Background

• Intranasal steroids (INS) are widely accepted as safe and effective for the management of inflammatory nasal conditions, including allergic rhinitis (AR)/chronic rhinosinusitis with or without nasal polyposis (CRSwNP).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 utilizing 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 polyposis 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 nasal endoscopy tend to report a higher incidence of local nasal AEs compared with studies that only report 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 ostomeatal complex region, where the sinuses drain and ventilate and polyps originate (Figure 1). EDS-FLU contains fluticasone propionate (methyl alcohol free).

• The MOA is described here: http://www.optinose.com.

Methods

• The efficacy and safety of EDS-FLU for the treatment of moderate-to-severe CRSwNP has been demonstrated in phase 3 trials (NAVIGATE I and II).1,2

• 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 inclusion, including nasal endoscopy.

• NAVIGATE I and II are similarly designed, randomized, double-blind (DB), parallel-group, multicenter, EDS-placebo-controlled trials with a 15-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).

• 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 (performed by nasal speculum), ocular examinations (alitis 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, or perforation, as well as nasal candidiasis by nasal endoscopic examination at each scheduled visit. Findings identified on nasal endoscopic examinations 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, a clot on endoscopy), irrespective of amount or severity.

  • Active bleeding: range of observations from bleeding-tined mucus (with blowing of the nose or on endoscopy), to active bleeding (intervention not indicated), to clinical nosebleed with intervention indicated.

• Baseline demographics and characteristics (Table 1) were similar among groups. Patients had previously used steroids (91.1%) and/or undergone surgery (32.2%).

• Based on the risk-benefit profiles, 186- and 372-µg doses were selected for further clinical development and commercialization, and are reported here.

Results

• There were no deaths, discontinuations, serious AEs, or AEs leading to withdrawal of consent.

• The most common AEs were epistaxis, nasal septum ulceration, nasopharyngitis, rhinorrhea, 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.

• 10% of reports of “active bleeding” identified by nasal endoscopy were categorized as blood-tined 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).

• 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 observed with EDS-FLU more frequently than EDS-placebo. Nearly all of these events were mild, and most resolved with continued exposure to study drug. Among EDS-placebo patients, 80% of “epistaxis” AEs resolved.

• With the exception of headache, the most commonly reported AEs were epistaxis, nasal septum ulceration, nasopharyngitis, rhinorrhea, nasal congestion, acute sinusitis, nasal septum disorder, headache, and pharyngitis. Further detail on “epistaxis” and “ulceration” events are shown in Table 2.

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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.

• The safety profile of EDS-FLU is comparable with other intranasal steroids when studied in a similar population for similar durations.3

Table 3. Incidence of Epistaxis by Treatment Group

<table>
<thead>
<tr>
<th>Week</th>
<th>EDS-FLU 186 µg BID (n = 161)</th>
<th>EDS-FLU 372 µg BID (n = 161)</th>
<th>EDS-placebo BID (n = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>6/154 (3.8)</td>
<td>19/153 (12.4)</td>
<td>35/154 (21.9)</td>
</tr>
<tr>
<td>Week 8</td>
<td>14/153 (9.1)</td>
<td>12/153 (7.8)</td>
<td>37 (23.0)</td>
</tr>
<tr>
<td>Week 12</td>
<td>10/149 (6.7)</td>
<td>37/149 (25.2)</td>
<td>40 (24.7)</td>
</tr>
<tr>
<td>Week 16</td>
<td>3/156 (1.9)</td>
<td>13/156 (8.4)</td>
<td>17/156 (10.9)</td>
</tr>
<tr>
<td>Week 24</td>
<td>6/152 (3.8)</td>
<td>13/152 (8.5)</td>
<td>15/152 (9.8)</td>
</tr>
</tbody>
</table>

Table 2. Categorization of “Epistaxis” Events

<table>
<thead>
<tr>
<th>Category</th>
<th>EDS-FLU 372 µg (n = 160)</th>
<th>EDS-FLU 186 µg (n = 160)</th>
<th>Placebo (n = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonactive bleeding, n (%)</td>
<td>3 (1.9)</td>
<td>5 (3.1)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Active bleeding, n (%)</td>
<td>1 (0.6)</td>
<td>3 (1.9)</td>
<td>2 (1.2)</td>
</tr>
</tbody>
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Conflicts of Interest: Contact: John Messina, PharmD, OptiNose US, Inc. Address: 1020 Stony Hill Rd, Suite 300, Yardley, PA 19067. E-mail: john.messina@optinose.com, Phone: 267-364-3500.

References:

3. Djupesland PG, Messina J, Mahmoud R. Enhanced nasal drug delivery with new exhalation delivery systems (EDS). Poster session presented at: Annual Scientific Meeting of the American College of Allergy, Asthma, & Immunology; November 10-14, 2016; Chicago, IL.