

Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder

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Abstract

Objectives: Endoxifen is a protein kinase C inhibitor. The objective of the present phase III study was to demonstrate the safety and efficacy of endoxifen in treating bipolar I disorder (BPD I) patients.

Methods: A multicenter, double-blind, active-controlled study was conducted using a daily dose of 8 mg endoxifen compared to 1000 mg divalproex, the current standard treatment, in patients with BPD I acute manic episodes with/without

mixed features. The primary endpoint of our study was the mean change in total Young Mania Rating Scale (YMRS) score at day 21.

Results: Endoxifen (n = 116) significantly ($p < 0.0001$) reduced total YMRS score (from 33.1 to 17.8). A significant ($p < 0.001$) improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) score was observed for endoxifen (4.8 to 2.5). Early time to remission of the disease was observed with endoxifen compared to divalproex. None of the patients required rescue medication and there was no drug-associated withdrawals. Changes in Clinical Global Impressions-Bipolar Disorder and Clinical Global Impression-Severity of Illness scores showed that treatment with endoxifen was well-tolerated.

Conclusions: Endoxifen at a low daily dose of 8 mg was as efficacious and safe in patients with BPD I acute manic episodes with/without mixed features.

KEYWORDS

bipolar I disorder, endoxifen, valproate, YMRS Score

1 | INTRODUCTION

Bipolar disorder is a mental health condition that cause moods cycle from extreme highs to extreme lows. There are two main types for bipolar disorders, which include type one bipolar and type two bipolar illnesses. Bipolar I disorder (BPD I), also known as a manic-depressive disorder is a chronic, disabling, and serious mental illness. The disease is characterized by the occurrence of acute manic or mixed episodes. It causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks.^{1,2} Bipolar II disorder is associated with at least one hypomanic period as well as a severe depressive period that lasts for at least 14 days. BPD I also known as bipolar mania is associated with overactive protein kinase C (PKC) intracellular signaling. Many studies have recognized the major role PKC plays in the pathophysiology of the disease.²⁻⁴ The approved treatments for BPD I such as lithium (a monovalent cation) and valproate (a small fatty acid) are known inhibitors of PKC.^{2,5,6} Tamoxifen, a drug approved for prevention and treatment of breast cancer, is a central nervous system permeant PKC inhibitor is effective in the treatment of BPD I.⁶⁻¹¹ The second-generation antipsychotics¹² are not only effective but are also associated with challenges such as tolerability, adherence, and adverse effects, which necessitates the development of novel, safer, and effective treatments.^{13,14}

Endoxifen, 4-OH-N-desmethyltamoxifen, is an active metabolite of tamoxifen and has shown a four-fold inhibitory activity of PKC compared to tamoxifen.¹⁵ The pharmacokinetics of this molecule was evaluated in humans.¹⁶ It is highly lipid-soluble, small enough to readily cross the blood-brain barrier and is found along with other metabolites of tamoxifen in the human brain.¹⁷ Tamoxifen is metabolized in the liver by cytochrome P450 enzymes including CYP3A, CYP2C9, and CYP2D6. The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs including drugs used for the treatment of BPD I. It is one of the main enzymes involved in converting tamoxifen

into its major active metabolite, endoxifen. Genetic variations in the CYP2D6 gene are known and result in a large interindividual and ethnic variability in bioavailability and functions owing to the CYP2D6 metabolic pathway. However, endoxifen is independent of CYP2D6 genetic polymorphism.¹⁸ Endoxifen, a new chemical entity, is synthesized and manufactured as enteric-coated tablets. The efficacy and safety of endoxifen in BPD I patients with current manic episodes with/without mixed features was shown in a Phase II study.¹⁴ In this 3-arm study, endoxifen 8 mg dose showed improvement in total YMRS score compared to baseline and were similar to divalproex. Endoxifen arm had lower incidence of adverse events versus divalproex indicative of better safety profile. This study reports a Phase III randomized controlled trial (RCT) in a larger patient population to establish the safety and efficacy of endoxifen in BPD I patients. An active-control arm is used which consists of divalproex, a well-established drug for the disease.¹⁹⁻²¹

2 | PATIENTS AND METHODS

This phase III trial was conducted at 18 study centers in India. The final study protocol and amendments were approved by the ethics committees and appropriate regulatory authorities of all participating centers. The study was performed following the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines, Indian Council of Medical Research (ICMR) guidelines, and applicable regulatory requirements, and all patients provided written informed consent.

