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CONTINUATION RATES WITH DIFFERENT DOSAGES OF DESMOPRESSIN ORAL LYOPHILISATE IN A LARGE PHASE III TRIAL OF NOCTURIA THERAPY

Hypothesis / aims of study

Nocturia is a highly prevalent condition which can have a detrimental impact on sleep, quality of life, daytime functioning and overall health. Effective management should seek to address the etiology of the condition for each patient, which can include such disorders as uncontrolled diabetes mellitus and hypertension. If these can be ruled out, the key urologic factors which can contribute to nocturia include nocturnal polyuria (NP) in up to ~80% of patients (1), benign prostatic obstruction (BPO), and overactive bladder (OAB). Effective therapies are available for each of these conditions.

The level of patient compliance and continuation with medication is a key factor influencing the success of any given treatment strategy. Discontinuation of medication may be attributable to many different causes, including a perceived lack of efficacy, unacceptable side effects, or cost. Persistence with therapy in naturalistic settings is reported to be low in some areas of urology, eg OAB (2, 3). Clinical trials which evaluate efficacy, tolerability and optimal dosing would do well to consider factors which might help to maximize persistence with the treatment regimen in order to facilitate the best possible outcome for the patient.

Desmopressin is a synthetic analog of the body's own antidiuretic hormone, arginine vasopressin. It concentrates the urine and reduces urinary output in patients, thus enabling fewer voids during the night. This study investigated the levels of continuation with a range of doses of desmopressin oral lyophilisate in nocturia patients participating in a large Phase III clinical trial. Retention during three phases of the trial was evaluated in order to ascertain whether the dosage groups differed in the extent of patient persistence with medication.

Study design, materials and methods

This was a 3-part, multicenter study investigating the efficacy and safety of four doses of a fast-dissolving (MELT) formulation of desmopressin for the treatment of nocturia in adults. All treatments were administered orally once per night approximately 1 hour prior to bedtime; subjects were instructed to limit their fluid intake prior to drug self administration. Part I (Weeks 1–4) had a randomized, double-blind, placebo-controlled, parallel group design. A centralized web-based randomization system (WebEZ) was used to randomly assign subjects to 1 of 5 treatment groups: placebo or desmopressin MELT 10 µg, 25 µg, 50 µg, or 100 µg. Randomization was stratified by age (<65, ≥65 years) and by the absence/presence of NP, defined as a ratio of night-time urine volume/24-hour urine volume ≥33%. Part I was conducted with 7 visits (screening, Day 1 [dosing], Days 4, 8, 15, 22, and 28 [end of Part I]). Immediately upon completion of Part I, all subjects on active treatment continued into Part II on the same treatment for 1 to 6 months. Subjects assigned to placebo in Part I were randomly assigned to 1 of the 4 desmopressin groups in Part II and blinding was maintained throughout Parts I and II. Part II follow-up visits were on Days 4, 8, 15, 29 and every 4 weeks thereafter until the database was locked for Part I. The total treatment duration for each subject in Part II therefore depended on when that subject was randomized in Part I and was estimated to be a minimum of 4 weeks and a maximum of 6 months. Upon completion of Part II, subjects were given the option to participate in an extension study (Part III). Subjects were assigned to the same treatment group as in Part II, initially in a blinded manner. Subjects were unblinded and the study became open label only when all subjects in Parts I and II remaining in the study had entered Part III. The expected total treatment duration was at least 12 months. Part III of the study is ongoing. Full continuation data are available up to Week 35 of treatment. It was planned that 750 subjects should be enrolled into Part I, with 150 subjects per treatment group.

Results

There was a high rate of continuation for all groups in Part I (Table 1), with 89% of patients completing this phase of the trial. The completion rate was highest (94%) for the 25 µg group.

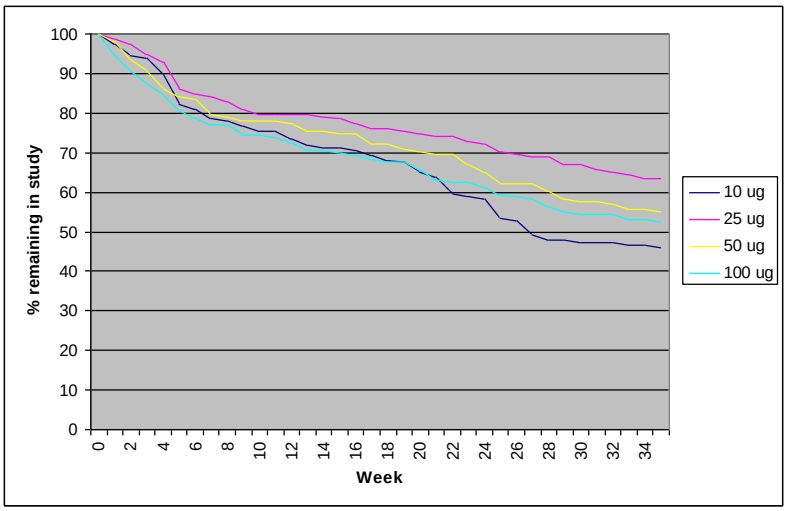
Table 1. Subject disposition, Part I (to Day 28)

	Placebo	**10 µg**	**25 µg**	**50 µg**	**100 µg**	**Total**
Randomized	160	163	158	158	160	799
Completed	145 (91%)	144 (88%)	148 (94%)	138 (87%)	135 (84%)	710 (89%)

Of the 710 subjects who completed Part I of the study, 665 subjects (93.7%) continued into Part II. A total of 566/665 subjects (85%) completed Part II. The most common reasons for discontinuation overall were withdrawal of consent (8%), adverse event (2%) and lost to follow-up (2%).

Figure 1 shows the percentage of patients in each desmopressin dosage group remaining in the study over time. Although all groups had similarly high rates of continuation for the first 4 weeks, by 35 weeks, a smaller proportion of patients (46.0%) remained in the lowest dosage group (10 µg) than in the other dosage groups (63.3%, 55.1% and 52.5% for the 25 µg, 50 µg and 100 µg treatment groups respectively). The 25 µg group again demonstrated the highest rate of continuation over the longer term.

Figure 1: patients remaining in the study over time



Interpretation of results

Continuation rates during the first 4 weeks of this study of desmopressin therapy for nocturia were high for all dosage groups, with the greatest level of persistence (94%) in one of the lower dosage groups (25 µg). At 35 weeks, less than half (46%) receiving the lowest dose (10 µg) remained, as compared with 63.3% who remained in the 25 µg group – again this was the highest rate of continuation amongst the treatment groups. This suggests that patients chose to continue with treatment at this dose, despite the possibility that higher doses of desmopressin may be more likely to satisfy formal efficacy endpoints. This may reflect the fact that low dosing achieves clinically meaningful improvements in nocturia, and that patients recognize the benefits of persisting with even low-dose treatment in order to maintain the reduction in night-time voiding that is achieved.

Concluding message

Persistence with therapy in some areas of urology, eg OAB (2, 3), is reported to be low. This is the first study to look at nocturia patients' long-term persistence with desmopressin oral lyophilisate therapy stratified by treatment dose. The rate of continuation was high, which supports the hypothesis that patients accept this treatment as an effective therapy for this bothersome condition. The relatively low dose of 25 µg was found to have the highest rate of persistence, indicating the perceived value of treatment in this dose range.

References

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Specify source of funding or grant	**Ferring Pharmaceuticals**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Clinicaltrials.gov NCT00477490, NCT00615836**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Approved by Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB) at each participating centre**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**