

VISUALIZE: a 24-week, open-label study using nasal endoscopy video to evaluate the efficacy and safety of EDS-FLU 186 µg twice daily in adults with bilateral nasal polyps*

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Abstract

Background: In prior phase 3, randomized, placebo-controlled trials, fluticasone propionate exhalation delivery system (EDS-FLU) over 24 weeks showed significant reduction in total polyp score compared with EDS-placebo. The goal of this study was to observe nasal endoscopy improvement(s) along with patient-reported symptoms associated with EDS-FLU administration over 24 weeks.

Methods: This open-label, multicenter study enrolled adults with bilateral nasal polyp grade of ≥ 3 (out of 6), 22-Item Sino-Nasal Outcome Test (SNOT-22) scores ≥ 20 , and previous sinus surgery. All patients received EDS-FLU 186 µg BID for 24 weeks. Nasal endoscopy was performed, and disease-specific quality of life and sense of smell were assessed with SNOT-22 and “Sniffin’ Sticks” at baseline, 3 months, and 6 months. An independent reviewer evaluated videos and performed blinded polyp grading and Lund-Kennedy (LK) assessments.

Results: Eleven patients were enrolled. At baseline, mean polyp grade was 3.1/6. SNOT-22 scores were 48.8, and Sniffin’ Sticks measurements were 11.8/48. A clinically meaningful reduction in SNOT-22 was noted at 24 weeks. Olfaction improved by 4.7 points. The mean polyp grade was reduced from 3.1 to 2.4 at week 24. LK edema scores were reduced by 2.2.

Conclusion: EDS-FLU 186 µg BID given over 24 weeks resulted in clinically meaningful reduction in SNOT-22 scores and polyp grade improvement in most subjects. Endoscopic documentation showed reduced inflammation and edema not adequately captured with polyp-scoring methodology.

Key words: nasal obstruction, nose, rhinitis, diagnostic techniques, nasal polyps, sinusitis, smell

Introduction

Chronic rhinosinusitis (CRS) is a persistent health condition characterized by inflammation of the sinus nasal mucosa, affecting 10% to 15% of the US population^(1–3). Amongst patients with

CRS, 18% to 20% have nasal polyposis (CRSwNP)⁽⁴⁾. Intranasal corticosteroids (INS) have become a mainstay of medical therapy in the management of CRSwNP due to their broad anti-inflammatory activity and documented clinical efficacy. Clinical

Abbreviations: AE, adverse event, BID, twice daily, CI, confidence interval, COPD, chronic obstructive pulmonary disease, CRS, chronic rhinosinusitis, CRSwNP, chronic rhinosinusitis with nasal polyps, EDS-FLU, exhalation delivery system with fluticasone, ESS, endoscopic sinus surgery, INS, intranasal corticosteroids, LK, Lund-Kennedy, NP, nasal polyp, PGIC, Patient Global Impression of Change, QoL, quality of life, SD, standard deviation, SNOT-22, 22-Item Sino-Nasal Outcome Test, TDI, Threshold, Discrimination, and Identification

guidelines for CRSwNP recommend topical steroids, due to their low systemic bioavailability and favorable safety profiles^(5,6).

Unfortunately, most patients with CRS do not achieve adequate symptom control with currently available intranasal steroid therapy delivered via nasal sprays^(7,8). This has been attributed to the inability of conventional nasal sprays to adequately deliver the drug beyond the nasal valve and above the inferior turbinate, leaving key sinonasal regions obstructed due to persistent inflammation and polyposis^(9–13). As a result, many patients with CRS remain symptomatic, report frustration with the limited symptom relief associated with conventional medical treatment and are ultimately considered for endoscopic sinus surgery (ESS) to relieve their symptoms^(5,6,14,15). However, as much as 40% of patients undergoing ESS can experience polyp recurrence at 18 months, indicating a need for improved medical therapies even in the early post-operative state^(16,17).