2.1 | Study design

This was a Phase III prospective, multicenter, randomized controlled trial (1:1), double-blind, double-dummy, endoxifen

(experimental arm) and active-controlled, parallel clinical study. The study consisted of a 1-week screening phase (including a 2-day prospective drug-free observation phase before randomization), a 3-week double-blind treatment phase in a hospital setting, and a 2-week post-treatment follow-up phase. The trial was registered with the Clinical Trials Registry-India (CTRI/2017/07/009163).

2.2 | Study population

A total of 228 adult patients (18–65 years) diagnosed with BPD I experiencing current manic episodes with/without mixed features were randomized in the study. This was based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association; 2013), total Young Mania Rating Scale (YMRS) score of ≥ 20 and ≥ 4 on two of four core items (irritability, speech, content, disruptive/aggressive behavior), total Clinical Global Impressions-Bipolar Disorder (CGI-BP) score of ≥ 4 , and who were previously treated with and responsive to ≥ 1 of the following drugs: lithium/valproate/carbamazepine/atypical (except for clozapine) or typical antipsychotics, were included in an inpatient setting.

Key exclusion criteria were history of seizures, obsessive-compulsive disorder/other anxiety disorder, retinal vein thrombosis, hypersensitivity/intolerance to tamoxifen/endoxifen or any other ingredients, recent diagnosis of BPD I without previous treatment, and $\geq 20\%$ improvement in YMRS score between screening and randomization.

2.3 | Study drugs and administration

Patients were orally administered endoxifen enteric-coated tablet 8 mg or divalproex sodium extended-release tablet 1000 mg (Divaa® OD) once daily. Dummy tablets of both drugs were used to maintain the blinding.

2.4 | Concomitant medications

Concomitant medications were allowed as per the investigator's discretion. Oral lorazepam (up to 5 mg/day) as an adjunctive medication within the first 10 days after study drug administration was permitted to control events like acute agitation/akathisia. Benzodiazepines were allowed but avoided within 12 hours of scheduled mania ratings. Oral diazepam (up to 10 mg/day) was allowed in the case of akathisia. Risperidone/haloperidol was allowed as "rescue medication" for symptomatic worsening or agitation not controlled by study medications. In these patients, ratings were to be considered from their last assessment before the rescue intervention and these patients would be discontinued.

2.5 | Study assessments

2.5.1 | Efficacy assessments

The primary endpoint was the mean change in the total YMRS²² (11-item YMRS, scoring range: 0–60) score at day 21 from baseline. Secondary endpoints included changes in Clinical Global Impression-Bipolar (CGI-BP),²³ Montgomery-Åsberg Depression Rating Scale (MADRS),²⁴ Clinical Global Impression-Severity of Illness scale (CGI-S),²⁵ and Columbia-Suicide Severity Rating Scale (C-SSRS)²⁶ scores, patients requiring lorazepam/diazepam for controlling acute agitation or akathisia, and patients requiring rescue medications and associated withdrawal. Response ($\geq 50\%$ decrease in YMRS), remission (YMRS ≤ 12).

2.5.2 | Safety assessments

Safety variables included adverse events (AEs), clinical laboratory parameters, vital signs, physical examinations, and treatment-emergent depression (MADRS ≥ 18 and increase of ≥ 4 from two consecutive post-baseline visits or at final visit).

