AIMS),[39] and the Barnes Akathisia Rating Scale (BARS),[40] as well as the Columbia-Suicide Severity Rating Scale (C-SSRS)[41] and concomitant medication usage.

Analysis Populations

All efficacy analyses were based on the modified-intent-to-treat (mITT) population. The mITT population was defined as any randomized patient who received ≥ 1 dose of study medication and completed ≥ 1 post-baseline efficacy measurement. All safety measures were based on the safety population, defined as any randomized patient who received ≥ 1 dose of study medication.

Statistical Methods

The primary efficacy parameter for the double-blind phase was change from baseline to week 4 (day 28) in YMRS total score. A restricted maximum likelihood (REML)-based mixed-effects model for repeated measures (MMRM) was applied to analyze the primary efficacy endpoint in the mITT population and included the following time points: days 7, 10, 14, 21, and 28. The MMRM model included the fixed, categorical effects of treatment group, visit, treatment group–by-visit interaction, and pooled sites, as well as the fixed, continuous covariates of baseline score and the baseline score–by-visit interaction.

Secondary efficacy endpoints included change from baseline in YMRS total, CGI-S, and MADRS total score and were analyzed in a similar manner to the primary endpoint. CGI-C was collected post-baseline only and therefore analyzed using a similar model without including baseline terms. For the categorical endpoints, such as YMRS response, the Cochran-Mantel-Haenszel test was applied adjusting for pooled site at each visit.

Safety analysis assessed significant changes from baseline in vital signs, clinical laboratory results, ECG results, and SAS, AIMS, BARS, and C-SSRS evaluations. Fridericia's QT correction was performed using the equation QTcF = QT interval/(RR interval)$^{1/3}$.

Tests for statistical significance were performed at 2-sided 5% significance level; confidence intervals (CIs) were 2-sided 95% CIs.

RESULTS

Participants

Patient disposition, demographics, and disease characteristics at baseline are characterized in Table 1 and Figure 1. Of 392 patients in the mITT population, 333 (85%) were enrolled at 20 sites in the United States, 49 (12.5%) were enrolled at 6 sites in Bulgaria, and 10 (2.5%) were enrolled at 1 site in Poland. Disorder characteristics were similar between groups at baseline. Mean YMRS total score, CGI-S, and MADRS scores were similar between iloperidone and placebo groups at baseline evaluation.

Table 1.
Patient Demographics and Clinical Characteristics at Baseline (mITT Population)

	Iloperidone	Placebo	Total
Patient demographics			
Age, mean (SD), y	42.9 (12.80)	43.5 (12.80)	43.2 (12.79)
Male, n (%)	113 (57.1)	105 (54.1)	218 (55.6)
Race			
White, n (%)[a]	129 (65.2)	121 (62.4)	250 (63.8)
Black or African American, n (%)	59 (29.8)	55 (28.4)	114 (29.1)
Other, n (%)[b]	10 (5.1)	18 (9.3)	28 (7.1)
Weight, mean (SD), kg	85.6 (18.1)	87.1 (19.0)	86.3 (18.6)
BMI, mean (SD), kg/m^2	29.0 (5.72)	29.5 (5.62)	29.3 (5.67)
Disorder characteristics			
***DSM-5* classification of bipolar I disorder, n**	198	194	392
Bipolar I disorder; manic, n (%)	154 (77.8)	163 (84.0)	317 (80.9)
Bipolar I disorder; mixed features specifier, n (%)	44 (22.2)	31 (16.0)	75 (19.1)
With psychotic features	67 (33.8)	75 (38.7)	142 (36.2)
Baseline efficacy variables			
Baseline YMRS total score, mean (SD)	29.2 (5.27)	28.8 (4.64)	29 (4.97)
Baseline CGI-S, mean (SD)	4.6 (0.71)	4.6 (0.7)	4.6 (0.7)
Baseline MADRS total score, mean (SD)[c]	10.2 (3.66)	9.9 (3.95)	10 (3.8)

[a]White includes Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown ethnic groups.
[b]Other includes all other racial groups besides White and Black or African American, including American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander races.
[c]Patients with MADRS scores ≥18 were excluded from the study.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity, mITT = modified intent-to-treat, MADRS = Montgomery-Asberg Depression Rating Scale, SD = standard deviation, YMRS = Young Mania Rating Scale.

