EDS-FLU (Exhalation Delivery System With Fluticasone) Improves Peak Nasal Inspiratory Flow (PNIF) in Chronic Rhinosinusitis With Nasal Polyps (CRSwNP)

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BACKGROUND

- Chronic rhinosinusitis (CRS) is a high-prevalence condition characterized by chronic mucosal inflammation of the nose and paranasal sinuses.[1]
- CRS is associated with substantial morbidity. The detrimental impact of CRS on quality of life (QoL) is similar in magnitude to other serious diseases, such as CHF, COPD, and Parkinson's disease.[2]
- The chronic inflammation of CRS is sometimes complicated by nasal polyps (NP), which can further contribute to the nasal obstruction caused by underlying inflammation. Obstruction is an important part of the disease burden.[1]
- PNIF is an inexpensive objective assessment for quantifying nasal obstruction.[3]
- In patients with nasal polyps (NP) treated with intranasal steroids (INS), there is a correlation between increasing (improving) PNIF and subjective improvement of nasal blockage as well as reduction in NP size.[3] Additionally, PNIF was shown to correlate with QoL in CRS patients after functional endoscopic sinus surgery (FESS).[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 ostiomeatal complex region, where the sinuses drain and ventilate, and polyps originate **(Figure 1).**[5] The MOA is described at http://www.xhance.com/.

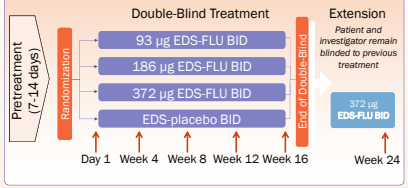
Figure 1. EDS MOA; Nasal Deposition by Gamma Scintigraphy[5]

- EDS-FLU was studied in 2 pivotal, phase 3, randomized, controlled trials (NAVIGATE I and II) in patients with CRSwNP. Patients had at least moderate symptoms, and most had previously been treated with steroids and/or surgery. Both trials demonstrated that EDS-FLU produces statistically and clinically significant improvement in both objective endoscopic assessments and in subjective patient-reported symptom scores (on all defining symptoms), compared with EDS-placebo. These treatment benefits are further supported by clinically significant improvements in QoL, functioning, and disease severity. In this analysis, we present results from NAVIGATE I and II on PNIF, a prespecified secondary outcome measure.

METHODS

- NAVIGATE I and II are similarly designed, randomized, double-blind (DB), parallel-group, multicenter, controlled trials with a 16-week, double-blind phase followed by an 8-week, active-treatment extension phase in which all patients received EDS-FLU 372 µg. All treatment was twice daily (BID) **(Figure 2)**.

Figure 2. Study Designs



- Results for the 186- and 372-µg BID doses, recommended in FDA-approved labeling, are presented here.
- 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) 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.[6]
- Eligible patients were ≥18 years old, with moderate to severe symptoms of nasal congestion/obstruction and NP at entry.
- Coprimary endpoints and other prespecified secondary endpoints have been previously reported.[7,8]
- PNIF was measured with an In-Check portable nasal inspiratory flow meter (Clement Clarke International, Ltd, Harlow, Essex, UK) at baseline and weeks 4, 8, 12, 16, and 24.
- To measure PNIF, a mask was placed over the nose and mouth, and the subject was instructed to inhale through his/her nose using maximum effort. Each patient performed the procedure 3 times, and the greatest of the 3 results at each time point was used.

RESULTS

- Baseline demographics and characteristics **(Table 1)** are representative of a moderate-severely symptomatic population. Many patients had previously used steroids and/or undergone surgery.

Table 1. Baseline Characteristics (NAVIGATE I and II)

Characteristic	EDS-Placebo (n = 161)	186 µg (n=160)	372 µg (n=161)
Age, mean, y (SD)	46.0 (12.5)	45.6 (12.8)	44.4 (12.4)
Male sex, n (%)	78 (48.4)	94 (58.8)	93 (57.8)
"White" race/ethnicity, n (%)	143 (88.8)	148 (92.5)	144 (89.4)
Prior INS treatment for CRSwNP (past 10 y), n (%)	149 (92.5)	146 (91.3)	144 (89.4)
Polyp removal surgery via polypectomy or sinus surgery, n (%)	91 (56.2)	85 (53.1)	77 (47.5)
7-Day morning nasal congestion/obstruction, at time of rating, (range 0-3), mean score (SD)	2.3 (0.42)	2.22 (0.39)	2.27 (0.43)
Bilateral endoscopic NP score, mean (SD)	3.8 (1.01)	3.9 (1.06)	3.8 (0.96)

- EDS-FLU decreased polyp grade starting at week 4, reaching statistical significance versus EDS-placebo at week 8 ($P < .01$, all comparisons). Polyp grade continued to improve monotonically with continued treatment through week 24 ($P \leq .006$, all comparisons vs EDS-placebo/372 µg BID).
- After 24 weeks, 25.9%/26.5% of subjects treated with EDS-FLU in NAVIGATE I/NAVIGATE II had polyps eliminated on at least 1 side of the nose, compared with 26.6%/8.7% with EDS-placebo at the end of the open-label phase.
- Baseline PNIF scores **(Table 2)** were worse than (below) the values reported in the literature for healthy people.[3]
  - Normal mean PNIF (L/min) in males: 143 ± 48.
  - Normal mean PNIF (L/min) in females: 121.9 ± 36.

