NAVIGATE I: A Randomized, Double-Blind Trial of an Exhalation Delivery System with Fluticasone (EDS-FLU) for Treatment of Chronic Rhinosinusitis With Nasal Polyps (CRSwNP)

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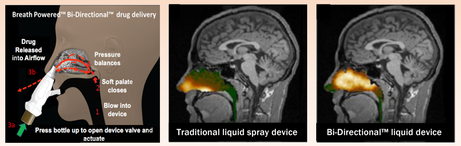
BACKGROUND

- Chronic rhinosinusitis (CRS), often accompanied by nasal polyps (CRSwNP), is a high-prevalence, chronic, inflammatory condition.
- CRSwNP is characterized by polyps in the nasal cavity plus 4 defining symptoms (nasal congestion/obstruction, rhinorrhea, facial pain/pressure, and reduction/loss of smell[1,2]), as well as a variety of other symptoms that collectively can adversely affect quality of life (QoL) to a degree similar to other serious diseases, such as CHF and COPD.[1,3]
- The overall annual economic burden of CRS in the United States was estimated at $22 billion (direct and indirect costs) in 2014.[4]
- Intranasal corticosteroids (INS) are recommended as a primary treatment for CRSwNP and its associated core symptoms; however, many CRS patients are highly dissatisfied with current INS therapy, primarily due to inadequate symptom relief.[1,2]
- Conventional INS sprays deliver the majority of topically acting drug to the anterior portion of the nasal cavity below the nasal valve, leaving much of the posterior/superior nasal regions—where polyps typically originate—undertreated[5] **(Figure 1).** EDS-FLU uses Breath-Powered® "Bi-Directional" delivery to optimize fluticasone propionate delivery to the entire nasal cavity, including key high and deep anatomical regions, such as the ostiomeatal complex.
- The primary purpose of this study in 323 patients was to compare the efficacy of intranasal EDS-FLU 93 µg, 186 µg, or 372 µg twice daily (BID) versus an EDS-placebo in the treatment of nasal polyposis.

Figure 1. EDS MOA; Nasal Deposition by Gamma Scintigraphy



METHODS

- The study design is presented in **Figure 2**.
- Eligible patients were at least 18 years of age and had CRSwNP, with a polyp grade of 1 to 3 in each of the nasal cavities and moderate-severe symptoms of nasal congestion/obstruction at entry.
- Nonsedating antihistamines were permitted as "rescue medication" after week 4.
- Polyps were graded according to the following scale:

Score	Description
0	No polyposis
1	Mild polyposis: polyps not reaching below the inferior border of the middle turbinate
2	Moderate polyposis: polyps reaching below the inferior border of the middle concha but not the inferior border of the inferior turbinate
3	Severe polyposis: large polyps reaching below the lower inferior border of the inferior turbinate

Coprimary Endpoints:

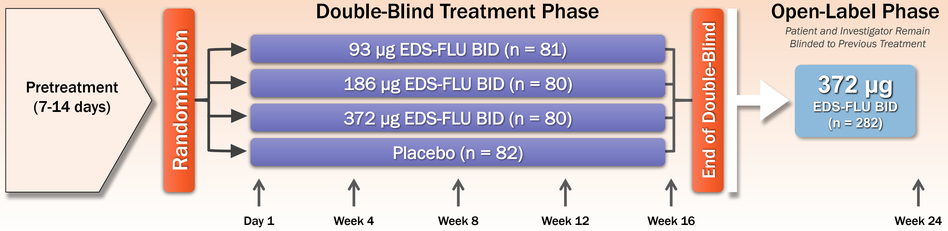
- **Reduction of nasal congestion/obstruction symptoms at week 4 measured by the "Average Diary Score, 7-day, Instantaneous AM"**
- **Reduction in total polyp grade at week 16 (nasal polyp grading score, scale 0-3 per nostril, summed) measured via nasoendoscopy**

Secondary Endpoints Include:

Key secondary endpoints (controlled for multiplicity):
- Sino-Nasal Outcome Test (SNOT-22) and Medical Outcomes Study Sleep Scale–Revised (MOS-Sleep-R)