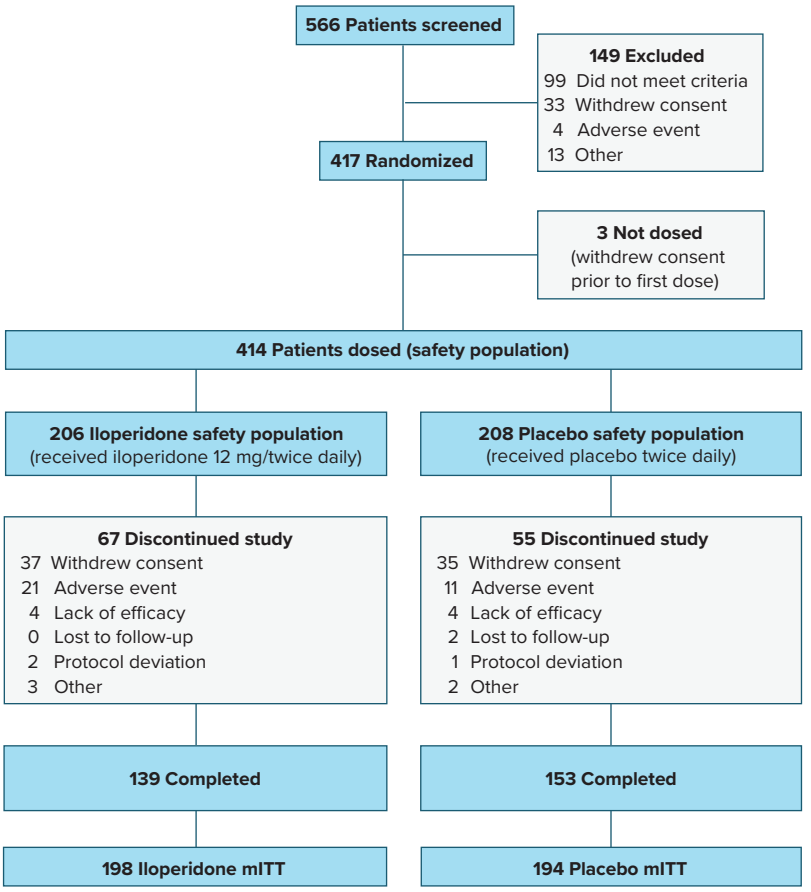
Primary Efficacy Endpoint: Week 4 YMRS Change From Baseline

Change in YMRS total score from baseline to week 4 was statistically significant for iloperidone compared with placebo using the MMRM approach (Figure 2A, Table 2).

Secondary Efficacy Endpoint: YMRS Change From Baseline Prior to Week 4

Statistically significant difference between iloperidone and placebo was observed on days 14, 21, and 28 (Figure 2A).

Figure 1.
CONSORT Flow Diagram[a]



[a]"Completed" represents patients who completed the short-term double-blind treatment phase per protocol. mITT includes any patient administered ≥1 dose of study medication who had ≥1 postbaseline efficacy assessment, excluding patients who enrolled multiple times.
Abbreviation: mITT = modified intent-to-treat.

Other Secondary Efficacy Endpoints

Statistically significant differences between iloperidone and placebo were also seen on all other secondary measures of efficacy at day 28 (CGI-S, CGI-C, YMRS responders), except for change from baseline in MADRS (Figure 2B–D, Table 2).

Safety Outcomes

In the iloperidone group, 67.5% of patients experienced at least 1 adverse event, compared to 48.6% of patients in the placebo group. Patients withdrew from the study at a rate of 32.9% for iloperidone treated patients and 27.1% for placebo treated patients. In the iloperidone group, 18 (8.7%) patients had TEAEs leading to study drug discontinuation, compared to 11 (5.3%) patients in the placebo group. No TEAE associated with discontinuation occurred in more than 2 patients in either treatment group. No patient in the study experienced any AE resulting in death.