2.6 | Statistical methods

2.6.1 | Sample size determination

Based on assumptions (maximum study duration and dropout rate), 228 patients were randomized (1:1) to obtain 204 subjects in the study (102 in each group), providing 95% power to detect a lower one-sided significance of 5% and null difference 0.10, assuming a common standard deviation of 11.01 for the two-sample pooled t-test.

2.6.2 | Efficacy endpoints and analyses

Efficacy was analyzed in a modified intent-to-treat (mITT) in patients who received ≥ 1 dose with ≥ 1 efficacy evaluation. The last-observation-carried-forward approach was used to compute missing data. The safety population included patients who received ≥ 1 dose of study medication.

The least square mean (LSM) change in total YMRS score was evaluated using point estimate and 95% confidence interval (CI) using analysis of covariance with treatment as a factor for YMRS score, and endoxifen was considered non-inferior to divalproex if the lower limit of 95% CI was greater than -10 . For YMRS and MADRS, the Wilcoxon signed-rank test was used for the within-group and the Wilcoxon rank-sum test for between-group comparisons. For CGI-BP and CGI-S, Fisher's exact test was used for within-group and Wilcoxon rank-sum test for between-group comparisons. All

	All patients N = 228	Endoxifen N = 116	Divalproex N = 112
Age, years (mean ± SD)	34.9 ± 10.50	35.9 ± 10.88	33.8 ± 10.03
Sex, n (%)			
Male	159 (69.7)	84 (72.4)	75 (67)
Female	69 (30.3)	32 (27.6)	37 (33)
Weight, kg, (mean ± SD)	59.8 ± 11.31	60.2 ± 10.48	59.4 ± 12.14
Age diagnosed with BPD I (years), (mean ± SD)	31.3 ± 10.89	30.2 ± 10.35	32.4 ± 11.33
Length of illness, years, (mean ± SD)	4 ± 4.85	4 ± 5.11	3.9 ± 4.61
Most common medical history n (%)			
Tubectomy	7 (3.1)	2 (1.7)	5 (4.5)
Hypertension	3 (1.3)	2 (1.7)	1 (0.9)
Hypothyroidism	3 (1.3)	1 (0.9)	2 (1.8)
Most common previous medication used n (%)			
Valproate	139 (60.9)	70 (60.3)	69 (61.6)
Lorazepam	130 (57.0)	64 (55.2)	66 (58.9)
Olanzapine	106 (46.5)	57 (49.1)	49 (43.8)
Lithium	83 (36.4)	47 (40.5)	36 (32.1)
Haloperidol	44 (19.3)	21 (18.1)	23 (20.5)
Promethazine	42 (18.4)	17 (14.7)	25 (22.3)
Clonazepam	36 (15.8)	21 (18.1)	15 (13.4)
Risperidone	34 (14.9)	15 (12.9)	19 (17)
Trihexyphenidyl	30 (13.2)	13 (11.2)	17 (15.2)
Risperidone + Trihexyphenidyl	26 (11.4)	14 (12.1)	12 (10.7)
Quetiapine	24 (10.5)	10 (8.6)	14 (12.5)
Nitrazepam	23 (10.1)	12 (10.3)	11 (9.8)
Baseline scores, mean ± SD			
Total YMRS score	-	33.1 ± 8.35	32.7 ± 8.31
MADRS	-	4.8 ± 3.31	4.6 ± 3.02

Abbreviations: BPD, bipolar disorder; MADRS, Montgomery-Åsberg Depression Rating Scale, SD, standard deviation; YMRS, Young Mania Rating Scale.

