Effective relief of menopausal symptoms with ultra low dose HRT

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Summary

The efficacy on postmenopausal symptom relief during 24 weeks of therapy with oral continuous-combined hormone replacement therapy (HRT) formulations containing 0.5mg 17ß-estradiol (E2) plus 0.1mg norethisterone acetate (NETA) or 0.5mg E2 plus 0.25mg NETA has been investigated in a randomised, double-blind, placebo-controlled trial conducted in 577 postmenopausal women. The number and severity of hot flushes were recorded daily. The change in mean number of moderate to severe hot flushes was calculated per week. Additionally, a sensitivity analysis was performed to analyse the mean changes in frequency and severity of moderate to severe hot flushes. Furthermore the Hot Flush Weekly Weighted Score (HFWWS) and the Greene Climacteric Scale were evaluated for each woman.

A rapid and significant reduction in the frequency of moderate to severe hot flushes as well as in the severity score was already achieved at week 3 versus placebo (p = 0.001) with both ultra low continuous-combined formulations. A significant improvement was also reported in the Hot Flush Weekly Weighted Score and the total Green Climacteric Scale compared to placebo (p = 0.001). These effects were maintained over the whole study period. Overall there was no statistically significant difference in efficacy between the two active treatment groups. During the whole observation period, the treatment was very well tolerated with no difference in adverse events between the groups and only 1% of serious adverse events being reported.

Introduction

The decline of oestrogen production associated with the menopause leads to the emergence of oestrogen deficiency symptoms such as vasomotor instability and symptoms related to urogenital atrophy.[1,2] For many women, these symptoms may compromise their overall well-being and quality of life.[3,4] Therefore treatment with oestrogens is logical and, because of its efficacy, is the therapy of choice.[5] Clinical efficacy as well as tolerability aspects are to be considered when establishing the optimal dose of oestradiol for symptom relief.

Objectives

The aim of the ***CHOICE*** (***C***linical Study on ***H***ormone Dose ***O***ptimisation ***i***n ***C***limacteric Symptoms ***E***valuation) trial was to assess the efficacy and safety of two ultra low continuous-combined formulations, containing 0.5mg E2 plus 0.1mg NETA or 0.5mg E2 plus 0.25mg NETA, compared to placebo in postmenopausal women with moderate to severe vasomotor symptoms.

Methods

The trial was a double-blind, randomised, placebo-controlled, multinational study with a duration of 24 weeks. A total 577 postmenopausal women experiencing at least 50 moderate or severe hot flushes per week were prospectively randomised to treatment with 0.5mg E2 plus 0.1mg NETA, 0.5mg E2 plus 0.25mg NETA or placebo. Women were asked to record the number and severity of hot flushes on the diary card throughout the trial. The severity was scored as mild, moderate or severe. The primary endpoint was the change in the mean number of moderate to severe hot flushes per week. A sensitivity analysis was also performed, analysing the mean changes in frequency and severity of moderate to severe hot flushes, in order to validate the results. The secondary efficacy endpoints were the Hot Flush Weekly Weighted Score (HFWWS) and the Greene Climacteric Scale.

The HFWWS takes into account the weekly number of hot flushes and their severity and was calculated using the formula: Hot Flush Weekly Weighted Score = (Number of mild hot flushes × 1) + (Number of moderate hot flushes × 2) + (Number of severe hot flushes × 3). The Green Climacteric Scale is comprised of 21 symptoms or events categorised into 4 groups: psychological, somatic, vasomotor symptoms and sexual interest. Each woman completed the Green Climacteric Scale at study entry and after 4, 8, 12 and 24 weeks of treatment. Each symptom was graded according to the extent to which the woman was bothered by the specific symptom (none = 0, slight = 1, moderate = 2 or severe = 3) and the scores of each group of symptoms were calculated. Changes from start to the end of the trial were analysed using the Kruskal-Wallis test. Paired treatment comparisons were performed using the Wilcoxon test stratified by country. The demographic data are summarized in *Table 1.*

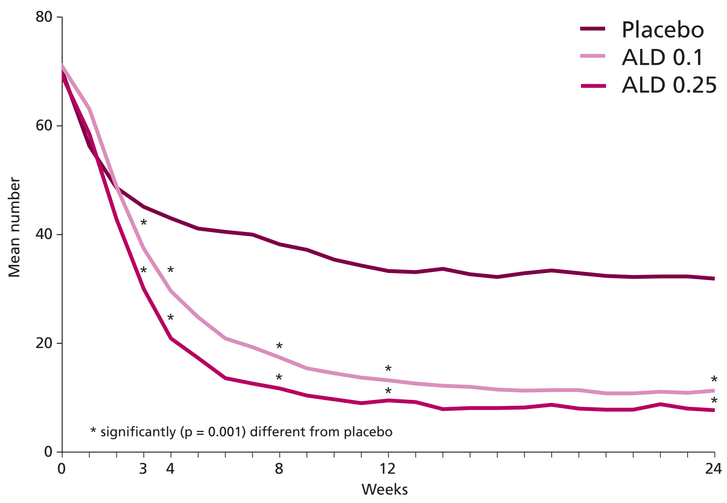
Table 1. Subject disposition and baseline subject characteristics

