Exhalation Delivery System With Fluticasone (EDS-FLU) for Chronic Rhinosinusitis (CRS): Integrated NAVIGATE I and NAVIGATE II Results

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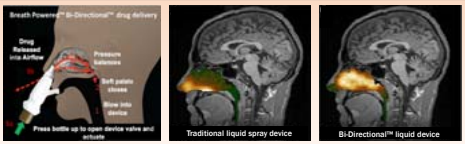
BACKGROUND

- CRS is a high-prevalence condition characterized by chronic mucosal inflammation of the nose and paranasal sinuses; most CRS patients fall in 1 of 2 subtypes based on the presence or absence of nasal polyps (CRSwNP and CRSsNP, respectively).[1,2]
- The overall detrimental impact of CRS on quality of life (QoL) has been measured to be similar in magnitude to other serious diseases, such as CHF, COPD, and Parkinson's disease.[2]
- Intranasal corticosteroid (INS) sprays are widely recommended for first-line treatment of CRS[2]; however, many patients are highly dissatisfied with conventional INS therapy, primarily due to inadequate symptom relief.[1]
- The limited efficacy of conventional INS sprays has been attributed to their inability to deliver topically acting steroid high and deep enough into the nasal cavity to reliably and regularly reach key anatomical regions, such as the ostiomeatal complex (OMC), which is the principal location for sinus ventilation and drainage, and for nasal polyp development.[3]
- EDS-FLU uses a novel mechanism of action (MOA), closed-palate bi-directional™ delivery with an exhaler, shown to deposit drug deep (posteriorly and superiorly) in regions affected by chronic inflammation, including the OMC region, where the sinuses drain and ventilate and polyps originate **(Figure 1).**[3] EDS-FLU contains fluticasone propionate (phenylethyl alcohol free). The EDS MOA is described here: http://www.optinose.com/.

Figure 1: EDS MOA; Nasal Deposition by Gamma Scintigraphy[3]

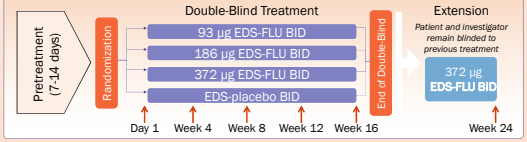


- EDS-FLU has been extensively studied. This includes 2 pivotal, phase 3, randomized, EDS–placebo-controlled trials (NAVIGATE I and II) in CRSwNP.[4,5] Studied patients were moderate to severe, and most had previously been treated with steroids and/or surgery. Results of both trials demonstrate that EDS-FLU produced statistically and clinically significant improvements in 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 integrated efficacy and safety results from NAVIGATE I and II.

METHODS

- NAVIGATE I and II are similarly designed, randomized, double-blind, parallel-group, multicenter, placebo-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 BID **(Figure 2)**.
- The 186- and 372-µg doses were selected for further clinical development and commercialization and are reported here.

Figure 2. Study Design



- The EDS-placebo comparator was "active" in the sense that twice-daily saline may offer therapeutic benefit in CRS.
- Eligible patients were ≥ 18 years old, with a polyp grade of 1 to 3 in each of the nasal cavities and moderate to severe symptoms of nasal congestion/obstruction at entry. The comparator in both trials was an EDS-placebo delivering a saline-like deep nasal "lavage" BID using an EDS.
- For this integrated analysis, data were pooled by treatment group.
- Coprimary endpoints: reduction of mean 7-day instantaneous morning (AM) nasal congestion/obstruction score at week 4; reduction in total polyp grade at week 16 (using a nasal polyp grading scale of 0-3 per nostril, then summed), measured via nasoendoscopy.
- Other key prespecified secondary endpoints included nasal polyp elimination, all defining nasal symptoms (by diary), SNOT-22 total score, patient global impression of change (PGIC), and SF-36.

RESULTS

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

Table 1: Baseline Characteristics

Characteristic	EDS-Placebo (n = 161)	186 µg (n=160)	372 µg (n=161)
Prior INS treatment for CRSwNP (past 10 y), n (%)	149 (92.5)	146 (91.3)	144 (89.4)
Sinus surgery for polyp removal or sinus surgery, n (%)	53 (32.9)	52 (32.5)	50 (31.1)
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 nasal polyp score, mean (SD)	3.8 (1.01)	3.9 (1.06)	3.8 (0.96)

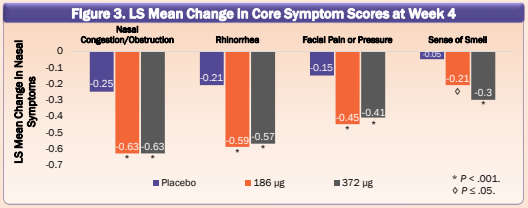
- A total of 445 of 484 randomized patients (91.9%) completed the double-blind phase. The 372-µg group had the fewest discontinuations (n = 4) whereas EDS-placebo had the most (n = 22). Of the 431 patients entering the extension phase, 422 (97.9%) completed the extension phase (89.0% of randomized cohort).

- As with each individual study, EDS-FLU treatment in the integrated analysis was statistically superior to EDS-placebo for both coprimary endpoints.
  - The least square (LS) mean change in congestion/obstruction at week 4 was -0.61 and -0.62 in the EDS-FLU 186-µg and 372-µg BID groups, respectively, versus -0.23 in the EDS-placebo group ($P < .001$, all comparisons).
  - The LS mean change in total polyp grade at week 16 was -1.11 and -1.23, in the EDS-FLU 186-µg and 372-µg BID groups, respectively, versus -0.51 in the EDS-placebo group ($P < .001$, all comparisons). The 372-µg BID group had the largest treatment effect.