TABLE 2 Site-wise patient enrollment

Site No.	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118
Patient No.	25	28	27	11	0	18	24	11	15	27	9	12	4	1	0	7	5	4

	Medication	Endoxifen, n(%)	Divalproex, n(%)
Prior to randomization and continued with lorazepam/diazepam	Diazepam	0 (0.00%)	0 (0.00%)
	Lorazepam	8 (6.90%)	12 (10.71%)
Post-randomization	Diazepam	1 (0.86%)	1 (0.89%)
	Lorazepam	2 (1.72%)	1 (0.89%)
Total patients administered with lorazepam/diazepam in the study	Diazepam	1 (0.86%)	1 (0.89%)
	Lorazepam	10 (8.62%)	13 (11.61%)

TABLE 3 Percent of patients administered with lorazepam or diazepam for controlling acute agitation or akathisia

statistical testing was two-sided at $\alpha = 0.05$. SAS® Version 9.4 (SAS Institute Inc., USA) was used for statistical analysis.

3 | RESULTS

A total of 276 patients were screened and out of which 228 were included in the study (endoxifen: $n = 116$; divalproex: $n = 112$). Demographic and baseline characteristics were comparable between the two treatment groups (Table 1). A total of 18 sites were open for patient enrolment. Patients' recruitment at each site is listed in Table 2. Out of 18 sites in the study, each 7 sites had provided ≥ 15 randomized patients. Lorazepam was given to 10 out of 116 patients in the endoxifen arm and 13 out of 112 patients in the divalproex arm. All patients who were administered lorazepam or diazepam came from one site. Considering very low number of patients that were given lorazepam, the overall effect to concomitant medication in the outcome of the endoxifen is negligible (Table 3). None of the patients required rescue medications and no patients were withdrawn from the study due to the intake of lorazepam or diazepam.

3.1 | Primary endpoint

Endoxifen demonstrated a significant ($p < 0.001$) reduction in the mean total YMRS score from baseline to day 21 (33.1 to 17.8). The mean change in total YMRS score for endoxifen was significant (15.2) at day 21. The divalproex also showed significant reduction in the mean total YMRS score from baseline to day 21 (32.7 to 17.2). The YMRS scores of patients from both endoxifen and divalproex were taken at various time period as shown in the Figure 1. The LSM change from baseline to day 21 for total YMRS score between endoxifen and divalproex was 15.6 vs. 15.8 (point estimate: -0.17 ; 95% CI: $-2.50, -2.16$).

3.2 | Secondary endpoints

A significant ($p < 0.0001$) improvement in MADRS scores from baseline to day 21 for endoxifen and divalproex were observed. At day 21, the changes in CGI-BP, MADRS, and CGI-S scores with endoxifen and divalproex are presented in Figure 2. The improvement in disease severity as in CGI-BP and CGI-S score was also comparable in both treatment arms.

FIGURE 1 Improvement in the Young Mania Rating Scale (YMRS) scores. Footnote: YMRS change from baseline over time. The Least Square Mean (LSM) changes from baseline to days 4, 7, 14, and 21 ($p < 0.0001$)

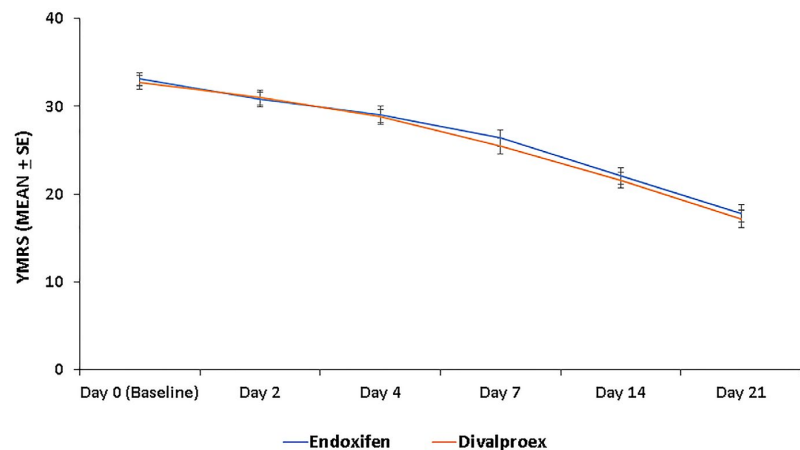
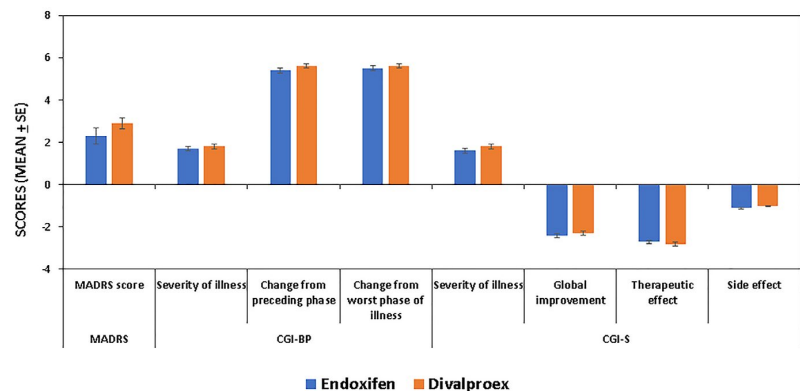


