EXHANCE-3: A Phase III, 3-Month Study of Safety and Efficacy of an Exhalation Delivery System with Fluticasone (EDS-FLU) in Patients With Chronic Rhinosinusitis With (CRSwNP) and Without Nasal Polyps (CRSsNP)

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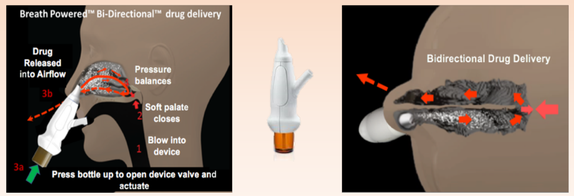
BACKGROUND

- Chronic rhinosinusitis (CRS) with (CRSwNP) and without (CRSsNP) nasal polyps is common (11.5-27.9 million persons in the United States) and is associated with substantial disease burden. The overall annual economic burden of CRS in the United States was estimated at $22 billion (direct and indirect costs) in 2014.[1,2]
- Defining symptoms include nasal congestion/obstruction, rhinorrhea (postnasal drip and runny nose), facial pain/pressure, and hyposmia (reduction/loss of smell). Extrasinal manifestations are common and include fatigue and bodily pain, sleep dysfunction, and depression. The overall effect is an impairment of quality of life (QoL), which has been measured to be similar in magnitude to other serious diseases, such as CHF, COPD, and Parkinson's disease.[3,4]
- CRS is characterized by widespread nasal mucosal inflammation involving key anatomical structures, including the ostiomeatal complex (OMC), where the sinus ostia drain and ventilate and where nasal polyps most commonly originate.[5]
- Intranasal corticosteroids (INS) are recommended as standard-of-care in multiple treatment guidelines; however, conventional INS sprays are relatively inefficient and ineffective in delivery of topically acting drug to key disease sites beyond the nasal valve area (including the OMC), potentially reducing treatment benefit, and are associated with low treatment satisfaction.[2]
- EDS-FLU uses Breath-Powered® "Bi-Directional" delivery to optimize deposition of fluticasone propionate to the entire nasal cavity, including key high and deep anatomical regions, such as the OMC (**Figure 1**).
- EDS has been shown to deposit drug deeper and more broadly in the nasal cavity (particularly superiorly/posteriorly, eg, the OMC), with less drug loss to drip-out and swallowing, compared with conventional nasal sprays.[6,7] EDS-FLU aims to meaningfully improve outcomes by using an EDS to substantially modify delivery of locally acting steroid, including to the OMC.

Figure 1. EDS Mechanism of Action



- The objective of this study was to assess the safety and efficacy of EDS-FLU 372 µg twice daily in patients with symptoms of moderate-severe CRS, with or without nasal polyps.

METHODS

- 12-week, open-label, multicenter, repeat endoscopy study.
- Eligible patients were ≥18 years of age, with CRSwNP or CRSsNP, as determined by nasoendoscopy plus history of diagnostic symptoms for ≥12 weeks, and were currently experiencing ≥2 defining symptoms of CRS, one of which had to be nasal congestion/obstruction or rhinorrhea.

Efficacy Assessments

- Lund-Kennedy endoscopic assessment
- Nasal Polyp Grading Scale (CRSwNP patients)
- Sino-Nasal Outcome Test (SNOT-22)
- Surgical intervention assessment
- Medical evaluation questionnaire
- Patient Global Impression of Change (PGIC)

Safety Assessments

- Adverse events (AEs)
- Nasal endoscopy
- Ocular examination by ophthalmologist
- Clinical laboratory parameters
- Vital signs
- Physical examination

RESULTS

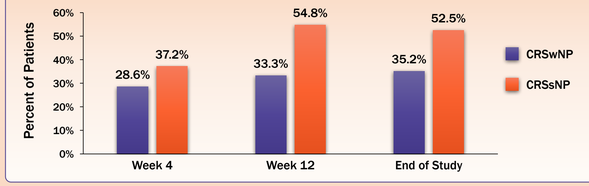
- 966 patients were screened, and 706 patients were enrolled at 38 centers in the United States. Seven hundred five patients received study drug, of which 601 (85.2%) completed the study.
- Baseline characteristics are shown in **Table 1**.

