CLINICAL STUDY REPORT

A 6-week open label cross-over study with 2 different daily doses of Minirin® oral lyophilisate (120 µg and 240 µg) and 2 different daily doses of Minirin® tablet (0.2 mg and 2 x 0.2 mg) in children and adolescents with primary nocturnal enuresis (PNE)

FE992026 CS022

EudraCT No.: 2004-000593-32

Investigational Medicinal Product: Desmopressin (FE992026) oral lyophilisate (120 µg and 240 µg) and desmopressin tablet (0.2 mg and 2 x 0.2 mg)

Indication: Primary Nocturnal Enuresis

Phase: IIIb

Study Initiation Date: 07 December 2004
Study Completion Date: 11 September 2005

Name and Affiliation of Chief Investigator:

[redacted]

Name and Address of Sponsor:

[redacted]
Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark
[redacted]

GCP Statement: This study has been performed in compliance with GCP.

SYNOPSIS

TITLE OF STUDY: A 6-week open label cross-over study with 2 different daily doses of Minirin® oral lyophilisate (120 µg and 240 µg) and 2 different daily doses of Minirin® tablet (0.2 mg and 2 x 0.2 mg) in children and adolescents with primary nocturnal enuresis (PNE).

CHIEF INVESTIGATOR: [redacted]

STUDY CENTRES: The study was conducted in 30 centres in 8 countries: France (5), Germany (8), The Netherlands (7), Sweden (1), Denmark (1), Norway (1), Finland (1) and the United Kingdom (6).

PUBLICATION (REFERENCE): Not applicable.

STUDIED PERIOD (YEARS):	**PHASE OF DEVELOPMENT:**
07 December 2004 11 September 2005	IIIb

OBJECTIVES:

Primary Objective:

To evaluate the preference of subjects for Minirin® oral lyophilisate treatment compared with Minirin® tablet treatment after 6 weeks.

Secondary Objectives:

- To compare efficacy of the 2 formulations at the end of the 6-week treatment period using diary card data.
- To compare ease of use of both formulations at 3 and 6 weeks using a visual analogue scale (VAS).
- To validate a PNE Quality of Life (QoL) questionnaire (not applicable for Norway and Sweden).
- To evaluate safety.
- To compare compliance with the 2 formulations.

METHODOLOGY:

This was a randomised, 6-week, open label, daily dose, cross-over study. Subjects with PNE who had been taking desmopressin tablets for a minimum of 2 weeks, and who were stabilised on a dose of either 0.2 mg or 2 x 0.2 mg, were screened for inclusion in the study. At screening (Week -2, Visit 0) a diary was issued for the subject to record daily enuretic events and dose of desmopressin during a 2-week screening treatment period. At baseline (Week 0, Visit 1), the subject had to have completed at least 7 diary days during the 2-week screening treatment period to be randomised into the cross-over treatment period. Eligible subjects were randomised to receive the study treatments in the order oral lyophilisate/tablet or tablet/oral lyophilisate, the dose during the study was equivalent to the dose being taken at the screening visit. At Week 0, a second diary was issued. Subjects attended the centre after a further 3 weeks (Week 3, Visit 2) when diaries were collected and reviewed, ease of use of the formulation was assessed using a VAS and a QoL questionnaire was completed. A third diary was issued for completion during the second study treatment period. Subjects returned to the centre at Week 6 (Visit 3) when the Week 3 assessments were repeated, the preference for either of the 2 formulations was recorded, a physical examination was performed and vital signs were assessed. A post-study safety evaluation was performed by telephone at Week 7 to Week 9, *i.e.*7 to 21 days after the last dose.

NUMBER OF SUBJECTS:

It was planned that 230 subjects would be recruited to the study and that 200 subjects would be randomised into the cross-over period.