Other secondary endpoints:
- Patient-reported nasal symptom assessments
- Objective endoscopic assessments of polyp grades
- QoL assessments
- Surgical intervention assessment
- Medication evaluation questionnaire

Figure 2. Study Design



RESULTS

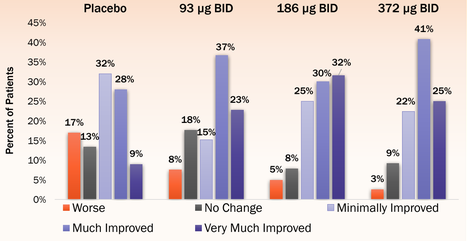
- Baseline demographics and characteristics **(Table 1)** are representative of the CRSwNP population and were similar among the 4 treatment groups. Many subjects had previously used steroids and/or undergone surgery.

Table 1. Baseline Characteristics

Characteristic	Placebo (n = 82)	All EDS-FLU (n = 241)
Age, mean (SD), y	45.3 (13.0)	45.1 (12.7)
Male sex, n (%)	36 (43.9)	126 (52.3)
"White" race/ethnicity, n (%)	68 (82.9)	215 (89.2)
Any corticosteroid treatment in past 10 y, n (%)	77 (93.9)	228 (94.6)
Sinus surgery for polyp removal or sinus surgery, n (%)	31 (37.8)	82 (34.0)
Bilateral endoscopic nasal polyp score, mean (SD)	3.8 (0.9)	3.7 (1.04)
SNOT-22 total score, mean (SD)	53.7 (18.1)	50.1 (19.5)

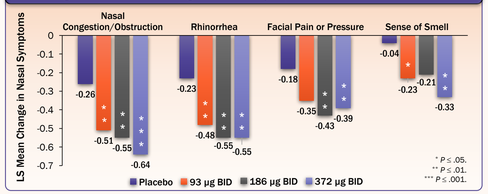
- The placebo group had the highest dropout rate (14.6%), largely due to lack of efficacy. The percentage of EDS-FLU recipients who discontinued during the double-blind phase was 7.9%.
- Changes in both coprimary endpoints were significantly superior to placebo for each EDS-FLU dose versus placebo ($P < .01$).
  - At week 4, the least squares (LS) mean change in congestion was -0.49, -0.54, and -0.62, in the 93-µg, 186-µg, and 372-µg groups, respectively, compared with -0.24 in the placebo group.
  - At week 16, the LS mean change in summed polyp grade was -0.96, -1.03, and -1.06 in the 93-µg, 186-µg, and 372-µg groups, respectively, compared with -0.45 in the placebo group. The 372-µg group produced the largest average reduction in polyp grade.
- Higher doses of EDS-FLU (186 µg and 372 µg) produced faster onset of action and numerically larger improvement in congestion and polyp grade than the lowest dose (93 µg).
- Almost twice the proportion of EDS-FLU patients reported very much/much improvement in symptoms compared with placebo ($P < .005$). Almost 90% of patients in the 372-µg group reported improvement **(Figure 3)**.

Figure 3. Patient-Reported Change in Symptoms (PGIC)



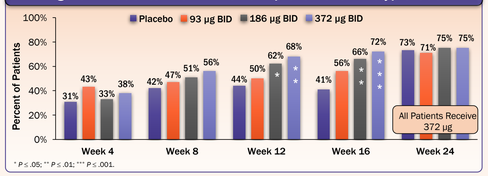
- Improvements in all 4 defining nasal symptoms, as assessed by average AM instantaneous diary scores, **(Figure 4)** and in multiple measures of QoL were statistically superior in all EDS-FLU groups versus placebo.

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



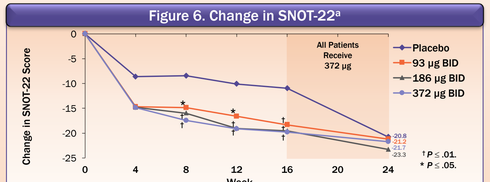
- The proportion of patients with an improvement in total bilateral polyp grade ≥-1 point increased monotonically in the active dose groups from week 4 through week 16 during the double-blind phase. By the end of the 372-µg open-label extension phase, the percent of responders increased further **(Figure 5)**.

