

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-795

STATISTICAL REVIEW(S)

12/14/05



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-795
Name of drug: Minirin (desmopressin acetate) Tablets, 0.1 mg and 0.2 mg
Applicant: Ferring Pharmaceuticals
Indication: 1. Central diabetes insipidus 2. Primary nocturnal enuresis 3.
Renal concentrating capacity test
Documents reviewed: Vols. 1.29-1.43
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Keywords: NDA review, clinical studies

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS

Minirin 0.6 mg tablet was noninferior to the nasal spray 20 µg in the renal concentrating capacity test (RCCT) according to the pre-specified noninferiority margin equal to 7% of the mean nasal spray osmolality. Both formulations were better than placebo for the test.

The study for primary nocturnal enuresis extending the results to patients 45 years of age was not statistically significant comparing the 0.4 mg to 0.2 mg ($p=0.08$) using analysis of covariance adjusting for baseline. However, the 0.4 mg dose does not need to be superior to 0.2 mg to be a useful dose. Minirin 0.4 mg was associated with a least square mean reduction from baseline of 3.7 wet nights per week and the 0.2 mg dose was associated with a least square mean reduction of 2.9 wet nights per week.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

This review pertains to 2 studies of desmopressin tablets for the proposed 2 new indications: 1. use as a renal concentrating capacity test (RCCT), and 2. Management of primary nocturnal enuresis (PNE) in adults _____

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The renal concentration capacity is a vital function of kidney to maintain water homeostatis. Intranasal Minirin was used as a night-time Renal Concentrating Capacity Test (RCCT) to determine the extent of renal impairment in children with urinary tract disorders. The sponsor conducted a crossover study to investigate noninferiority of Minirin tablets (0.6 mg) to intranasal Minirin in inducing the kidneys to concentrate urine.

This submission relies on NDA 19-776 that was approved and delisted for the intranasal dosage form (Concentraid, 0.1 mg/ml solution, single use pipettes) to test RCCT for safety and efficacy and NDA 19-955 that is approved for DDAVP tablets (0.1 mg and 0.2 mg) for the treatment of PNE in children 6 years of age and older and for the treatment of Central Diabetes Insipidus.

Minirin tablets are _____ to the currently approved DDAVP tablets (NDA 19-955) which Ferring AB is the approved manufacturer for the NDA-holder, Aventis. The clinical data is to support approval of a tablets dosage form for the indication of RCCT and the extension of PNE indication to adults. Table 1 displays the two randomized studies for the 2 new indications, respectively.

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Figure 2 Median urine osmolality by treatment group and treatment sequence

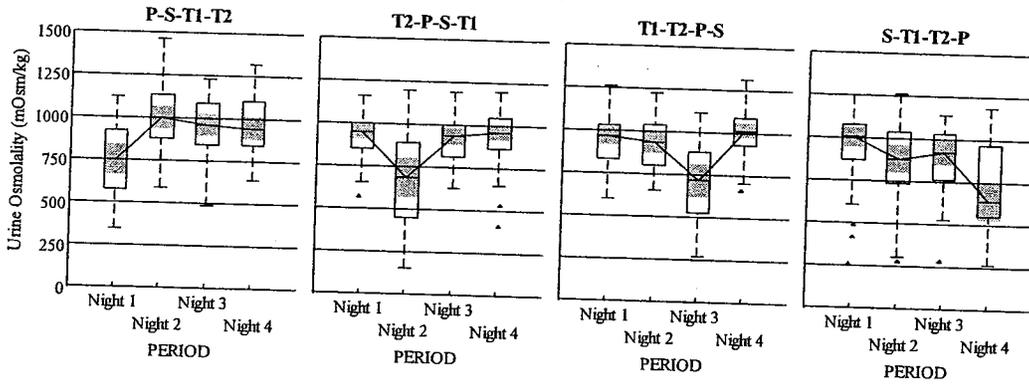
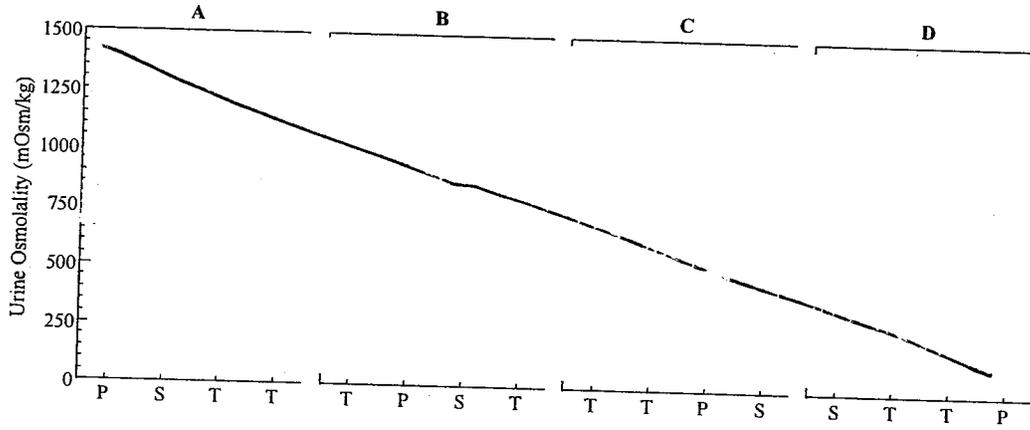


Figure 3 Patient level urine osmolality over the 4 periods grouped by sequence



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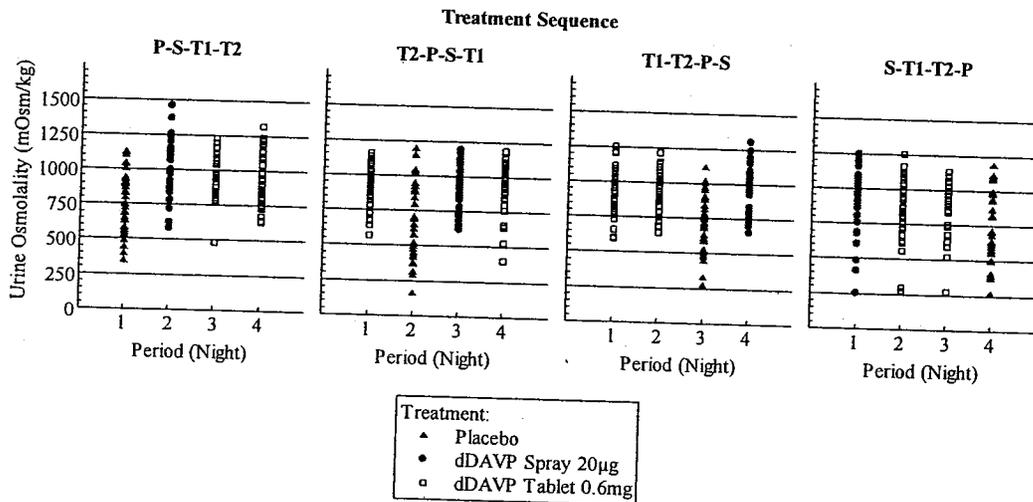