Adverse events were classified as common if they occurred in > 5% of any given group. In iloperidone treated patients, these events were tachycardia 17.5% (36/206 patients), dizziness 11.2% (23/206 patients), dry mouth 9.2% (19/206), alanine aminotransferase increased 7.3% (15/206 patients), nasal congestion 6.3% (13/206), increased weight 5.8% (12/206 patients), and somnolence 5.3% (11/206 patients) (Table 3).

There were 5 total serious adverse events (SAEs) in the safety population, with 4 occurring in iloperidone group (4/206 patients) and 1 occurring in the placebo group (1/208 patients) (Table 3). Two SAEs reported in the iloperidone group were identified as related to study medication (sedation and spontaneous penile erection), and 2 SAEs were identified as unrelated (gastrointestinal hemorrhage and respiratory distress). One patient in the placebo group had an SAE of bipolar disorder (depression).

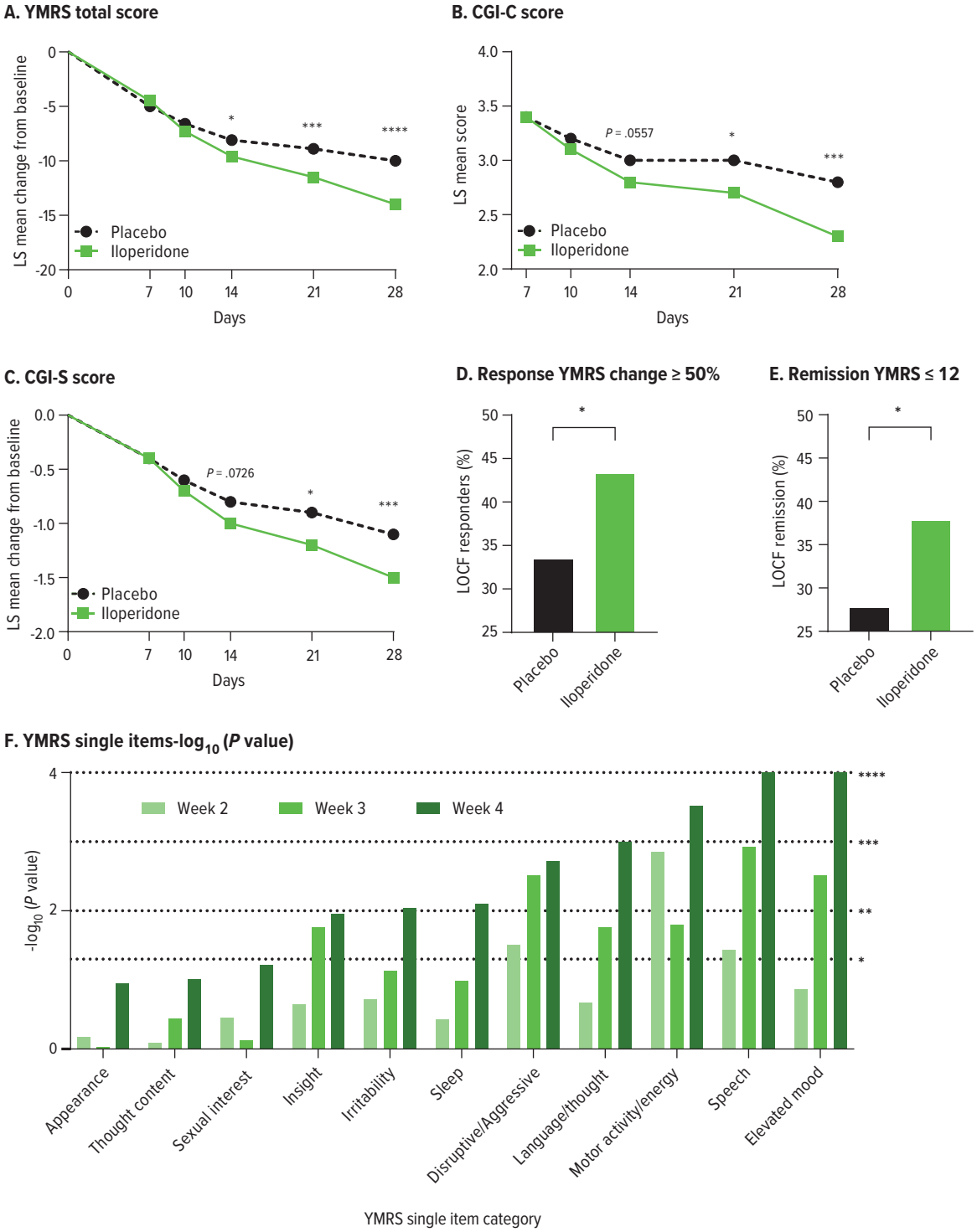
Change from baseline in clinical laboratory parameters was generally similar across treatment groups. Compared to placebo, mild to moderate increases in alanine aminotransferase (ALT) and prolactin were observed in some iloperidone treated patients. A mean weight increase (SD) was observed for iloperidone treated patients (4.60 ± 4.271 kg) compared to placebo (1.63 ± 3.578 kg). No major differences were seen in mean fasting glucose for iloperidone and placebo from baseline to day 28 (iloperidone: 0.39 ± 0.933 mmol/L; placebo: 0.30 ± 1.240 mmol/L).