The US Food and Drug Administration–approved exhalation delivery system with fluticasone (EDS-FLU; XHANCE®) is designed to facilitate deposition of topical corticosteroid deeper into the paranasal sinuses (e.g., the ostiomeatal complex, frontal recess) at a concentration higher than conventional prescription and over-the-counter INS^(18,19). Multiple clinical trials of EDS-FLU (NAVIGATE I, NAVIGATE II, EXHANCE-3, and EXHANCE-12) have demonstrated a broad improvement in symptoms and polyp burden^(20–23). A detailed description of the mechanism of EDS-FLU has been published^(19–23), and is available at <https://www.optinose.com/exhalation-delivery-systems/liquid-delivery-device>.

Current polyp-grading systems are crude measures of changes in polyp tissue that do not reflect the overall changes in polyp mass or inflammation/edema⁽²⁴⁾. The available grading systems assign scores based on polyp tissue relative to anatomical landmarks (e.g., inferior border of middle turbinate) and do not account for total polyp bulk within the nasal cavity or the associated swelling of nasal tissues. Therefore, we sought to directly assess the effect of twice-daily EDS-FLU treatment on nasal polyp (NP) burden using nasal endoscopy video to document changes in NP size as well as the associated edema that can be overlooked on currently available measures. We also collected patient-reported outcome measurement data over the course of the study to demonstrate possible associations with reduction in NP burden.

Methods

Objectives and assessments

This prospective, 24-week, open-label, multicentre study documented the effects of EDS-FLU on polyp burden over a 6-month period using nasal endoscopy video. Polyp grading of each side

Table 1. Polyp-grading scale.

Polyp grade score	Description
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 lower inferior border of the inferior turbinate

was determined using the Lildholdt nasal polyp-grading scale,^(25,26) a 3-point scale that evaluates the extent of middle meatus obstruction (Table 1). Each side was scored independently by a blinded rhinologist who reviewed nasal endoscopy videos recorded during study visits. In addition, the independent reviewer scored each video with the Lund-Kennedy (LK) Scoring System (which assesses polyps, edema discharge, scarring/adhesions, and crusting on a 0 to 2 scale for a maximum total of 10 for each side)⁽²⁷⁾. Secondary objectives evaluated at each study visit included change from baseline to each time point in patient-reported symptoms and quality of life (QoL), as measured by the 22-Item Sino-Nasal Outcome Test (SNOT-22)⁽²⁸⁾, Sniffin' Sticks (expressed as the sum of the results of the Threshold, Discrimination, and Identification tests [TDI score])^(29,30), and the Patient Global Impression of Change (PGIC) scale (graded on a Likert scale from 1 to 7, with 1 signifying "very much improved" and 7 signifying "very much worse")^(31,32). The safety of EDS-FLU was evaluated via adverse-event (AE) reports, vital signs, and nasal examination.

Participants

Eleven adult patients, aged 18 years or older, were enrolled between June 2018 and September 2018. Inclusion criteria were presence of bilateral NP with a grade of ≥ 2 in at least 1 side of the nasal cavity at baseline (assessed by nasal endoscopy) and a baseline SNOT-22 score ≥ 20 . Patients were also required to have received INS sprays for ≥ 1 month within the 3 months prior to study enrollment. All patients discontinued prior steroid treatment for NP at study enrollment, but patients were permitted to continue oral inhaled steroids, if necessary, to treat asthma or chronic obstructive pulmonary disease (COPD), consistent with inclusion criteria from published studies^(20–23).

Exclusion criteria included current or prior use of EDS-FLU at time of screening, uncontrolled COPD and/or asthma, COPD/asthma exacerbations in the preceding 3 months, nasal or sinus surgery (in the prior 3 months), and nasal or sinus surgery planned during the study period and specific comorbidities (nasal

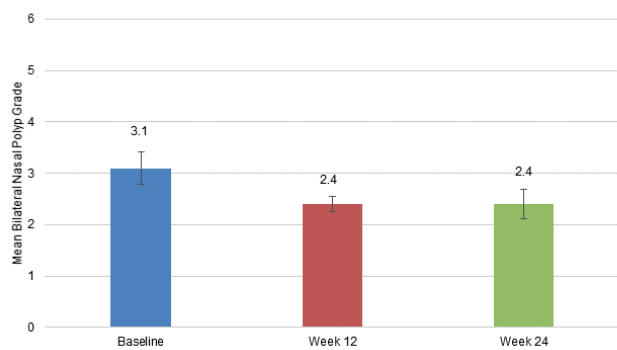


Figure 1. Mean change in bilateral nasal polyp grade.