Table 1 BRIEF SUMMARY OF CONTROLLED TRIAL

Study ID	Study population n	Treatment	Type of Study & Control	No. of patients for efficacy analysis
45A03-008	Children aged 3-18 years with an indication for RCCT for renal disease	dDAVP tablets 0.6 mg dDAVP spray 20 µg Placebo	4-period, 4 sequence crossover, randomized, double-blind, double-dummy (placebo nasal spray, placebo tablet), multicenter (6 centers). 0.6mg Mimirin tablets (T) 2 nights, 20µg Mimirin nasal spray (S) one night and placebo (P) one night. Sequence A: P, S, T1, T2 Sequence B: T2, P, S, T1 Sequence C: T1, T2, P, S Sequence D: S, T1, T2, P	ITT: 145 PP: 118
45A06-53	Patients 12 to 45 years of age with PNE	dDAVP tablets 0.2 mg dDAVP tablets 0.4 mg	1. 2-week observation period 2. 2-week Mimirin nasal spray 20 µg 3. randomize patients achieving ≥50% reduction in # of wet nights/week to 200 µg or 400 µg tablets 4. 1-week washout (≥1 wet night during washout) 5. 4-week double-blind treatment 6. 2-week washout 7. 12-week open label 400 µg 8. 2-week washout	ITT: 63 PP: 56

RCCT – Protocol 45A03-008

The primary objective was to show noninferiority of tablet to the intranasal formulation in inducing the kidneys to concentrate urine in the assessment of a RCCT performed during the night. The primary efficacy variable was urine osmolality. The placebo treated night served as baseline. All treatments in the sequence were separated by at least one washout medication-free night.

Disposition of patients

A total of 154 patients aged 3 to 18 years with renal disease were randomized to the 4 treatment sequences in 6 centers in Sweden. Nine patients were excluded (1 included twice, 7 not exposed and 1 had no efficacy measurement) and leaving 145 patients in the ITT population. Eleven patients did not complete the study.

Demographic and Baseline Characteristics

Most patients were Caucasians (97.5%) and females (67.8%). Table 2 displays the descriptive statistics for age, weight, and height.

Table 2 Patient demographics

	n	Mean (SD)	Median	Min, Max
Age (yrs)	145	9.5 (3.5)	9.3	3.5, 17.2
Weight (kg)	139	34.7 (15)	31.8	15, 86.6
Height (cm)	143	135.4 (20)	134	100, 183

Primary efficacy evaluation

The sponsor stated that ‘finding a higher variability in urine osmolality after placebo than after Minirin was not expected and precluded the use of the four periods, four treatments high order cross-over model. Since the variability after Minirin tablets and nasal spray was equivalent a normal model for the Minirin formulations excluding placebo, could still have been employed. This would give marginally higher power and shorter confidence intervals, which would however just strengthen the already clear conclusions. Therefore, the only the analyses considering each contrast separately, which were pre-specified in the statistical analysis plan, have been performed. Since Minirin is used for a diagnostic test in this study it is questionable whether the standard method to establish non-inferiority for therapeutic treatment drugs is the best way to compare different diagnostic methods.’ The sponsor’s analysis was valid as long as it was prespecified. However, the aforementioned separated statistical analysis plan was not evidently presented in the submission.

The sponsor’s analysis was based on within-patient contrast which was robust in making no assumptions about the covariance structure. Under the assumption of no carry-over effect, the primary analysis was a one-way ANOVA with sequence group as the factor and the contrast $((T1+T2)/2)-S$ as paired observations for the dependent variable. The last column of Table 3 displays the results of the analysis based on the ITT population and the PP population. The placebo group was not in the ANOVA analysis.

The sponsor designated the PP population as the primary population for analysis. However, the intent-to-treat population is the primary population of choice regardless of the study design (superiority or noninferiority) for reducing the bias and increasing the power of the test.

Table 3 ANOVA* analysis on Urine Osmolality (mOsm/kg)

	Placebo	Tablet mean (T1+T2)/2 0.6 mg (3x0.2 mg)	Nasal Spray mean 20 µg (2x10µg)	(T1+T2)/2 minus Spray LSM (95% CI)
PP	N=118	N=118	N=118	
Mean (SD)	721.4 (245.5)	933.5 (150.0)	978.0 (175.5)	-44.5 (121.4) (-67.0, -22.0)
p-value				0.0002 Margin=-68.5
ITT	N=141	N=137	N=144	N=137
Mean (SD)	718.3 (239.4)	930.4 (149.1)	961.7 (187.0)	-40.7 (127.1) (-62.2, -19.2)
p-value				0.0003 Margin=- 67.3

* treatment sequence as independent variable and $(T1+T2)/2$ minus S as dependent variable

The prespecified non-inferiority margin was -7% of the mean osmolality after nasal spray. For ITT population the margin was -67.3 (-961.7x.07). The -62.2 lower confidence limit was within the margin, therefore the tablet was noninferior to the nasal spray in RCCT, but on the other hand, the nasal spray is statistically better than the tablet (p=0.0003).

This reviewer performed cross-over analysis as sensitivity analysis. The least mean and confidence interval for the ITT population was -38.4 (-66.6, -10.1) and the PP population was -44.9 (-75.5, -14.2). The lower limit of the PP analysis exceeded the margin.

The sponsor did not include the center in the model. This reviewer found that the treatment-by-center interaction was not significant ($p=0.78$) which justifies it not being included in the model.

