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Achieving clinically meaningful response in endometriosis pain symptoms is associated with improvements in health-related quality of life and work productivity: Analysis of 2 phase III clinical trials

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Achieving clinically meaningful response in endometriosis pain symptoms is associated with improvements in health-related quality of life and work productivity: Analysis of 2 phase III clinical trials

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Clinical Trial Registration: NCT01620528 and NCT01931670

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CONDENSATION:

Women with moderate-to-severe endometriosis-related pain who respond to clinical treatment also have improvements in health-related quality of life and employment-related and household-related productivity.

SHORT TITLE: HRQoL and productivity among clinical responders in endometriosis trials.

AJOG AT A GLANCE:

A. Why was this study conducted?

- The objective of this post hoc analysis was to address the question, if patients show a clinical response (in dysmenorrhea or non-menstrual pelvic pain), does that mean they also have an improvement in health-related quality of life (HRQoL) and in productivity?

B. What are the key findings?

- Patients characterized as dysmenorrhea or non-menstrual pelvic pain *responders* also met HRQoL thresholds for responders on all of the Endometriosis Health Profile-30 (EHP-30) domains; nonresponders did not meet the HRQoL thresholds for EHP-30 responders.
- Productivity was improved among women who were dysmenorrhea or non-menstrual pelvic pain responders.

C. What does this study add to what is already known?

- The analysis results indicated that women with moderate-to-severe pain associated with endometriosis who experienced improvements in disease-related pain (based on dysmenorrhea and non-menstrual pelvic pain responders) also experienced improvements in HRQoL (as assessed by the EHP-30) and

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employment- and household-related productivity (as assessed by the HRPQ) when compared with clinical nonresponders.

KEY WORDS: endometriosis, Endometriosis Health Profile-30, health-related quality of life, Health-Related Productivity Questionnaire, absenteeism.

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ABSTRACT (462/500 MAX)

Background: Endometriosis-related pain symptoms negatively impact health-related quality of life (HRQoL) and productivity. In fact, as endometriosis-related symptom severity and the number of symptoms experienced increases, HRQoL decreases. Dysmenorrhea and non-menstrual pelvic pain are prominent symptoms experienced by women with endometriosis and were shown to have improved with the oral, nonpeptide GnRH antagonist, elagolix.

Objective: The objective of this post hoc analysis was to address the question, if patients show a clinical response (in dysmenorrhea or non-menstrual pelvic pain), do they also have improvements in HRQoL and in productivity?

Study Design: This post hoc analysis used data from the Elaris Endometriosis (EM)-I and EM-II phase III, randomized, placebo-controlled studies. A surgical diagnosis of endometriosis (in the past 10 years), premenopausal, age 18-49 years, and moderate to severe endometriosis-associated pain were among the inclusion criteria for both trials. Women self-reported pain daily using a scale ranging from 0 (no pain) to 3 (severe pain); daily pain was assigned to either dysmenorrhea or non-menstrual pelvic pain based on self-reported bleeding on that particular day. In addition, their self-reported endometriosis-associated pain must have been an average of moderate or severe during the month leading to baseline for inclusion in the trial program.

Patients were characterized as achieving a clinical response for dysmenorrhea or non-menstrual pelvic pain (i.e. “responder” or “nonresponder”) which was defined as women who did not have an increase in analgesic use and who met the pain reduction score threshold at month 3. Pain reduction score thresholds were defined separately for dysmenorrhea and non-menstrual pelvic pain in the trial using receiver operating characteristics analysis. HRQoL was assessed using the

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Endometriosis Health Profile-30 (EHP-30); work productivity assessed using the Health-Related Productivity Questionnaire (HRPQ).

Results: Women enrolled in EM-I (n=871) and EM-II (n=815) were included in this analysis. Patients with a clinical response during treatment to dysmenorrhea or non-menstrual pelvic pain also experienced a meaningful improvement in all domains of the EHP-30 at month 3. Patients who did not show a dysmenorrhea or non-menstrual pelvic pain clinical response at month 3 did not exhibit mean improvements in EHP-30 domain scores that indicate an EHP-30 responder. Productivity improved among dysmenorrhea clinical responders. In the EM-I study, clinical responders lost a total of 5.9 hours compared with a total of 13.0 hours for nonresponders of employment-related work at month 3 ($p<0.0001$). Among women in the EM-II study, a total of 4.1 hours and 10.4 employment-related hours were lost at month 3 for dysmenorrhea responders vs. nonresponders ($p<0.001$). Similar results were obtained when analyzed by non-menstrual pelvic pain responder status.

Conclusion: Women with moderate-to-severe endometriosis-related pain, who are clinical responders based on dysmenorrhea and non-menstrual pelvic pain, also experience significant and clinically meaningful improvement in HRQoL and productivity as measured by the EHP-30 and HRPQ, respectively.

