# Exhalation Delivery System With Fluticasone (EDS-FLU) for Treatment of Chronic Rhinosinusitis With Nasal Polyps (CRSwNP): Integrated Safety Results From NAVIGATE I and NAVIGATE II

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## BACKGROUND

- Intranasal steroids (INS) are widely accepted as safe and effective for the management of inflammatory nasal conditions, including allergic rhinitis (AR) and chronic rhinosinusitis with or without nasal polyps (CRSw/sNP).[1]
- Local adverse events (AEs), such as epistaxis, are the most commonly reported drug-related AEs associated with INS treatment in clinical trials.[1] However, the method of assessment (eg, spontaneous report vs scheduled physician assessment using serial nasal endoscopy) as well as patient population (severity of disease, treatment history) and duration of treatment, are important considerations when interpreting safety results.
- For example, most studies reporting the safety of INS are performed in healthier patients with AR, rather than in chronic rhinosinusitis (CRS).[2]
  - Results from placebo-controlled studies with INS demonstrate that there is generally a higher-reported incidence of epistaxis in patients with nasal polyps than patients with AR.[3]
  - Patients with more-severe nasal/sinus disorders, such as CRS with or without nasal polyps, previous nasal/sinus surgery (a risk factor for nasal septum ulceration/perforation), and extensive prior nasal steroid use, may be excluded from AR trials.
- In addition, trials that assess AEs actively via frequent serial nasal endoscopy tend to report a higher incidence of local nasal AEs compared with studies—often older—that collect only spontaneously reported AEs or that use nasal speculum examinations instead of endoscopy.
- EDS-FLU uses a novel mechanism of action (MOA), closed-palate bi-directional™ delivery with an exhaler, shown to deposit drug deep (posteriorly and superiorly) in regions affected by chronic inflammation, including the ostiomeatal complex region, where the sinuses drain and ventilate and polyps originate **(Figure 1).**[4] EDS-FLU contains fluticasone propionate (phenylethyl alcohol free).
- The MOA is described here: http://www.optinose.com/.

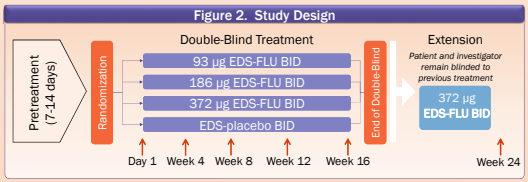
**Figure 1. EDS MOA; Nasal Deposition by Gamma Scintigraphy[4]**


- The efficacy and safety of EDS-FLU for the treatment of moderate-severe CRSwNP has been demonstrated in phase 3 trials (NAVIGATE I and II).[5,6]
- We present integrated safety results from NAVIGATE I and II, which examined the safety of EDS-FLU in patients with moderate to severe CRSwNP over an extended period with active surveillance, including serial nasal endoscopy.

## METHODS

- NAVIGATE I and II are similarly designed, randomized, double-blind (DB), parallel-group, multicenter, EDS–placebo-controlled trials with a 16-week DB phase followed by an 8-week, active-treatment, extension phase in which all patients received EDS-FLU 372 µg. All treatments were twice daily **(Figure 2)**.

**Figure 2. Study Design**




- Based on the risk-benefit profiles, 186- and 372-µg doses were selected for further clinical development and commercialization, and are reported here.
- Safety assessments included AE reports, nasal endoscopic examinations (not simply by nasal speculum), ocular examinations (slit-lamp and tonometry), vital signs, and concomitant medication use.
- In addition to spontaneously reported AEs, trained investigators were instructed to specifically look for evidence of any blood ("epistaxis"), septal erosion, ulceration, and perforation, as well as nasal candidiasis by nasal endoscopic examination at each scheduled visit. Findings identified on nasal endoscopic examination were reported as AEs, regardless of whether they would have been clinically apparent without directed examination.
- The term "epistaxis" in these trials was an AE code used as a catch-all for evidence of current or past blood in the nose; although nosebleed was included, other findings were also categorized as "epistaxis."
- More specifically, the coding term "epistaxis" in these trials included:
  - *Non active bleeding*: any observation suggesting prior bleeding (eg, evidence of a clot on endoscopy), irrespective of amount or significance
  - *Active bleeding*: range of observations from blood-tinged mucus (with blowing the nose or on endoscopy), to mild bleeding (intervention not indicated), to clinical nosebleed with intervention indicated
- Nasal septal ulceration-related event severity was defined as follows:
  - *Mild*: evidence of erosion of the epithelium
  - *Moderate*: evidence of ulceration through epithelial layer with exposed cartilage
  - *Severe*: perforation of the septum