FIGURE 2 Mean changes in MADRS, CGI-BP, and CGI-S scores of endoxifen and divalproex. Footnote: MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-BP, Clinical Global Impression-Bipolar; CGI-S, Clinical Global Impression Severity. Data are presented as mean and standard error



Day	Responders		Remission	
	Endoxifen N = 116, n (%)	Divalproex N = 112, n (%)	Endoxifen N = 116, n (%)	Divalproex N = 112, n (%)
2	1 (0.9)	0	0	0
4	3 (2.6)	1 (0.9)	3 (2.6)	0
7	7 (6.1)	5 (4.5)	8 (6.9)	4 (3.6)
14	27 (23)	30 (27)	19 (16)	21 (19)
21	57 (49)	56 (50)	43 (37)	38 (34)

TABLE 4 Responders and Remission in patients treated with endoxifen and divalproex

	All Patients N = 228, n (%)	Endoxifen N = 116, n (%)	Divalproex N = 112, n (%)
At least one TEAE	64 (28.1)	32 (27.6)	32 (28.6)
TEAE reason for discontinuation	1 (0.4)	1 (0.9)	0 (0)
TEAEs occurring in ≥1% patients			
Headache	13 (5.7)	9 (7.8)	4 (3.6)
Insomnia	9 (3.9)	4 (3.5)	5 (4.5)
Vomiting	9 (3.9)	5 (4.3)	4 (3.6)
Mania	5 (2.2)	4 (3.5)	1 (0.9)
Pyrexia	5 (2.2)	1 (0.9)	4 (3.6)
Abdominal Pain	4 (1.8)	1 (0.9)	3 (2.7)
Somnolence	3 (1.3)	1 (0.9)	2 (1.8)
Restlessness	3 (1.3)	3 (2.6)	0 (0)
Increased TSH	2 (0.9)	0 (0)	2 (1.8)
Depression	2 (0.9)	2 (1.7)	0 (0)

TABLE 5 Treatment-emergent adverse events during double-blind treatment phase (safety population)

TEAE, treatment emergent adverse events; TSH, thyroid stimulating hormone.

3.3 | Additional efficacy endpoints

Time to remission was observed as early as on day 4 with endoxifen when compared to day 7 with divalproex (Table 4). Additional endpoints evaluated through response rate showed improvements with endoxifen (49.1%) similar to the findings reported for cariprazine, 57%, and aripiprazole 10 and 30 mg/d (45% and 64%, respectively).^{27,28} Remission rates reported with atypical antipsychotics such as cariprazine, aripiprazole, haloperidol, and quetiapine, are similar to that observed for endoxifen (37.1%).²⁹ Remission was achieved earlier with endoxifen compared with divalproex, as early as at day 4. Significant differences ($p < 0.0001$) on YMRS measures were evident at the first post-baseline assessment and were maintained throughout the duration of the study, suggesting an early onset of effect with endoxifen treatment.