Table 1. Baseline Characteristics

Characteristic	CRSwNP (n = 102)	CRSsNP (n = 603)
Age, mean (SD), y	45.2 (13.7)	45.4 (13.7)
Male sex, n (%)	56 (54.9)	246 (40.8)
White race, n (%)	91 (89.2)	461 (76.5)
Used corticosteroids for CRS (within last 10 y), n (%)	99 (97.1)	549 (91.5)
Bilateral endoscopic nasal polyp score, mean (SD)	2.9 (1.2)	NA
Lund-Kennedy total score, mean (SD)	2.1 (1.2)	1.7 (1.4)
SNOT-22 total score, mean (SD)	43.8 (19.2)	43.2 (19.5)
≥1 sinus surgery for polyp removal or sinus surgery, n (%)	41 (40.2)	47 (7.8)

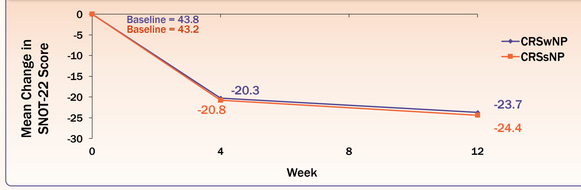
- Among patients with baseline Lund-Kennedy edema scores >0, EDS-FLU treatment was associated with complete resolution of edema in 33.3% of CRSwNP and 54.8% of CRSsNP patients at week 12 (**Figure 2**).

Figure 2. Patients With Complete Resolution of Edema



- Mean SNOT-22 scores improved dramatically, and similarly, in CRSwNP (-23.7) and CRSsNP (-24.4) patients by week 12. Importantly, this magnitude of improvement far exceeds the clinically significant threshold of a 9-point improvement and is comparable to that of postoperative SNOT-22 reductions in CRS patients[8] (**Figure 3**).
- A similar relative magnitude of improvement was also observed for the SNOT-22 subscales, regardless of the presence of nasal polyps at baseline.

Figure 3. Mean Change in SNOT-22



- By week 12, >90% of patients receiving EDS-FLU reported symptom improvement as assessed by PGIC, with >70% reporting "much" or "very much" improvement. Rates of improvement were similar for patients with and without nasal polyps (**Figure 4**).

Figure 4. Patient-Reported Change in Symptoms

- For CRSwNP, the percentage observed to have polyp elimination in at least 1 nostril (Grade 0, no polyps seen) by nasal endoscopy increased over the course of the study (**Figure 5a**). Among those completing 12 weeks of treatment, 48% of CRSwNP patients had polyp elimination in at least 1 nostril.
- Patients with nasal polyps at study entry experienced a large reduction in polyp grade, with a mean decrease in bilateral nasal polyp score of -0.8 and -1.3 at week 4 and week 12, respectively (**Figure 5b**); 63% of CRSwNP patients had >1-point improvement in polyp grade.
- Using standardized assessments of surgical eligibility, at end-of-study, the number of CRSwNP patients eligible for surgery decreased from 42.2% to 18.2%.
- Approximately 90% of patients reported that the EDS-FLU delivery device was somewhat or very easy to use. At week 4, the majority of patients reported much less/less drip out of the nose (67%) and drip down the throat (74%) with EDS-FLU compared to that of their most recent conventional INS.

Figure 5. Endoscopic Assessments of Polyp Grades (CRSwNP)

Figure 5a. Polyp Elimination

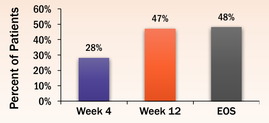
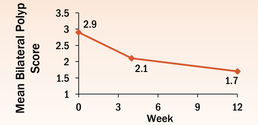


Figure 5b. Mean Polyp Score



EOS, end of study.

- EDS-FLU was well tolerated, with a safety profile similar to that reported with traditional intranasal steroids studied in patients with CRS for a similar duration.
- The most common AEs (>5%) included infections and infestations (16.0%), epistaxis [all types (14.5%), identified on nasal endoscopic examination (7.7%) and spontaneously reported (6.8%)], nasal mucosal disorder (10.2%), nervous system disorders (5.7%), and nasal septum disorder (5.5%).

CONCLUSIONS

- EDS-FLU 372 µg twice daily substantially improved subjective symptoms and objective local signs of disease with a similar magnitude of improvement in patients who have symptoms of CRS with and without nasal polyps.
- Patients with nasal polyps at study entry experienced an extensive reduction in polyp grade, and nearly 50% of patients experienced polyp elimination in at least 1 nostril after only 12 weeks of treatment.
- Based on the PGIC, a very high proportion of patients treated with EDS-FLU reported improvement, and very few reporting worsening—a result reinforced by the large improvement measured by SNOT-22.
- The AEs reported were generally local in nature, tended to be mild in severity, and were largely transient. AEs did not increase in frequency or severity with increasing duration of exposure to study drug. One of the most common AEs was epistaxis.
- Improvement in symptoms, QoL, and objective signs of disease, including polyp grade, is likely due to the ability of EDS-FLU to deliver fluticasone superiorly and posteriorly throughout the nasal cavity, including the OMC, where polyps originate and sinuses drain.
- In patients with moderate to severe symptoms of CRS (with and without nasal polyps) and frequent past use of conventional INS sprays, EDS-FLU was well tolerated and significantly improved symptoms and objective measures of disease, indicating the important role of superior/posterior drug delivery via EDS.

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Funding: This study was funded by OptiNose US, Inc., Yardley, PA, USA and OptiNose AS, Oslo, Norway