NAVIGATE I: EDS-FLU (Exhalation Delivery System With Fluticasone) for Symptoms of Chronic Rhinosinusitis With Nasal Polyps

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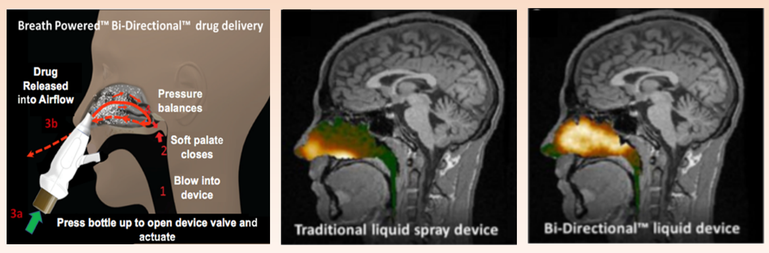
BACKGROUND

- Chronic rhinosinusitis (CRS), often accompanied by nasal polyps (CRSwNP), is a high-prevalence chronic inflammatory condition creating substantial quality-of-life (QoL), economic, and societal burden.
- CRSwNP is characterized by polyps in the nasal cavity plus at least 2 of 4 defining symptoms (nasal congestion/obstruction, rhinorrhea, facial pain/pressure, and reduction/loss of smell[1,2]) and a variety of other symptoms that collectively can adversely affect key domains of QoL to a degree similar to other serious diseases, such as CHF and COPD.[1,3]
- Intranasal corticosteroids (INS) are recommended as a first-line treatment for CRS, including CRSwNP; however, many CRS patients are highly dissatisfied with current INS therapy, primarily because of inadequate symptom relief.[1,2]
- Conventional INS nasal sprays deliver the majority of topically acting drug to the anterior portion of the nasal cavity below the nasal valve or to the floor of the nasal cavity, leaving superior/posterior nasal regions—where polyps typically originate and sinuses drain—undertreated.[4]
- EDS-FLU (Exhalation Delivery System with Fluticasone) uses an exhaler device with a Breath-Powered® "Bi-Directional" mechanism of action (MOA) to optimize fluticasone propionate delivery to the entire nasal cavity, including high/deep regions important in CRS, such as the ostiomeatal complex **(Figure 1)**.[5]
- The purpose of NAVIGATE I (n = 323) was to compare the efficacy and safety of EDS-FLU 93 µg, 186 µg, or 372 µg twice daily (BID) versus EDS-placebo in treatment of nasal polyposis. Primary results were recently reported.[6]
- In this analysis, we report the effect of EDS-FLU on the changes in severity over time of all 4 defining symptoms of the disease reported both for morning and evening and both on an instantaneous and "reflective" (over the past 12 hours) basis.

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



METHODS

- The study design is presented in **Figure 2**.
- Eligible patients were at least 18 years of age with CRSwNP, 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.

Coprimary Endpoints

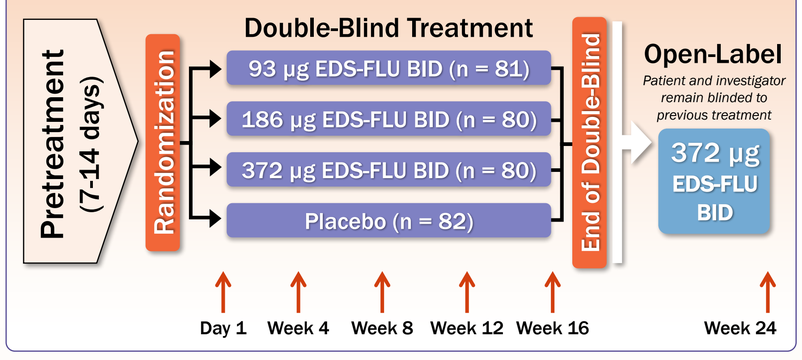
- **Reduction of nasal congestion/obstruction symptoms at week 4 measured by the "Average Diary Score, 7-day, Instantaneous AM"**
- **Reduction in total polyp grade at week 16 (nasal polyp grading score, scale 0-3 per nostril, summed) measured via nasoendoscopy**

Secondary Endpoints Included in This Analysis

- **Onset of action**
- **AM and PM instantaneous and reflective symptom scores**
- **≥0.5-point improvement in AM instantaneous symptom scores**
- **Sino-Nasal Outcome Test (SNOT-22)**

- Patients used an electronic diary twice daily immediately before dosing (morning and evening) to report both instantaneous (evaluation of symptom severity immediately preceding the time of scoring) and reflective (evaluation of symptom severity over the previous 12 hours) scores for all 4 defining symptoms of CRS on an ordinal 4-point scale (none, mild, moderate, severe).
- Nasal polyp grade was scored by nasoendoscopy on a 3-point scale for each nostril.