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INTRODUCTION

Endometriosis is estimated to affect 176 million women globally, including seven million in the United States.[1,2] Women of all socio-ethnic groups are impacted by this estrogen-dependent disease, which is characterized by the presence of tissue resembling endometrium outside the uterus.[3,4] Dysmenorrhea (DYS), dyspareunia, and chronic non-menstrual pelvic pain (NMPP) are the most prominent symptoms experienced by women with endometriosis.[1,5] These symptoms negatively impact health-related quality of life (HRQoL) and productivity.[1,5-7] The burden of endometriosis symptoms on HRQoL has been documented in a web-based survey among 1,269 women and showed that as symptom severity, and as the number of symptoms experienced increased HRQoL deteriorated.[2] Another study, the Global Study of Women's Health, a cross-sectional study conducted in 10 countries, increased absenteeism, (p=0.019), presenteeism (p=0.033), and overall work productivity losses (p=0.014) were reported by women with symptomatic endometriosis when compared with asymptomatic controls; it was also observed that productivity losses rose with increasing disease severity.[6]

Elagolix, an oral, nonpeptide GnRH antagonist, has been shown to be effective in managing DYS and pelvic pain in women with endometriosis in the Elaris Endometriosis (EM)-I (NCT01620528) and EM-II (NCT01931670) studies.[4] These were, double-blind, randomized, placebo-controlled, phase III studies conducted to evaluate the effects of elagolix (150 mg once daily and 200 mg twice daily) in women with moderate-to-severe endometriosis-associated pain. Both treatment groups showed significantly reduced symptoms of DYS and NMPP in the Endometriosis Daily Pain Impact Electronic Diary (eDiary) after three months (primary endpoint) and six months of elagolix therapy when compared with the placebo group.[4] The objective of this post hoc analysis was to address the question, if patients show a clinical

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response (in dysmenorrhea or non-menstrual pelvic pain), do they also have improvements in HRQoL and in productivity?

MATERIALS AND METHODS

Study Design and Data Source

This post hoc analysis utilized data from two phase III, randomized, double-blind, placebo-controlled clinical studies (EM-I and EM-II) which evaluated the efficacy of elagolix among women with moderate-to-severe endometriosis-related pain. Eligibility included women with a surgical diagnosis of endometriosis (in the past 10 years), being premenopausal, age 18-49 years, and moderate to severe endometriosis-associated pain. Moderate to severe endometriosis-associated pain for trial entry was based on the mean pain scores of the month leading to baseline using the self-reported Endometriosis Daily Pain Impact eDiary (described in detail below) and diagnosed as endometriosis associated pain by the investigator.[4,7] EM-I included 151 sites in the US and Canada and enrollment was between July 2012 and May 2014; EM-II included 187 sites on five continents and enrollment was between November 2013 and July 2015. These studies were conducted in accordance with the principles set by the Helsinki Declaration and approved by an institutional review board. Shulman Associates IRB conducted the majority of the IRB approvals (EM-I/M12-665 IRB approval number 201202559 approval date April 11, 2012; EM-II/M12-671 IRB approval number 201208471, approval date on November 16, 2012). Informed consent was obtained from all individual participants included in the study.

A total of 872 women were randomized to one of three treatment arms in a 3:2:2 ratio and received either placebo (n=374), elagolix 150 mg once daily (n=249), or elagolix 200 mg twice daily (n=248) for six months in the EM-I study. The EM-II study enrolled 817 women who were

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randomly assigned in a ratio of 3:2:2 to receive placebo (n=360), elagolix 150 mg once daily (n=226), or elagolix 200 mg twice daily (n=229) for six months.[4] Treatment continued for six months with a post-treatment, follow-up period of 12 months. The co-primary endpoints for efficacy were the proportion of women who exhibited a clinical response in DYS and NMPP as assessed by an Endometriosis Daily Pain Impact eDiary at three months.[7] The study design and primary results have been previously described.[4] Both studies also included assessment with the Endometriosis Health Profile-30 (EHP-30) among other patient-reported outcome (PRO) measures that were used to capture the patient's perspective.

Patient-Reported Outcome Measures

Endometriosis Daily Pain Impact eDiary

The Endometriosis Daily Pain Impact eDiary is composed of mutually exclusive DYS and NMPP items[7] and was completed daily during the EM-I and EM-II studies. The DYS item asks, "Choose the item that best describes your pain during the last 24 hours when you had your period" and the NMPP item asks, "Choose the item that best describes your pain during the last 24 hours without your period." For both DYS and NMPP, responses of "None (no discomfort)", "Mild (mild discomfort but I was easily able to do the things I usually do)", "Moderate (moderate discomfort or pain, I had some difficulty doing the things I usually do)", and "Severe (severe pain, I had great difficulty doing the things I usually do)" were assigned a score of 0, 1, 2, and 3, respectively. Baseline scores were calculated based on the average during the 35 calendar days immediately prior to and including the first study drug dose date. Subsequent monthly pain scores for DYS and NMPP were averaged over the number of days when the patient reported DYS or NMPP within each respective time frame. Pain was assigned based upon

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the patient's response to the question: "Did you have your period in the last 24 hours?" If yes, the pain was attributed to DYS; if no, then the pain was attributed to NMPP.

Dyspareunia data were collected during the EM-I and EM-II trials but were not reported as part of this analysis. Dyspareunia will be reported in future analysis and publication. Patients completed the eDiary at baseline (monthly average based on daily assessment was used for the analysis), monthly during the treatment period, and every three months during the post-treatment, follow-up period.

Defining a DYS or NMPP Responder and Nonresponder

The EM-I and EM-II coprimary endpoints for DYS and NMPP were evaluated separately at month 3; thus a patient could be a responder for both or one and not the other; or a nonresponder for both DYS and NMPP.

