NAVIGATE II: A Randomized Double-Blind Trial of Fluticasone Propionate Exhalation Delivery System (FLU-EDS) for Treatment of Chronic Rhinosinusitis (CRS) with Nasal Polyps (Nasal Polyposis)

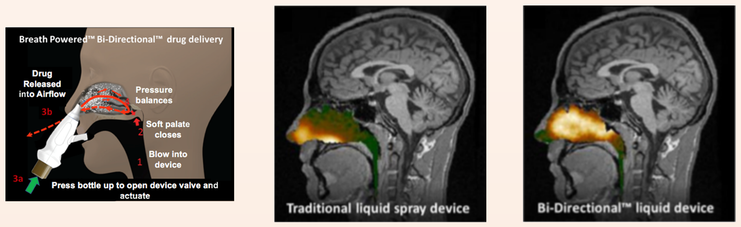
Donald Leopold, MD, FACS[1]; David Elkayam, MD[2]; John Messina, PharmD[3]; Colette Kosik-Gonzalez, BS, MA[3]; Per Djupesland, MD, PhD[3]; Ramy Mahmoud, MD, MPH[3]

1. Department of Surgery, College of Medicine, University of Vermont, Burlington, VT; 2. Bellingham Asthma Allergy & Immunology Clinic, Bellingham, WA; 3. OptiNose US Inc. Yardley, PA, USA and OptiNose AS, Oslo, Norway

BACKGROUND

- CRS with nasal polyps (CRSwNP), is a high-prevalence chronic inflammatory condition 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 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]
- Intranasal corticosteroids (INCS) are recommended as a primary treatment but conventional INCS 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.[4]
- FLU-EDS (fluticasone propionate exhalation delivery system) is a novel intranasal drug delivery system capable of deeply and broadly distributing fluticasone in the nasal cavity, including much greater deposition of drug in the ostiomeatal complex (OMC) where sinus ostia drain/ventilate and polyps typically originate.[5,6] **(Figure 1)**
- The primary objective of this study was to compare the efficacy of intranasal administration of 93 µg, 186 µg, and 372 µg of FLU-EDS twice daily (BID) with placebo EDS in nasal polyposis.

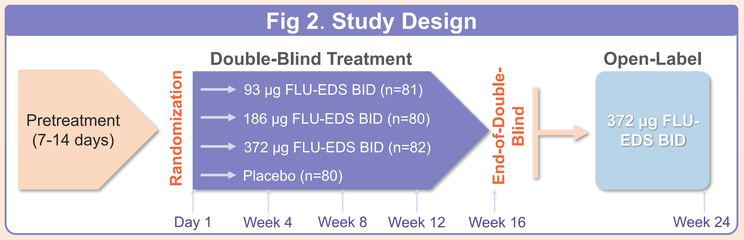
Fig 1. EDS MOA; Gamma Scintigraphy Nasal Deposition Studies[6]



METHODS

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

Fig 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.

Two Co-Primary Endpoints

- **Reduction of nasal congestion/obstruction symptoms** at Week 4 measured by the "7-day instantaneous AM average diary score" ("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 Included

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

- Polyp grading
  - 0 = no polyps
  - 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 inferior border of the inferior turbinate
  - Findings and scores were reviewed by a central reviewer
- Active assessment of the nasal cavity by a specialist using nasal endoscopy (not simply speculum exam) for findings such as epistaxis, septal erosion, ulceration, and perforation, was performed throughout the study and all were recorded as adverse events (AEs) irrespective of clinical correlation.

RESULTS

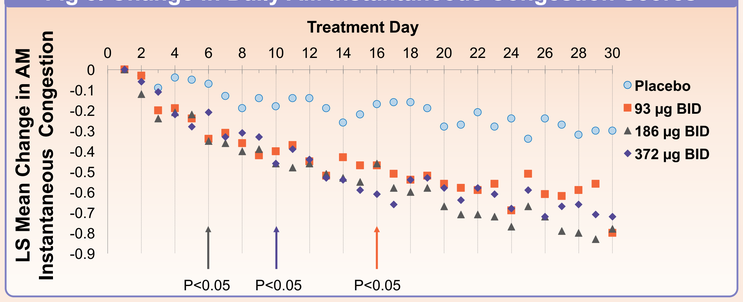
- Baseline demographics and characteristics **(Table 1)** are representative of the CRSwNP population and were similar among the 4 treatment groups.
- The placebo group had the highest drop-out rate (12.5%).

Table 1. Baseline, Including Reported Med/Surgical History

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)

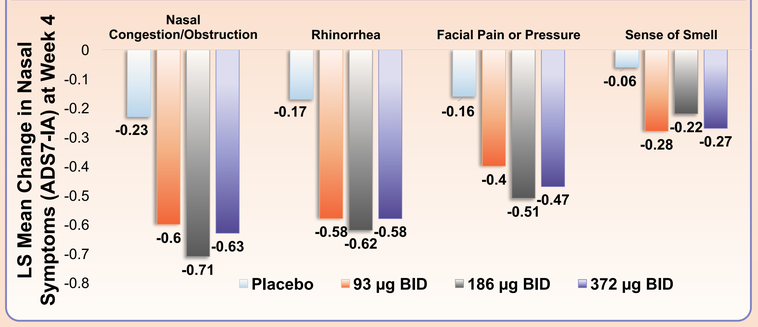
- Changes in both co-primary endpoints were significantly superior to placebo for each FLU-EDS dose versus placebo (p<0.001)
  - At Week 4, the LS mean change in congestion (by ADS7-IA) was -0.59, -0.68, and -0.62 in 93 µg, 186 µg, and 372 µg groups, respectively, compared to -0.24 in the placebo group.
  - 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.
- Higher doses of FLU-EDS (186 µg and 372 µg) produced faster onset of action and numerically larger improvement in congestion **(Figure 3)** and polyp grade than the lowest dose (93 µg).