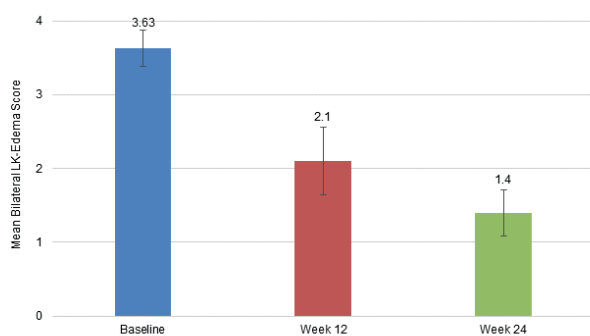


Figure 2. Mean change in Lund-Kennedy edema score.

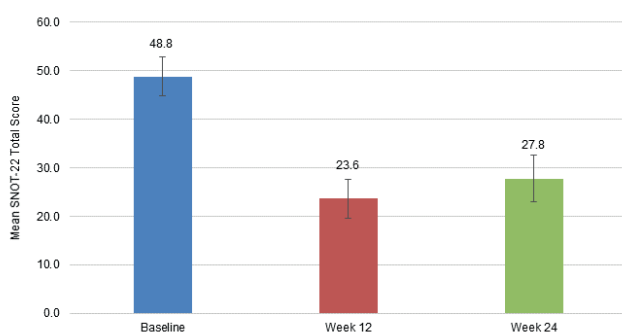


Figure 3. Mean change in SNOT-22 total score.

candidiasis, cystic fibrosis, glaucoma, or ocular hypertension). Patients with significant oral structural abnormalities, such as a cleft palate, were excluded. In addition, patients who were unable to have each nasal cavity examined were also excluded. Pregnant or lactating women were excluded, and women of childbearing age were required to provide a negative pregnancy test and, if sexually active, to practice an effective method of birth control during the study period.

Study design

All patients received EDS-FLU 186 µg twice daily (BID) (i.e., 1 spray containing 93 µg of the study drug in each nostril twice daily) and were instructed to administer the medication every 12 hours. Patients were assessed on day 1 (baseline), at week 12,

Table 2. Week 24 efficacy outcomes versus baseline.

	Baseline (n=11)	Week 24 (n=11)
NP grade, mean	3.1*	2.4
Difference in means (95% CI; P-value)		-0.73 (-1.33 to -0.12; p=0.02)
LK total score, mean	10.8	7.4
Edema	3.6	1.4
Discharge	2.7	2.0
Crusting	0.3	0.2
Scarring/adhesion	0.2	0.2
NP	4.0	3.6
SNOT-22 total score, mean	48.8	27.8
Difference in means (95% CI; P-value)		-21.0 (-32.64 to -9.36; p=0.002)
Sniffin' sticks TDI score, mean	11.8	16.5
Difference in means (95% CI; P-value)		4.7 (0.82 to 8.59; p=0.02)

*There was a difference in mean polyp grading between the investigator's assessment and the independent rater's at screening (3.5 vs. 3.1). The ratings from the independent rater are included here. BID = twice daily; LK = Lund-Kennedy; NP = nasal polyps; SNOT-22 = 22-Item Sino-Nasal Outcome Test; TDI = threshold, discrimination, identification.

and at week 24 of the study. At each visit, patients completed SNOT-22 questionnaires and PGIC scores, and underwent nasal endoscopy and Sniffin' Sticks testing. To maintain consistency, physical examinations and nasal endoscopies were performed by the same physician for each subject. Patients were contacted at weeks 4, 8, 16, and 20, separate from the site visits, to collect treatment compliance, AEs, and concomitant medications information.

Safety analysis

At each study visit, researchers assessed patients for occurrences of AEs and AEs of special interest, which included epistaxis, nasal septal ulceration, and other potential emergent AEs. AEs were reported as mild, moderate, or severe.

