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AN EVALUATION OF SER120 NASAL SPRAY IN PATIENTS WITH NOCTURIA – RESULTS OF THE POOLED ANALYSES OF 2 PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDIES

Hypothesis / aims of study

SER120 nasal spray was evaluated in 2 Phase III clinical studies (DB3 and DB4) in patients with nocturia. The objective of this investigation was to explore the efficacy and safety of SER120 two doses of 1.5 and 0.75 mcg in these studies.

Study design, materials and methods

The design of the DB3 and DB4 studies were identical except for 1) the DB3 study had 1 more dose level (1.0 mcg) of SER120 and 2) the DB4 study used a validated QOL instrument (Impact of Night-time Urination – INTU questionnaire) in compliance with current FDA guidelines which will be presented here.

Eligible patients at least 50 years old with a history of 2 or more nocturic voids per night were enrolled into a 2-week double-blind placebo lead-in period to identify placebo responders (at least 50% reduction in mean nocturic voids per night or less than 1.8 voids per night) and placebo non-responders. On Day 15, all patients were randomized to one of the SER120 groups or placebo for a 12-week treatment period. Patients completed 3-day voiding diaries weekly during Screening and the 2-week placebo lead-in period and at Weeks 1, 2, 4, 6, 8, 10 and 12. For the DB4 study, patients completed a QOL instrument (INTU questionnaire) corresponding to each voiding diary completed during Screening and at Weeks 6 and 12.

The co-primary efficacy endpoints were mean change in nocturic voids and percentage of patients who achieved at least 50% reduction in mean nocturic voids. Secondary endpoints were the change from baseline in INTU total score (DB4 study only), time from bedtime to first nocturic void, percentage of patients with 0 or 1 or less nocturic voids and reduction in nocturnal urine volume. Efficacy analyses were conducted on the ITT and the modified ITT (mITT, a subset of ITT that comprised of placebo non-responders) populations.

Sample size calculations for each study were based on the 2 co-primary efficacy endpoints. For the DB3 study, using 80% power and a 2-sided alpha level of 0.05, a sample size of 180 ITT patients per group was needed based on a mean difference of 0.3 in nocturic voids (SD = 1.0) and a treatment responder percentage difference of 15% (42.5% vs. 57.5%) between the 1.5 mcg group and placebo group. The sample size calculation for the mITT population was 120 patients per group assuming a 30% placebo responder rate. For the DB4 study, using 90% power and a 2-sided alpha level of 0.05, a sample size of 175 mITT patients per group was needed based on a mean difference of 0.35 nocturic voids (SD = 1.0) and a treatment responder percentage difference of 15% (33% vs. 18%) between the 1.5 mcg group and placebo. Assuming 30% of randomized patients were placebo responders, therefore, 250 patients per group would be needed in the ITT population. The Analysis of Covariance and the Cochran-Mantel-Haenszel methods were used to test for significance for the co-primary endpoints of reduction in nocturic voids and percentage of patients with 50% reduction in nocturic voids, respectively. The analyses were based on all available data.

Results

The results of the co-primary and secondary efficacy endpoints for the pooled analyses of the 1.5 and 0.75 mcg doses of SER120 for the ITT and mITT populations are shown in Table 1. The results of the change in INTU total score (DB4 study) are shown in Table 2.

