APPENDICES

Appendix 1. Principal Study Investigators

The following principal investigators participated in the study:

Canada

Dr. Jaime Del Carpio: Jaime Del Carpio; CHUM Hôtel-Dieu: Martin Desrosiers; Gordon Sussman Clinical Research Inc: Gordon Sussman; Ottawa Allergy Research Corporation: William Yang

Czech Republic

ENT Department University Thomayer Hospital with Polyclinic: Pavel Chrbolka; VFN-Department ENG: Radim Kana; Stredomoravska nenocnicna as – odstepeny zavod Nemocnice Prostejov: Pavel Navratil; University Hospital Hradec Kralove, ORL: Victor Chrobok; Oblastni nemocnice Kladno: Monika Plaskova; ENT Department Charles University Prague: Ales Hahn; Alergologie Trebonska sro: Lenka Pennigrova

South Africa

Tiervlei Trail Centre: Maria Pretorius; JOSHA research : Johannes Jurgens Lombaard; Wits Clnical Research: Alana Hemus; Phoenix Pharma: Daniel Rudolph Nalan; Randles Road Medical Centre: Uttam Govind; M-Care Medical Centre: Mare Botha

Ukraine

Kyiv City Clinical Hospital #9: Bogdan Bil; Municipal Treatment and Prophylactic Institution: Oleg Malyayev; Regional Clinical Hospital: Vyacheslav Vanchenko; Clinic of State Institustion: Dmytro Zabolotnyi; Municipal Healthcare Institution Regional Clinical Hospital Center of Urgent Medical Care and Medicine of Catastrophes: Anatoliy Ahuralov

United Kingdom

Guys' Hospital: Claire Hopkins; Wrightington Hospital: Nirmal Kumar; Norwich and Norfolk University Hospital: John Phillips; Derriford Hospital: Hisham Khalil; Sheffield Teaching Hospital NHS Foundation Trust: Jaydip Ray; University College Hospital: Valerie Lund; James Paget University Hospital NHS Trust: Carl Philpott; Addenbrooke's Hosptial: Shuaib Nasser; Hinchingbrooke Hospital: Jose Tavares

United States

California Medical Clinic for Headache: David Kudrow; Optimed Research, Ltd: Donald McNeil; Ear Nose & Throat Associates of Texas, PA: Neelesh Mehendale; Costal Ear, Nose and Throat, LLC: Mary Mitskavitch; Charlotte Eye Ear Nose and Throat Associates, PA: Jonathan J. Moss; University of Chicago: Robert Naclerio; Allergy Associates Research Center: Michael Noonan; Colorado ENT & Allergy: Lewis J. Romett; Cleveland Clinic: Raj Sindwani; New York Medical College: Catherine Small; Clinical Research Group of Montana, PLLC: Alan Wanderer; PMG Research of Wilmingot LLC: Gregory Zwack; PMG Research of Winston Salem: Ronald Shealy; Rush University Medical Center: James Moy; Kern Allergy and Medical Research, Inc.: Tonny Tanus; NEQ Baptist Clinic: Bryan Lansford; NU Feinberg School of Medicine: Rakesh Chandra; ENG & Allergy Associates, LLP: Richard DeMalo; Chicago ENT: Michael Friedman; Physicians Regional Medical Group: James Hadley; EVMS Department of Otolaryngology: Joseph Han; Vital Prospects Conical Research Institute: Iftikhar Hussain; ENT and Allergy Associates, LLP: Nagalingam Jeyalingam; The Center for Pharmaceutical Research, P.C.: John Ervin; ENTTEX: Lav Kapadia; Center California Clinical Research: Brent Lanier; University of South Florida: Richard Lockey; Allergy, Asthma & Sinus Center, S.C.: Gary Steven; Focus Conical Research: Joseph Kasper; Intermountain Ear Nose and Throat: Steven Miller; SC

Clinical Research, Inc.: James Gordon; TOSH Medical Towers: Justin Gull; Choc PSF, AMC, Division of AA & I: Sherwin Gillman; AARA Research Center: William Lumry; Northeast Medical Research Associates, Inc: David S. Miller; Colorado allergy and Asthma Centers, P.C.: Shaila Gogate; Peninsula Research Associates, Inc.: Lawrence Sher; Asthma & Allergy Associates, PC: Daniel Soteres; California Allergy & Asthma Medical Group, Inc: Sheldon Spector; Allergy, Asthma & Clinical Research Center: Martha Tarpay; Allergy & Asthma Specialists Medical Group: Steven Weinstein; National Allergy, Asthma & Urticaria Centers of Charleston, PA: Thomas Murphy; California Allergy and Asthma Palmdale: Ricardo Tan; Bensch Research Associates

Appendix 2. Detailed entry criteria

1. Men or women 18 years of age and older.
2. Women had to:
    - be practicing an effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel], or male partner sterilization) before entry and throughout the study, or
    - be surgically sterile (have had a hysterectomy or bilateral oophorectomy, or tubal ligation at least 1 year before Visit 1 [screening]) or otherwise have been incapable of pregnancy, or
    - be postmenopausal (spontaneous amenorrhea for at least 1 year).
3. Women of child-bearing potential had to have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at Visit 1 (screening).
4. Must have had bilateral nasal polyposis with a grade of 1 to 3 in each of the nasal cavities as determined by a nasal polyp grading scale score measured by nasoendoscopy at Visit 1 (screening).
5. Must have had at least moderate symptoms of nasal congestion/obstruction as reported by the subject, on average, for the 7-day period preceding Visit 1 (screening).
6. At Visit 2, Day 1 (baseline), subjects must have had a morning score of at least 2 (moderate) on nasal congestion/obstruction recorded on the subject diary for at least 5 of the last 7 days of the 7- to up to 14-day run-in phase.