The 227 (SD 213.7) mosm/kg mean difference between Minirin $(T1+T2+S)/3$ (948.3 mosm/kg and placebo (721.4 mosm/kg) was statistically significant ($p<0.000005$) which confirmed the efficacy of Minirin for RCCT.

Table 4 displays the mean, standard deviation of urine osmolality by treatment group for the 4 treatment sequences. In each sequence the standard deviation in the placebo group was the greatest among the groups. The mean urine osmolality of the nasal spray was greater than the tablet except in sequence B (T2-P-S-T1). Figures 1-5 display the urine osmolality by patient, period or sequence.

Table 4 Mean (SD) of osmolality (m osm/kg) by sequence and treatment – ITT population

Sequence	n	P	T1	T2	S	$(T1+T2)/2$	$(T1+T2)/2 - S$
A. P-S-T1-T2	36	762 (218)	967 (153)	963 (178)	1014 (187)	965 (146)	-49 (124)
B. T2-P-S-T1	34	685 (271)	933 (126)	945 (145)	929 (144)	939 (119)	10 (123)
C. T1-T2-P-S	34	697 (204)	928 (154)	932 (147)	984 (152)	930 (119)	-54 (124)
D. S-T1-T2-P	33	739 (260)	884 (228)	885 (201)	954 (227)	885 (196)	-70 (136)

Figure 1 Mean (SD) urine osmolality by treatment sequence and period – ITT population

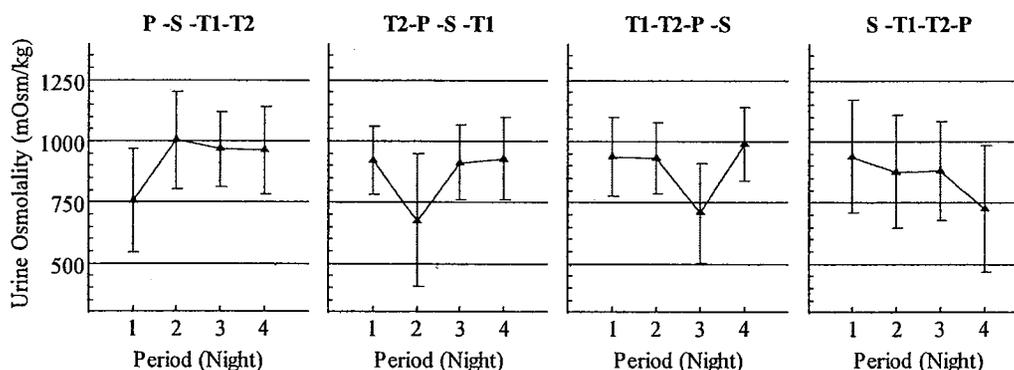
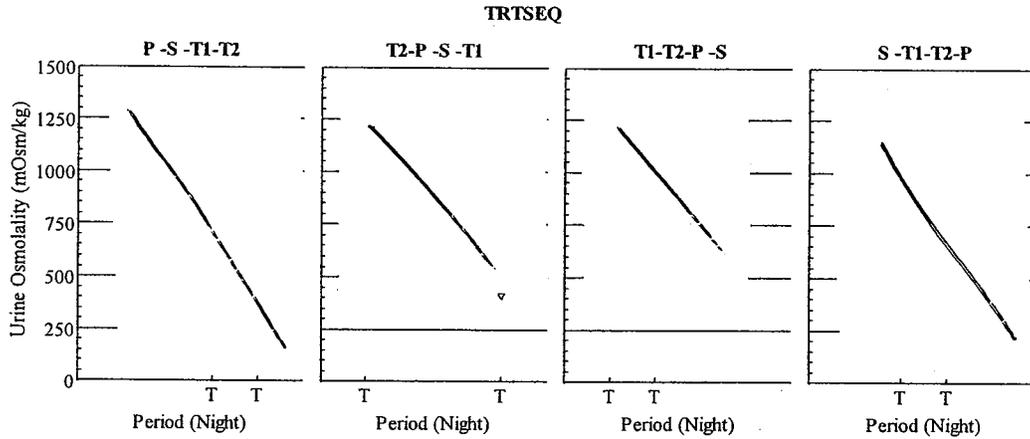
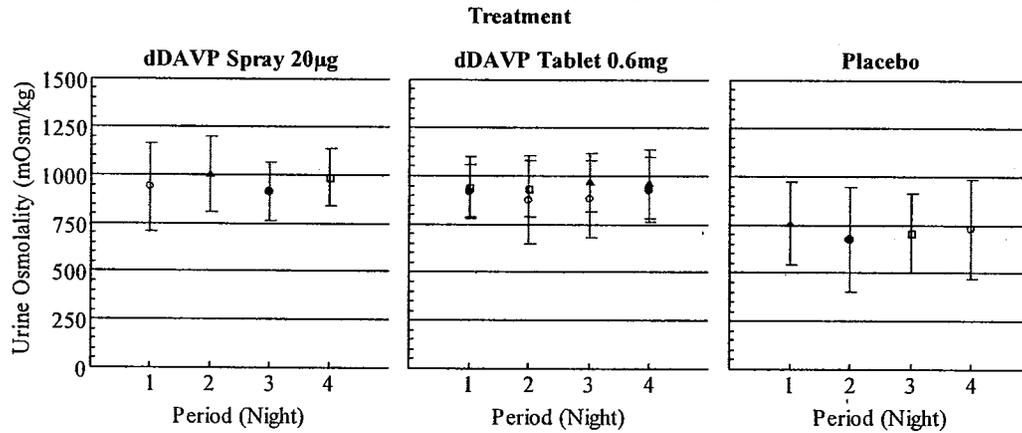


Figure 4 Urine osmolality by patient for the 2 Tablet periods for each sequence



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Figure 5 Mean (SD) urine osmolality by period grouped by treatment



Treatment Sequence:
 ▲ P-S-T1-T2
 ● T2-P-S-T1
 □ T1-T2-P-S
 ○ S-T1-T2-P

Figures 6 and 7 explore the agreement between the 2 nights using tablets for RCCT. The histogram for the difference of T1-T2 showed the differences are normally distributed with the second sequence least variable (bell shape narrower).