Table 1: Pooled Analyses Results of the Primary and Secondary Efficacy Endpoints

Efficacy Endpoints (LS Mean)	mITT Population			ITT Population		
	1.5 mcg SER120 (n = 327)	0.75 mcg SER120 (n = 334)	Placebo (n = 326)	1.5 mcg SER120 (n = 439)	0.75 mcg SER120 (n = 448)	Placebo (n = 446)
Reduction in Nocturic Voids	-1.4 [p=<0.0001]	-1.3 [p=0.0009]	-1.0	-1.5 [p=<0.0001]	-1.4 [p=< 0.0001]	-1.2
% of Patients with at least 50% Reduction in Nocturic Voids	37.3% [p=<0.0001]	25.1% [p = 0.0062]	16.3%	48.7% [p = <0.0001]	37.9% [p = 0.0159]	30.3%
Time (Change) from Bed-time to First Void (min)	234 (+96) [p=<0.0001]	216 (+72) [p=0.0003]	192 (+54)	252 (+108) [p=<0.0001]	240 (+96) [p=<0.0001]	216 (+72)
Change in Percentage of Nights with 0 Nocturic Void (%)	+6.87 [p=<0.0001]	+3.81	+2.98	+10.86 [p=<0.0001]	+8.16 [p=0.0197]	+5.28
Change in Percentage of Nights with 1 or Less Nocturic Void (%)	+38.14 [p=<0.0001]	+29.59 [p=0.0243]	+23.88	+46.58 [p=<0.0001]	+39.94 [p=0.0121]	+33.75
Reduction in Nocturnal Urine Volume (mL)	-251.3 [p=<0.0001]	-172.8	-129.0	-259.7 [p=<0.0001]	-195.2 [p=0.0025]	-132.7

Table 2: Results of the Change in INTU Total Score (DB4 Study QOL Instrument)

Secondary Efficacy Endpoint (LSM ± SEM)	mITT Population			ITT Population		
	1.5 mcg SER120 (n = 196)	0.75 mcg SER120 (n = 197)	Placebo (n = 193)	1.5 mcg SER120 (n = 260)	0.75 mcg SER120 (n = 262)	Placebo (n = 260)
Change in INTU Total Score	-12.0	-9.7	-9.5	-14.1 [p=0.0225]	-12.4	-11.5

The singular adverse event associated with SER120 was low serum sodium. Table 3 shows the number of patients with nadir serum sodium levels in the DB3 and DB4 pooled analysis.

Table 3: Number of Patients with Nadir Serum Sodium Levels Less than 135 mmol/L

Serum Sodium Levels (mmol/L)	1.5 mcg SER120 (n = 448)	0.75 mcg SER120 (n = 454)	Placebo (n = 454)
130 – 134	50 (11.2%)	38 (8.4%)	20 (4.4%)
126 - 129	9 (2.0%)	9 (2.0%)	0 (0%)
125 and Below	5 (1.1%)	0 (0%)	1 (0.2%)

Interpretation of results

The pooled analyses of the 1.5 and 0.75 mcg doses of SER120 were significant for all primary and the 4 secondary efficacy endpoints in the ITT population. The 1.5 mcg dose also showed significance in the QOL (INTU) endpoint in the ITT population and demonstrated clinical benefit with SER120. Similar treatment effect was seen at the 1.5 mcg dose in the mITT population for the QOL endpoint; the lack of statistical significance ($p = 0.0653$) is likely due to the smaller sample size. The mITT population also showed statistical significance for all the primary and all other secondary endpoints at the 1.5 mcg and most of the efficacy endpoints at the 0.75 mcg dose. Again, the lack of significance for 2 of the 4 secondary endpoints at the 0.75 mcg in the mITT population may be due to the smaller sample size.

There were no patients with serum sodium equal to or less than 125 mmol/L at the 0.75 mcg dose. Incidences of 1.1% and 0.2% were seen with the 1.5 mcg and placebo groups, respectively. SER120 showed a modestly higher incidence of patients with low serum sodium at the 130 to 134 and 126 to 129 mmol/L ranges. The results showed that SER120 is well tolerated at these doses.

Concluding message

SER120 at doses of 1.5 and 0.75 mcg demonstrated statistically significant results for the primary and most of the secondary efficacy endpoints. SER120 treatment effect correlated with clinical benefit as demonstrated by the INTU results. No incidence of serum sodium at 125 mmol/L or below was seen at the 0.75 mcg dose. Results suggest that 0.75 mcg might be an appropriate starting dose for all patients. SER120 at doses of 1.5 and 0.75 mcg had an acceptable safety profile, was well tolerated and effective for the treatment of nocturia.

Disclosures

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