	All Subjects	Number of Subjects by Dose Group		Number of Subjects by Treatment Sequence	
		D1	D2	Oral Lyophilisate/ Tablet	Tablet/ Oral Lyophilisate
Entered Study	236	76	160		
Dosed in Screening Period	232	76	156		
Randomised	221	72	149	111	110
Dosed in Period 1	220	72	148	110	110
Dosed in Period 2	214	70	144	107	107
Completed Study	210	66	144	105	105

D1=120 µg oral lyophilisate and 0.2 mg tablet; D2=240 µg oral lyophilisate and 2 x 0.2 mg tablet.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Children and adolescents (age 5 to15 years, or as determined by marketing authorisation in each country) with monosymptomatic PNE who had been on a stable dose level of 0.2 mg or 2 x 0.2 mg desmopressin tablet for at least 2 weeks.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

FE992026 (desmopressin [Minirin®]) provided by Ferring Pharmaceuticals A/S, 120 µg or 240 µg oral lyophilisate, was administered sublingually once a day at bedtime without water (unless specifically requested by the subject). The dose of oral lyophilisate was determined by the dose of desmopressin tablet that subjects were stabilised on at entry to the study: subjects stabilised on 0.2 mg desmopressin tablet were allocated to receive 120 µg desmopressin oral lyophilisate, and subjects stabilised on 2 x 0.2 mg desmopressin tablets were allocated to receive 240 µg desmopressin oral lyophilisate.
Batch number: 100096 (120 µg) and 95198 (240 µg).

DURATION OF TREATMENT:

During a 2-week screening treatment period, subjects received 0.2 mg or 2 x 0.2 mg Minirin® tablet. Subjects then received study treatment for 6 weeks during the cross-over treatment period: each of the 2 formulations (oral lyophilisate and tablet) was administered for 3 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Desmopressin (Minirin®), 0.2 mg or 2 x 0.2 mg tablet depending on the stabilised dose at study entry, was administered orally once a day at bedtime with a little water.
Batch number: FB 8170, FH 8482, FI 8552 and FK 8600.

CRITERIA FOR EVALUATION:

Efficacy: Preference for one of the 2 formulations at the end of the 6-week treatment period; difference between the 2 formulations in incidence of bedwetting episodes; and ease of use of formulation assessed by VAS score.
Safety: Adverse events (AEs), physical findings and vital signs.
Primary Endpoint: The proportion of subjects who preferred one of the formulations at the end of the 6-week treatment period, evaluated by asking a question as to which treatment was preferred.
Secondary Endpoints: Difference between treatment groups for the average incidence of bedwetting episodes in each 3-week treatment period; ease of use of each formulation rated by a 100 mm VAS (0 = I find it very easy to use this medicine and 100 = I find it very difficult to use this medicine); QoL questionnaire responses (to be reported separately); and compliance with use of each formulation.

STATISTICAL METHODS:

The primary efficacy endpoint was analysed using the exact binomial test for a single proportion. This analysis was performed using both the ITT and PP datasets. A sensitivity analysis was also performed using the ITT dataset only. The approach of the sensitivity analysis was as follows: (1) All subjects with missing data were assigned the best possible outcome (*i.e.* they all preferred oral lyophilisate); (2) All subjects with missing data were assigned the worst possible outcome (*i.e.* they all preferred tablet); (3) All subjects with missing data were divided equally between the best and worst possible outcomes. A *post-hoc* statistical analysis of the primary endpoint by age group (<12 years and 12+ years) using the exact binomial test was also performed for the ITT dataset.

Logistic regression was performed on the primary efficacy endpoint using this variable as a binary response 'oral lyophilisate/tablet'. The model included terms for sequence, age and dose group and the analysis provided a p-value of significance for sequence and dose group. This secondary analysis investigated if there was any dose, sequence or age effect on the preference proportions. The effect size, 95% CI and p-value were provided in the table for the factors in the model, sequence and dose group. These analyses were produced using the ITT and PP datasets.