## RESULTS

- Baseline demographics and characteristics (**Table 1**) were similar among the 3 treatment groups. Many patients had previously used steroids (91.1%) and/or undergone surgery (32.2%).

**Table 1. Baseline Characteristics**

| Characteristic | EDS-Placebo (n = 161) | 186 µg (n = 160) | 372 µg (n = 161) |
|---|---|---|---|
| Age, mean (SD), y | 46.0 (12.5) | 45.6 (12.8) | 44.4 (12.4) |
| Male sex, n (%) | 78 (48.4) | 94 (58.8) | 93 (57.8) |
| "White" race/ethnicity, n (%) | 143 (88.8) | 148 (92.5) | 144 (89.4) |
| Prior INS treatment for CRSwNP (in past 10 y, n (%)) | 149 (92.5) | 146 (91.3) | 144 (89.4) |
| Sinus surgery for polyp removal or sinus surgery, n (%) | 53 (32.9) | 52 (32.5) | 50 (31.1) |
| Bilateral endoscopic nasal polyp score, mean (SD) | 3.8 (1.01) | 3.9 (1.06) | 3.8 (0.96) |

- 13.6% of all EDS-placebo patients and 5.3% of EDS-FLU patients discontinued during the DB treatment phase. Reasons included:
  - EDS-placebo: lack of efficacy (6.8%), AEs (3.7%), and withdrawal by patient (3.1%)
  - EDS-FLU: lack of efficacy (1.6%), AEs (1.6%), and withdrawal by patient (1.6%)
- Serious AE reports were rare with EDS-FLU (2/321 [0.6%], positional vertigo, menorrhagia), and none were related to treatment.
- The most common AEs were epistaxis, nasal septum ulceration, nasopharyngitis, erythema, nasal congestion, acute sinusitis, nasal septum disorder, headache, and pharyngitis. Further detail on "epistaxis" and "ulceration" events are shown in **Table 2.**
- The majority of "epistaxis" events were identified by nasal endoscopy rather than clinical report.
- Findings coded as "epistaxis" (including both non active and active) were reported from nasal endoscopic examination in 18.2% and 21.7% of patients in the 186-µg and 372-µg groups, respectively, compared with 3.8% in EDS-placebo patients (**Table 2**).
  - 100% of reports of "active bleeding" identified by nasal endoscopy were categorized as blood-tinged mucus or mild bleeding, with no medical intervention required.
  - Only 1 patient received intervention for epistaxis (372-µg group: minor intervention, cotton ball placed in nasal vestibule).

**Table 2. Categorization of "Epistaxis" AE Reports**

| Category | EDS-Placebo (N = 161) | 186 µg (N = 160) | 372 µg (N = 161) |
|---|---|---|---|
| All patients with "epistaxis" AE, n (%) | 10 (6.2) | 35 (21.9) | 37 (23.0) |
| Patients with epistaxis upon nasal endoscopic examination, n/N (%) | 6/160 (3.8) | 29/159 (18.2) | 35/161 (21.7) |
| Patients spontaneously reporting epistaxis AE, n (%) | 4 (2.5) | 19 (11.9) | 16 (9.9) |
| Patients with both spontaneously reported epistaxis AE and nasal examination epistaxis finding, n/N (%) | 0/160 (0) | 13/159 (8.2) | 14/161 (8.7) |
| Number of "epistaxis" AEs | 10 | 69 | 70 |
| Epistaxis AEs observed to resolve spontaneously (~93% of resolved events resolved with continuing use of EDS-FLU) | 8/10 (80.0) | 64/69 (92.8) | 65/70 (92.9) |
| Active and nonactive bleeding on nasal examination | | | |
| N | 160 | 159 | 161 |
| Nonactive bleeding, n (%) | 5 (3.1) | 28 (17.6) | 32(19.9) |
| Active bleeding, n (%) | 1 (0.6) | 3 (1.9) | 3 (1.9) |