- EDS-FLU significantly improved morning (and evening, not shown) symptom scores for all 4 defining symptoms at week 4 **(Figure 3)**, with improvement continuing throughout the double-blind phase. EDS-FLU improved current and 12-hour-recall severity of all 4 defining symptoms of CRS, as reported both for morning and evening ($P < .01$, all comparisons).

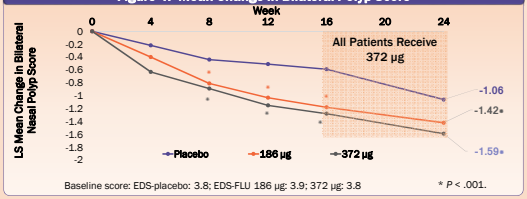
- Statistical onset of effect (symptom improvement reached, and permanently retained, significance) was day 3 with 186 µg and day 4 with 372 µg.

Figure 3. LS Mean Change in Core Symptom Scores at Week 4



- EDS-FLU decreased total polyp grade. The reduction in polyp grade increased through 24 weeks **(Figure 4).**

Figure 4. Mean Change in Bilateral Polyp Score

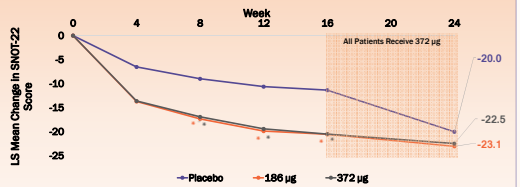


Baseline score: EDS-placebo: 3.8; EDS-FLU 186 µg: 3.9; 372 µg: 3.8 * $P < .001$.

- 14.1% of EDS-FLU recipients were observed to have polyps entirely eliminated in at least 1 nostril at the end of the double-blind phase (compared with 7.8% of EDS-placebo recipients). This percentage increased throughout the study: at 24 weeks of EDS-FLU, 26.2% of patients had polyp elimination in at least 1 nostril.

- Overall symptom/functioning as measured by SNOT-22 was substantially improved with EDS-FLU ($P \leq .001$ vs EDS-placebo, all comparisons). Total scores progressively improved with increasing duration of treatment through week 24 (**Figure 5**). This magnitude of SNOT-22 improvement is comparable with the magnitude reported for CRS patients after surgery.[6]

Figure 5. LS Mean Change in SNOT-22 Score



Baseline score: EDS-placebo: 52.9; EDS-FLU 186 µg: 49.9; 372 µg: 49.7 * $P < .001$.

- The percentage of subjects receiving EDS-FLU who rated their symptoms "very much improved" or "much improved" was higher than EDS-placebo and increased with dose (64.9% and 66.9% for 186 µg and 372 µg, respectively, vs 33.1% EDS-placebo). This difference was statistically significant (active/placebo odds ratios for response distributions at end of double blind; all $P < .001$).

- The safety profile of EDS-FLU was similar to that of conventional INS studied in similar populations for similar durations. Adverse events were almost entirely local, and the most common adverse event was coded as "epistaxis," with most "epistaxis" identified by nasal endoscopy rather than clinically **(Table 2).**

Table 2: Adverse Events ≥5% and Greater Than EDS-placebo

Adverse Event	EDS-Placebo (n = 161) n (%)	186 µg (n = 160) n (%)	372 µg (n = 161) n (%)
Epistaxis	10 (6.2)	35 (21.9)	37 (23.0)
Identified other than by endoscopy	4 (2.5)	19 (11.9)	16 (9.9)
Identified by nasal endoscopy	6 (3.8)	29 (18.2)	35 (21.7)
Erythema	8 (5.0)	15 (9.4)	11 (6.8)
Nasal septum ulceration	3 (1.9)	11 (6.9)	12 (7.5)
Nasal congestion	6 (3.7)	7 (4.4)	9 (5.6)
Nasal septum disorder (erythema)	3 (1.9)	6 (3.8)	7 (4.3)
Headache	5 (3.1)	8 (5.0)	6 (3.7)
Acute sinusitis	6 (3.7)	7 (4.4)	8 (5.0)
Nasopharyngitis	8 (5.0)	3 (1.9)	12 (7.5)

CONCLUSIONS

- In an integrated analysis of 2 large trials in CRSwNP, patients with moderate to severe symptoms, including those with a history of prior steroid use and/or surgery, EDS-FLU reduced subjective and objective evidence of inflammation (symptoms of CRS and polyp grade).
- Secondary outcomes were consistent with the primary outcomes, demonstrating broad, clinically significant improvement in multiple signs and symptoms of the disease, as well as in various functional, physical, and emotional domains related to QoL.
- Longer treatment with EDS-FLU produced greater improvement (measured by SNOT-22 and polyp regression), with polyp elimination rates (in at least 1 nostril) increasing through at least 6 months.
- All tested doses were effective; however, the highest dose produced the largest effect size and fastest onset of action.
- The safety/tolerability of EDS-FLU in these trials was consistent with expectations for topically-acting intranasal steroid.
- These 2 large, 24-week studies demonstrate that EDS-FLU may be an important new tool in maximizing medical management of diseases characterized by chronic nasal inflammation, such as CRSwNP.

References:

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