The average increase in ventricular rates from baseline was slightly higher for iloperidone treated patients compared to placebo during titration, but progressively decreased for iloperidone patients, with an average increase in ventricular rate of 4.7 and 1.5 beats per minute for iloperidone and placebo at week 4, respectively. The mean change in QT interval and QT interval corrected for heart rate using Fridericia's correction (QTcF) from baseline to day 28 was −0.1 msec and +8.3 msec for iloperidone treated patients, respectively, and −3.5 msec and −1.0 msec for placebo treated patients, respectively. Post-randomization changes in QTcF interval of ≥ 60 msec from baseline were observed for 3 iloperidone patients and 0 placebo patients (1 instance for each patient).

Incidence of orthostatic response was higher for iloperidone patients than placebo patients during titration (range of 1.5%–6.4% vs 2.4%–3.1% for

Figure 2.

Primary, Secondary, and Post Hoc Efficacy[a]



[a]YMRS Total Score (A) and CGI-S (C) are shown as LS mean change from baseline. CGI-C score (B) is shown as LS means at each visit. YMRS responders (D) represents LOCF proportions of patients with change of ≥ 50% in YMRS from baseline. YMRS remitters (E) represents LOCF proportions of patients with YMRS ≤ 12 at week 4. YMRS single items (F) significance shown as $-\log_{10}$(*P* value). *P* values represent iloperidone versus placebo (**P* < .05, ***P* < .01, ****P* < .001, *****P* ≤ .0001). All data were calculated using MMRM model in mITT populations. Significance for response and remission calculated using CMH. Panels (E) and (F) represent post hoc analysis.

Abbreviations: CGI-C = Clinical Global Impression of Change, CGI-S = Clinical Global Impressions-Severity, CMH = Cochran-Mantel-Haenszel test, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, mITT = modified intent-to-treat, MMRM = mixed model for repeated measures, REML = restricted maximum likelihood, SE = standard error, YMRS = Young Mania Rating Scale.

Table 2.
Efficacy Outcomes at Week 4[a]

	Iloperidone (n = 198)	Placebo (n = 194)	LS mean difference or adjusted relative risk (95% CI)	*P* value
Primary efficacy outcome, change in YMRS total score from baseline to week 4				
YMRS, LS mean change (SE)	−14.0 (0.64)	−10.0 (0.63)	−4.0 (−5.70 to −2.25)	.000008
Secondary efficacy outcomes at week 4				
CGI-S, LS mean change (SE)	−1.5 (0.08)	−1.1 (0.08)	−0.4 (−0.62 to −0.17)	.0005
CGI-C, LS mean (SE)	2.3 (0.09)	2.8 (0.09)	−0.5 (−0.70 to −0.23)	.0002
MADRS, LS mean (SE)	−2.7 (0.45)	−1.8 (0.44)	−0.9 (−2.13 to 0.29)	.1365
YMRS response, n/N (%)	86/198 (43.4)	65/194 (33.5)	1.32 (1.037 to 1.688)	.0248
Post hoc efficacy outcomes at week 4				
YMRS remission, n/N (%)	75/198 (37.9)	54/194 (27.8)	1.39 (1.049 to 1.841)	.0198

