International Journal of Gynecology and Obstetrics 117 (2012) 228–233

Contents lists available at SciVerse ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Detailed analysis of a randomized, multicenter, comparative trial of dienogest versus leuprolide acetate in endometriosis

Thomas Strowitzki [a,*], Joachim Marr [b], Christoph Gerlinger [c], Thomas Faustmann [d], Christian Seitz [b]

[a] Department of Gynecological Endocrinology and Reproductive Medicine, University of Heidelberg, Vossstrasse 9, 69115 Heidelberg, Germany
[b] Global Clinical Development, Women's Healthcare, Bayer HealthCare, Berlin, Germany
[c] Global Biostatistics, Women's Healthcare, Bayer HealthCare, Berlin, Germany
[d] Global Medical Affairs, Women's Healthcare, Bayer HealthCare, Berlin, Germany

ARTICLE INFO

Article history:
Received 20 October 2011
Received in revised form 12 January 2012
Accepted 22 February 2012

Keywords:
Dienogest
Endometriosis
Gonadotropin-releasing hormone analog
Pain relief

ABSTRACT

Objective: To analyze the secondary efficacy and safety outcomes from a recent trial comparing dienogest (DNG) with leuprolide acetate (LA) in women with endometriosis. *Methods:* A 24-week, open-label, randomized, multicenter study of DNG versus LA in women with endometriosis-related pain was assessed for outcomes such as responder rates (using predefined thresholds of pain relief), changes in single symptoms/signs and sum scores from the Biberoglu and Behrman (B&B) scale, clinical laboratory parameters, and measures of quality of life. *Results:* Dienogest was non-inferior to LA for treatment response using all predefined thresholds of pain relief and provided equivalent improvements in B&B symptoms and signs. No clinically relevant changes in laboratory parameters were observed during DNG treatment, whereas estrogen levels decreased in the LA group. Compared with LA, DNG was associated with pronounced improvements in specific quality-of-life measures. *Conclusion:* The analyses provide supportive evidence that the efficacy of DNG is equivalent to that of LA for treating endometriosis symptoms, with specific quality-of-life benefits and a favorable safety profile.

1. Introduction

Endometriosis is a painful chronic disease affecting approximately 10% of women [1]. Symptoms such as dysmenorrhea, dyspareunia, and pelvic pain are common and, for many patients, have a severe impact on quality of life (QoL) [2]. Symptomatic treatment with nonspecific pain medications (e.g. nonsteroidal anti-inflammatory drugs) and off-label use of oral contraceptives are common, although trial evidence to support the efficacy of these approaches in endometriosis remains limited. Specific indicated treatments for endometriosis include gonadotropin-releasing hormone (GnRH) analogs and some progestins. Although effective in many women, medications in these classes are associated with adverse effects that limit patient compliance and long-term use [3].

Dienogest (DNG [Visanne; Bayer HealthCare, Berlin, Germany]) is a selective progestin that has recently been approved—at a low oral dose of 2 mg/day—for the treatment of endometriosis in Europe, Japan, and other countries. Dienogest reduces endometriotic lesions by creating a local progestogenic environment, while only moderately suppressing systemic estrogen levels [4]. It has no significant androgenic, mineralocorticoid, or glucocorticoid activity owing to its specific receptor binding [4,5].

Two clinical trial programs in Europe and Japan investigated the efficacy and safety of DNG 2 mg/day in the treatment of endometriosis [6–11]. A randomized multicenter trial comparing oral DNG 2 mg/day with the GnRH analog leuprolide acetate (LA [3.75-mg depot intramuscular injection every 4 weeks]) demonstrated the non-inferiority of DNG based on the predefined primary endpoint (i.e. improvement of pelvic pain after 24 weeks of treatment) [11]; the study also showed that DNG offers advantages in safety and tolerability, including a reduced incidence of hypoestrogenic effects and minimal change in bone mineral density (BMD) [11].

The aim of the present paper was to analyze further the results from the study on the efficacy and safety of DNG versus LA [11], using secondary outcomes and sensitivity analyses.

2. Materials and methods

Study methods for the comparative trial of DNG and LA have been described in detail previously [11]. The study protocol was approved by the local independent ethics committees, and all participants provided written informed consent before study enrollment. The study was conducted in accordance with the amended version of the Declaration of Helsinki and in compliance with the principles of Good Clinical Practice.

Women aged 18–45 years experiencing de novo or recurrent pain associated with a confirmed diagnosis of endometriosis were

* Corresponding author. Tel.: +49 6221 567910; fax: +49 6221 564099.
E-mail address: thomas_strowitzki@med.uni-heidelberg.de (T. Strowitzki).

0020-7292/$ – see front matter
doi:10.1016/j.ijgo.2012.01.009

eligible for study enrollment. Exclusion criteria included amenorrhea (≥3 months), need for surgical treatment, previous use of hormonal treatments within specified times, abnormal findings (other than endometriosis) at gynecologic examination, pregnancy or breast feeding, and risk factors for decreased BMD.

The study was a multicenter, randomized, open-label, parallel-group, non-inferiority comparison of DNG and LA. Patients were randomized (1:1 ratio) to receive DNG 2 mg/day orally or standard-dose intramuscular LA. The study was limited to 24 weeks, which is the maximal recommended treatment duration for depot LA in endometriosis when no estrogen add-back therapy is used.