A patient was considered a responder if 1) she did not have an increase of $\geq$15% in analgesic use and 2) if her absolute change from baseline score for DYS or NMPP met the respective score threshold. Clinical responder/nonresponder status was defined in the EM-I and EM-II clinical trials for DYS and NMPP separately by using a receiver operating characteristics analysis, among all randomized and treated patients, using the Patient Global Impression of Change anchor month 3. The threshold values that represented a meaningful reduction in pain were: -0.81 for DYS and -0.36 for NMPP and -0.85 for DYS and -0.43 for NMPP for EM-I and EM-II respectively.[4] If the patient's month 3 score change for DYS or NMPP met their respective threshold the patient was characterized as a "responder" for DYS or NMPP; if the threshold was not met the patient was a nonresponder for DYS or NMPP.

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Endometriosis Health Profile-30

The EHP-30 was developed using patient interviews and has been evaluated for its reliability, validity, and responsiveness.[8] Minimally important scoring changes have also been explored among women with medical and surgical interventions.[9] The EM-I and EM-II trials included the EHP-30 core items (Pain; Control and Powerlessness; Emotional Well-Being; Social Support; Self-Image) and the EHP-30 Sexual Relationship domain. The recall period for the EHP-30 was the previous four weeks. Responses include "Never", "Rarely", "Sometimes", "Often", and "Always" and the scores for each domain range from 0 to 100 (0 represents best health status). The EHP-30 was administered to patients at baseline, month 1, month 3, and month 6 during the treatment period, and every three months during the post-treatment, follow-up period of the EM-I and EM-II studies.

A study based on EM-I and EM-II recently established the score changes, by domain, that indicates a treatment response for the EHP-30 in this patient population.[10] To arrive at responder thresholds for the EHP-30 domains, a three method approach, or "triangulation approach"[11] was used. Specifically, anchor-based, distribution-based, and endpoints that are clinically relevant data were utilized to recommend the threshold score changes that indicate an EHP-responder. The anchor-based approach used a 7-response level Patient Global Impression of Change questionnaire at months 3 and 6. The distribution-based approach used two approaches which were 0.5 standard deviation at baseline calculation and one standard error of measurement. The clinically relevant indicators were DYS and NMPP responder status. The EHP-30 score change threshold by domain is a change from baseline of at least: Pain -30; Control and Powerlessness -35; Emotional Well-Being -20; Social Support -20; Self-Image -20; and Sexual Relationship -20).[10]

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Health-Related Productivity Questionnaire

The Health-Related Productivity Questionnaire (HRPQ) is a validated, nine-item, self-reported questionnaire that has been used to evaluate health-related productivity.[12,13] The HRPQ includes items on employment status; hours scheduled to work; effect of health issues or treatment on working scheduled hours (absenteeism); effect of health issues or their treatment on work output (presenteeism); hours of household chores planned; effect of health issues or their treatment on planned hours of household chores; effect of health issues or their treatment impact work output for household chores actually performed; how long since health issues developed; and effect of health issues on life. The questionnaire follows a skip pattern so that patients can answer only the items applicable to them according to whether they work outside the home (e.g., full- or part-time employment). Two patient groups were defined for this study: employed and household (employed and not employed, combined). Patients completed the HRPQ at baseline, monthly during the treatment period, and every three months during the post-treatment, follow-up period.

Analytic Approach

All analyses were run in SAS™ version 9.4 (SAS Institute Inc., Cary NC, USA) using the modified intention-to-treat sample from EM-I and EM-II separately. Missing PRO data were not imputed for this analysis; if a patient did not have an evaluation on a scheduled assessment, she was excluded from the analyses. Descriptive analyses were conducted to describe the sample (mean, standard deviation, range, frequencies for categorical data). PRO instruments were scored according to the developer's manuals.

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Impact of Clinical Response on HRQoL and Productivity Loss Outcomes

The relationship between clinical endpoints such as DYS and NMPP and PRO data over time is a facet of construct validity called responsiveness.[11,14] The dichotomous "responder" or "nonresponder" status for DYS and NMPP were determined based on the Endometriosis Daily Pain Impact eDiary[7] data from EM-I and EM-II.[4] Changes in PRO scores after three months of treatment were used to assess EHP-30 domain responder status by DYS and NMPP clinical responder status. Specifically, patients were grouped by DYS and NMPP responder status and the mean differences in PRO scores evaluated. General linear models with pairwise comparisons between least square (LS) means were performed using Scheffe's test adjusting for multiple comparisons to evaluate the EHP-30 domains or productivity (absenteeism or presenteeism for employed or household hours or percent using the HRPQ data) by responder status. The models included covariates (e.g., age, race, body mass index [BMI], baseline analgesic use, baseline DYS, baseline NMPP).

RESULTS

Complete sociodemographic and clinical information for the patients enrolled in the EM-I (n=871) and EM-II (n=815) studies have been previously reported.[4] The sample is summarized in EM-I and EM-II, respectively, by mean age (31.5 years and 33.2 years), race (87.1% and 89.2% White), and mean cycle length (28.3 days for both).

Baseline scores from DYS and NMPP, the EHP-30 domains, and HRPQ scores for EM-I and EM-II are presented in Table 1. The patients in both EM-I and EM-II had DYS scores of 1.5 ± 0.8 and NMPP scores of 1.6 ± 0.5. The patient Control and Powerlessness domain scores from the EHP-30 showed the most negative impact (69.8 ± 19.4 for EM-I and 62.4 ± 23.2 for EM-II).