Fig 3. Change in Daily AM Instantaneous Congestion Scores



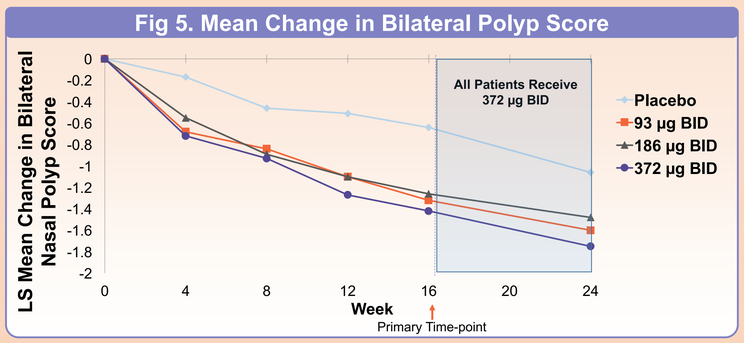
- Improvements in all core nasal symptoms **(Figure 4)**, patient global impression of change (PGIC) and multiple measures of functioning and QoL were superior in all FLU-EDS groups versus placebo (p<0.05, all comparisons).

Fig 4. Mean Change in Core Symptom Scores (ADS7-IA) at Week 4



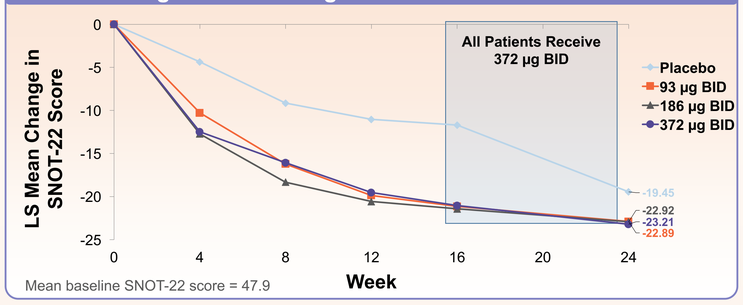
- Polyp grade was notably reduced at Week 4, reaching statistical significance versus placebo at week 8 (p<0.01, all comparisons). Polyp grade continued to monotonically improve with continued treatment through Week 24 (p≤0.006, all comparisons versus placebo/372 µg BID). **(Figure 5)**

Fig 5. Mean Change in Bilateral Polyp Score



- At Week 24, the proportion of patients with polyps eliminated 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 sequences, respectively, as compared with 8.7% in the placebo/372 µg sequence (p<0.05 for all comparisons versus placebo/372 sequence).
- SNOT-22 improvement was large in all FLU-EDS groups and statistically superior to placebo (p<0.001). SNOT-22 scores (total and subscale) progressively improved through Week 16, with incremental improvement through Week 24. **(Figure 6)**

Fig 6. Mean Change in SNOT-22 Total Score



- AEs associated with FLU-EDS were local in nature and similar in frequency to that reported with conventional INCS when studied in similar populations for similar durations.[7]
- The most frequent AEs in FLU-EDS 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 meds. **(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

- FLU-EDS, at doses of 93 µg, 186 µg, and 372 µg intranasally BID, significantly reduced both co-primary endpoints of nasal congestion/obstruction and total polyp grade.
- FLU-EDS resulted in clinically significant improvements in a broad range of objective and subjective outcome measures, including in all four core symptoms of CRS, QoL, and polyp elimination in some patients.
- Higher doses of FLU-EDS (186 µg and 372 µg) resulted in numerically greater responses for some endpoints and a more rapid onset of action.
- Subjective and objective measures of CRS continued to improve throughout the course of 24 weeks of follow-up.
- Treatment with FLU-EDS was well tolerated with an adverse event profile similar to that of other intranasal steroids studied in patients with CRSwNP.

References:

1. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;6:S22-S209.
2. Palmer J, Messina J, Biletch R, Grosel K, Mahmoud R. A Cross-Sectional Population-Based Survey of the Prevalence, Disease Burden, and Characteristics of the US Adult Population with Symptoms of Chronic Rhinosinusitis (CRS). Poster session presented at: the 62nd Annual Meeting of the American Rhinologic Society; 2016 Sept 16-17; San Diego, CA.
3. Soler ZM, Wittenberg E, Schlosser RJ, et al. Health state utility values in patients under- going endoscopic sinus surgery. *Laryngoscope.* 2011;121:2672–2678.
4. Merkus P, Ebbens FA, Muller B, et al. The 'best method' of topical nasal drug delivery: comparison of seven techniques. *Rhinol.* 2006;44:102-7.
5. Djupesland PG, Messina J, Mahmoud R. Novel Nasal Exhalation Delivery Systems (EDS) May Produce Beneficial Activity Independent of Delivered Drug in Inflammatory Nasal Diseases and Migraine via Exhaled CO2 and Mucosal pH Changes. Poster session presented at: the 62nd Annual Meeting of the American Rhinologic Society; 2016 Sept 16-17; San Diego, CA.
6. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective – a review. *Drug Deliv and Transl Res. 2013;3:42-62*
7. Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol.* 2005;116:1275-1281

Contact: John Messina, PharmD, OptiNose US Inc. Yardley, PA, USA.
Address: 1010 Stony Hill Rd., Yardley, PA, 19067
Email: john.messina@optinose.com, Phone: (267) 364-3500