[a]LS mean change for YMRS, CGI-S, CGI-C, and MADRS were calculated using MMRM model using the mITT population. YMRS response and remission were calculated using the mITT population with LOCF to account for missing data due to dropouts. Adjusted relative risk, 95% CI, and *P* values for response and remission were calculated based on the ratio of response rates for iloperidone vs placebo, with *P* values calculated based on CMH test for the association between treatment and responder rate. YMRS responders are the proportion of patients who achieved ≥ 50% reduction in YMRS total score from baseline. YMRS remission is calculated as the proportion of patients who achieved a YMRS total score of ≤12 at endpoint. All *P* values represent iloperidone versus placebo. Refer to Table 1 for baseline efficacy variables.

Abbreviations: CGI-C = Clinical Global Impression of Change, CGI-S = Clinical Global Impressions-Severity, CMH = Cochran-Mantel-Haenszel test, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, mITT = modified intent-to-treat, MMRM = mixed models for repeated measures, REML = restricted maximum likelihood, SE = standard error, YMRS = Young Mania Rating Scale.

iloperidone and placebo treated patients, respectively), but was low and placebo-like on week 2, 3, and 4 visits, observed in 5.6% and 4.5% of iloperidone and placebo treated patients at week 4, respectively.

An AE of akathisia was reported in 9 (4.4%) and 0 iloperidone and placebo patients, respectively, and no patient discontinued due to akathisia. No statistically significant difference was identified between iloperidone and placebo groups for proportions of patients with worsening from baseline to any visit for BARS scores (Table 3).

Rates of EPS were low and similar to placebo for iloperidone patients. Mild TEAE of extrapyramidal disorder occurred in 2 patients in the iloperidone group and 0 patients in placebo group but did not result in dose modification or permanent discontinuations. No statistically significant difference was identified between iloperidone and placebo groups for change from baseline to any endpoint on the SAS or AIMS.

A total of 6 (3.4%) and 0 (0%) of patients in iloperidone and placebo groups received benztropine (3/6 patients for 1 to 4 total days and 3/6 patients for 18 to 23 total days); all 6 patients completed the study. One additional iloperidone patient had initiated benztropine ≥ 6 days before baseline and continued anticholinergic treatment throughout the study and completed.

No suicidal behavior was reported, and C-SSRS results were similar for patients receiving iloperidone and placebo throughout the study. Suicidal ideation was reported in 1 iloperidone patient and in 1 placebo patient.

DISCUSSION

In this phase 3 study, 24 mg/d iloperidone demonstrated efficacy for the acute treatment of bipolar mania in adults compared to placebo. Iloperidone was observed to be safe and well tolerated in adult patients with bipolar mania, consistent with previous evidence demonstrating iloperidone is safe and well tolerated in individuals with schizophrenia,[42] and no new safety risks were identified.

YMRS total score change from baseline to 4 weeks was significantly greater for the iloperidone group compared to placebo. Statistical significance was detected as early as 14 days from the initial dose of study medication and was maintained throughout the remainder of the double-blind phase. A post hoc analysis of change from baseline in YMRS total score excluding patients given benzodiazepines revealed no difference in treatment effect for iloperidone mITT patient subgroups (Supplementary Table 1). Post hoc analysis also showed statistically significant improvement regardless of the presence or absence of psychotic features at baseline for iloperidone subgroups (Supplementary Table 2).

Other outcome measures provide further support for the efficacy of iloperidone in treating bipolar mania. Improvement on CGI-S, CGI-C, and YMRS response was greater for iloperidone vs placebo. Numerically higher change on MADRS score was observed at endpoint for iloperidone compared to placebo, although

Table 3.