Figure 6 Agreement of the osmolality of the 2 tablet treatments
 Treatment Sequence

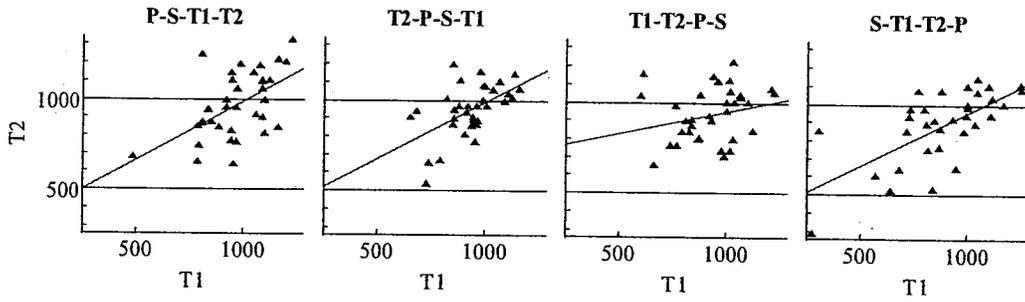
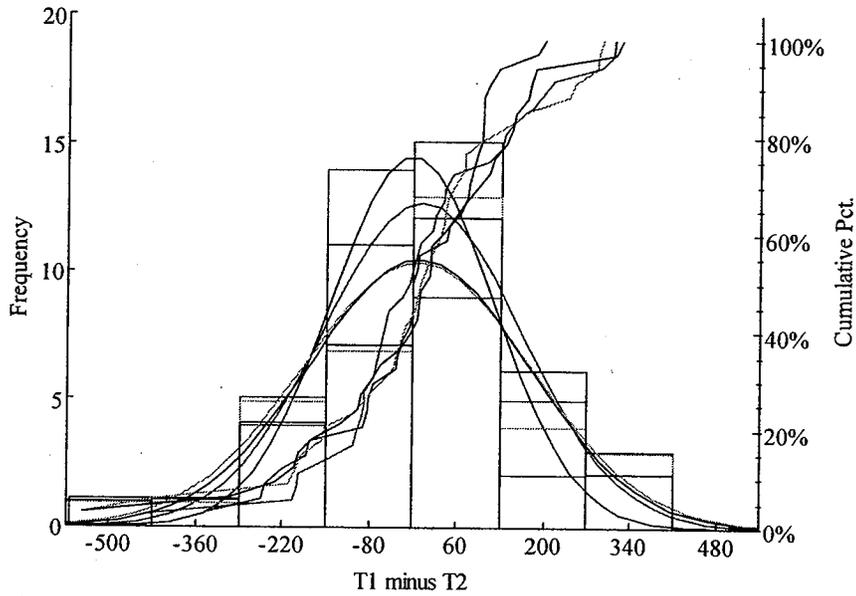


Figure 7 Histogram and Cumulative distribution of the difference in osmolality between the 2 tablet treatment nights (Tablet 1 minus Tablet 2)



Treatment Sequence:
 — P-S-T1-T2
 - - T2-P-S-T1
 . . T1-T2-P-S
 - . S-T1-T2-P

Subgroups

Figure 8 displays no treatment-by-gender effect of Minirin in urine osmolality. Figure 9 shows the treatment-by-age interaction was not significant ($p=0.5$).

Figure 8 Mean (SD) urine osmolality by treatment and gender

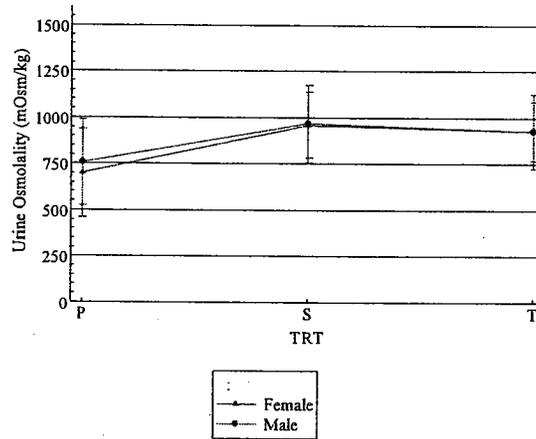
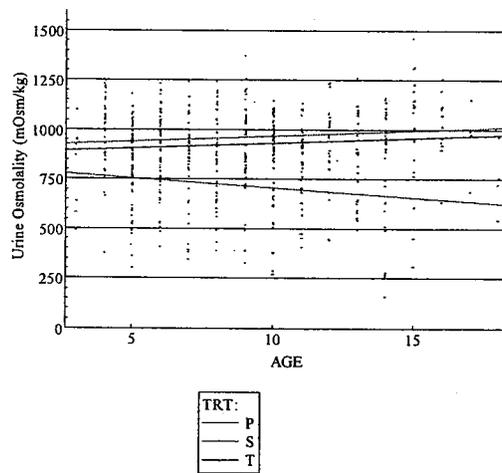


Figure 9 Regression of urine osmolality by age



Study 45A06-53

The primary objective of the study was to compare 2 doses of desmopressin tablets (200 and 400 μg) in the management of primary nocturnal enuresis in adolescents and adults (12-45 years of age) that are known responders to 20 μg Minirin nasal spray.

This multicenter, randomized, double-blind, parallel group study began with a 2-week observation period (baseline) followed by a 2-week period of treatment with Minirin nasal spray 20 μg . The responders (achieving $\geq 50\%$ reduction in wet nights/week) were

randomized to 4 weeks of treatment with desmopressin tablets 200 µg or 400 µg at bedtime after a 1 week washout period during which there was at least 1 wet night.

The sample size of 40 patients per group was to detect a 10% (0.57 units) difference in mean wet nights between patients on 200 µg and 400 µg with 80% power and a standard deviation of the difference of 0.8 unit.

The null hypothesis of the analysis was that there was no difference between the 2 oral strengths in reducing the number of wet nights against the alternative hypothesis that there was a difference between the 2 strengths.