Data analysis

Study outcomes were summarized descriptively, and differences in mean values were compared using a paired t test (GraphPad QuickCalcs Web site: <https://www.graphpad.com/quickcalcs/ttest1/> (accessed April 2020). Data listings were produced using SAS® Version 9.0 or higher. No inferential statistics were performed for this study.

Results

The study enrolled 11 patients from 2 study sites. The group included 8 men and 3 women; 82% were white (9 of 11), 1 patient was black/African American, and 1 patient was Hispanic/

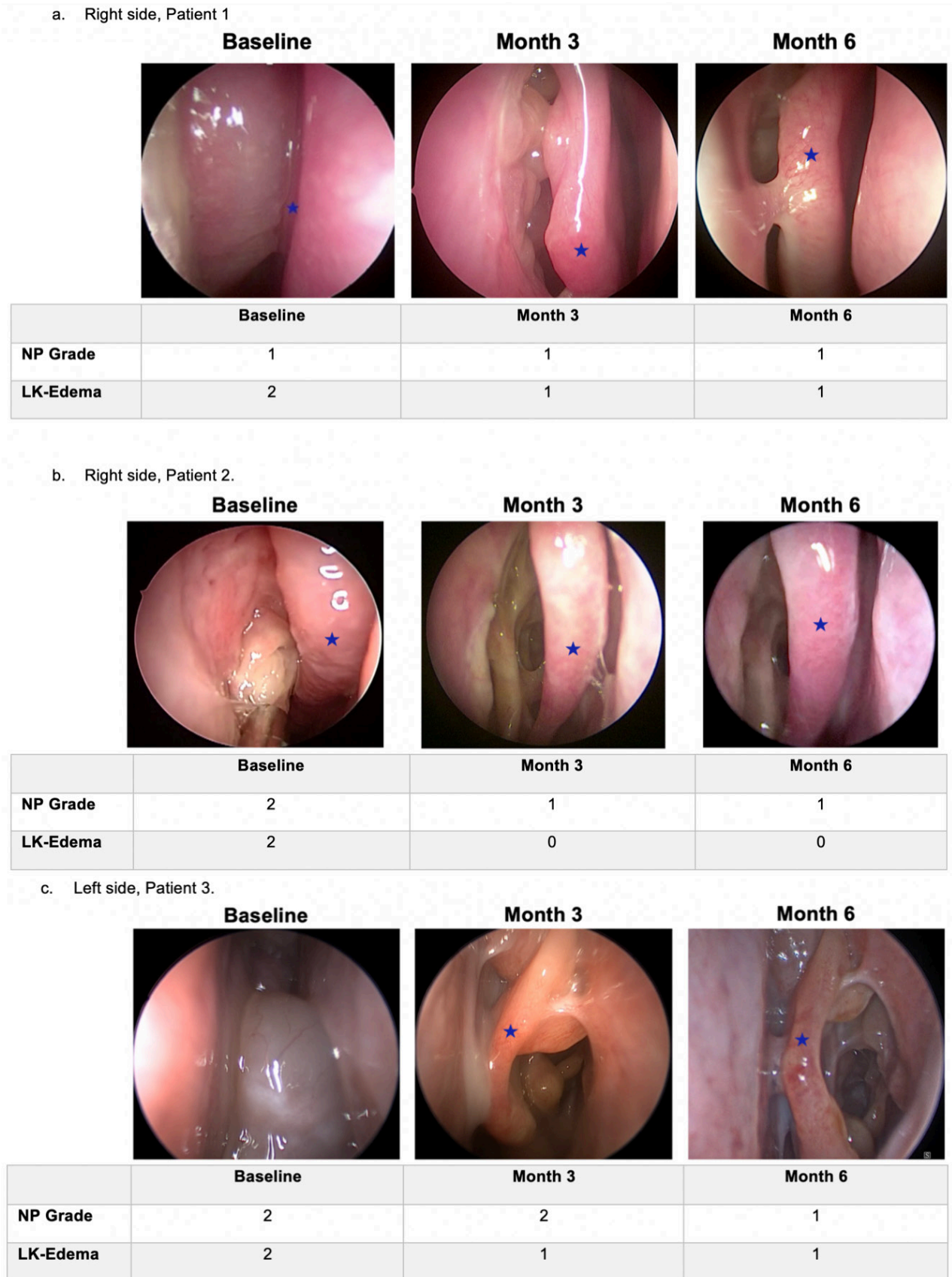
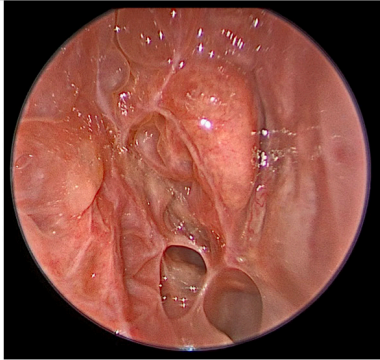
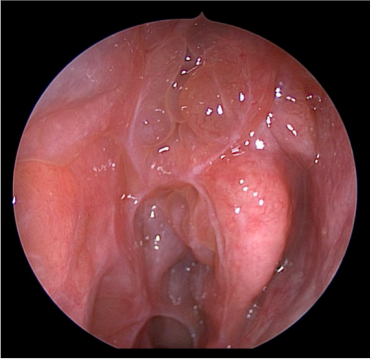