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At day 1, the patients reported employment-related absenteeism as losing an average of 3.2 (±5.3) hours per week and 2.9 (±5.6) hours per week for EM-I and EM-II respectively. The absenteeism from work reflected 9.2% (±15.6%) and 9.5% (±18.7%) of their working week for EM-I and EM-II, respectively. At day 1, the patients reported losing 13.4 (±9.9) hours due to presenteeism which reflected 36.3% (±23.2%) of their employed working week (EM-I; EM-II reported 12.5 ±10.1 hours lost due to presenteeism which was 34.7% ± 23.8% of their employed working week).

Patients who were categorized as a DYS responder in the EM-I study experienced a decrease in EHP-30 scores, indicative of an increase in HRQoL, across all domains at month 3 (Table 2). All changes in LS mean change from baseline in EHP-30 scores for DYS responders were above the previously defined thresholds of clinical meaningfulness. A mean (standard error [SE]) change of -38.0 (1.1), -47.7 (1.3), -26.5 (1.1), -29.2 (1.4), -24.4 (1.6), -29.5 (1.6) points was observed for the domains of Pain, Control and Powerlessness, Emotional Well-Being, Social Support, Self-Image, and Sexual Relationship, respectively. Similar results were observed for the DYS responders in the EM-II study with DYS responders having EHP-30 score improvements that indicated a meaningful treatment benefit (Table 2). DYS nonresponders did not exhibit a clinically meaningful change in EHP-30 scores at month 3 in either EM-I or EM-II study because the LS mean difference from day 1 to month 3 did not reach any of the EHP-30 meaningful score changes. The proportion of patients who met the EHP-30 domain threshold among the DYS responders and nonresponders is also reported in Table 2. The proportion of EHP-30 domain responders among the DYS responders ranged from 48.0% in the Self-Image domain from EM-II to 70.2% in the Control and Powerlessness domain from EM-I. The

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proportion of EHP-30 domain responders among the DYS nonresponders ranged from 19.3% from the Pain domain from EM-I to 36.5% from the Sexual Relationship domain from EM-II.

Similar observations were noted when patients in the EM-I and EM-II study were categorized by NMPP responder status (Table 3); clinically meaningful improvements in HRQoL were observed across all domains of the EHP-30 at month 3. LS mean (SE) changes at month 3 observed among NMPP responders in the EM-I study were -36.2 (1.0) in the Pain domain; -46.2 (1.3) in Control and Powerlessness; -24.7 (1.1) in Emotional Well-Being; -28.2 (1.3) in Social Support; -25.3 (1.3) in Self-Image; and -29.2 (1.4) in Sexual Relationship. Similar to the DYS responders, NMPP responders in the EM-II study also exhibited clinically meaningful improvements across all domains of the EHP-30. No mean domain scores showed clinically meaningful improvements in EHP-30 domains among patients in either study that were categorized as NMPP nonresponders. The proportion of patients who met the EHP-30 domain threshold among the NMPP responders and nonresponders is also reported in Table 3. The proportion of EHP-30 domain responders among the NMPP responders ranged from 47.1% in the Self-Image domain from EM-II to 67.4% in the Control and Powerlessness domain from EM-I. The proportion of EHP-30 domain responders among the NMPP nonresponders ranged from 18.9% from the pain domain from EM-I to 33.6% from the Sexual Relationship domain from EM-II.

Productivity was improved among women who were DYS or NMPP responders as well. Overall, DYS and NMPP responders in both studies lost fewer hours due to absenteeism and presenteeism in the workplace and at home (Figures 1 and 2). The hours lost due to absenteeism and presenteeism for the group of employed patients and the household (workplace and at home) group are presented by responder status in Figure 1 for EM-I and EM-II. Employed patients who were clinical DYS responders lost 0.6 (SE 0.4) hours per week compared with the DYS

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nonresponders who lost 3.2 (SE 0.4) hours per week (EM-I, p<0.0001; EM-II results were similar p=0.0065). Employed patients who were clinical NMPP responders lost 0.2 (SE 0.4) hours per week as compared with the NMPP nonresponders who lost 3.2 (SE 0.4) hours per week (EM-I, p<0.0001; EM-II group differences were not statistically significant p=0.0605). Similar findings were true of the household group with statistically significant differences between the DYS and NMPP responders vs. nonresponders for absenteeism and presenteeism (Figure 1).

DYS responders lost a mean (SE) of 2.4% (1.0%) of their planned work hours compared with a loss of 8.4% (1.1%) of planned working hours for DYS nonresponders due to absenteeism in EM-I (Figure 2). Presenteeism accounted for higher losses in productivity; however, DYS responders still lost fewer hours of planned work when compared with DYS nonresponders in both EM-I and EM-II studies. Similar results were observed when considering hours of planned household work lost. Consistent with what was observed with DYS responders, NMPP responders lost fewer hours of employment-related and household-related work in the EM-I and EM-II studies (Figures 1 and 2). The only exception for statistically significant differences between the DYS and NMPP responders vs. nonresponders in terms of percent of lost productivity in EM-II was among the employment-related absenteeism: NMPP responders lost 3.5% (SE 1.2%) and NMPP nonresponders lost 6.4% (SE 1.2%), p=0.0856.

STRUCTURED DISCUSSIONS/COMMENT

Principal Findings

Women with endometriosis-related pain are negatively affected in a variety of ways relating to daily tasks, intimate sexual relationships, social activities, mental health, and employment.[3,5,15,16] This post-hoc analysis provided substantial evidence that demonstrated that significantly

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lowering moderate-to-severe endometriosis-related pain levels results in significant improvements in HRQoL and productivity. A greater proportion of women who were clinical responders to treatment, as defined by DYS and NMPP in the EM-I and EM-II studies achieved the thresholds for clinical meaningfulness[10] for the EHP-30 domains and the Sexual Relationship module when compared with women who were not clinical responders, indicating treatment efficacy across all the domains. While some DYS or NMPP nonresponders meet the thresholds for clinical meaningfulness, the group LS means for the EHP-30 domain scores did not indicate a change in domain score that met the threshold for clinical meaningfulness.