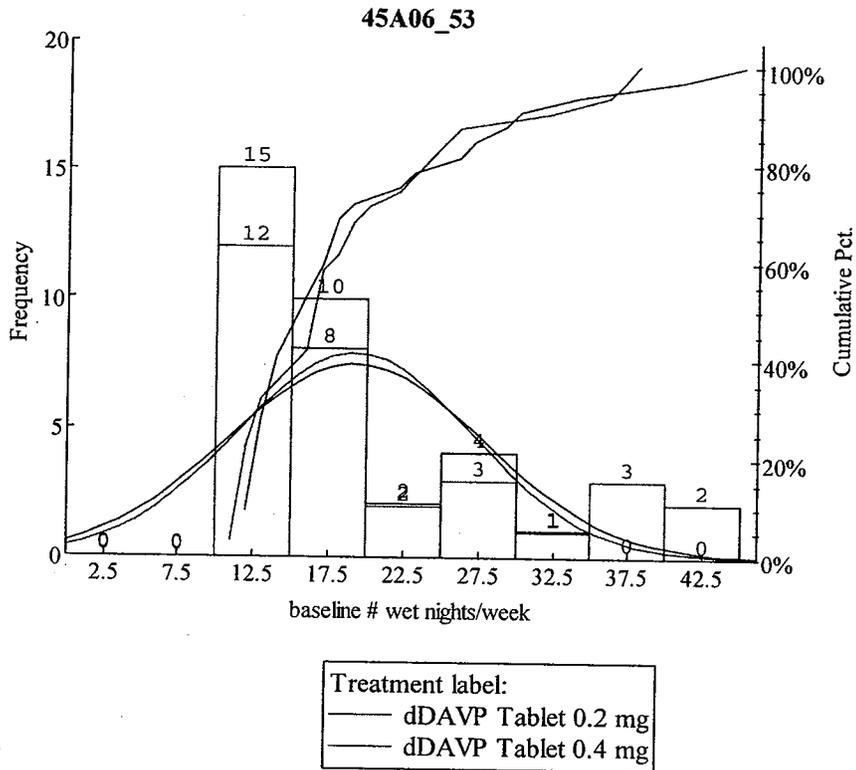
Patient disposition

Of the 90 patients who were selected and began a 2-week observation run-in period, 10 were excluded. Nine of the 10 patients experienced <6 wet nights during run-in and one failed to provide consent. Eighty patients began a 2-week period of treatment with Minirin nasal spray. Fourteen patients were removed from the study (10 failed to respond, 2 became dry during washout and 2 lacked cooperation). The remaining 66 were randomized to receive 4 weeks of double blind treatment (200 µg or 400 µg). Three of the 66 patients were excluded from the efficacy analysis: 1 due to adverse event (0.2 mg), 1 patient lost to follow up and 1 due to non-cooperative attitude (0.2 mg).

Fifty-seven percent of patients were male and 42% were female. The mean age for patients was approximately 19.2 years for both of the treatment groups. The range was from 11 years to 45 years. The median age was 17 years and 16 years for the 0.2 mg group and the 0.4 mg group, respectively. Figure 10 displays the histogram for age with cumulative distribution curves.

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Figure 10 Histogram of age with cumulative distribution



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Efficacy Results

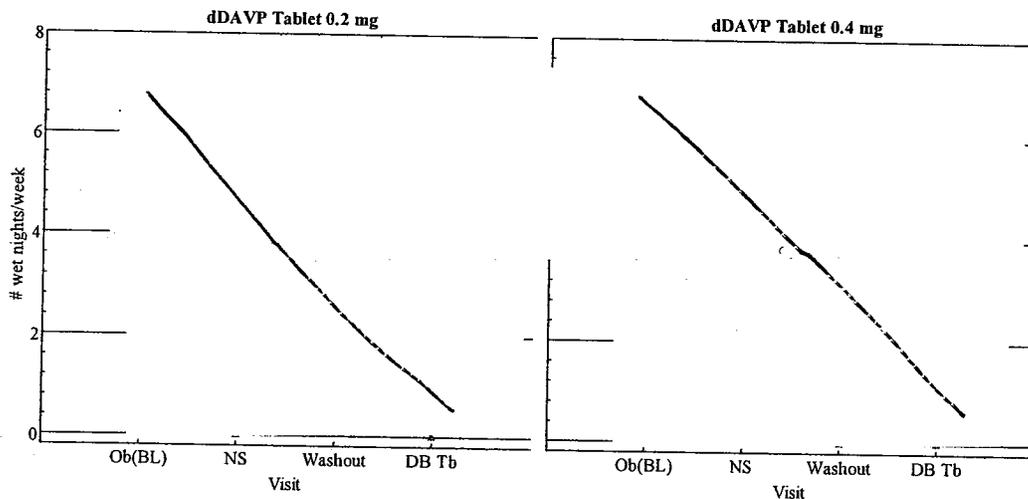
Table 5 displays the mean number of wet night per week during each study period.

Table 5 Descriptive statistics of number of wet night/week by period

	N	dDAVP Tablet 0.2 mg				dDAVP Tablet 0.4 mg			
		mean	SD	Min	Max	Mean	SD	Min	Max
1. Observation (baseline)	31	5.6	(1.1)	(3.5, 7)	32	4.7	(1.4)	(2.5, 7)	
2. dDAVP Spray 20 µg	31	1.5	(1.5)	(0, 5.9)	32	0.8	(1.0)	(0, 3.2)	
3. Wash-out	31	4.9	(1.8)	(1, 7)	32	4.2	(1.7)	(0, 7)	
4. Tablet(0.2 mg or 0.4 mg)	31	2.4	(2.1)	(0, 6.5)	32	1.3	(1.6)	(0, 6.8)	
4a. Change from baseline	31	-3.2	(2.3)	(-6.7, 2)	32	-3.4	(1.9)	(-6.7, 0.5)	
5. Wash-out/Observation	29	3.9	(2.2)	(0, 7)	31	3.6	(1.8)	(1, 7)	
6. Open-follow-up with tablets	26	1.1	(1.3)	(0, 4.5)	25	0.8	(1.3)	(0, 4.3)	
7. Wash-out/Observation	28	4.0	(1.9)	(1, 7)	28	3.5	(2.2)	(0, 7)	

