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

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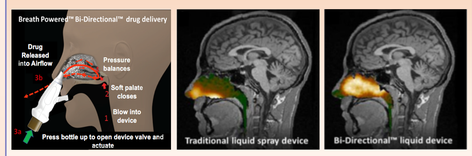
BACKGROUND

- CRS, often accompanied by nasal polyps (CRSwNP), is a high-prevalence chronic inflammatory condition. CRSwNP is characterized by polyps in the nasal cavity and core symptoms of nasal congestion/obstruction, rhinorrhea, facial pain/pressure, and reduction/loss of smell[1,2] and a variety of other symptoms which collectively can adversely affect quality of life (QoL) to a similar degree as other serious chronic diseases such as CHF, COPD, and Parkinson's disease.[1,3]
- The overall annual economic burden of CRS in the U.S. was estimated at $22 billion (direct and indirect costs) in 2014.[4]
- Intranasal corticosteroids (INCS) are recommended as a primary treatment for CRSwNP and its associated core symptoms.
- Conventional INCS nasal 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 and superior nasal regions, where polyps typically originate, undertreated.[5]
- A significant proportion of patients treated with conventional INCS remain unacceptably symptomatic and report considerable impact on daily activities and need for ongoing healthcare.[2] Several aspects of the disease, including but not limited to loss of sense of smell and polyp burden are especially refractory.

Figure 1. EDS MOA; Gamma Scintigraphy Nasal Deposition



- EDS-FLU (Exhalation Delivery System for fluticasone) is a novel intranasal drug delivery system capable of deeply and broadly distributing fluticasone in the nasal cavity, including deposition of drug in the ostiomeatal complex (OMC) where sinus ostia drain/ventilate and polyps typically originate.[6,7] **Figure 1**
- The primary objective of this RCT in 323 patients was to compare the efficacy of intranasal EDS-FLU 93 µg, 186 µg, and 372 µg twice daily with placebo EDS in nasal polyposis. Primary results of NAVIGATE-II were recently reported.
- In this analysis we report the effect of EDS-FLU on the severity scores for morning and evening core symptoms (congestion, rhinorrhea, facial pain and pressure, and sense of smell), both instantaneous and "reflective" (over the past 12 hours). Additionally, the onset of action of EDS-FLU and response rates and magnitude of benefit as reported by patients using the Patient Global Impression of Change (PGIC) are examined.

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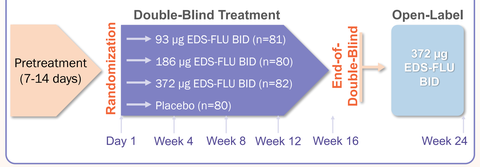
METHODS

- The study design is presented in **Figure 2**.

Figure 2. Study Design



- 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-severe symptoms of nasal congestion/obstruction at entry.
- Non-sedating antihistamines were permitted as 'rescue medication' after week-4.
- Patients reported both **instantaneous** (evaluation of symptom severity immediately preceding the moment of scoring) and **reflective** (evaluation of symptoms severity over the 12 hours prior to scoring) scores for all 4 core defining symptoms (**nasal congestion/obstruction, rhinorrhea, facial pain/pressure, and reduction/loss of smell**) of CRSwNP in both the AM and PM.
- Nasal Symptom Score:
  - **0 = None**
  - **1 = Mild:** Symptoms clearly present, but minimal awareness, and easily tolerated
  - **2 = Moderate:** Definite awareness of symptoms that is bothersome but tolerable
  - **3 = Severe:** Symptoms that are hard to tolerate, cause interference with activities or daily living
- Patients reported their global impression of change in the disease since starting the study drug using the PGIC scale at weeks 4, 16, and 24.

