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Original Research Article

A multicentre phase III study comparing efficacy and safety of novel extended-release versus conventional formulation of dydrogesterone in Indian patients with endometriosis

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ABSTRACT

Background: The aim of the study was to compare the efficacy and safety of novel once-daily extended-release (ER) dydrogesterone 20 mg versus conventional twice-daily dydrogesterone 10 mg in Indian patients with endometriosis.
Methods: A phase III prospective, randomized, double-blind, single-dummy, two-arm, active-controlled, parallel, multicenter study was performed in six gynecology centers across India. The patients of 18 to 45 years of age with a confirmed diagnosis of endometriosis on ultrasonography (USG) and having endometriosis-associated pelvic pain score (EAPP) of at least 30 mm on a 100 mm visual analog scale (VAS) were randomly assigned to a 1:1 ratio to either once-daily dydrogesterone ER 20 mg or twice-daily dydrogesterone 10 mg arms for a treatment period of 90 days. The primary outcome was a change from baseline in EAPP score at the end of the treatment.
Results: A total of 228 patients with a mean age of 31.8±6.9 years were enrolled in the study. At day 90, both the treatment arms showed a significant reduction ($p<0.05$) in EAPP score from baseline (i.e. -34.2±15.3 mm and -33.1±14.8 mm in once daily dydrogesterone ER and twice daily dydrogesterone 10 mg, respectively), with no significant difference between the two arms ($p=0.53$). With both formulations, patients experienced a significant reduction in the size of endometrioma, serum vascular endothelial growth factors (VEGF) levels, use of rescue analgesics, and significant improvement in the health-related quality-of-life parameters. A favorable safety profile of dydrogesterone was confirmed, and no significant safety concerns were reported during the study.
Conclusions: Once daily dydrogesterone ER 20 mg and twice daily dydrogesterone 10 mg demonstrated a significant and similar reduction in EAPP and all other secondary parameters along with marked improvements in parameters related to quality of life.

Keywords: Dydrogesterone, Endometriosis, Extended-release, Pelvic pain, Progesterone

INTRODUCTION

Endometriosis is a chronic illness that impairs the quality of life of the patients.[1] According to estimates, between 2 and 10% of women who are of reproductive age and between 25 and 50% of women suffering from infertility have endometriosis.[2,3] It is estimated that endometriosis affects ~247 million girls and women globally and ~42 million girls and women in India.[4] Endometriosis patients often appear with one or more related symptoms, such as dysmenorrhea, profound dyspareunia, cyclical intestinal problems, fatigue/weariness, and infertility, while some may not exhibit any symptoms at all.[1] The symptoms of endometriosis gradually make it more difficult for women to do specific everyday tasks, which worsens their general health and well-being.[5] Furthermore, this condition may result in sexual dysfunction in 2-4% of sexually active women.[6] Lastly, symptoms associated with endometriosis significantly hinder afflicted women's ability to work, frequently leading to many lost workdays.[5]

Symptomatic endometriosis remains the prime indication for treatment. Ideally, treatment should provide pain relief and allow pregnancy to occur safely while undergoing treatment. The current treatments for endometriosis include surgery (ablation using either laser or electrosurgery if laparoscopy is performed), pharmacological therapy, or a combination of both. Symptomatic patients always receive pharmacological therapy, which can include analgesics for women with endometriosis-related pain, hormonal treatments such as hormonal contraceptives, progestogens (e.g., progesterone), anti-progestogens (e.g., gestrinone), or gonadotropin-releasing hormone agonists (e.g., leuprolide) as it reduces endometriosis-associated pain or alternative treatments such as aromatase inhibitors (e.g., letrozole).[7]

Dydrogesterone (6-dihydro-retroprogesterone) is a retro progesterone derived from progesterone that is similar in structure and pharmacology to endogenous progesterone. It acts as a selective progesterone receptor agonist and has better oral bioavailability compared with oral micronized progesterone.[8] Dydrogesterone has been on the market since the 1960s and is used as postmenopausal hormone replacement as well as for the treatment of menstrual disorders and endometriosis.[9]

As per the approved package insert of dydrogesterone, it has to be used in a dose of 10 mg to be taken two times daily for the management of endometriosis.[10] Taking these tablets two times in a day may lead to inconvenience and non-compliance, thus impacting the efficacy of the drug in real-world clinical practice. Taking this into consideration, an extended-release (ER), once-daily formulation of dydrogesterone 20 mg has been developed by M/s Zydus Healthcare Limited.