Table 1	Placebo	E2 0.5mg/NETA 0.1mg	E2 0.5mg/NETA 0.25mg
Randomised Completed Discontinued	201 160 (80%) 40 (20%)	194 177 (91%) 17 (9%)	182 171 (94%) 10 (5%)
Age (years) Mean (SD)	 56.1 (4.7)	 55.2 (4.8)	 55.3 (4.4)
Time since last menses Distribution < 1 year > 1–2 years > 2–5 years > 5–10 years > 10 years	 31 (17%) 19 (11%) 39 (22%) 50 (28%) 39 (22%)	 29 (17%) 20 (12%) 40 (24%) 51 (31%) 26 (16%)	 31 (19%) 20 (12%) 46 (28%) 39 (23%) 30 (18%)
BMI Mean (SD)	 25.3 (3.6)	 25.0 (3.6)	 25.4 (3.5)
Moderate-severe hot flushes per week Mean (SD)	 70.0 (26.4)	 70.9 (27.4)	 69.2 (30.5)
Hot flush weekly weighted score Mean (SD)	 183.5 (79.4)	 185.8 (75.8)	 180.5 (87.7)

Results

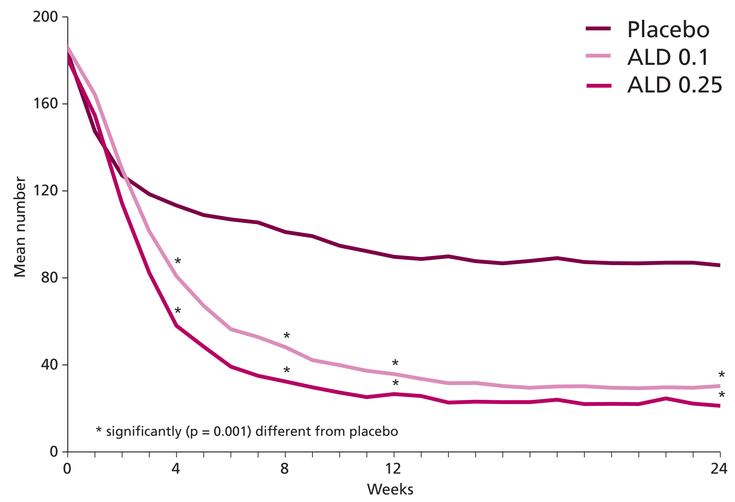
575 women took a study medication and 573 documented hot flushes in the diary, out of a total of 577 postmenopausal women. A rapid and significant reduction in the frequency of moderate to severe hot flushes as well as in the severity score was already achieved at week 3 versus placebo (p = 0.001) with both ultra low combinations of E2 0.5mg and NETA 0.1 or 0.25mg in the intention to treat population. There was no difference between the two groups. This effect was maintained over the whole study period *(Figure 1).*

Figure 1. Mean number of moderate to severe hot flushes (per week)



A similar significant improvement (p = 0.001) was also reported in the Hot Flush Weekly Weighted Score in both ultra low dose groups *(Figure 2).*

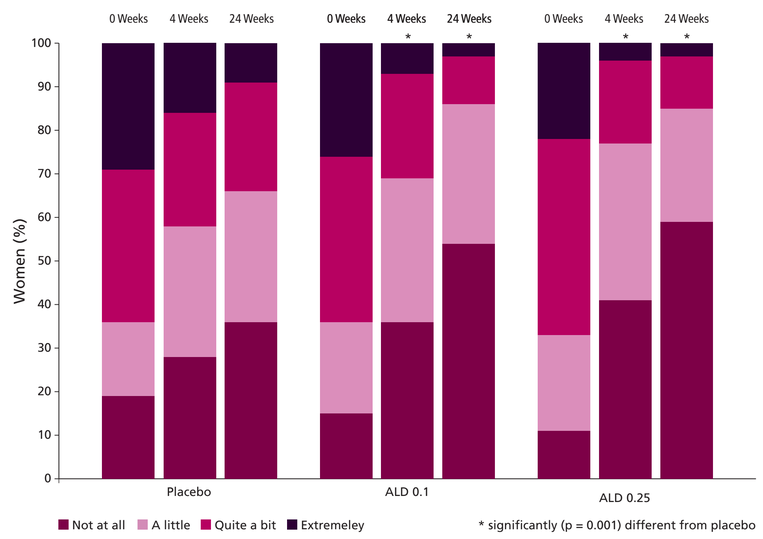
Figure 2. Hot flush weekly weighted score (per week)



The same statistically significant improvement (p = 0.001) was also reported in the total Green Climacteric Scale and this effect was maintained over the whole study period.

Additionally, significant differences in difficulty in sleeping were seen at all time points between both treatment groups and placebo *(Figure 3).*

Figure 3. Greene Climacteric Scale – difficulty in sleeping (per week)



During the whole observation period the treatment was very well tolerated in all treatment arms. Only 1% of serious adverse events were reported in the safety population, equally distributed among the groups.

Conclusions

- The new ultra low dose combinations effectively reduce the frequency and severity of hot flushes within the initial weeks of treatment.
- This significant improvement was also confirmed by the Hot Flush Weekly Weighted Score and the Green Climacteric Scale.
- Overall there was no statistically significant difference in efficacy between the two active treatment groups.
- These ultra low dose combinations are a new milestone in offering postmenopausal women effective symptom relief while minimizing safety concerns.

References: 1. Oldenhave A, Jaszmann IJ, Haspels AA, Everaerd WT. Impact of climacteric on well-being. A survey based on 5213 women 39 to 60 years old. *Am J Obstet Gynecol* 1993; 168:772-80. 2. Kuh DI, Wadsworth M, Hardy R. Women's health in midlife: the influence of the menopause, social factors and health in earlier life. *Br J Obstet Gynaecol* 1997; 104:923-33. 3. Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M. Measuring the impact of menopausal symptoms on quality of life. *BMJ* 1993; 307:836-40. 4. Zethraeus N, Johannesson M, Henriksson P, Strand RT. The impact of hormone replacement therapy on quality of life and willingness to pay. *Br J Obstet Gynaecol* 1997; 104: 1191-5. 5. Burger H. et al. Practical recommendatios for hormone replacement therapy in the peri- and postmenopause. *Climacteric* 2004; 7:210-216.