Results

Pain associated with endometriosis is a critical aspect of the disease. Soliman, et al. documented as the symptom severity and number of symptoms of endometriosis increase, the woman's HRQoL decreases.[2] Research about the impact of endometriosis shows that pelvic pain, specifically, has negative effects on HRQoL, anxiety, and depression. Facchin et al 2015, enrolled 110 women with surgically diagnosed endometriosis of whom 78 experienced pelvic pain and 32 did not experience pelvic pain (as well as 61 healthy controls). They found that women with endometriosis-related pelvic pain (DYS, dyspareunia, NMPP and dyschezia) reported poorer HRQoL (as measured by the SF12) and more depression and anxiety (as measured by the Hospital Anxiety and Depression Scale) than the women with endometriosis but no pelvic pain and the healthy controls.

Decrements in HRQoL due to endometriosis-related pain have been well-characterized by several studies.[2,3,6] This study evaluated a more specific comparison between clinical responders and nonresponders.

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The improvement in HRQoL, as measured by the EHP-30, among clinical responders indicated that the EHP-30 performed as expected and that its results aligned with those based on clinical endpoints. This is an important finding given the subjectivity of clinical endpoints for endometriosis treatments and is in line with patient-centered drug development.[10] Interventions should address the patient experience and these results provide further evidence that the EHP-30 is well-suited for monitoring patient treatment goals.

Clinical responders in EM-I and EM-II also experienced improvements in their workplace and household productivity. When considering clinical responders for these studies, approximately 8% (EM-I and EM-II) of planned work hours were lost due to absenteeism and 26% (EM-I) and 22% (EM-II) of planned work hours were lost due to presenteeism.

The findings were consistent with other studies[6] and higher than results in the study by Soliman et al. which reported the average loss for a general endometriosis population and was not limited to patients with moderate-to-severe endometriosis-related pain.[5] Nevertheless, both studies outlined that workplace productivity remains a major burden among women with endometriosis. The results of the current analysis showed that clinical responders in the EM-I and EM-II studies lost fewer hours of planned employment-related productivity, based on assessments made with the HRPQ. Similar results were observed for household-related productivity. Pain may be only one of the mechanisms by which endometriosis affects productivity. Further, elagolix may have effects on other aspects of the disease that also correlate with pain. Therefore, while pain reduction would clearly be expected to improve productivity, so might improvements in other aspects of the disease.

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Clinical Implications

From a patient care perspective, these findings demonstrate that symptom improvements in dysmenorrhea and non-menstrual pelvic pain lead to improvements in HRQoL and productivity which is vital information for patients to hear. Such data should be shared with patients in the treatment decision making process so that the patients can make informed decisions.

Research Implications

While this research demonstrates the distal impact of a pharmacologic intervention on patients' lives using standardized questionnaires, more can be gained in understanding the implications of this impact. Exploring the patient's perspective about treatment benefits; specifically, qualitative data collection about changes in symptoms and the value and impact on daily activities, would provide additional insight into understanding patient priorities and treatment decision making process.

Strengths and Limitations

The strength of including PRO research into the EM-I and II trials is the rigor in which the research is conducted and the fairly large sample size which provides strength to these findings. Of course, the clinical trial requirements limit the generalizability of these findings as the patient population may not fully reflect what is observed in a real-world setting. In this trial pain was diagnosed as endometriosis-associated by each clinical investigator, however the etiology of pain cannot always be attained with certainty; some pain may have been misdiagnosed as being due to endometriosis. However, we believe that this is reflective of clinical practice where diagnosis of pain recurrence due to endometriosis in the setting of prior surgically confirmed disease is routine. These analyses were conducted using binary grouping of responder or nonresponder and

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those are irrespective of treatment arm assignment. Consistent with other previously conducted endometriosis trials, a threshold for response was defined based on the trials' data.[17,18]

Conclusion

The analysis results indicated that women with moderate-to-severe endometriosis-associated pain who experienced improvements in disease-related pain (based on DYS and NMPP responders) also experienced improvements in HRQoL (as assessed by the EHP-30) and employment- and household-related productivity (as assessed by the HRPQ) when compared with clinical nonresponders. These results emphasized that changes in HRQoL and productivity were aligned with expectations for treatment goals. Furthermore, the EHP-30 and HRPQ performed as expected in this patient population thus providing further evidence these PRO measures can be used to measure and monitor treatment progress in women with endometriosis.

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DECLARATIONS

Conflict of Interest

Robin Pokrzywinski, Karin Coyne, and Jun Chen are employees of Evidera, who were paid consultants to AbbVie in connection with this study. Ahmed Soliman and Michael Snabes are employees of and own stock/stock options in AbbVie. Hugh Taylor received grant support and consulting fees from Pfizer and Ovascience, consulting fees from Bayer, AbbVie, and Dot Lab. Eric Surrey serves on medical advisory boards and speakers' bureau for AbbVie and speakers' bureau for Ferring.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. Access is provided to anonymized, patient and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports) from AbbVie-sponsored Phase II-IV global interventional clinical trials conducted in patients (completed as of May 2004, for products and indications approved in either the United States or the European Union), as long as the trials are not part of an ongoing or planned regulatory submission). This includes requests for clinical trial data for unlicensed products and indications.

