

WHEN IS TREATMENT CLINICALLY RELEVANT COMPARED TO PLACEBO FOR STUDIES IN NOCTURIA?

Hypothesis / aims of study

Composite endpoints are frequently used in many disease areas to gain an overview of the full benefit of a treatment. According to the FDA, a composite score is relevant if each component is clinically meaningful and contributes equally to the treatment effect.

Lower urinary tract symptoms (LUTS) such as overactive bladder (OAB) and nocturia have traditionally been assessed by counting the number of voids. Number of voids is a surrogate marker of the symptom rather than a measure of clinical benefit itself and several disease specific quality of life (QoL) tools have therefore been developed (e.g. the NI Diary, the N-QoL and the OAB-q). However, QoL assessments relate to the patient's current situation and do not correlate fully with treatment benefit as QoL questionnaires also measure personality, patient/physician interaction, etc. Furthermore, increasing evidence highlights that nocturia has severe long-term health effects due to sleep disturbance (1).

Extremely high placebo responses are often observed in the primary endpoint of LUTS trials, with rates of 32–65% being reported in OAB trials (2). We therefore wanted to use the inspiration from composite endpoint to develop a totality of key endpoints to identify the true clinical benefit of nocturia treatment compared to placebo.

Study design, materials and methods

This *post hoc* analysis was based on two 3-month, randomised, double-blind, parallel group studies in males and females with nocturia (2 or more nocturnal voids) who were treated once daily with desmopressin 50 µg and 25 µg, respectively, compared to placebo (3).

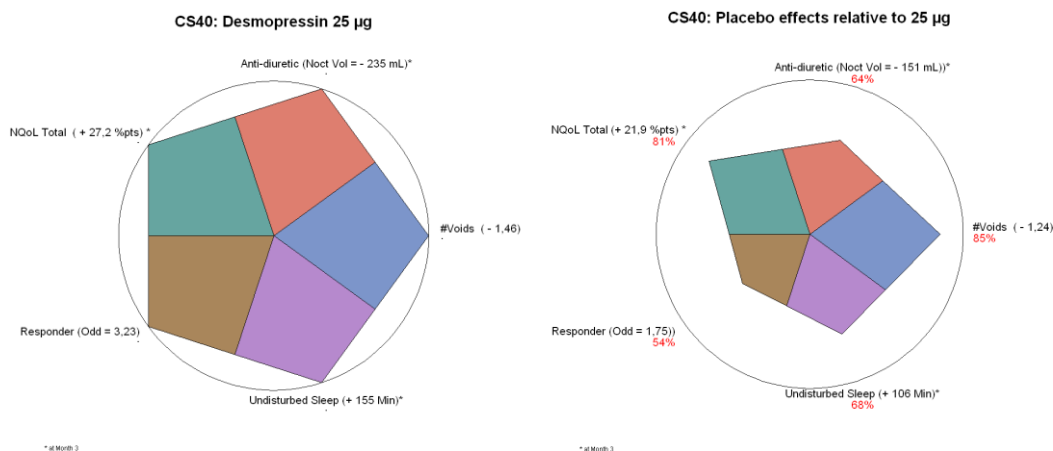
To investigate the totality of the treatment benefit compared to placebo the effect on the following key endpoints were graphically displayed and evaluated with a multivariate star plot.

- 1) Mean change from baseline
- 2) 33% responder status
- 3) FUSP (a surrogate marker of long-term health effect of disturbed sleep)
- 4) Change in N-QoL (a marker of short-term treatment benefit)
- 5) Change from baseline in nocturnal urine volume (an objective assessment of the mode of action of the drug)

The various effects size, being of different dimensions, are for each respective active treatment arm represented in a star plot where all endpoints are dimensioned as rays of equal size (100%). To express the amount of placebo effect for each of these endpoints, accompanying star plots (figure 1) are presented for the respective placebo arms, where the placebo effect sizes are expressed as a percentage of the active-treatment arm effect sizes. This provides a 'at one glance' display of the totality of various treatment effects as superimposed to placebo.

Results

The full analysis set comprised 261 females (age range 19 to 87 years) and 385 males (age range 20 to 87 years). The star plot represents the adjusted mean change from baseline for each of the five key endpoints (except for the responder status, which is in terms of odds) listed above for the desmopressin treatment and for the placebo (Figure 1).



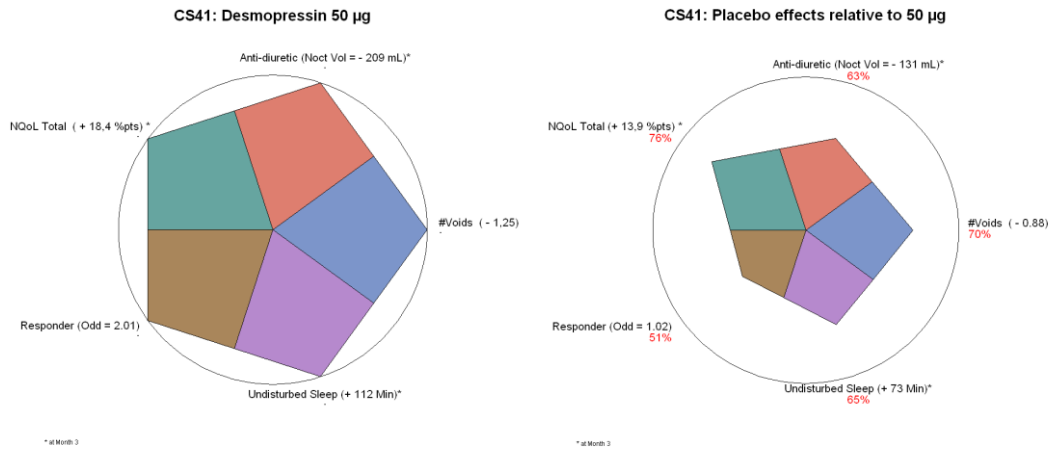


Figure 1. Total clinical benefit of treating nocturia with desmopressin

Interpretation of results

The 33% responder status analysis generated the lowest placebo response in both the female and male trials. Number of voids generated a high placebo response, which may stem from patients being most aware that this is assessed. The short-term benefit assessment (N-QoL) also showed a high placebo response, which may be due to increased physician contact. The sleep marker of long-term consequences (FUSP) showed a relatively low placebo response.

Concluding message

The full clinical benefit of treating nocturia with desmopressin versus placebo becomes clearer when considering all the key endpoints together. We recommend that the clinical benefit is assessed by the totality of results from key endpoints with for example star plots in LUTS treatment, for which placebo response can be really high and vary between endpoints.

References

1. Rosen RC, Holm-Larsen T, Kupelian V, Wein AJ (2013) Consequences of nocturia.
2. van Leeuwen JHS. (2006) The placebo effect in the pharmacological treatment of patients with LUTS. Eur Urol:50: 440-53.
3. Sand PK, Dmochowski RR, Reddy J, van der Meulen EA (2013) Efficacy and safety of low dose desmopressin orally disintegrating tablet in women with nocturia: results of a multicenter, randomized, double-blind, placebo controlled, parallel group study. J Urol 190: 958-964.

Disclosures

Funding: Ferring Pharmaceuticals **Clinical Trial:** Yes **Registration Number:** study NCT01223937 and NCT01262456 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** It was a multicenter study which was approved by the institutional review board/ethics committee for each site **Helsinki:** Yes **Informed Consent:** Yes