7. Must have demonstrated an ability to correctly complete the daily diary during the run-in phase to be eligible for randomization.

8. Subjects with comorbid asthma or chronic obstructive pulmonary disease (COPD) must have been stable with no exacerbations (eg, no emergency room visits, hospitalization, or oral or parenteral steroid use) within the 3 months prior to Visit 1 (screening). Inhaled corticosteroid use must have been limited to stable doses of no more than 1000 µg/day of beclomethasone (or equivalent) for at least 3 months prior to Visit 1 (screening) with plans to continue use throughout the study.

9. Must have been able to cease treatment with intranasal medications including, but not limited to, intranasal steroids, intranasal sodium cromolyn, nasal atropine, nasal ipratropium bromide, and inhaled corticosteroids (except permitted doses listed above for comorbid asthma and COPD) at Visit 1 (screening).

10. Must have been able to cease treatment with oral and nasal decongestants and antihistamines at Visit 1 (screening).

11. Must have been able to use the OptiNose device correctly; all subjects were required to demonstrate correct use of the practice placebo at Visit 1 (screening).

12. Must have been capable, in the opinion of the investigator, of providing informed consent to participate in the study. Subjects must have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study.

Appendix 3. Detailed exclusion criteria

- Pregnancy/lactation.
- Complete or near-complete obstruction of the nasal cavities.
- Inability to achieve bilateral nasal airflow.
- Inability to have each nasal cavity examined.
- Nasal septum perforation.
- >1 episode of epistaxis with frank bleeding in the month prior to screening
- Evidence of significant mucosal injury, ulceration or erosion on screening nasal examination/nasoendoscopy.
- History of >5 sinonasal surgeries for either nasal polyps or nasal/sinus inflammation (lifetime).
- History of sinus or nasal surgery within 6 months prior to screening.
- History of any surgical procedure that prevented the accurate grading of polyps.
- Symptoms of seasonal allergic rhinitis at screening or baseline, and/or, based on time of year, anticipated onset of symptoms within 4 weeks of randomization.
- Current, ongoing rhinitis medicamentosa.
- Significant oral structural abnormalities.
- Diagnosis of cystic fibrosis.
- History of Churg-Strauss syndrome or dyskinetic ciliary syndromes

- Purulent nasal infections, acute sinusitis, or upper respiratory tract infection within 2 weeks prior to screening.
- Planned sinonasal surgery during the period of the study.
- Allergy, hypersensitivity, or contraindication to corticosteroids or steroids.
- Allergy or hypersensitivity to any excipients in the study drug.
- Exposure to any glucocorticoid treatment with potential for systemic effects within 1 month prior to screening; except as noted in inclusion criteria for patients with comorbid asthma or COPD.
- Nasal candidiasis.
- Use of potent cytochrome P3A4 (CYP3A4) inhibitor within 14 days before screening.
- History or current diagnosis of any form of glaucoma or ocular hypertension.
- History of intraocular pressure elevation on any form of steroid therapy.
- Current diagnosis of the presence (in either eye) of a cataract of grade 1 or greater as defined on the eye examination worksheet or, less than a grade 1 cataract with associated visual impairment.
- Any serious or unstable concurrent disease, psychiatric disorder, or any significant condition that, in the opinion of the investigator, could confound the results of the study or could interfere with the subject's participation or compliance in the study.
- A recent (within 1 year of screening) clinically significant history of drug or alcohol use, abuse, or dependence that, in the opinion of the investigator could interfere with the subject's participation or compliance in the study.

- Positive urine drug screen at screening for drugs of abuse, with the exception of prescribed medications for legitimate medical conditions.
- Participation in an investigational drug clinical trial within 30 days of screening.
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

