EDS-FLU (Exhalation Delivery System With Fluticasone) Improves Sleep in Patients With Chronic Rhinosinusitis (CRS) With Nasal Polyps

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BACKGROUND

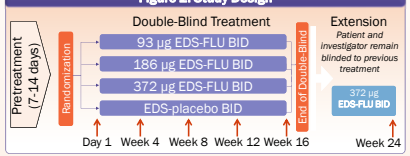
- Chronic rhinosinusitis (CRS) is a high-prevalence condition (~15% in the United States) characterized by chronic mucosal inflammation of the nose and paranasal sinuses.[1,2]
- In addition to the 4 defining symptoms of CRS (facial pain/pressure, congestion/obstruction, rhinorrhea, hyposmia), patients suffer extrasinal manifestations including fatigue and bodily pain, sleep dysfunction, and depression.[1]
- Up to three-quarters of CRS patients suffer from sleep impairment and report worse sleep quality than patients with serious chronic diseases such as inflammatory bowel disease, HIV, chronic kidney disease, and Sjogren's syndrome.[3]
- Deficient sleep negatively affects daily performance, mood, and quality of life (QoL).[3] The overall impact of CRS on QoL is similar in magnitude to other serious diseases, such as CHF, COPD, and Parkinson disease.[1]
- Given the high prevalence of poor sleep quality, there is significant interest in the effect of different treatments on sleep-specific outcomes in CRS, including medical management alone and surgery combined with postoperative medical management.[3]
- Intranasal steroids (INS) are recommended for first-line treatment of CRS (with or without polyps)[1]; however, many patients are highly dissatisfied with conventional INS therapy, primarily due to inadequate symptom relief.[2]
- The limited efficacy of traditional nasal sprays has long been attributed to their inability to deliver steroid high and deep into the nasal cavity and reliably reach key anatomical regions, such as the ostiomeatal complex (OMC), above the inferior turbinate and behind the uncinate process.[4]
- EDS-FLU uses a novel mechanism of action (MOA), closed-palate delivery with an exhaler, to deposit drug deep (posteriorly and superiorly) in regions affected by chronic inflammation, including the OMC region, where sinuses drain and ventilate and polyps originate **(Figure 1).**[4] The MOA is described at http://www.xhance.com/.
- In 2 pivotal, phase 3, randomized, controlled trials (NAVIGATE I and II), EDS-FLU produced statistically and clinically significant improvements in objective assessments and in patient-reported symptom scores compared with EDS-placebo.[5,6]
- In this analysis, we report the effect of EDS-FLU on patient-reported sleep measures in NAVIGATE II.

Figure 1. EDS MOA; Nasal Deposition by Gamma Scintigraphy[4]

METHODS

- NAVIGATE II is a randomized, double-blind (DB), parallel-group, multicenter, controlled trial with a 16-week DB phase followed by an 8-week, active-treatment extension phase in which all patients received EDS-FLU 372 µg twice daily (BID) **(Figure 2).**
- Results for the 186- and 372-µg BID doses, which are recommended in FDA-approved product labeling, are presented here.

Figure 2. Study Design



- The comparator (EDS-placebo) was "active" in the sense that, 1) BID delivery of liquid (eg, saline) has been shown to provide symptomatic benefit, and 2) because evidence suggests that other direct EDS effects (eg, delivery of CO_2 from exhaled breath to the upper/posterior nasal cavity, removal of nitric oxide, positive pressure, change in pH) may contribute to efficacy in all EDS groups.[7]
- Medical Outcomes Study Sleep Scale—Revised (MOS Sleep-R) and Sinonasal Outcomes Test (SNOT-22) were assessed.
  - MOS Sleep-R is a brief, validated questionnaire measuring key aspects of sleep. The 12-item version with 4-week recall was used. The score range is 12 to 71,[8] and the scale yields a sleep problem index and scores on 6 subscales **(Table 1).**
  - SNOT-22 is a validated questionnaire consisting of 22 symptoms and social/emotional consequences of the nasal disorder.[9] The Sleep Function subscale consists of 3 questions on a standardized 6-point scale from 0, indicating no problem, to 5, indicating a problem as bad as it can be.
- MOS Sleep-R and SNOT-22 were assessed at baseline and weeks 4, 8, 12, and 16. SNOT-22 was also assessed at week 24.

Table 1. MOS Sleep-R Subscales

Dimensions and Sleep Problems Index	Item No.	Item Contents
Sleep disturbance	07	Trouble falling asleep
	03	Sleep restlessness
	08	Awaken during sleep
	01	Time to fall asleep
Somnolence	09	Trouble staying awake
	11	Take naps
	06	Feel drowsy
Sleep adequacy	04	Enough sleep, feel rested
	12	Amount sleep needed
Snoring	10	Snore during sleep
Awaken short of breath or headache	05	Awaken short of breath or headache
Quantity of sleep/optimal sleep	02	Quantity of sleep
Sleep Problems Index	*Item Nos. 01, 03, 04, 05, 06, 07, 08, 09, 12*	

RESULTS

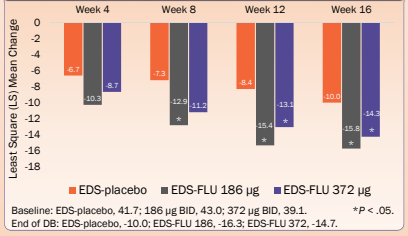
- Baseline demographics and characteristics **(Table 2)** were similar among the groups and are representative of the CRSwNP population.