Access to this clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-

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trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

Data analysis plans, data, and study-related materials may be made available upon request to the corresponding author. Each request will be carefully considered by the study sponsor.

Contributions

RMP, KSC, and JC developed the statistical analysis plan. JC ran the analyses under the direction of RMP and KSC. RMP and KSC oversaw the medical writing of the results. AMS and MS provided strategic oversight in the clinical trial design, data collection, and analyses. HST served as a clinical consultant and site investigator.

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FIGURES LEGENDS

Figure 1. Change in Hours Lost by Responder Status for DYS and NMPP for Absenteeism and Presenteeism

Significance *** p<0.0001; ** p<0.01; * p<0.05

Figure 2. Change in Percent of Lost Productivity by Responder Status for DYS and NMPP for Absenteeism and Presenteeism

Significance * p<0.0001; ** p<0.01; *** p<0.05

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TABLES

Table 1. Baseline/Day 1 Pain Scores, EHP-30 Scores, and HRPQ Scores

Characteristic	EM-I Total		EM-II Total	
	n=871	mean ± SD	n=815	mean ± SD
Monthly assessment of endometriosis pain				
Dysmenorrhea*	722	1.5 ± 0.8	662	1.5 ± 0.8
Non-menstrual Pelvic Pain†	871	1.6 ± 0.5	815	1.6 ± 0.5
EHP-30 Core				
Pain domain	858	58.2 ± 14.3	807	55.3 ± 16.2
Control and powerlessness	863	69.8 ± 19.4	809	62.4 ± 23.2
Emotional well-being	864	49.2 ± 19.9	810	46.2 ± 20.8
Social support	866	54.8 ± 25.6	812	50.5 ± 26.8
Self-image	864	51.0 ± 27.6	811	45.6 ± 28.3
Sexual relationship	668	64.5 ± 24.7	639	58.2 ± 26.1
HRPQ				
Employment-related (Employed only)				
Employment-related Absenteeism				
Hours Lost ‡	661	3.2 ± 5.3	609	2.9± 5.6
Percent Lost §	661	9.2± 15.6	609	9.5± 18.7
Employment-related Presenteeism				
Hours Lost ‡	658	13.4 ± 9.9	600	12.5±10.1
Percent Lost §	658	36.3± 23.2	600	34.7± 23.8
Household (Employed and Non-Employed)				
Household Absenteeism				
Hours Lost ‡	826	4.7± 5.5	737	4.8± 6.0
Percent Lost §	826	39.9± 29.1	737	37.0± 28.6
Household Presenteeism				
Hours Lost ‡	825	3.6± 4.9	730	3.7± 4.7
Percent Lost §	825	26.5± 19.5	730	26.1± 18.7

EM, Elaris Endometriosis; SD, standard deviation; EHP, endometriosis health profile; HRPQ, health-related productivity questionnaire

* Description of pain due to endometriosis in preceding month

† Description of pain due to endometriosis in preceding month

‡ Hours of lost work due to absenteeism or presenteeism

§ Percent of scheduled work lost due to absenteeism or presenteeism

Note: Each domain has a 0–100 scale range where 0 indicates the best health status.

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Table 2. Change in EHP-30 Domain Score by Responder Status for DYS at Month 3

Change in EHP-30 domain*	DYS† - EM-I Study				DYS† - EM-II Study			
	DYS Responder		DYS Nonresponder		DYS Responder		DYS Nonresponder	
	n	LS Mean (SE) [n, % meeting threshold‡]	n	LS Mean (SE) [n, % meeting threshold‡]	n	LS Mean (SE) [n, % meeting threshold‡]	n	LS Mean (SE) [n, % meeting threshold‡]
Pain domain	317	-38.0§ (1.1) [207, 65.3%]	404	-16.0 (0.9) [78, 19.3%]	304	-36.1§ (1.1) [182, 59.9%]	390	-18.1 (1.0) [100, 25.6%]
Control and powerlessness	322	-47.7§ (1.3) [226, 70.2%]	403	-22.9 (1.2) [111, 27.5%]	303	-40.3§ (1.5) [172, 56.8%]	400	-23.0 (1.3) [117, 29.3%]
Emotional well-being	318	-26.5§ (1.1) [201, 63.2%]	408	-11.2 (1.0) [131, 32.1%]	300	-21.2§ (1.2) [153, 51.0%]	396	-12.4 (1.1) [124, 31.3%]
Social support	326	-29.2§ (1.4) [187, 57.4%]	409	-9.5 (1.3) [113, 27.6%]	303	-25.1§ (1.5) [155, 51.2%]	400	-10.7 (1.3) [117, 29.3%]
Self-image	325	-24.4§ (1.6) [172, 53.2%]	405	-9.9 (1.3) [120, 29.6%]	304	-20.9§ (1.5) [146, 48.0%]	397	-10.3 (1.3) [112, 28.2%]
Sexual relationship	213	-29.5§ (1.6) [135, 63.4%]	310	-9.5 (1.3) [87, 28.1%]	220	-25.7§ (1.6) [128, 58.2%]	277	-12.6 (1.4) [101, 36.5%]

EHP, endometriosis health profile; DYS, dysmenorrhea; EM, Elaris Endometriosis; LS, least square; SE, standard error

* Each domain has a 0–100 scale range where 0 indicates the best health status, the change in each domain was month 3 to day 1.