Figure 2. Study Design



RESULTS

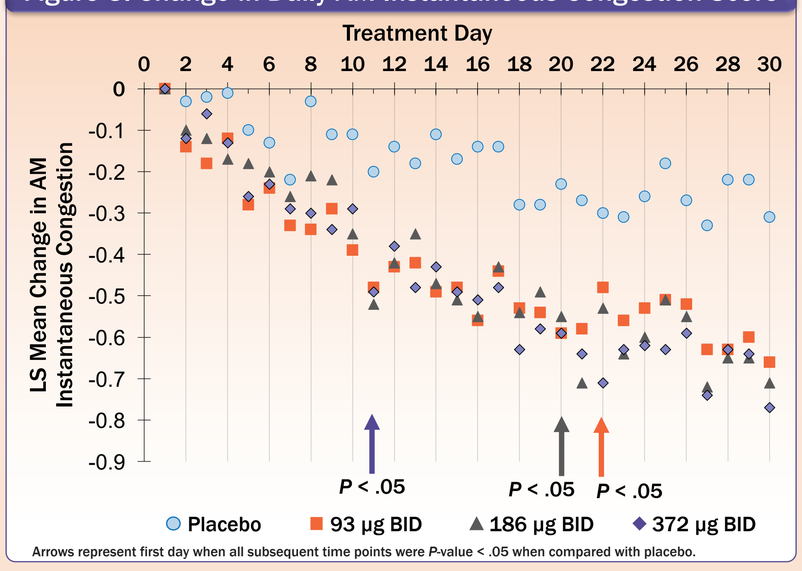
- Baseline demographics and characteristics (**Table 1**) are representative of the CRSwNP population and similar among the 4 treatment groups. Many subjects had previously used steroids and/or undergone surgery.

Table 1. Baseline Characteristics

Characteristics	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 12 months, 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)
Asthma, n (%)	33 (40.2)	101 (41.9)

- The placebo group had the highest drop-out rate (14.6%), compared with 7.4%, 11.3%, and 5.0% in the EDS-FLU 93-µg, 186-µg, and 372-µg groups, respectively.
- Each dose of EDS-FLU was significantly superior to placebo in both coprimary outcomes ($P < .01$). The EDS-FLU 372-µg dose produced the numerically largest mean improvement in both outcomes.
  - At week 4, the LS mean change in 7-day average AM instantaneous congestion score was -0.49, -0.54, and -0.62, in the EDS-FLU 93-µg, 186-µg, and 372-µg groups, respectively, versus -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 EDS-FLU 93-µg, 186-µg, and 372-µg groups, respectively, versus -0.45 in the placebo group.
- Higher doses of EDS-FLU (186 µg and 372 µg) produced faster onset of action and a numerically larger improvement in congestion than the lowest dose (93 µg) (**Figure 3**).

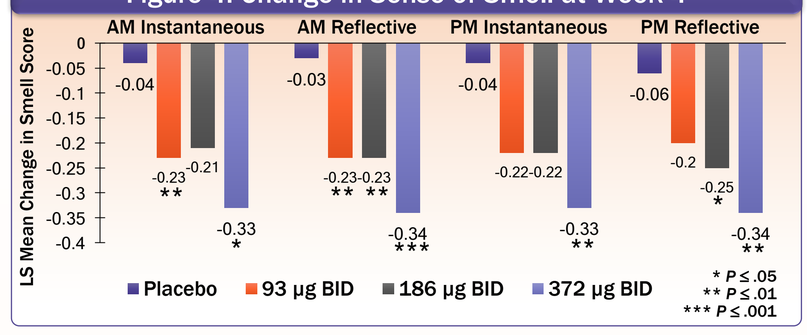
Figure 3. Change in Daily AM Instantaneous Congestion Score



Arrows represent first day when all subsequent time points were *P*-value < .05 when compared with placebo.