Figure 4. Endoscopic images from 3 nostrils. This is an endoscopic image of the nasal cavity at baseline, 3 months, and 6 months following treatment with EDU-FLU in 3 patients. The star represents the middle turbinate. In patient 3, the middle turbinate cannot be visualized due to the polyp and associated edema. As it can be seen in the image panels, the polyp decreases with the use of EDU-FLU and its efficacy is sustained at 6 months. *Signifies middle turbinate.

Patient 4, right side	Baseline	Month 3
		
SNOT-22 total score	42	21
NP grade	1	1
LK-edema score	1	0

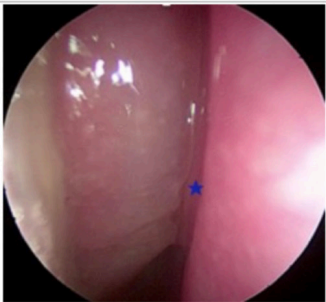
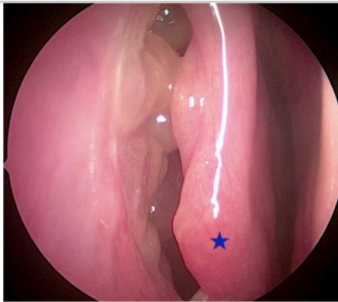
Patient 1, right side	Baseline	Month 3
		
SNOT-22 total score	39	5
NP grade	1	1
LK-edema score	2	1

Figure 5. Endoscopic changes from baseline to month 3 in patients with improvement in edema. *Signifies middle turbinate.

Latino. Mean age at enrollment was 54.0 years. All patients had a previous sinus surgery, 73% (8 of 11) had asthma, and 18% (2 of 11) had COPD. All patients were on standard topical steroid treatment for at least 1 month within the previous 3 months from study start date. Specifically, 5 patients were on INS and 6 patients were on budesonide irrigation/rinse at enrollment. Mean polyp grade score was 3.1 (standard deviation [SD]: 1.0, range: 2-5), mean SNOT-22 score was 48.8 (SD: 13.3, range: 26-74), mean total LK score was 10.8 (SD: 1.7, range: 8-13), and mean Sniffin' Sticks TDI score was 11.8 (SD: 6.5, range: 5.5-27.8). Two patients were terminated early from the study. One patient who was enrolled in error (baseline summed nasal polyp score of 2) but was allowed to continue in the study, was dropped at week 24 due to receiving oral prednisone for an asthma exacerbation; the other patient was dropped at week 15 after developing an exacerbation of COPD.