Co-Primary Endpoints:	Reduction of nasal congestion/obstruction symptoms at Week 4 measured by the "Average Diary Score, 7-day, Instantaneous AM" (ADS7-IA) Reduction in total polyp grade at Week 16 (nasal polyp grading score, scale 0-3 per nostril, summed) measured via nasoendoscopy
Secondary Endpoints Include:	• Patient-reported nasal symptom assessments • Objective endoscopic assessments of polyp grades • Quality of life (QoL) assessments • Surgical intervention assessment • Medication evaluation questionnaire

RESULTS

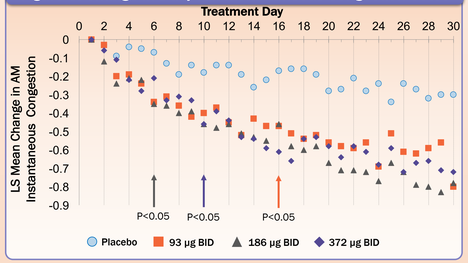
- Baseline demographics and characteristics (**Table 1**) were similar among the 4 treatment groups and representative of the CRSwNP population.

Table 1. Baseline Characteristics

Characteristic	Total (n=323)
Age, mean (SD), y	45.8 (12.7)
Male sex, No. (%)	186 (57.6)
"White" Race/Ethnicity, No. (%)	304 (94.1)
Oral steroids used for nose, sinus in past 12 months (%)	280 (86.7)
Sinus surgery for polyp removal or sinus surgery, No. (%)	97 (30)
Bilateral endoscopic nasal polyp score, mean (SD)	3.8 (1)
SinoNasal Outcomes Test (SNOT-22) total score, mean (SD)	47.9 (20)

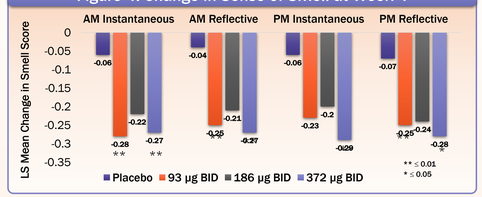
- The placebo group had the highest drop-out rate (12.5%), compared to 3.7%, 5%, and 0% in 93 µg, 186 µg, and 372 µg groups, respectively.
- Changes in both co-primary endpoints were significantly superior to placebo for each EDS-FLU dose versus placebo (p<0.001).
  - At Week 4, the LS mean change in congestion (by ADS7-IA) was -0.59, -0.68, and -0.62 in 93 µg, 186 µg, and 372 µg groups, respectively, compared to -0.24 in the placebo group.
  - At Week 16, the LS mean change in summed polyp grade was -1.31, -1.22, and -1.41 in the 93 µg, 186 µg, and 372 µg groups, respectively, compared to -0.61 in the placebo group.
- **Figure 3** displays the mean ADS7-IA scores for nasal congestion/obstruction over the first 30 days of double-blind treatment. Results indicate the patients in the 186 µg BID dose group had the earliest onset of action (at Day 6). The 93 µg BID group had the slowest onset of action (at Day 26).

Figure 3. Change in Daily AM Instantaneous Congestion Score



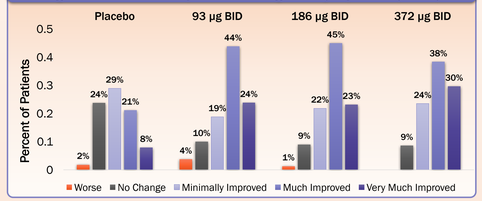
- Both the mean instantaneous and mean 12-hour reflective assessment scores, both AM and PM, improved in each treatment group at each successive time point from Week 4 through the end of double-blind treatment, with improvement generally increasing over time, indicating that patients experienced consistently improved morning and evening nasal symptoms (p<0.05).
- With respect to impairment of sense of smell, which is often difficult to treat, the 372-µg dose consistently demonstrated the largest treatment benefit (P < 0.05 for instantaneous and reflective AM and PM assessments). **Figure 4**