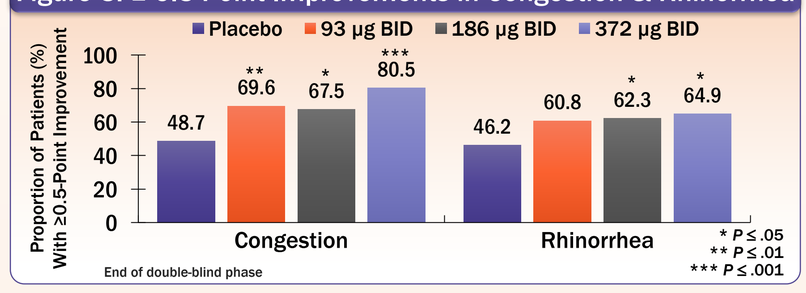
- At both AM and PM assessments, EDS-FLU produced statistically significant benefits (LS mean changes from baseline at week 4) in both instantaneous and 12-hour reflective reports of nasal congestion/obstruction versus placebo (all doses, all comparisons; $P < .05$). The effect of EDS-FLU on both instantaneous and reflective AM/PM assessments of rhinorrhea, facial pain and pressure, and sense of smell was similarly superior to placebo for the majority of comparisons at week 4 ($P < .05$). Across these comparisons, the 372-µg group consistently had the largest treatment effect.
- With respect to impairment of sense of smell, which is often particularly refractory to treatment, the 372-µg dose consistently demonstrated the largest treatment benefit ($P < .05$ for instantaneous and reflective AM and PM assessments at all time points) (**Figure 4**). Mean baseline scores were 2.42, 2.31, 2.49, and 2.44 in the placebo, 93-µg, 186-µg, and 372-µg groups, respectively.

Figure 4. Change in Sense of Smell at Week 4



- The proportion of patients with a ≥0.5-point improvement in AM instantaneous scores for congestion/obstruction was consistently >50% in all 3 EDS-FLU dose groups beginning at week 4. At the end of the double-blind phase, >80% of patients randomized to the highest dose of EDS-FLU (372 µg BID) achieved ≥0.5-point improvement in congestion scores (**Figure 5**).
- The proportion of patients with ≥0.5-point improvement in AM instantaneous scores for rhinorrhea was consistently >50% in all 3 EDS-FLU dose groups beginning at week 8. The 186-µg and 372-µg groups were statistically significant compared to placebo at the end of the double-blind phase (**Figure 5**).

Figure 5. ≥-0.5 Point Improvements in Congestion & Rhinorrhea



- SNOT-22 improvement was large (-18.3 to -19.8) in EDS-FLU groups and superior to placebo (all groups, $P \leq .003$). Scores progressively improved through week 16, with increasing improvement through week 24.
- The most frequent adverse event codes 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. In most cases, these events were observed to resolve with continued use of study medication (**Table 2**).

Table 2. AEs >5% and Greater Than Placebo

Adverse Events	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)
Nasal endoscopic findings	3 (3.7)	8 (9.9)	9 (11.3)	13 (16.5)
Nasal mucosal disorder,[a] n (%)	5 (6.1)	11 (13.6)	6 (7.5)	6 (7.6)
Acute sinusitis,[b] 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,[c] 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)

[a] Erythema and ulceration/erosion in areas other than the septum.
[b] In another study of identical design and duration, acute sinusitis was higher in the placebo group.
[c] All cases of septal ulceration resolved spontaneously with continued use of study medication.

CONCLUSIONS

- EDS-FLU significantly reduced nasal congestion/obstruction and total polyp grade.
- EDS-FLU treatment improves all 4 defining symptoms of CRSwNP. This includes significant improvement in sense of smell, a symptom of CRS often considered refractory to topical steroid treatment.
- For all symptoms, improvement was reported throughout the day, as evidenced by consistent effects on both instantaneous and reflective assessments in both AM and PM.
- A substantial percentage of patients treated with EDS-FLU met responder criteria (≥0.5-point improvement) for congestion/obstruction and rhinorrhea.
- EDS-FLU produced a large and statistically significant improvement in a global measure of symptoms, functioning, and QoL often used to assess treatment of CRS (the SNOT-22).
- Treatment with EDS-FLU was well tolerated, with an AE profile similar to that of other intranasal steroids studied in patients with CRSwNP.

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