3.3.1 | Safety evaluation

Of 100 AEs (in 64 [28.1%] patients), 48 were reported with endoxifen (in 32 [27.6%] patients) and 52 with divalproex (in 32 [28.6%] patients).

The most common AEs reported with endoxifen were headache, vomiting, insomnia, mania, and restlessness, and divalproex were insomnia, headache, vomiting, pyrexia, and abdominal pain (Table 5). One patient treated with endoxifen had grade 3 AE, which led to study discontinuation. Most AEs were mild-to-moderate and resolved within the same day. Significant increases in the total cholesterol levels (156.3 to 166.0), low-density lipoprotein (LDL) cholesterol levels (93.6 to 101.1), and non-high-density lipoprotein (HDL) cholesterol (115.2 to 127.1) were observed with endoxifen, whereas a significant decrease in HDL cholesterol (42.8 to 38.1) was seen with divalproex. Increase in LDL/HDL ratio, low-density lipoprotein (VLDL) levels, and triglyceride levels were observed in both the groups, though not significant ($p < 0.05$). Compared to endoxifen (2.3 to 2.4), divalproex showed a significant increase in thyroid-stimulating hormone (TSH) levels (1.8 to 3.1). A significant decrease in the platelet counts ($287.5 \times 10^3/\mu\text{L}$ to $233.7 \times 10^3/\mu\text{L}$) was also observed with divalproex compared to endoxifen ($268.6 \times 10^3/\mu\text{L}$ to $266.8 \times 10^3/\mu\text{L}$). None of the patients reported treatment emergent depression. There were no deaths, serious or significant AEs. Furthermore, none of the patients required rescue medications and associated withdrawal from the study and showed no suicidal behavior.

4 | DISCUSSION

In this study, endoxifen was effective and generally well tolerated in the treatment of acute manic or mixed episodes associated with BPD I. The change in total YMRS score at day 21 was similar to the results of the earlier Phase II study.¹⁴ Similar changes in the total YMRS score were observed with lithium/valproate and other agents such as olanzapine, paliperidone, risperidone, and quetiapine (range: 10–16).^{30–34}

In previous phase II clinical trial, we demonstrated for the first time an antimanic activity of endoxifen in BPD I patients and its promise as a novel monotherapy option for mania.¹⁴ The other first-line treatment options with significant improvement for mania include divalproex, lithium, typical, and atypical antipsychotics such as recently approved cariprazine. Overall, these agents show comparable efficacy to endoxifen.³⁵

The endoxifen crosses the blood–brain barrier and it is a direct inhibitor of PKC. Endoxifen is independent of CYP2D6-mediated metabolism, and hence interpatient variability in efficacy and safety may not exist¹⁴ and prevent potential interactions with several agents often used for the treatment of comorbid conditions, which also use the CYP2D6 pathway for metabolism.^{36,37}

The early time to remission in acute mania is a desirable feature and suggestive of a faster mode of action, and the central PKC inhibition by endoxifen could have attributed to the early remission in this study. The time to remission was 14 days with the combination of olanzapine +lithium/valproate and 22 days with valproate/lithium.³⁸

Patients with BPD I are at a higher risk of gaining weight, developing metabolic illnesses, and pharmacologic intervention may further increase this risk.³⁹ Furthermore, weight gain with the use of antipsychotic drugs has also been reported. The weight gain is not expected with endoxifen as it is a metabolite of tamoxifen, which has been used for a long time in breast cancer patients with no significant weight gain.⁴⁰ Valproic acid is known to alter thyroid functions,⁴¹ and a significant increase in TSH levels was reported with divalproex, which can be attributed to the rise in TSH levels in two patients on day 21. Endoxifen was not associated with any such changes. Low incidence of somnolence (endoxifen: 0.9% vs. divalproex: 1.8%) suggests that the antimanic effect of endoxifen was not due to sedation or somnolence.