The secondary efficacy endpoints (*i.e.* mean incidence of bedwetting episodes and VAS score) in each treatment period were analysed using an analysis of covariance (ANCOVA) model with terms for sequence, age, treatment, dose group, treatment by dose group interaction, period and a random factor for subject. Using the error variance from the ANCOVA model, the overall treatment effect was estimated and presented along with the CIs. If the treatment by dose group interaction was found to be non-significant at the 10% level then it was to be removed from the model and the results based on the model excluding this term presented in the table. The residual normality was investigated using the Sharpiro-Wilk test and if the p-value for this test was significant then it was to be concluded that the normality assumption had not been satisfied. The residual normality was also investigated using normal probability plots and the homogeneity of variance was investigated using a plot of the studentised residuals *vs* the predicted values. If either assumption was clearly not satisfied, the non-parametric method by Hauschke, Steinijans and Diletti was to be performed. If the results from the non-parametric method were similar to the results from the ANCOVA, (*i.e.* both analyses reached the same conclusion) the results from the ANCOVA were to be presented and a footnote added to the analysis table to clarify the situation. A point estimate, p-value, and appropriate CI for the adjusted treatment differences were reported. For the factors in the model, sequence, age, dose group and period, the effect size, 95% CI and p-value were provided. The within-subject differences were calculated as the mean for each subject for oral lyophilisate minus the mean for tablet.

The mean volume of water taken with IMP was summarised for the ITT and PP datasets.

In the planned analysis, the mean incidence of bedwetting episodes and mean volume of water taken with IMP were calculated including days where no data were recorded in the denominator of the calculation (effectively imputing days with missing data as a 'wet night' and '0 ml of water taken with IMP'). A *post-hoc* sensitivity analysis was performed using a revised calculation for these variables which excluded days where no data were recorded.

All safety parameters were summarised by treatment group and timepoint (where appropriate) using the safety dataset. No formal statistical analysis on safety variables was performed.

EFFICACY RESULTS:

Overall, a higher proportion of subjects preferred oral lyophilisate to tablet (55.7% [95% CI: 48.7%, 62.5%] and 53.8% [95% CI: 46.0%, 61.4%] for the ITT and PP datasets, respectively) although these differences were not statistically significant. The proportion of subjects preferring each formulation in the sensitivity analysis of the preference assessment (which included missing data with 3 different approaches) was similar to those in the primary analysis and thereby confirmed the results.

Age was found to be a statistically significant factor on preference of formulation in both the ITT and PP datasets, with younger subjects being more likely to prefer oral lyophilisate to tablet. Consequently, a *post-hoc* statistical analysis by age group (<12 years and 12+ years) was performed on the ITT dataset. For subjects <12 years, the proportion of subjects preferring oral lyophilisate was statistically significantly higher than the proportion preferring tablet (60.6% [95% CI: 52.6%, 68.2%]; p-value=0.009). For subjects

aged 12+ years, the proportion of subjects preferring oral lyophilisate was lower than the proportion preferring tablet (40.0% [95% CI: 26.4%, 54.8%]) but the difference was not statistically significant.
The sequence in which the subjects received the treatments had no effect on preference for either of the formulations in either the ITT or PP dataset. Dose group was found to be statistically significant for subjects in the PP dataset, where subjects in the low dose group were more likely to prefer oral lyophilisate compared with tablet (parameter estimate -0.694 [95% CI: -1.375, -0.014]; p-value=0.046). There was also a tendency toward this in the ITT dataset although the difference was not statistically significant (parameter estimate -0.548 [95% CI: -1.162, 0.066]; p-value=0.080).
There was no statistically significant difference between oral lyophilisate and tablet in the mean incidence of bedwetting episodes per week for the ITT or PP datasets indicating that the efficacy of the formulations was similar. However, for the ITT dataset there was a significant treatment by dose group interaction at the 10% significance level in the statistical analysis which implied that the treatment effect was not consistent across dose groups (mean treatment differences of -0.26 [95% CI: -0.53, 0.01] and -0.05 [95% CI: -0.21, 0.10] episodes per week for the analyses including and excluding the treatment by dose group interaction term, respectively). Because the interaction was essentially quantitative (the parameter estimates indicated that the difference across dose groups within each formulation was in the same direction, but of a different magnitude) and the treatment by dose group interaction was not statistically significant for the PP dataset, the effect of treatment is primarily assessed from the model without the interaction. Age and dose group had a statistically significant effect on the incidence of bedwetting episodes in the ITT dataset with younger subjects and subjects in the high dose group being more likely to have a higher mean incidence of bedwetting episodes, for both formulations.
There was no statistically significant difference between formulations in mean ease of use of formulation evaluated by VAS score (mean treatment difference -0.4 [95% CI: -5.6, 4.7] mm and 1.4 [95% CI: -4.0, 6.8] mm for the ITT and PP datasets, respectively). Mean ease of use of formulation VAS scores for the ITT dataset were 21.4 and 21.8 mm for oral lyophilisate and tablet, respectively (where 0 mm = I find it very easy to use this medicine and 100 mm = I find it very difficult to use this medicine). Dose group and period had a statistically significant effect on VAS score with subjects in the high dose group and in the second treatment period, being likely to report higher values (*i.e.* found the formulation more difficult to use) irrespective of formulation.
Mean treatment compliance and the proportion of compliant subjects were similar for oral lyophilisate and tablet overall and in both dose groups. Overall, 94.5% and 88.9% of subjects were compliant *(i.e.* ≥80% compliant) for oral lyophilisate and tablet, respectively.
The median of the mean volume of water taken per week with oral lyophilisate was lower than that taken with tablet for those subjects who recorded a value. The median of the mean volume of water taken with IMP per week was 26.7 ml (oral lyophilisate) and 189.6 ml (tablet) using the original formula to calculate mean volume. The median of the mean volume of water taken per week with oral lyophilisate was also lower than that taken with tablet using a revised formula to calculate the mean volume of water taken per week but the difference between formulations was smaller (median values of 140.0 ml [oral lyophilisate] and 175.0 ml [tablet]).
The percentage of dosing occasions where fluid intake was recorded was lower for the oral lyophilisate than for the tablet formulation (13.1% *vs* 76.9%). Where fluid intake was recorded, the median volume of water taken per dosing occasion was the same for the oral lyophilisate and tablet formulations (both 30.0 ml).

