The “DRY” Study

Desmopressin Response in the Young: A double-blind, randomised, placebo-controlled, dose-titration study with three different doses (120 µg, 240 µg and 360 µg) of desmopressin administered as a new melt tablet in children and adolescents with Primary Nocturnal Enuresis (PNE)

Investigational product: Desmopressin melt tablet 120 µg
Placebo melt tablet (identical appearance)

Indication: Primary Nocturnal Enuresis

Phase: III

Name and address of Sponsor: Ferring, Inc
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North York, Ontario
M2J 5C1
Canada
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Study Initiation Date: First Patient First Visit: 10 August 2004
Study Completion Date: Last Patient Last Visit: 10 January 2006

GCP statement: This study has been performed in compliance with GCP.
SYNOPSIS

**TITLE OF STUDY:**
Desmopressin Response in the Young: A double-blind, randomised, placebo-controlled, dose-titration study with three different doses (120 µg, 240 µg and 360 µg) of desmopressin administered as a new melt tablet in children and adolescents with Primary Nocturnal Enuresis (PNE)

**INVESTIGATOR(S):**
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**STUDY CENTRE(S):**
Ten sites in Canada.

**PUBLICATION (REFERENCE):**
N/A

**STUDIED PERIOD (YEARS):**
(first subject first visit): 10 Aug 2004  
(last subject last visit): 10 Jan 2006

**PHASE OF DEVELOPMENT:**
III

**OBJECTIVES:**

*Primary Objective:*
To evaluate the efficacy of desmopressin administered as a melt tablet compared to placebo in terms of reducing the number of wet nights in children and adolescents with primary nocturnal enuresis.

*Secondary Objectives:*
To evaluate the efficacy of desmopressin administered as a melt tablet compared to placebo in terms of percentage baseline reduction in the number of wet nights.

To evaluate the efficacy of desmopressin administered as a melt tablet compared to placebo in terms of the proportion of full, partial and non-responders.

To investigate the safety and tolerability of desmopressin, administered as a melt tablet compared to placebo, for all doses tested.

**METHODOLOGY:**
A double-blind, randomised, placebo-controlled, dose-titration study with three different doses of desmopressin and placebo. Doses were administered once daily at bedtime.

**NUMBER OF SUBJECTS:**
169 subjects were screened in order to randomise a total of 132 subjects: 32 subjects in the placebo group and 100 in the desmopressin treatment group.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:**
Children and adolescents (age 5-16 years) with diagnosed primary monosymptomatic nocturnal enuresis were included in the study. For inclusion in the study the subject must have had a minimum of 3 wet nights per week in the 2-week screening period without treatment.

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:**
Desmopressin melt tablet 120 µg administered sublingually.  
Batch number: 100096
**DURATION OF TREATMENT:**
54 days

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:**
Placebo in the melt tablet formulation administered sublingually.
Batch number: 136447

**CRITERIA FOR EVALUATION:**

**Primary Endpoint**

**Efficacy:**
The reduction in number of wet nights from baseline (two-week screening period) to last two weeks at the end of treatment: (wet nights at treatment end) - (wet nights during screening).

Subject diaries were used to measure the number of wet nights.

**Secondary Endpoint**

**Efficacy**
Percentage baseline adjusted reduction in number of wet nights from the two-week screening period to last two weeks at the end of treatment: \[ \frac{[(\text{wet nights at treatment end}) - (\text{wet nights during screening})]}{(\text{wet nights during screening})} \times 100. \]

Frequency of response, based on the percentage reduction in the number of wet nights from the screening period to the last two weeks of treatment, in terms of full responders (≥ 90% reduction), partial responders (≥ 50% and < 90% reduction) and non-responders (< 50% reduction).

**Safety**
Frequency and type of adverse events.
Changes in other safety parameters (laboratory parameters, urinalysis, vital signs, physical examination).

**STATISTICAL METHODS:**
The efficacy analysis was based on the intent-to-treat population. Randomisation was planned as 3:1 for desmopressin versus placebo to provide maximum information on the subjects in the active treatment group.