† DYS responder status based on 1) no increase in analgesic use during trial period and 2) change from baseline score meeting a change score threshold, detailed above.

‡ EHP-30 domain responder threshold

§ EHP-30 responder threshold score change for the domain has been met.

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Table 3. Change in EHP-30 Domain Score by Responder Status for NMPP at Month 3

Change in EHP-30 domain*	NMPP† - EM-I Study				NMPP† - EM-II Study			
	NMPP Responder		NMPP Nonresponder		NMPP Responder		NMPP Nonresponder	
	N	LS Mean (SE) [%meeting threshold‡]	N	LS Mean (SE) [%meeting threshold‡]	N	LS Mean (SE) [%meeting threshold‡]	N	LS Mean (SE) [%meeting threshold‡]
Pain domain	355	-36.2§ (1.0) [216, 60.8%]	366	-15.5 (1.0) [69, 18.9%]	342	-35.7§ (1.0) [205, 59.9%]	352	-16.5 (1.0) [77, 21.9%]
Control and powerlessness	359	-46.2§ (1.3) [242, 67.4%]	366	-21.9 (1.2) [95, 26.0%]	343	-41.0§ (1.3) [194, 56.6%]	360	-20.5 (1.3) [95, 26.4%]
Emotional well-being	356	-24.7§ (1.1) [216, 60.7%]	370	-11.4 (1.0) [116, 31.4%]	340	-22.6§ (1.1) [185, 54.4%]	356	-10.1 (1.1) [92, 25.8%]
Social support	363	-28.2§ (1.3) [207, 57.0%]	372	-8.6 (1.3) [93, 25.0%]	343	-24.3§ (1.4) [168, 49.0%]	360	-9.9 (1.4) [104, 28.9%]
Self-image	360	-25.3§ (1.3) [196, 54.4%]	370	-7.7 (1.3) [97, 26.2%]	344	-20.9§ (1.4) [162, 47.1%]	357	-9.1 (1.4) [96, 26.9%]
Sexual relationship	245	-29.2§ (1.4) [151, 61.6%]	278	-7.3 (1.4) [71, 25.5%]	241	-27.0§ (1.5) [143, 59.3%]	256	-10.3 (1.4) [86, 33.6%]

EHP, endometriosis health profile; NMPP, non-menstrual pelvic pain; EM, Elaris Endometriosis; LS, least square; SE, standard error

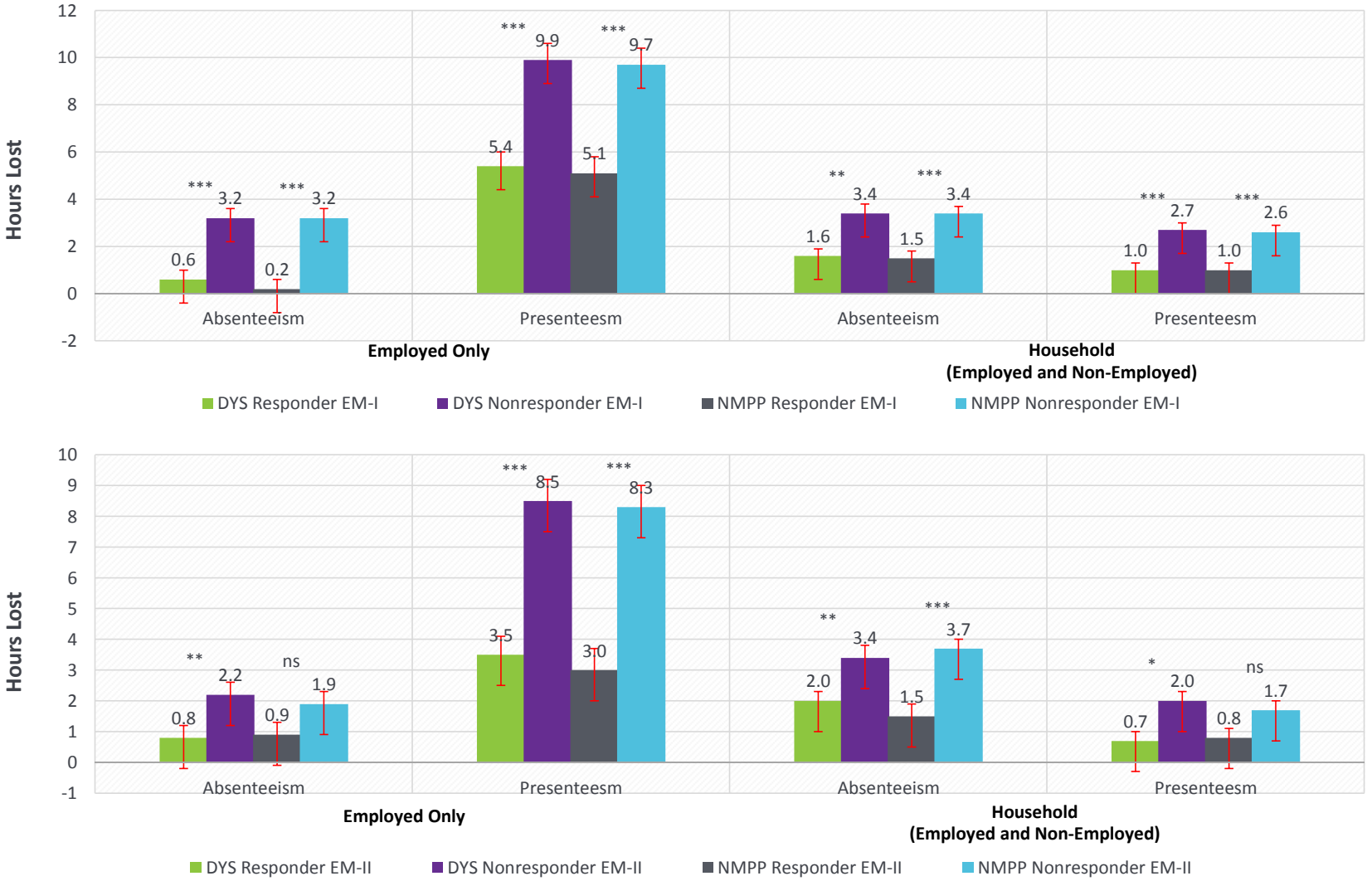
* Each domain has a 0–100 scale range where 0 indicates the best health status, the change in each domain was month 3 to day 1.