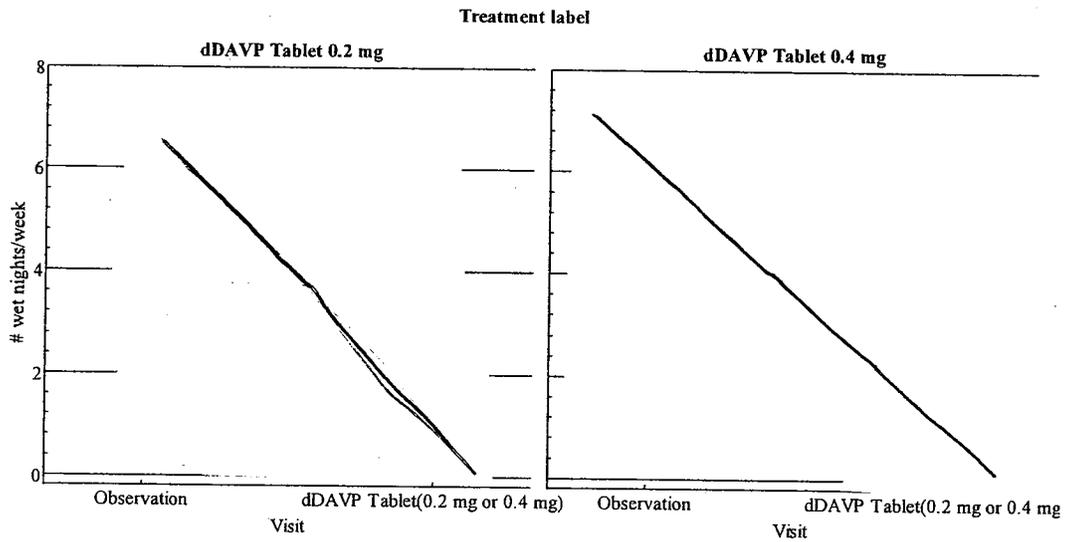
Figure 11 displays the number of wet night per week for each patients over the first 4 periods; observation (baseline), 20 µg nasal spray, washout and double-blind treatment. Figure 12 displays only the baseline and the double-blind treatment periods and figure 13 the mean number of wet night per week over the 7 study periods.

Figure 11 # wet nights/week by the first 4 periods for each patient
 Treatment label



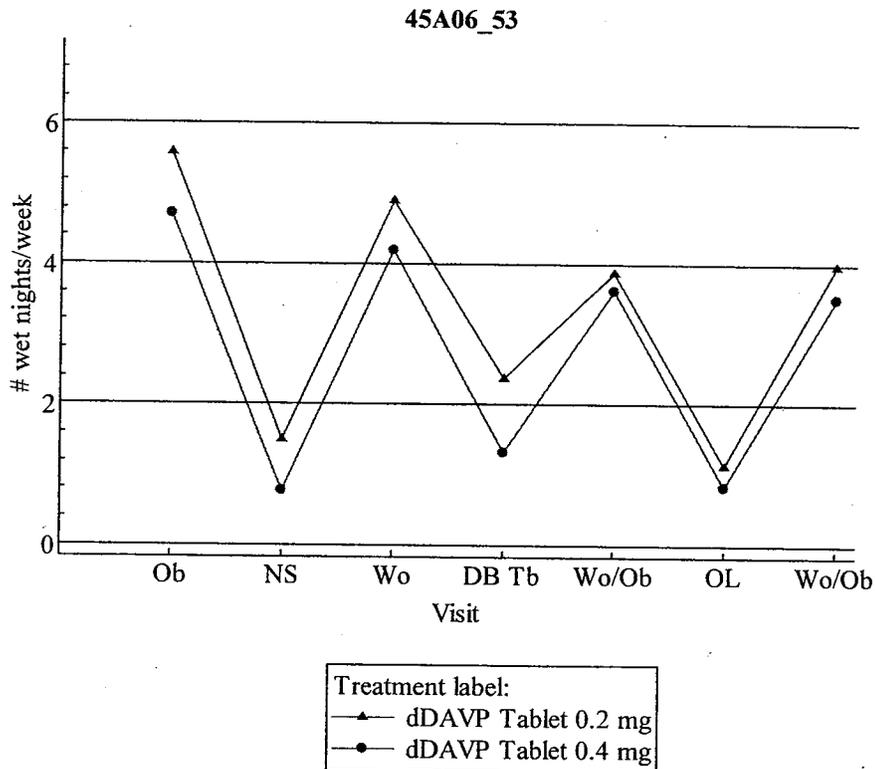
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Figure 12 # wet nights/week for baseline period and double blind treatment period



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Figure 13 Mean # wet nights/week by the 7 periods



The baseline number of wet nights per week was statistically significant different between the 2 treatment groups (Table 6 , Fig 14). In addition, the correlation of wet nights per week between baseline and the treatment phase was significantly different from zero. This reviewer therefore performed analysis of covariance to adjust for baseline number of wet nights per week. The change in number of wet nights per week between 0.2 mg group and 0.4 mg group was not statistically significant ($p=0.08$) but compared to not adjusting ($p=0.74$) the model had a better fit with less variability (Table 7). Figures 14 and 15 display the histograms for number of wet nights/week and change from baseline number of wet nights per week for the double-blind treatment period. Figure 16 displays the linear regression of change in number of wet nights/week by baseline wet nights/week.

Table 6 Summary of efficacy analyses

	Tablet 0.2 mg	Tablet 0.4 mg	0.4 mg minus 0.2 mg (SE) (CI), p value
ITT	N=31	N=32	
Baseline mean (SE)	5.6 (0.23)	4.7 (0.22)	-0.88 (0.32) (-1.52, -0.24), $p=0.008$
ANOVA LSM change (SE)	-3.2 (0.37)	-3.4 (0.37)	-0.17 (0.52) (-1.22, 0.87), $p=0.74$
ANCOVA LSM change (SE)	-2.9 (0.33)	-3.7 (0.33)	-0.87 (0.49) (-1.85, 0.10), $p=0.08$

Figure 14 Histogram of baseline # of wet nights/week with cumulative distribution curve