The primary analysis was the analysis of covariance (ANCOVA) using the MIXED model with centre as a random effect and gender and age group (5-8 years, 9-11 years, 12-16 years) as the covariates. The reduction in the number of wet nights and the percentage reduction in wet nights were analyzed using this model; the percent reduction analysis also included baseline number of wet nights as a covariate. The rate of responders was analyzed by the Fisher’s Exact test.

The safety profile was analysed primarily by means of descriptive statistics and qualitative analysis. The safety assessment was based on the safety population. Treatment emergent adverse events were classified according to their intensity and relationship to the investigational product and by body system organ class. Laboratory values were assessed via mean values and pre-post shifts in the rate and type of abnormality.
**EFFICACY RESULTS:**

**Primary efficacy variable**

For the ITT population, the mean±SD reduction in number of wet nights from baseline to the last 14 days in the treatment period, was 3.2±4.69 per 14 days in the desmopressin melt group and 2.7±4.62 per 14 days in the placebo group. The adjusted between treatment group difference (with 95% CIs) was 0.50 (-1.77, 2.76); (p=0.6527).

For the PP population, the mean±SD reduction in number of wet nights from baseline to the last 14 days in the treatment period, was 3.7±4.76 per 14 days in the desmopressin melt group and 3.3±4.84 per 14 days in the placebo group. The adjusted between treatment group difference (with 95% CIs) was 0.26 (-2.63, 3.15); (p=0.8528).

**Secondary efficacy variables**

The mean±SD percentage reduction in number of wet nights from baseline to the last 14 days in the treatment period was 29.8%±42.36 in the desmopressin group and 25.4%±42.42 in the placebo group. The covariate adjusted LSmean difference (with 95% CIs) was 2.26 (-22.24, 26.77); (p=0.8489).

The percentage of full responders, partial responders and non-responders was 15.0%, 21.0% and 64.0%, respectively, in the desmopressin melt group, and 12.5%, 18.8% and 68.8%, respectively, in the placebo group. When the full and partial responders were combined into a responder category, the odds ratio (with 95% CIs) was 1.238 (0.528, 2.900).

In the desmopressin melt group, 10.0% of the subjects achieved complete dryness, as did 9.4% of subjects in the placebo group; the odds ratio (with 95% CIs) was 1.074 (0.277, 4.170).

**SAFETY RESULTS:**

In the desmopressin melt treatment arm, 29 subjects (29.3% of the safety population) experienced 44 treatment-emergent AEs. In the placebo group, 8 subjects (25.0% of the safety population) experienced 13 AEs. None of the AEs was judged to be possibly or probably related to study medication. There were no serious AEs. None of the AEs led to discontinuation of study medication. The majority of AEs were mild and only one event (nausea) was classified as severe.

Clinically significant abnormal changes in biochemistry parameters (elevations in creatinine and BUN) were reported in one subject, and in haematology parameters in two subjects (decrease in platelet and white blood cell count). There were no clinically significant changes in urinalysis parameters, vital signs or physical findings.
CONCLUSIONS:
The efficacy of desmopressin melt was consistent with the level of reduction in wet nights as reported in previous placebo-controlled studies involving bioequivalent doses of the tablet formulation. However, for both the primary and secondary endpoints, there was no significant difference between desmopressin melt tablet and placebo as the placebo patients exhibited a higher than expected response.

The unexpected and unprecedented placebo response has been investigated and the conclusion reached is that no single cause can be found to explain the response.

Desmopressin was well-tolerated. The percentages of adverse events were comparable across both treatment groups and the majority of AEs were mild. There were no serious AEs. None of the AEs was judged to be possibly or probably related to study medication. None of the AEs led to discontinuation of study medication. Changes in laboratory parameters, urinalysis, vital signs and physical findings were also similar in both treatment groups.

The safety and efficacy of desmopressin administered as a melt tablet at doses up to 360 µg is consistent with longstanding historical data for bioequivalent formulations used in the treatment of primary nocturnal enuresis.