This pre-licensure phase III study was designed to evaluate the efficacy and safety of the new formulation of dydrogesterone ER tablets 20 mg for the treatment of endometriosis in women as compared to the dydrogesterone 10 mg twice daily.

METHODS

Study design

This was a prospective, randomized, double-blind, single-dummy, two-arm, active-controlled, parallel, and multicenter, phase III clinical trial from March 2023 to August 2023. This study was conducted in accordance with 'New Drugs and Clinical Trials Rules 2019 and Indian Good Clinical Practices guidelines. The study was approved by the institutional ethics committees of all the participating centers and registered in the clinical trials registry India (CTRI/2023/03/050698). All participants provided written informed consent prior to enrollment.

Study subjects

The participants were female patients, 18-45 years of age, diagnosed with endometriosis based on ultrasonography, with an endometriosis pain score of at least 30 mm on a 100 mm visual analog scale. These patients were willing to give written informed consent and comply with the study procedures.

The key exclusion criteria of the study were women who were pregnant, lactating, having childbearing potential unwilling to use effective barrier contraception, menopausal, having premature ovarian insufficiency, had undergone laparoscopic surgery for endometriosis in the last 6 months, had taken hormonal therapy in the last 6 months or oral contraceptives in the last 3 months, any other significant concomitant gynecological disorder or uncontrolled systemic diseases.

Study conduct

At the end of 3 days of screening period, the eligible endometriosis patients were randomized to either of the two study groups; test arm received dydrogesterone ER 20 mg tablet in the morning and a matching placebo for dydrogesterone 10 mg tablet in the evening, while patients in reference arm received dydrogesterone 10 mg tablets twice daily for the total treatment duration of 90 days. Patients were also dispensed paracetamol 500 mg tablets for use as rescue medication only. The patients were instructed to take one tablet of paracetamol in case of unbearable endometriosis-associated pelvic pain. A maximum of 4 tablets of paracetamol were allowed in a day. In case the patients still had unbearable pain, the patient was withdrawn from the study.

Study endpoints

The primary endpoint was the change in EAPP from baseline to end of study i.e. at day 90 as assessed on a 100 mm VAS scale in the two groups. The secondary endpoints

included the consumption of rescue pain medication and change from baseline in the health-related quality of life using the HRQoL-4 questionnaire (Table 1) in the two groups during the study period. The secondary endpoints also included the changes from baseline in the size of endometrioma as assessed by USG and serum VEGF levels at the end of the study. The safety was assessed based on the reported adverse events (AEs) throughout the study.

Table 1: The HRQoL-4 questionnaire included the following four questions.

S. no.	Questions
1	Health as self-assessed (excellent 1; very good 2; good 3; fair 4; poor 5)
2	Number of days feeling physically unhealthy
3	Number of days feeling mentally unhealthy
4	Lost days (defined as days when work or other daily activities are not possible)

Statistical analysis

The sample size was calculated based on the primary endpoint of the study i.e., change from baseline in EAPP at the end of the study. At least 204 patients (test: 102, reference: 102) were required to achieve 90% power with 2.5% one-sided level of significance, considering a non-inferiority margin of 10 mm on VAS and assuming no difference between the test and the reference groups in the change in EAPP from baseline and common standard deviation of 22.[11] Considering a treatment allocation ratio of 1:1 and an attrition rate of 10%, 228 subjects are required to be enrolled in the study (test: 114, reference: 114).

For efficacy analysis, both per protocol (PP) and modified intention to treat (mITT) analyses were planned. The PP population was comprised of all the randomized patients who had completed all the post-randomization visits as per the protocol including the patients with minor protocol deviations. The mITT population was comprised of all the randomized patients who had completed at least one post-randomization visit including the patients with major protocol deviations. The PP analysis was considered as the primary analysis while the mITT analysis was considered as the supportive analysis. The test drug was considered non-inferior to the reference drug if the upper bound of 95% confidence interval (CI) for the difference between the study groups (test - reference) for the change in EAPP from baseline to the end of the study was below the non-inferiority margin of 10 mm. From the safety perspective, all the randomized subjects who had used at least a single dose of the study drug were considered for the safety analysis.

RESULTS

A total of 228 patients with confirmed diagnoses of endometriosis were evaluated for efficacy and safety. The baseline demographics and characteristics of the patients are mentioned in Table 2. The flow of patients in the two study groups is shown in Figure 1.