Hyperlipidemia has been reported with tamoxifen.⁴² In our current study, significant increases in the total cholesterol, LDL, and HDL levels were observed with endoxifen, whereas a significant decrease in HDL was seen with divalproex that was also reported earlier with valproic acid.⁴³

Thrombocytopenia is a known AE of divalproex⁴⁴ and significant ($p < 0.001$) reduction in platelet counts was observed with divalproex in this study, whereas it was not significant with endoxifen, corroborating that thrombocytopenia is a rare AE with tamoxifen.⁴⁵ Also, no unexpected safety concerns were observed with endoxifen 8 mg.

Headache was reported in 7.8% patients with endoxifen versus 3.6% with divalproex; however, these AEs were mild-to-moderate

in severity and resolved without any dose modifications. The incidence of headache reported in this study was lower than previously reported for aripiprazole (10.9%); haloperidol³⁶ (11.8%), and ziprasidone (21.4%).⁴⁶

Non-adherence to the drugs during long-term treatment of BPD I is noted in about 50% of patients with AEs being one of the most common reasons.⁴⁷ The long-term use of endoxifen is not expected to result in significant toxicities as evidenced by long-term use of tamoxifen.⁴⁸ The use of potential drugs with fewer AEs may ensure treatment adherence in patients with this chronic disease.

5 | LIMITATIONS

While the 21-day study duration was sufficient to assess endoxifen in the treatment of acute bipolar mania, data from longer studies are needed to evaluate the long-term outcomes. Rather than including a placebo arm in the trial, we included an active control arm of divalproex as it is reported to be more effective in treating acute mania in adults when compared to a placebo (45% vs. 29%).^{49,50}

6 | CONCLUSION

Endoxifen (8 mg/day) was found to be safe and effective for improving mania symptoms in patients with BPD I with acute manic episodes with/without mixed features. It showed significant improvements in the total YMRS score, disease severity assessed by CGI-BP and CGI-S score, and treatment response and remission rates. Thus, endoxifen is a potential treatment option for managing BPD I disease.

PRIOR PRESENTATION

Results presented in part at the American Society of Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting 2019, March 13–16, 2019, Washington D.C. USA.

SIGNIFICANT STATEMENT

Bipolar I Disorder (BPD I) is a chronic debilitating illness characterized by drastic swings in mood, energy, and functional ability that affects the adult population. Endoxifen, a protein kinase C inhibitor offers distinct advantages and unlike valproate and lithium, does not require the need for therapeutic drug monitoring considering its wide therapeutic index. Most of the drug–drug interactions involving antipsychotics such as cariprazine, aripiprazole, and risperidone occur at the metabolic levels involving alterations in metabolism by cytochrome P450 enzymes. However, endoxifen is not subjected to metabolism in the liver by CYP450 s. Endoxifen offers a distinct advantage over other medications. In addition, endoxifen showed efficacy at a much lower dose

(8 mg) compared to divalproex (1000 mg) and offers a unique advantage of achieving a pharmacological target more potently.

ACKNOWLEDGMENTS

We acknowledge Mr. Shreekanth Sharma, Dr. Venugopal Madhusudhana, and Ms. Ankita Shah (Lambda Therapeutic Research Ltd.) for medical writing assistance, additional editorial assistance, and statistical analysis, respectively. The authors thank the study patients for their participation in this study.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

AUTHORS CONTRIBUTION

AA, SS, MAK, AC, PP, RP, and IA contributed to clinical trial design, data analysis and writing of the manuscript. BCB, RSA, TCS, VNV, VR, SR, Narendra K, BSVP, RS, KKV, VGJ, Nand K, Sandip S, PKD, BS, and PT were investigators in the clinical trial.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Ahmad A, Sheikh S, Khan MA, et al. Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. *Bipolar Disord*. 2021;23:595-603. <https://doi.org/10.1111/bdi.13041>