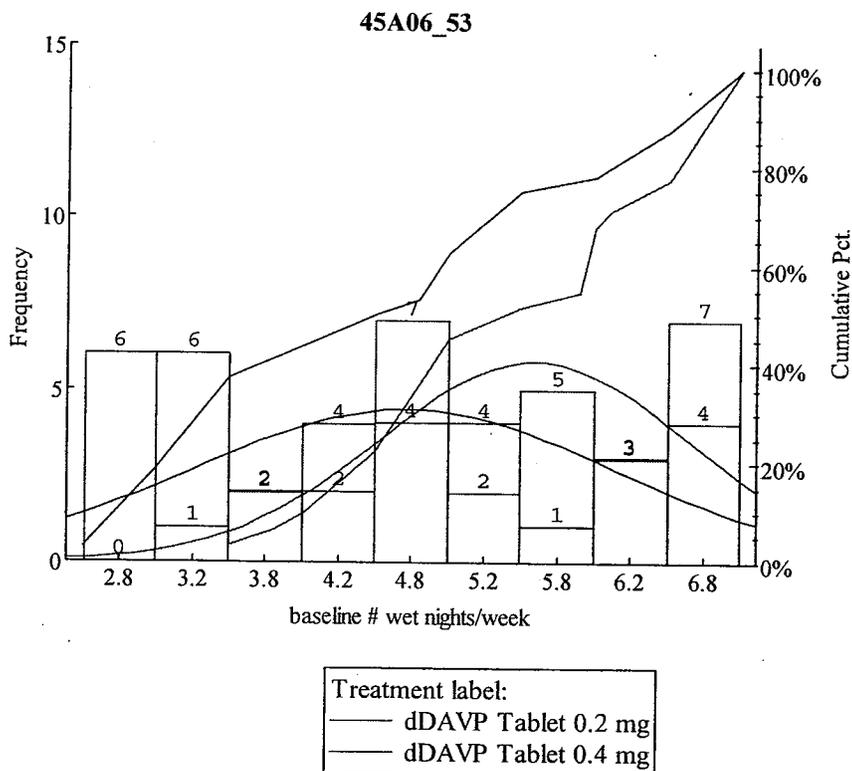
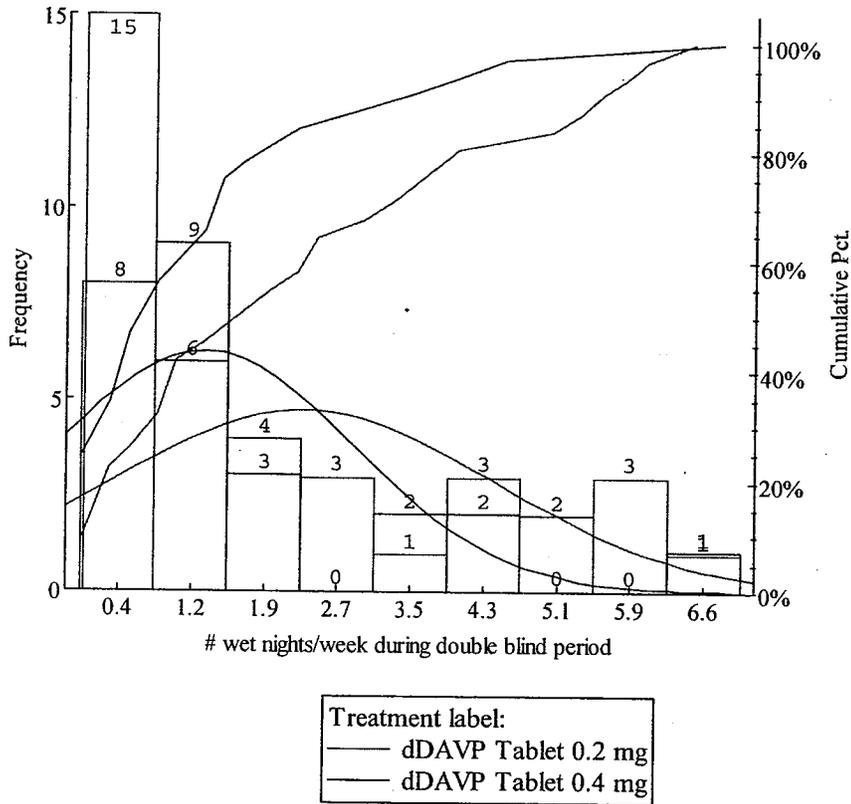
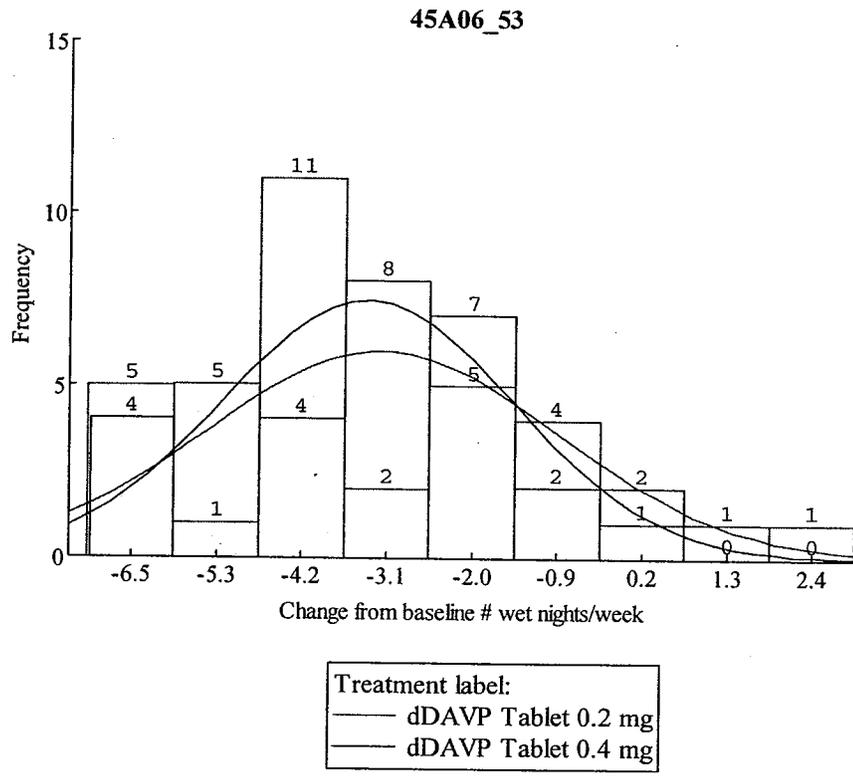