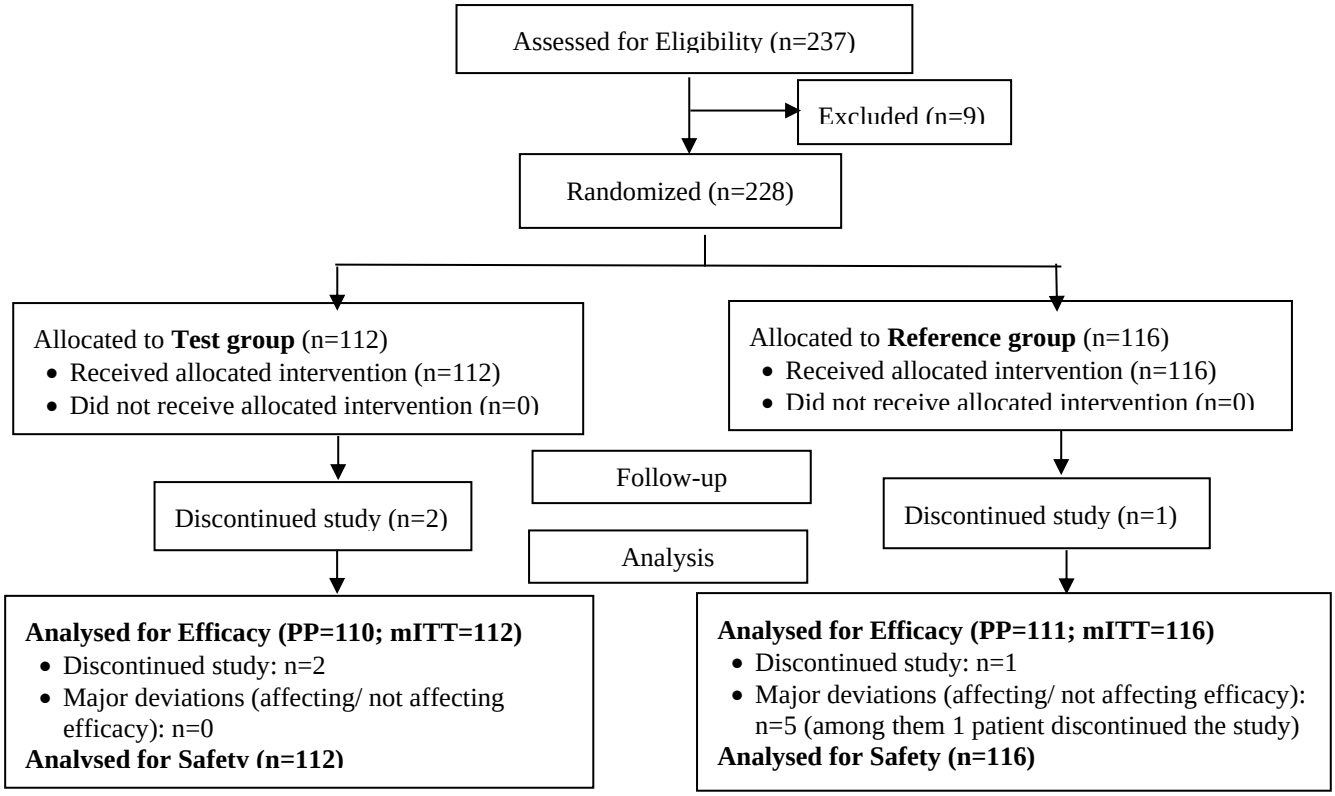

Figure 1: Patients in the two study groups.

Table 2: Demographics and baseline characteristics of the patients.

Parameters	Test group (n=112)	Reference group (n=116)	P value
Age (years)	31.8±6.9 (30.5 to 33.1)	32.0±6.3 (30.8 to 33.1)	0.85
Height (cm)	159.2±5.6 (158.2 to 160.2)	159.5±6.0 (158.3 to 160.6)	0.74
Weight (kg)	58.4±6.9 (57.1 to 59.7)	58.8±6.9 (57.5 to 60.0)	0.68
Body mass index (kg/m^2)	23.1±2.9 (22.6 to 23.6)	23.2±2.9 (22.7 to 23.7)	0.82

Data presented as mean±SD (95% CI), p value calculated using unpaired t test

Primary outcome

After 90 days of treatment, the mean change in EAPP from baseline was -34.2±15.3 mm (p<0.05 versus baseline) in the test group and -33.1±14.8 mm (p<0.05 versus baseline) in the reference group. The difference between the two groups for the mean change in EAPP at day 90 from baseline was statistically not significant (p=0.53) (Table 3). The upper limit of 95% CI for the difference between the test group and the reference group for the mean change in EAPP at day 90 from baseline was 2.8 mm which was well below the non-inferiority margin (10 mm). Hence, the test drug was found to be non-inferior to the reference drug for change in EAPP from baseline at the end of the study.