Summary of Adverse Events and Safety Results (Safety Population)[a]

	Iloperidone (n = 206)		Placebo (n = 208)	
Adverse events and discontinuations				
Patients with ≥ 1 AE that caused discontinuation[b]	18 (8.7)		11 (5.3)	
Deaths	0		0	
Patients with ≥ 1 serious adverse event[c]	4 (1.9)		1 (0.5)	
Patients with ≥ 1 treatment emergent adverse event[d]	131 (63.6)		83 (39.9)	
Maximum severity of treatment emergent adverse events				
Mild	84 (40.8)		49 (23.6)	
Moderate	42 (20.4)		30 (14.4)	
Severe	5 (2.4)		4 (1.9)	
Most frequent treatment emergent events ≥ 5% in any group				
Tachycardia	36 (17.5)		11 (5.3)	
Dizziness	23 (11.2)		2 (1.0)	
Dry mouth	19 (9.2)		4 (1.9)	
Alanine aminotransferase increased	15 (7.3)		1 (0.5)	
Nasal congestion	13 (6.3)		3 (1.4)	
Increased weight	12 (5.8)		3 (1.4)	
Somnolence	11 (5.3)		4 (1.9)	
BARS global clinical assessment score[e]				
Study day	n	Mean	n	Mean
Baseline	206	0.044	208	0.053
Day 28	143	0.063	156	0.077
Proportions of patients with BARS scores that worsened from baseline				
Day 28, n/N patients (%)	4/143 (2.8)		6/156 (3.8)	

[a]Values expressed as n (%) unless otherwise noted.
[b]The number of patients who had ≥1 adverse event that led to permanent discontinuation by an investigator. Three additional iloperidone patients who withdrew consent due to adverse events are represented under discontinuations due to adverse events in Figure 1.
[c]Serious adverse events are adverse events that may be life-threatening, be fatal, or result in hospitalization.
[d]An adverse event is any untoward medical occurrence in a patient administered a medicinal product and does not necessarily have to have a causal relationship with this treatment. A treatment emergent adverse event is one that occurs while the participant is taking the study medication or within 3 days after discontinuation of the study medication.
[e]BARS results in table depict results for observed cases at baseline and day 28.
Abbreviations: AE = adverse event, BARS = Barnes Akathisia Rating Scale.

the treatment difference did not achieve statistical significance. This likely reflects that the study was not designed to evaluate patients experiencing moderate to severe depressive symptoms, limiting the ability to draw conclusions about iloperidone's effect in this domain.

Post hoc analysis examined change from baseline to weeks 2, 3, and 4 in YMRS single items, which showed statistically significant superiority of iloperidone vs placebo groups as early as day 14 in the disruptive/aggressive behavior, increased motor activity energy, and speech items. Single item scores continued to improve on day 21 and achieved statistical significance in 8 of the 11 single items on day 28 ($P = .0110$ for insight, $P < .01$ for irritability, sleep, disruptive/aggressive behavior, language/thought disorder, increased motor activity energy, speech, and elevated mood) (Figure 2F).

Understanding the safety and tolerability of second-generation antipsychotics, particularly for long term or maintenance treatment, remains one of the major concerns for clinicians and patients.[3,43–45] Outcomes of interest include those related to weight gain and metabolic disturbances,[46] QT/QTc and cardiovascular safety,[18,47] akathisia/EPS and tardive dyskinesia,[48,49] and postural and non-postural changes in blood pressure.[50,51]

In this study, patients had mild to moderate weight gain compared to baseline, in alignment with previous studies of iloperidone in schizophrenia patient populations.

QTcF findings were similar to previously reported results at doses of 12 mg twice daily, including some adaptation to QTcF increases at day 28 evaluations[24] and mean change in QTcF decreasing to 7 to 9 ms within 4 weeks after initiating treatment.[24,47] The results of this study also support that QTc increases can be managed in practice by following recommended prescribing directions to avoid contraindicated metabolic inhibitors and to reduce the dosage by half in patients with impaired CYP2D6 metabolism.[23]

Though much improved compared to early antipsychotics, second-generation antipsychotics can still cause considerable adverse motor side effects.[48,49] However, among all second-generation antipsychotics, iloperidone's akathisia profile is favorable.[28] In this study, the incidence of patients whose BARS scores worsened from baseline was low in the iloperidone group, with an incidence similar to placebo. Antipsychotic-induced akathisia has been reported more frequently in patients with bipolar disorder relative to schizophrenia populations treated with the same medication.[29,52] The underlying reasons for observed differences in the two patient populations remains incompletely characterized, but clinical observations support that increased agitation and akathisia associated with depressive episodes complicates clinical evaluations of patients with bipolar disorder.[53–55]