Five of 11 subjects had at least a ≥ 1 polyp grade reduction over 24 weeks. At week 24, the mean NP score was 2.4 versus 3.1 at baseline (difference in means = -0.73 ; 95% confidence interval [CI], -1.33 to -0.12 ; $p=0.02$) (Table 2; Figure 1), and the mean total LK score was 7.36 versus 10.8 at baseline (difference in means = -3.45 ; 95% CI, -5.46 to -1.45 ; $p=0.003$). In addition, patients on EDS-FLU demonstrated improvements in LK subscores, assessing edema (Figure 2), discharge, crusting, and NP. A statistically significant difference in mean SNOT-22 scores was observed (Figure 3). At 24 weeks, the mean SNOT-22 score was 27.8, showing a 43% decrease. The difference in mean SNOT-22 total score at baseline and at week 24 was found to be -21.0 (95% CI, -32.64 to -9.36 ; $p=0.002$) (Table 2). Sniffin' Sticks score indicated an improvement in sense of smell by 39.8% from baseline to 24 weeks, with a mean TDI composite score of 16.5 compared with 11.8 at baseline (difference in means = 4.7 ; 95% CI, 0.82 to 8.59 ;

$p=0.02$) (Table 2). At week 24, 8 of 11 patients reported their symptoms as “much improved” or “very much improved” in their PGIC scores. Visual endoscopic evaluation was completed in all patients; results for 3 patients are shown in Figure 4 and Videos 1 to 3.

Overall, EDS-FLU was well tolerated. Sixteen AEs were reported by 7 patients; none were considered serious or severe. Epistaxis was detected in 1 patient at visit 2, during the second endoscopic evaluation.

Discussion

In this study, serial nasal endoscopy video recordings confirmed that EDS-FLU produces both a decrease in polyp grade and a decrease in associated inflammation. NP consist of edematous, swollen, and variably fibrous tissue associated with inflammation of the nasal cavity structures and adjacent paranasal sinuses⁽³³⁾. Topical corticosteroid nasal sprays are a mainstay of treatment due to their potent anti-inflammatory effects; however, treatment outcomes are often variable, presumably due to the suboptimal distribution of the medication at the targeted inflammation^(7,8). In contrast, EDS-FLU has been shown to achieve a distribution of fluticasone at the middle meatus and beyond⁽⁹⁾. In clinical trials, EDS-FLU has demonstrated clinically meaningful, statistically significant improvements in symptom severity, NP grade, and QoL measures in patients with CRSwNP, including those with high rates of prior intranasal steroid use and/or surgery^(20–23). The current study is the first to objectively document changes in nasal endoscopy among a small cohort of patients treated with EDS-FLU that are not reflected using currently available objective scoring measures.

In addition to the decrease in polyp size, substantial changes to swelling in both anterior and superior/posterior areas of the nasal cavity were observed. The combined effect of reducing the edema and swelling can allow for easier access of the endoscope as well as increased space in the nasal cavity for airflow and medication delivery. This likely explains the large increases in symptomatic improvement reported by subjects with either small changes or no changes in polyp grade.

Review of the endoscopy recordings highlighted findings that are not well captured in current polyp-grading systems that only crudely report overall polyp size and do not account for mucosal edema as a concurrent finding in the polyps and in adjacent nasal and sinus tissues (Figure 4). The endoscopic findings in the study highlight the need for improved measures of treatment effect for patients with NP, because this disease involves more than the presence of polyps alone. Furthermore, results also highlight that the lack of changes in polyp grade do not match the observed symptom changes (Figure 5). Current polyp-grading scales are based on 2-dimensional views of the nasal cavity; however, they fail to take into account the 3-dimensional

shape of NP occupying the sinonasal cavity. Ideally, volumetric assessment of polyp burden may better assess the impact of treatments such as EDS-FLU. Perhaps serial computed tomography can serve to document changes in the volume of air-containing spaces of the nose and paranasal sinuses.

The results of this small study are consistent with what has been observed with EDS-FLU in previous, placebo-controlled clinical trials^(24,25). In this study, patients experienced a mean reduction of NP grade score from 3.1 to 2.4—which is consistent with the ≈ 1 -point decrease seen in previous studies—and a 63% decrease in total mean LK edema score from 3.64 at baseline to 1.36 at week 24. Patients experienced a 57% decrease in SNOT-22 scores, from a baseline mean of 48.8 to 21 at 24 weeks, as seen in previous studies. Although the decrease in SNOT-22 scores was statistically significant, 3 of 11 patients enrolled in the study did not have a decrease in SNOT-22 score. The variability in response between patients may be due to some having steroid resistance or a different CRS endotype compared to the patients who had a more robust improvement.