Figure 4. Change in Sense of Smell at Week 4



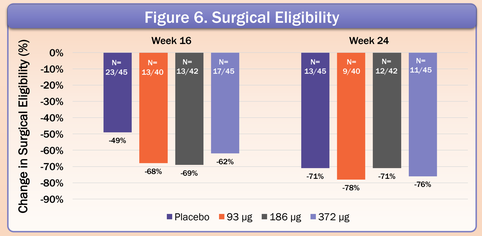
- At the end of the double-blind phase, two-thirds of subjects in each of the active treatment arms reported being "much improved" or "very much improved" compared with 29% of subjects treated with placebo. Over 90% of subjects reported being improved in the 372 µg BID group (p<0.001). **Figure 5**

Figure 5. Patient-Reported Change in Symptoms (PGIC)



- At Week 24, the proportion of patients with polyps eliminated (polyp grade 0;"no polyp seen") in at least 1 nostril was 24.7%, 24.6%, and 28.2% in the 93 µg+372 µg, 186 µg+372 µg, and 372 µg+372 µg BID sequences, respectively, as compared with 8.7% in the placebo+372 µg BID sequence (p<0.05 for all comparisons versus placebo+372 sequence).
- The number of subjects eligible for surgery (by standard *a priori* criteria) decreased in all 4 treatment groups over the course of the study. **Figure 6**

Figure 6. Surgical Eligibility



- Adverse Events (AEs) associated with EDS-FLU were largely local in the nose and similar frequency to that reported with conventional INCS when studied in similar populations for similar durations.[8]
- The most frequent AEs in EDS-FLU recipients were identified on nasoendoscopy rather than by clinical report, and were 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. Adverse Events >5% and Greater than Placebo

Adverse Event	Placebo (n=79)	93 µg BID (n=80)	186 µg BID (n=80)	372 µg BID (n=82)
Epistaxis, No. (%)	4 (5.1)	14 (17.5)	19 (23.8)	18 (22)
Spontaneously reported	1 (1.3)	4 (5)	12 (15)	10 (12.2)
Incidental finding on nasoendoscopy	3 (3.8)	10 (12.5)	7 (8.8)	8 (9.8)
Nasal Septal Ulceration, No. (%)	3 (3.8)	3 (3.8)	6 (7.5)	9 (11)
Nasopharyngitis, No. (%)	4 (5.1)	2 (2.5)	1 (1.3)	8 (9.8)
Nasal Erythema/Erosion, No. (%)	2 (2.5)	6 (7.5)	8 (10)	5 (6.1)
Headache, No. (%)	3 (3.8)	5 (6.3)	6 (7.5)	6 (7.3)
Nasal Septal Erythema, No. (%)	2 (2.5)	5 (6.3)	4 (5.0)	4 (4.9)
Atypical Nasal Congestion, No (%)	2 (2.5)	2 (2.5)	5 (6.3)	3 (3.7)

CONCLUSIONS

- EDS-FLU, at doses of 93 µg, 186 µg, and 372 µg intranasally BID, significantly improved the co-primary endpoints of nasal congestion/obstruction and total polyp grade relative to placebo.
- EDS-FLU treatment improved all four core defining symptoms of CRSwNP. This benefit was observed throughout the day as evidenced by the consistent positive effects on both instantaneous and reflective assessments taken both in the AM and PM.
- EDS-FLU treatment significantly improved sense of smell, a symptom of CRS often considered refractory to topical treatment.
- EDS-FLU treatment produced clinically significant improvement, as defined by the patient, in the great majority of treated patients (up to 90%), reduced eligibility for surgery, and even polyp elimination in some patients.
- Higher doses of EDS-FLU (186 µg and 372 µg BID) produced numerically greater responses for most endpoints, and a more rapid onset of action, than the lower dose. At the end of the double-blind period, the 372 µg dose remained numerically superior to both lower doses for improvement in sense of smell.
- Treatment with EDS-FLU was generally well tolerated with an adverse event profile similar to that reported with other intranasal steroids in patients with CRSwNP.

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