Secondary endpoints

During the last 30 days of the study period, there was a significant decrease in the use of rescue medication compared to the first 30 days of the study period in both the treatment arms (Figure 2a). The patients in both arms experienced a significant decrease size of endometrioma, and serum VEGF levels from baseline to the end of the study (Figures 2b and c). Significant improvements were also observed in measures of HR-QoL, including perceived health status, mental health, pain, and physical, role, and social functioning in both arms at the end of the treatment (Figure 2d). There were no significant differences observed between the two treatment groups in any of the secondary endpoints.

The efficacy results mentioned in Figure 2 belonged to PP population. The results in mITT population were similar to that reported in PP population (data not shown).

Safety

During the study, a total of 14 AEs were reported in 14 (12.5%) patients in the test group, and 14 AEs were reported in 12 (10.3%) patients in the reference group (Table 4). Two adverse events in the test group were moderate in severity, however, both were not related to the study medication. All the AEs in both the study groups resolved completely with or without treatment. There were no serious adverse event (SAE) reported during the study.

Table 3: Change in EAPP from baseline to end of study.

VAS score	Test group (n=110)	Reference group (n=111)	P value*
Day 0 (baseline)	61.8±10.0 (59.9 to 63.7)	61.8±8.8 (60.1 to 63.5)	0.98
Day 30	50.8±9.5 (49.0 to 52.6)	51.5±9.1 (49.8 to 53.2)	0.55
Day 60	41.0±11.2 (38.9 to 43.1)	41.7±11.5 (39.5 to 43.8)	0.67
Day 90 (end of study)	27.5±14.1 (24.9 to 30.2)	28.7±14.3 (26.0 to 31.4)	0.53

Data presented as mean±SD (95% CI), *p value calculated using unpaired t test

Table 4: Adverse events reported in the study.

Preferred term	Test group (n=112) (%)	Reference group (n=116) (%)	P value*
Headache	6 (5.4)	1 (0.9)	0.06
Weight gain	2 (1.8)	0 (0.0)	0.24
Back pain	2 (1.8)	0 (0.0)	0.24
Fever	1 (0.9)	3 (2.6)	0.62
Breast tenderness	1 (0.9)	1 (0.9)	1.0
Acidity	1 (0.9)	0 (0.0)	0.49
Dizziness	1 (0.9)	0 (0.0)	0.49
Nausea	0 (0.0)	3 (2.6)	0.25
Vomiting	0 (0.0)	3 (2.6)	0.25
Bloating	0 (0.0)	1 (0.9)	1.0
Cold	0 (0.0)	1 (0.9)	1.0
Myalgia	0 (0.0)	1 (0.9)	1.0

Data presented as n (%); % calculated from no. of subjects analyzed for safety, *Fisher's exact test (test group versus reference group)