SAFETY RESULTS:

The following conclusions were made from the results of safety assessments performed in this study.
No deaths were reported during the study and no subject was withdrawn from the study as the result on an AE. One SAE of tonsillitis was reported after the screening treatment period (2 x 0.2 mg) and before the subject received any randomised treatment (oral lyophilisate/tablet). The SAE was considered by the investigator to be unrelated to the study treatment and to be of severe intensity. One incidence of pneumonia, which occurred during the screening treatment period (2 x 0.2 mg) was reported to be of severe intensity. All other AEs were considered by the investigator to be of mild or moderate intensity.

There was no marked difference between oral lyophilisate and tablet in the proportion of subjects experiencing AEs or IMP-related AEs in either D1 or D2. The proportion of subjects experiencing AEs was higher in D2 than in D1 for both formulations.
In D1, there was no marked difference between oral lyophilisate and tablet in the proportion of subjects experiencing AEs or IMP-related AEs in any preferred term category. In D2, a slightly higher proportion of subjects experienced AEs of headache in the oral lyophilisate treatment period compared with the tablet treatment period (6 subjects [4.1%] *vs* one subject [0.7%]). None of the subjects who experienced an AE of headache had a marked abnormal weight gain (which may have indicated that water retention was a contributing factor). There were no marked differences between oral lyophilisate and tablet in the proportion of subjects who experienced AEs in any other preferred term category or IMP-related AEs in any preferred term category.
At the end of the study, 9 subjects had changes from screening on physical examination reported as AEs. None of these was considered to be related to IMP. There were no marked changes in mean values for any vital signs variable or in body weight, and no individual assessment was reported as an AE.

CONCLUSIONS:
The following overall conclusions were made from the results of this study.
A higher proportion of subjects prefer Minirin® oral lyophilisate to Minirin® tablet but the difference is not statistically significant. A statistically significantly higher proportion of younger subjects (*i.e.* <12 years of age) express a preference for Minirin® oral lyophilisate over Minirin® tablet.
Minirin® oral lyophilisate and Minirin® tablet are similar in terms of efficacy (assessed by incidence of bedwetting episodes) and in ease of use.
Compliance is similar in subjects treated with Minirin® oral lyophilisate or Minirin® tablets regardless of dose.
No safety concerns are associated with Minirin® oral lyophilisate administered at the 120 µg or 240 µg dose or with Minirin® tablets administered at the 0.2 mg or 0.4 mg dose. The safety profile is similar for the two formulations.
Results of QoL assessments performed in this study are not presented in this report.