Sniffin’ Sticks provide a measure of patient olfactory response⁽³⁴⁾. The patients in this study had improvement in olfaction, with mean TDI scores increasing from 11.8 to 16.5, a 39.8% improvement. Because a TDI score of 27.3 for ages 36 to 55 years and 19.6 for patients older than 55 years is classified as the border between normosmia and hyposmia⁽³⁵⁾, our results reveal an enduring impairment in smell for the average patient. As expected, the patients with the largest improvements in smell also experienced the greatest reductions in polyp grade and edema.

The major limitation of this study was the small sample size. In addition, the lack of a control group prevents the analysis of the impact of placebo. Lastly, this was an open-label study, which may introduce bias through unblinded patients.

Conclusion

EDS-FLU 186 μ g BID administered over 24 weeks for the treatment of symptomatic CRSwNP resulted in reductions in both polyp and inflammatory burden that cannot be characterized by the currently available polyp scoring methods, as documented in serial nasal endoscopy videos reviewed by a blinded, independent rhinologist. In addition, patients reported symptom improvements, as documented in clinically meaningful reductions in SNOT-22 scores. Although the small sample size likely precluded statistically significant results, this study also observed incremental improvement in olfaction and polyp grade.

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Authorship contribution

WCY: Participated in the design and conduction of the study, analysis of data, and manuscript preparation and editing. VRR: Participated in the design and conduction of the study, analysis of data, and manuscript preparation and editing. AUL: Participated in the design and conduction of the study, analysis of data, and manuscript preparation and editing. MJC: Participated in the design and conduction of the study, analysis of data, and manuscript preparation and editing.

Conflict of interest

M.J.C. serves as a consultant for Acclarent (Irvine, CA), Medical Metrics (Houston, TX), Medtronic (Jacksonville, FL), and Stryker (Kalamazoo, MI). A.L. serves as a consultant for Aerin Medical (Sunnyvale, CA), Lyra Therapeutics (Watertown, MA), Intersect ENT (Menlo Park, CA), and Stryker (Kalamazoo, MI). She is on the advisory board for ENTvantage (Austin, TX). She has participated in advisory board meetings for Sanofi (Paris, FA) and Novartis (Basel, CH). W.Y. serves as a consultant for Stryker (Kalamazoo, MI) and is part of the speakers' bureau for OptiNose US, Inc. (Yardley, PA). V.R.R. serves as a consultant for OptiNose US, Inc.

(Yardley, PA); and Medtronic, Inc. (Jacksonville, FL), which was not affiliated with the current study. The Department of Otolaryngology at University of Colorado received research funding from OptiNose US, Inc. The Department of Otorhinolaryngology at the McGovern Medical School received research funding from Gossamer Bio (San Diego, CA), Arrinex (Redwood City, CA), and OptiNose US, Inc. (Yardley, PA).

Ethics approval and consent to participate

The project received approval from The University of Texas Health Science Center at Houston institutional review board (HSC-MS-18-0130) and the University of Colorado School of Medicine institutional review board (IORG0000433). Informed consent was obtained from all patients in advance of their inclusion in the study

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPLEMENTARY DATA

Video 1. Video endoscopic improvement from baseline to month 6 in patient 1, right side. This is an endoscopic video of the right nasal cavity at baseline, 3 months, and 6 months following treatment with EDU-FLU. As seen here, there is reduction in the polyp as well as edema that allows the endoscope to pass into the middle meatus. One can see the multiple synechiae present in the 3- and 6-month images that were unrecognized at baseline due to the edema and polyp.

Video 2. Video endoscopic improvement from baseline to month 6 in patient 2, right side. This is an endoscopic video of the right nasal cavity at baseline, 3 months, and 6 months following treatment with EDU-FLU. As seen here, there is a reduction in the polyp as well as edema that allows the endoscope to pass into the middle meatus.

Video 3. Video endoscopic improvement from baseline to month 6 in patient 3, left side. This is an endoscopic video of the right nasal cavity at baseline, 3 months, and 6 months following treatment with EDU-FLU. As seen here, there is reduction in the polyp as well as edema that allows the endoscope to pass into the middle meatus. In this video, the previously obscured middle turbinate is now visible and the polyp that is within the olfactory cleft becomes visible.

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