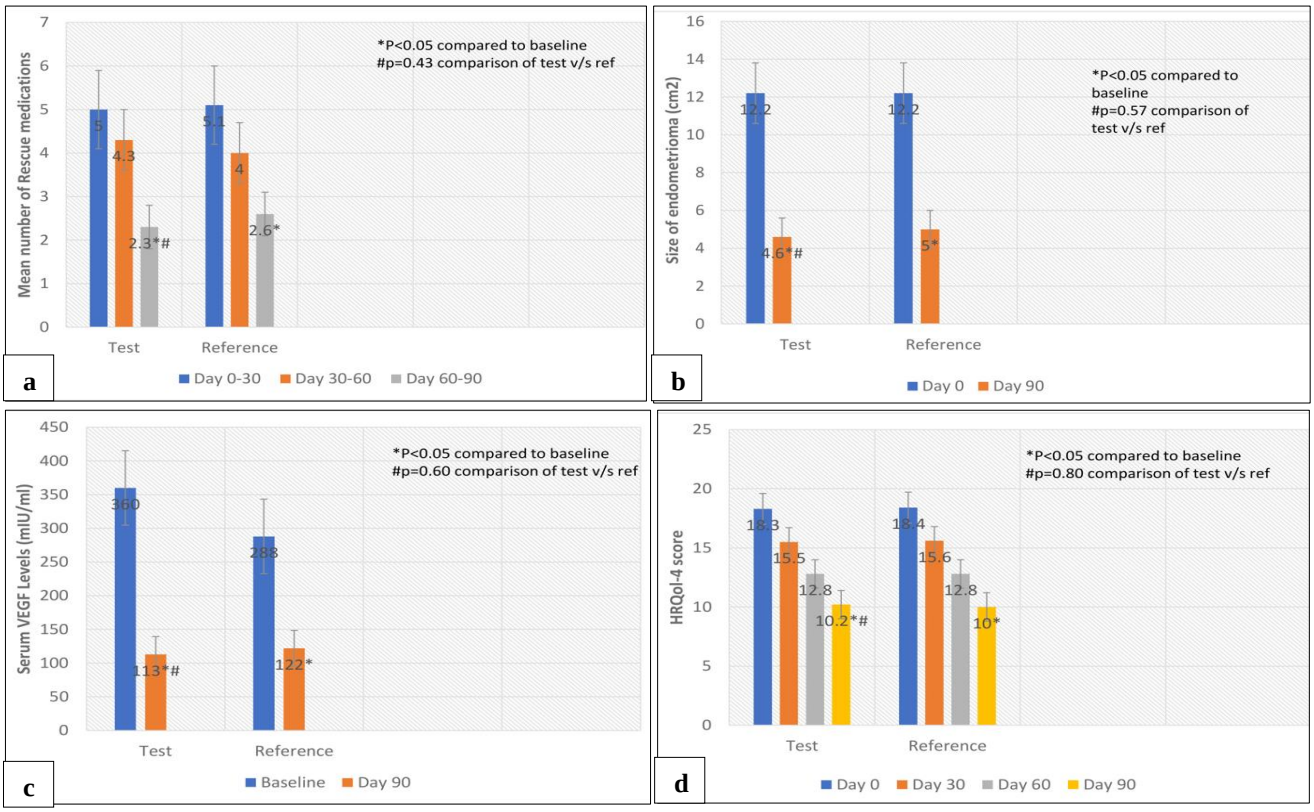

Figure 2: (a) Use of rescue medication, (b) size of endometrioma, (c) serum VEGF levels, and (d) HRQoL-4 questionnaire score.

DISCUSSION

Endometriosis is a condition that significantly affects HR-QoL and is linked to severe pain and morbidity. The objective of best-practice therapy is to control symptoms by avoiding recurrent surgical operations and making the most use of medical care through a personalized lifetime plan.[12,13] The difficulty in evaluating the efficacy of medical treatments for endometriosis and identifying specific patients' treatment options stems from the dearth of randomized controlled trials and the influence of the placebo effect, as noted in earlier research.[14,15]

Progestogens are advised as the first line of treatment for persistent pelvic discomfort associated with endometriosis, along with analgesics and oral contraceptives.[12-14] The use of progestogens in this situation is supported by high-quality evidence; however, when deciding which therapy is best for a given patient, clinicians are supposed to take into account the various side-effect profiles, such as irregular bleeding, as well as irreversible effects, like thrombosis and androgenic effects.[13,17,18]

Limited and low-to-moderate quality data supports other treatment alternatives, such as the use of combination oral contraceptives, which are also thought to be the first-line treatment for endometriosis pain-associated symptoms.[12,19] Additionally, there is insufficient data to support the use of some pharmaceutical treatments that are suggested as second-line therapies, such as aromatase inhibitors and gonadotropin-releasing hormone agonists, as they are linked to serious side effects like decreased bone mineral density or hypoestrogenic symptoms that necessitate add-back estrogen therapy.[12,13,20,21]

According to Schweppe et al dydrogesterone was typically dosed between 10 and 30 mg daily for varying numbers of days per cycle over a period of three to nine months is a successful endometriosis therapy that lessens persistent pelvic discomfort. The majority of women reported a significant decrease in the quantity and/or intensity of symptoms across studies, and laparoscopic inspection corroborated these results in many trials.[22-24]

This prospective, randomized, double-blind study evaluated the once-daily extended-release dydrogesterone 20 mg in comparison to dydrogesterone 10 mg twice daily in women with endometriosis. We observed significant and similar improvements in EAPP in both arms. All patients receiving dydrogesterone experienced significant improvements in the quality of life as well as a reduction in the size of endometrioma, serum VEGF levels, and, analgesic use.

Both formulations of dydrogesterone were well tolerated during the study, with a safety profile that was generally in line with previous studies of dydrogesterone in endometriosis.[22,25] All the AEs in both the study groups resolved completely with or without treatment.

Limitations

The shorter duration of the treatment in the study was a limitation.

CONCLUSION

In conclusion, the results of this prospective randomized controlled clinical study established the efficacy and safety of once-daily dydrogesterone ER 20 mg in patients with endometriosis. The study showed similar efficacy and safety of dydrogesterone ER 20 mg once daily compared to dydrogesterone 10 mg twice daily in the treatment of endometriosis.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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