Table 2. Baseline PNIF Scores

	NAVIGATE I		NAVIGATE II	
	Males	Females	Males	Females
EDS-placebo (L/min)	118.6	94.6	133.0	104.5
EDS-FLU 186 µg (L/min)	97.4	96.6	114.6	98.1
EDS-FLU 372 µg (L/min)	116.1	91.8	123.1	121.7

- EDS-FLU treatment improved (increased) PNIF statistically significantly more than EDS-placebo in both NAVIGATE I and II trials, in both males and females **(Figures 3 and 4).** Improvements were evident as early as the week 4 assessment and generally increased with longer duration of treatment. Improvements in PNIF tended to be larger in men than women.
- At week 16, male and female patients in both EDS-FLU groups achieved mean PNIF scores at or above those reported for healthy subjects **(Figures 5-8)**, but EDS-placebo groups did not.
  - PNIF values continued to improve during the extension phase, at which time all patients (irrespective of prior treatment group) were switched to receive EDS-FLU 372 µg BID.

Figure 3. Least Square Mean Change in PNIF: Males

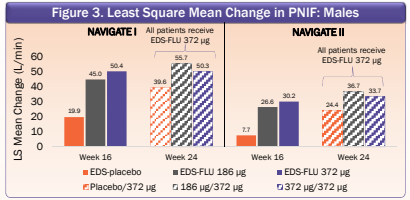


Figure 4. Least Square Mean Change in PNIF: Females

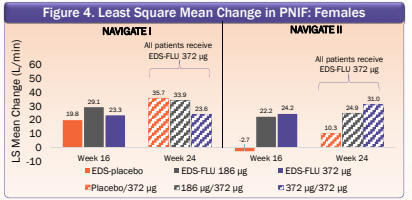


Figure 5: Mean PNIF Scores: Males, NAVIGATE I

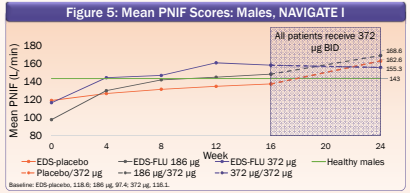


Figure 6: Mean PNIF Scores: Males, NAVIGATE II

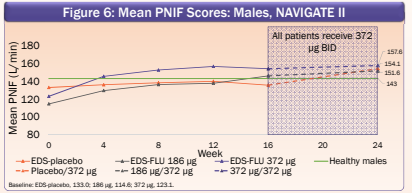


Figure 7: Mean PNIF Scores: Females, NAVIGATE I

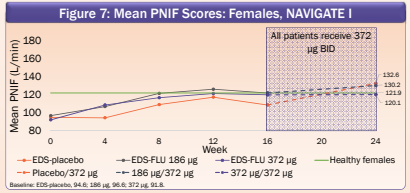
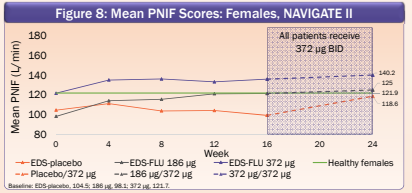


Figure 8: Mean PNIF Scores: Females, NAVIGATE II



CONCLUSIONS

- EDS-FLU uses a novel Exhalation Delivery System shown to deliver medication more broadly and more superiorly/posteriorly than conventional INS sprays. It has been found to be effective in relieving symptoms and polyps in CRSwNP patients in 2 independent, randomized, controlled trials.
- PNIF is an objective measure of nasal obstruction, and would be expected to improve with reduction in nasal inflammation and polyp mass.
- In both trials, EDS-FLU improved PNIF compared with EDS-placebo, in both men and women. The increase in PNIF paralleled patient-reported improvement in all 4 defining symptoms of CRS, including congestion and reduction in polyp grade.
- On average, males and females receiving EDS-FLU achieved PNIF values at or above reported values for healthy people.
- The ability of EDS-FLU to deliver steroid broadly to deep nasal mucosal surfaces, including the surface of polypoid tissue, results in reduced nasal passage obstruction and restoration of PNIF in patients with CRSwNP.

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