Iloperidone has a unique receptor binding profile that includes strong affinity for the α_1-adrenergic receptor.[23] α_1 Receptor antagonism is associated with a variety of physiological effects including decreased peripheral vascular resistance, which results in acute and sustained decreases in blood pressure. Selective α-adrenergic receptor antagonists have been developed to treat benign prostatic hyperplasia and hypertension.[56] Central α_1-adrenergic inhibition has also been postulated to have CNS effects. For example, some agents have been tested in the reduction of agitation in Alzheimer's disease patients and in the reduction of nightmares in posttraumatic stress disorder patients.[57–60] For iloperidone and other atypical antipsychotics, α-adrenergic receptor inhibition in the CNS has been hypothesized to contribute to their relatively

low rates of akathisia and EPS.[28–31,61] While the benefits of α-adrenergic inhibition vary across different conditions, antagonism of these receptors is also observed to result in decreased orthostatic response of blood pressure.[25] Similar to other α-adrenergic receptor antagonists, orthostatic responses were seen more frequently during titration in iloperidone treated patients and then declined substantially to placebo-like rates on evaluations conducted after day 10. This supports previous findings that patients adapt to symptoms of postural blood pressure changes associated with α_1-adrenergic inhibition despite the sustained decreases in blood pressure observed in hypertensive patients treated with such agents.[62–65]

This study provides evidence that iloperidone is effective as an intervention in acute treatment of bipolar mania in adults. Limitations include the exclusion of patients with significant comorbidities such as substance use disorders. Long-term efficacy in the prevention of manic or depressive episodes was not assessed. Of note, iloperidone has been approved for maintenance treatment of schizophrenia since 2016.[23]

This study provides evidence that iloperidone improves the symptoms of bipolar mania in adults and can be a useful treatment option for people with bipolar disorder. The safety profile for iloperidone was consistent with previous studies.

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Supplementary Material

Article Title: Efficacy and Safety of Iloperidone in Bipolar Mania: A Double-Blind, Placebo-Controlled Study

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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Supplementary Material

Supplementary Table 1: Efficacy analysis excluding patients treated with lorazepam or benzodiazepines (mITT population)

Supplementary Table 1: Efficacy analysis excluding patients treated with lorazepam or benzodiazepines					
	N (ILO:PBO)	ILO	PBO	LS mean difference	P-value
Population					
mITT population	392 (198:194)	-14.0	-10.0	-4.0	<0.0001
Excluding any lorazepam or other benzodiazepines	259(137:122)	-14.1	-10.6	-3.4	0.0017
Excluding any dose of lorazepam >2mg	342(172:170)	-14.1	-10.5	-3.6	0.0002
Excluding >7 doses of lorazepam >2mg	361(184:177)	-14.0	-10.6	-3.4	0.0003

Supplementary Table 1: Efficacy analysis excluding patients treated with lorazepam or benzodiazepines (mITT population). LS mean change for YMRS was calculated using mixed-effects model for repeated measures (MMRM) model using the mITT population. All p-values represent iloperidone vs placebo. Abbreviations: ILO = iloperidone; PBO = placebo.

Supplementary Table 2: Efficacy subgroup analysis by presence or absence of psychotic features at baseline (mITT Population)

Supplementary Table 2: Efficacy subgroup analysis by presence or absence of psychotic features at baseline					
	N (ILO:PBO)	ILO	PBO	LS mean difference	P-value
Population					
With Psychosis	142 (47:57)	-15.4	-10.5	-4.9	0.0009
Without Psychosis	250 (95:97)	-13.8	-10.2	-3.6	0.0015

Supplementary Table 2: Subgroup analysis by psychotic features (presence or absence at baseline): change in YMRS Total Score from baseline to endpoint (Week 4). Of the 392 patients in the ITT population, 142 (36.2%) were classified as having psychotic features and 250 (63.8%) were classified as not having psychotic features at baseline. LS mean change for YMRS was calculated using mixed-effects model for repeated measures (MMRM) model using the mITT population. N (ILO:PBO) = total mITT for category (ILO:PBO mITT observed cases at Day 28). All p-values represent iloperidone vs placebo. Abbreviations: ILO = iloperidone; PBO = placebo.

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