† NMPP responder status based on 1) no increase in analgesic use during trial period and 2) change from baseline score meeting a change score threshold, detailed above.

‡ EHP-30 domain responder threshold

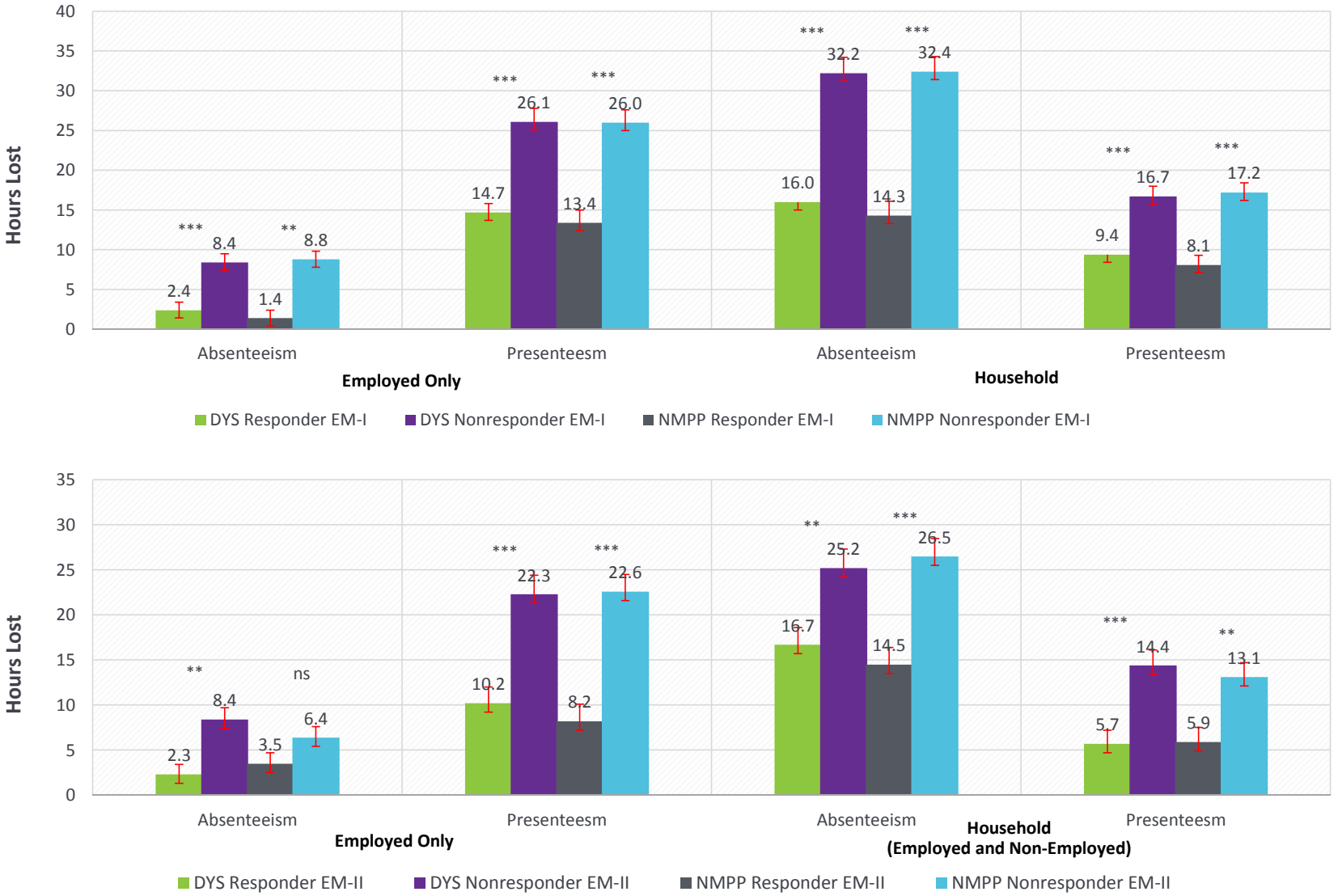
§ EHP-30 responder threshold score change for the domain has been met.

Figure 1. Change in Hours Lost by Responder Status for DYS and NMPP for Absenteeism and Presenteeism



Significance *** p<0.0001; ** p<0.01; * p<0.05

Figure 2. Change in Percent of Lost Productivity by Responder Status for DYS and NMPP for Absenteeism and Presenteeism



Significance * p<0.0001; ** p<0.01; *** p<0.05