Figure 15 Histogram of # of wet nights/week during double-blind treatment



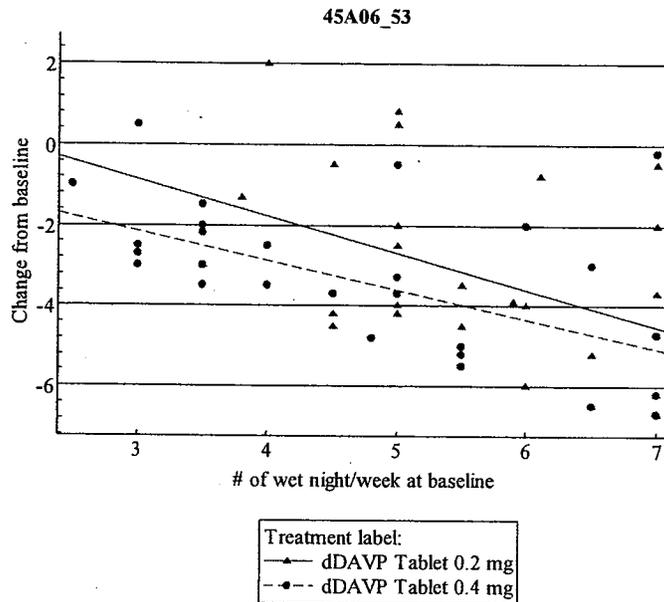
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Figure 16 Histogram of change from baseline # of wet nights/week, double-blind treatment



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Figure 17 Change in # wet nights/week by baseline # of wet nights/week



The treatment-by-age group (<17, ≥17) interaction was significant (p=0.08). Compared to the 0.2 mg group the mean number of wet nights/week for the 0.4 mg group was less in patients <17 years and more in patients ≥17 years (Table 7 & Fig 18). Fig 19 displays the regression of change from baseline # of wet nights/week by age of the patients.

Table 7 Descriptive statistics of number of nights/week by age group

	0.2 mg Tablet		0.4 mg Tablet	
Age (years)	<17 (n=13)	≥17 years (18)	<17 (n=17)	≥17 (n=15)
Baseline	5.5 (0.96)	5.7 (1.15)	4.5 (1.40)	4.9 (1.51)
Tablet	3.5 (1.88)	1.5 (1.78)	1.4 (1.24)	1.3 (1.97)
Change	-1.9 (1.63)	-4.2 (2.24)	-3.2 (1.73)	-3.7 (2.07)

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Figure 18 Mean change from baseline of # of wet nights/week for the 1st 4 periods

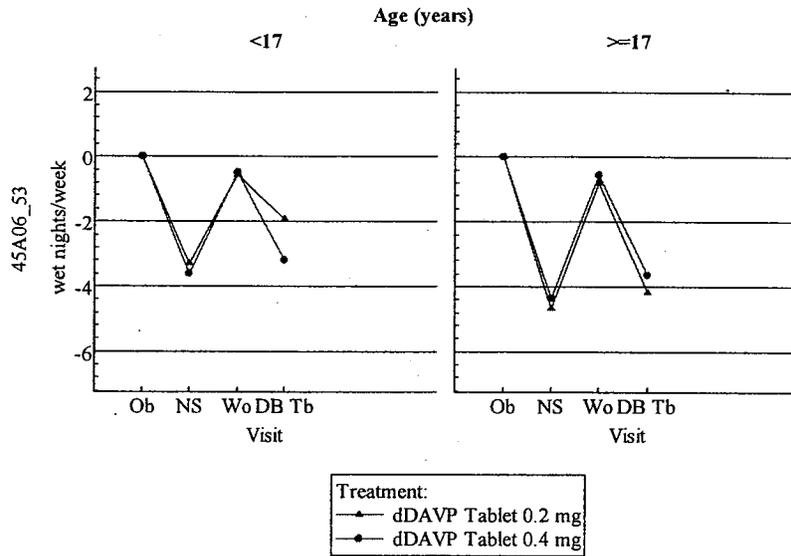
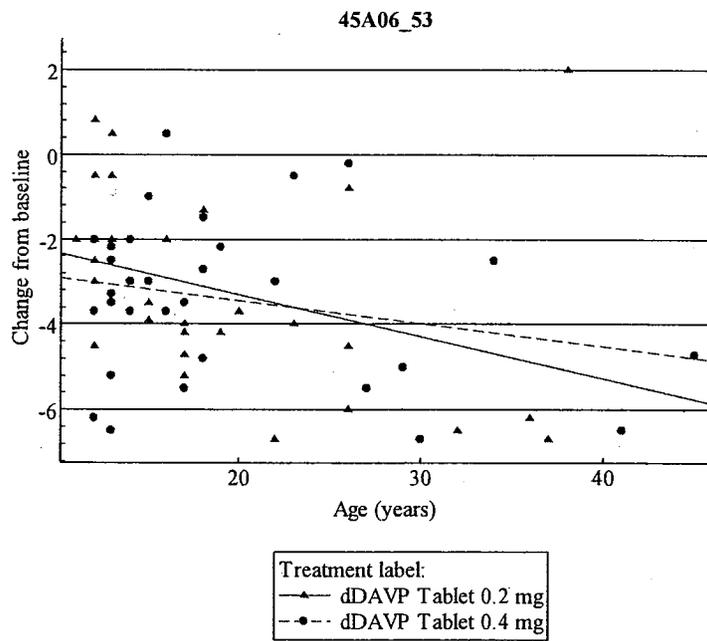


Figure 19 Change from baseline # of wet nights/week by age



2.2 LABELING COMMENTS

1. Under PNE in adults _____ the sponsor stated that Minirin tablets, 0.2 mg and 0.4 mg have similar efficacy (short and long term) in the treatment of PNE in adults, as in children. The study design was to show 0.4 mg is superior to 0.2 mg for patients _____. The sponsor should present the analysis results with the mean difference between treatment groups and the confidence intervals instead of claiming similarity in the treatment groups and the similarity in subgroups when the test was not statistically significant. All claims for similarity or better efficacy are therefore, not valid. **b(4)**
2. The sponsor presented both the randomized, double-blind response rate, 19/63 (30%) and the response rate from the extension study (26/51, 51%). The 'long-term' extension data did not compare randomized groups; therefore, the response rate should not be presented. **b(4)**
3. The statement "desmopressin decreased the number of wet nights from baseline in all supportive studies and the proportion of full responders ranged from 21-100%" is too general. Perhaps a more specific data presentation is more appropriate.

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