- Spontaneously reported (ie, clinically evident) "epistaxis" was reported in 11.9% and 9.9% in the 186-µg and 372-µg groups, respectively, compared with 2.5% in EDS-placebo patients (**Table 2**). Evaluation of verbatim terms for these events shows that ~40% were described as "nonactive," "minimal/small amount," or "trace amount in discharge" suggesting that these events were not clinically meaningful.
- The overall spontaneous report rate is similar to the rate of epistaxis reported in other studies of INS with similar populations and duration.[7,8]
- Longer duration of treatment was not associated with increased rate of epistaxis events **(Table 3)**. At week 4, 6% of EDS-FLU patients experienced epistaxis (similar to the rate reported with over-the-counter fluticasone furoate after 2 weeks [8.0%]).[9]
- Most patients with "epistaxis" had events reported to be "mild" in severity (~90% of patients); there were no reports of severe bleeding in any treatment group.

**Table 3. Incidence of Epistaxis by Treatment Visit**

| Visit | Placebo (n = 161) | 186 µg (n = 160) | 372 µg (n = 161) |
|---|---|---|---|
| Week 4 | 5/153 (3.3) | 8/154 (5.2) | 11/160 (6.9) |
| Week 8 | 1/143 (0.7) | 15/151 (9.9) | 15/159 (9.4) |
| Week 12 | 0 | 14/149 (9.4) | 12/157 (7.6) |
| Week 16/End of double blind/ Early termination | 3/159 (1.9) | 12/158 (7.6) | 17/161 (10.6) |
| Week 24 (all 372 µg twice daily) | 9/137 (6.6) | 12/138 (8.7) | 15/153 (9.8) |

- 92.8% (129/139) of all "epistaxis" events resolved spontaneously (no evidence of nonactive or active bleeding on subsequent nasal endoscopic examination). ~98% of events that resolved did so while the patient continued to use study medication. Among EDS-placebo patients, 80% of "epistaxis" AEs resolved.
- All events of septal erosion/ulceration/perforation in EDS-FLU patients were identified via scheduled endoscopic nasal examination rather than by symptoms or other clinical presentation. These AEs were generally not persistent; 93.3% resolved despite continued use of EDS-FLU. Only 1 event progressed in severity (from erosion to ulceration); this event subsequently resolved with continued use of medication. The rate of this AE did not increase with increasing duration of treatment through 24 weeks, and there was no dose-response relationship.
- One septal perforation was identified in a patient with a history of nasal surgery, a known risk factor for perforation.

## CONCLUSIONS

- EDS-FLU uses a novel exhaler shown to deliver medication more superiorly and posteriorly than conventional INS sprays. It has been found to be effective in relieving symptoms and signs of inflammation in CRSwNP patients in 2 pivotal controlled trials.
- With the exception of headache, the most commonly reported AEs were associated with local effects at the site of administration in the nasal cavity or with the underlying disease (acute sinusitis, nasopharyngitis).
- Most local AEs were identified by directed, active monitoring using scheduled nasal endoscopy and were not spontaneously reported.
- "Epistaxis" and nasal erosion/ulceration events were more commonly observed with EDS-FLU than EDS-placebo. Nearly all of these events were mild, and most resolved with continued exposure to study drug.
- The safety profile of EDS-FLU is comparable with other intranasal steroids when studied in a similar population for similar durations.

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