A range of efficacy, safety, and QoL outcomes were included in the study [11]. The primary efficacy outcome was absolute change in endometriosis-related pelvic pain from baseline to study end, measured on a visual analog scale (VAS; where 0 mm represented absence of pain and 100 mm represented unbearable pain), covering a recall period of 4 weeks. The VAS is a validated measure of endometriosis-related pain, which is widely used in clinical trials [12].

Secondary efficacy outcomes based on the VAS included responder rates (using predefined thresholds of pain relief as responder definitions) and time course of VAS score change. Response analysis represents a tangible method for measuring pain relief in clinical trials, in addition to absolute change in pain score [13].

The physician-assessed modified Biberoglu and Behrman (B&B) severity profile [14] was also included as a secondary efficacy outcome. The B&B scoring grades the severity of individual endometriosis symptoms (pelvic pain, dysmenorrhea, dyspareunia) and signs (pelvic tenderness, induration), which are then combined into sum scores for total pelvic symptoms and physical signs. Although not validated for measuring changes in endometriosis symptoms or signs, B&B scoring has been widely used historically and provides a useful subjective assessment. The present analysis assessed changes in B&B severity profile before and after DNG and LA treatment.

Safety variables recorded in the trial included adverse events, BMD and markers of bone metabolism, clinical laboratory parameters, and vital signs. The present analyses focused on comparisons of laboratory parameters before and after DNG and LA treatment.

Quality of life was assessed at screening and study end using the Short Form-36 (SF-36) Health Survey [15]. Assessments on a 0–100-point scale included overall physical and mental health scores

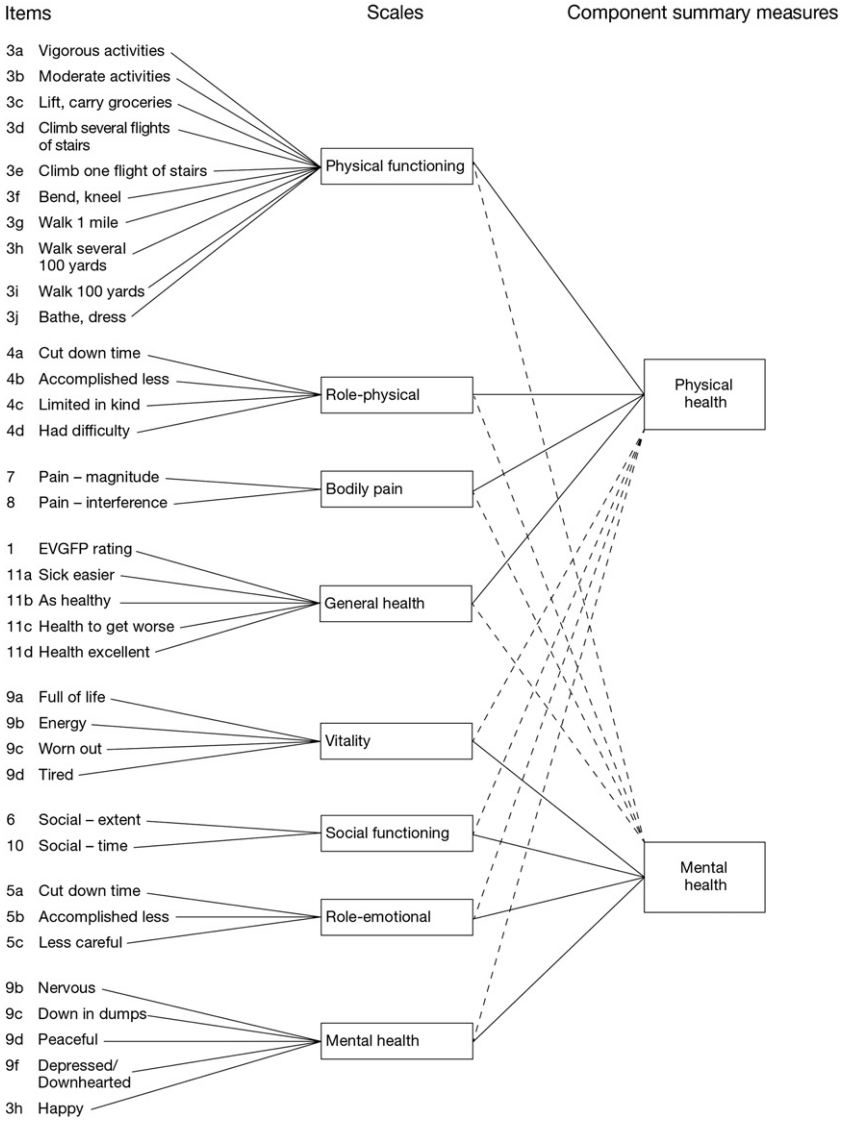

Fig. 1. Quality-of-life parameters in the Short Form-36 v2 Health Survey Measurement Model. Adapted from Ware et al. [15]. Figure is published with permission from QualityMetric Incorporated. SF-36, SF-36v2, SF-12, and SF-12v2 are registered trademarks of the Medical Outcomes Trust and are used under license. The SF-36v2 Health Survey is copyrighted 2000, 2002, 2007 by QualityMetric Incorporated.