Figure 5. Patients With ≥1-Point Improvement in Polyp Grade



- At the end of the double-blind treatment phase, 19.5% of patients in the EDS-FLU groups had a polyp grade of 0 (no polyps) in at least 1 nostril compared with 11.5% of patients in the placebo group. This further increased in the active-active sequences to approximately 30% of patients with no polyps in at least 1 nostril at 24 weeks.
- SNOT-22 improvement was substantial in all EDS-FLU groups and statistically superior to placebo ($P \leq .005$). SNOT-22 scores progressively improved through week 16, with continued incremental improvement through week 24 **(Figure 6)**.

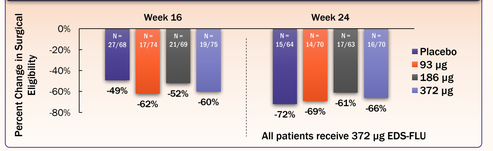
Figure 6. Change in SNOT-22[a]



[a] SNOT-22 baseline values: placebo = 53.7; 93 µg BID = 46.1; 186 µg BID = 51.8; 372 µg BID = 52.4.

- EDS-FLU treatment resulted in an approximately 60% reduction in the proportion of patients eligible for surgery at week 16 **(Figure 7)**.

Figure 7. Surgical Eligibility (by standardized assessment)



- The most frequent adverse events (AEs) in EDS-FLU recipients were identified by nasal endoscopy rather than by clinical report and included mild "epistaxis" (defined as any visualized blood, including, for example, streaked mucous or old clots) and nasal septal ulceration. Both typically resolved with continued use of study medications **(Table 2)**.

Table 2. AEs >5% and Greater Than Placebo

AE	Placebo (n = 82)	93 µg BID (n = 81)	186 µg BID (n = 80)	372 µg BID (n = 79)
Epistaxis, n (%)	6 (7.3)	11 (13.6)	16 (20.0)	19 (24.1)
Spontaneously reported	3 (3.7)	3 (3.7)	7 (8.8)	6 (7.6)
Incidental finding on nasoendoscopy	3 (3.7)	8 (9.9)	9 (11.3)	13 (16.5)
Nasal mucosal disorder, n (%)	5 (6.1)	11 (13.6)	6 (7.5)	6 (7.6)
Acute sinusitis, n (%)	4 (4.9)	5 (6.2)	6 (7.5)	8 (10.1)
Upper respiratory tract infection, n (%)	7 (8.5)	1 (1.2)	4 (5.0)	5 (6.3)
Nasal congestion, n (%)	4 (4.9)	3 (3.7)	2 (2.5)	6 (7.6)
Nasal septum ulceration, n (%)	1 (1.2)	5 (6.2)	5 (6.3)	4 (5.1)
Nasopharyngitis, n (%)	4 (4.9)	3 (3.7)	2 (2.5)	4 (5.1)
Gastrointestinal disorders, n (%)	4 (4.9)	1 (1.2)	2 (2.5)	4 (5.1)

CONCLUSIONS

- EDS-FLU doses of 93 µg, 186 µg, and 372 µg BID significantly reduced coprimary endpoints of nasal congestion/obstruction, total polyp grade, and SNOT-22.
- In a population in which many had previously used steroids or had surgery, EDS-FLU significantly improved a broad range of objective and subjective outcome measures, including all 4 defining symptoms of CRS (congestion, rhinorrhea, hyposmia, pain/pressure), PGIC, and QoL.
- SNOT-22 scores improved more with longer treatment, polyps continued to regress and disappear in some patients, and surgical eligibility decreased with all doses of EDS-FLU over the course of the study.
- Higher doses of EDS-FLU (186 µg and 372 µg) resulted in numerically greater responses for some endpoints and a more rapid onset of action.
- Treatment with EDS-FLU was well tolerated, with an AE profile similar to that of other intranasal steroids studied in patients with CRSwNP.

References:
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