Table 2. Baseline Characteristics

Characteristic	EDS-Placebo (n = 80)	EDS-FLU 186 µg (n = 80)	EDS-FLU 372 µg (n = 82)
Age, mean, y (SD)	46.7 (12.0)	44.8 (12.9)	45.0 (12.1)
Male sex, n (%)	42 (52.5)	46 (57.5)	56 (68.3)
"White" race/ethnicity, n (%)	76 (95.0)	76 (95.0)	76 (92.7)
Corticosteroid treatment for nasal polyps in past 10 y, n (%)	73 (91.3)	70 (87.5)	70 (85.4)
Sinus surgery for polyp removal or sinus surgery, n (%)	53 (32.9)	52 (32.5)	50 (31.1)
Number of polyp removal surgeries via polypectomy only, n (%)	30 (37.5)	25 (31.2)	27 (32.9)
Bilateral endoscopic nasal polyp score, mean (SD)	3.8 (1.08)	3.9 (1.05)	3.8 (0.98)
SNOT-22 total score, mean (SD)	52.0 (19.8)	48.1 (19.7)	47.1 (20.4)
SNOT-22 Sleep Function subscale score, mean (SD)	6.7 (4.0)	6.6 (4.3)	6.3 (4.5)
MOS Sleep-R Sleep Problems Index, mean (SD)	41.7 (19.2)	43.0 (19.5)	39.1 (16.7)

- EDS-FLU was statistically and clinically superior to EDS-placebo on both of the designated coprimary endpoints in NAVIGATE II.[6]
- EDS-FLU reduced/improved mean MOS Sleep-R Sleep Problems Index scores numerically more than EDS-placebo at each successive time point from week 4 through the end of the DB phase. Differences in Sleep Problems Index scores between EDS-FLU and EDS-placebo reached statistical significance starting at week 12 and remained significant thereafter (**Figure 3**).

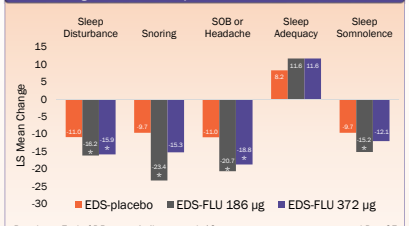
Figure 3. MOS Sleep-R Problems Index



Baseline: EDS-placebo, 41.7; 186 µg BID, 43.0; 372 µg BID, 39.1. End of DB: EDS-placebo, -10.0; EDS-FLU 186, -16.3; EDS-FLU 372, -14.7. *$P < .05$.

- Scores on the MOS Sleep-R subscales also decreased/improved with EDS-FLU (**Figure 4**).

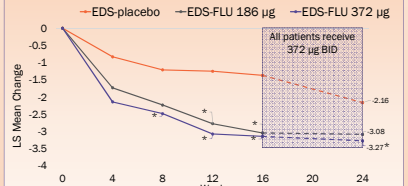
Figure 4. MOS Sleep-R Subscales at Week 16



Results at End of DB were similar to week 16. *$P < .05$.

- At week 16, EDS-FLU significantly decreased subscale scores for the Sleep Disturbance subscale (186- and 372-µg groups), the Snoring subscale (186-µg group), the Shortness of Breath (SOB) or Headache subscale (186- and 372-µg groups), and Sleep Somnolence subscale (186-µg group).
- Small increases in sleep quantity were noted in the 3 groups over the course of treatment.
- EDS-FLU significantly improved SNOT-22 compared with EDS-placebo ($P < .001$). Least square (LS) mean change in SNOT-22 score at week 16 was -11.7, -21.43, and -21.05 in EDS-placebo, EDS-FLU-186, and EDS-FLU-372 groups, respectively. SNOT-22 scores (total and subscale) progressively improved through week 16, with incremental improvement through week 24.
  - This magnitude of change in total SNOT-22 score is similar to the magnitude of improvement reported in patients who have undergone sinus surgery for the removal of polyps.[9]
- The SNOT-22 Sleep Function subscale scores decreased/improved compared with baseline over the course of the study with all EDS treatments.
- EDS-FLU significantly improved Sleep Function subscale scores compared with EDS-placebo starting at week 8 (372-µg group) (**Figure 5**).

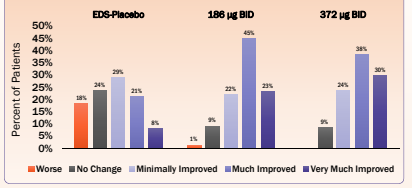
Figure 5. Change in SNOT-22 Sleep Function Subscale Score



Baseline: EDS-placebo, 6.7; 186 µg, 6.6; 372 µg, 6.3. *$P < .05$.

- At the end of the DB phase, two-thirds of subjects in both EDS-FLU groups reported being "much improved" or "very much improved" compared with 29% of subjects treated with EDS-placebo. According to the PGIC assessment, more than 90% of subjects in the 372-µg BID group reported being improved ($P < .001$) (**Figure 6**).

Figure 6. Patient Global Impression of Change (PGIC)



- Adverse events (AE) associated with EDS-FLU were largely local to the nose and similar in frequency to that reported with conventional INS when studied in similar populations for similar durations.[6,10] AE occurring in > 5% of the patients included epistaxis, nasal septal ulceration, nasopharyngitis, nasal erythema, headache, nasal septal erythema, and atypical nasal congestion.

CONCLUSIONS

- Most CRS patients report sleep dysfunction, which is known to negatively affect daily performance, mood, and QoL.
- EDS-FLU reduced/improved mean MOS Sleep-R Sleep Problems Index scores and subscale scores significantly more than EDS-placebo.
- SNOT-22 Sleep Function subscale scores also improved significantly more with EDS-FLU than EDS-placebo.
- In CRS patients with moderate to severe symptoms and polyps, EDS-FLU treatment significantly improved sleep across multiple measures.

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