146 ***Appendix 4.*** **Table 1. Additional baseline characteristics**

Baseline characteristics by treatment group (Intent-to-Treat Population)						
		EDS-FLU				
Variable Statistic	Placebo (n = 82)	93 µg (n = 81)	186 µg (n = 80)	372 µg (n = 80)	All EDS-FLU (n = 241)	Total (n = 323)
Number of steroid nasal spray treatments for polyps in past 10 years n (%)						
0	5 (6.1)	4 (4.9)	4 (5.0)	5 (6.3)	13 (5.4)	18 (5.6)
1	23 (28.0)	35 (43.2)	31 (38.8)	23 (28.8)	89 (36.9)	112 (34.7)
2	19 (23.2)	17 (21.0)	26 (32.5)	28 (35.0)	71 (29.5)	90 (27.9)
3	15 (18.3)	10 (12.3)	11 (13.8)	12 (15.0)	33 (13.7)	48 (14.9)
4	12 (14.6)	5 (6.2)	1 (1.3)	7 (8.8)	13 (5.4)	25 (7.7)
5	2 (2.4)	5 (6.2)	5 (6.3)	5 (6.3)	15 (6.2)	17 (5.3)
6	4 (4.9)	3 (3.7)	2 (2.5)	0	5 (2.1)	9 (2.8)
7	2 (2.4)	1 (1.2)	0	0	1 (0.4)	3 (0.9)
8	0	1 (1.2)	0	0	1 (0.4)	1 (0.3)
Total polyp grading score						
N	82	81	80	79	240	322
Mean	3.8	3.6	3.9	3.7	3.7	3.7
SD	0.94	1.07	1.08	0.94	1.04	1.01
Minimum, Maximum	2, 6	2, 6	2, 6	2, 6	2, 6	2, 6
Worst polyp grading score						
N	82	81	80	79	240	322
Mean	2.1	2.0	2.1	2.0	2.0	2.1
SD	0.58	0.57	0.60	0.48	0.55	0.56
Minimum, Maximum	1, 3	1, 3	1, 3	1, 3	1, 3	1, 3
Distribution of participants by polyp grade						
Grade 1	37	55	33	38	126	163
Grade 2	105	88	100	106	294	399
Grade 3	22	19	27	14	60	82

EDS-FLU = Exhalation Delivery System for Fluticasone; n = number of participants; n (%) = number (percentage) of participants; SD = standard deviation

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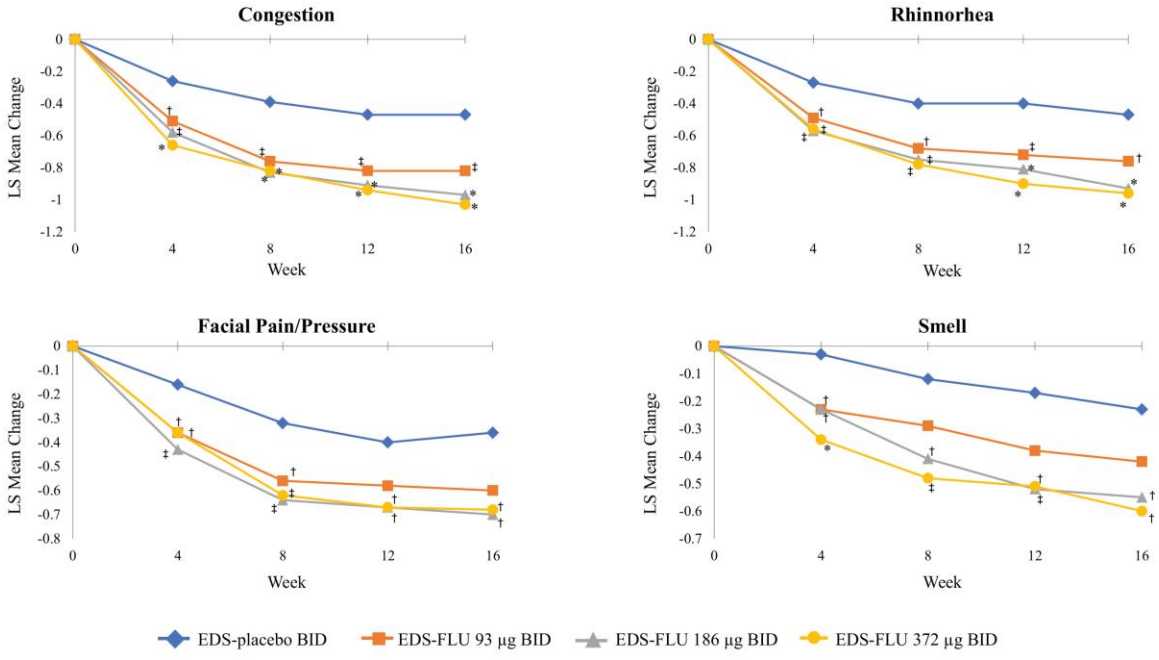
Appendix 5. Details of Missing Data

Trial-wide, for the co-primary outcome of nasal congestion there were a total of 2 MAR values, both in the 93-mcg treatment group, and 8 NMAR values, 5 in the EDS-placebo and 1 in each of the three active treatment groups. For the co-primary outcome of polyp grade, there were 2, 3, 5, and 0 MAR values in the EDS-placebo, EDS-FLU 93 mcg, EDS-FLU 186 mcg, and EDS-FLU 372 mcg treatment groups, respectively, for a total of 10 overall; there were 12, 3, 7, and 3 in the EDS-placebo, EDS-FLU 93 mcg, EDS-FLU 186 mcg, and EDS-FLU 372 mcg treatment groups, respectively, for a total of 25 overall NMAR.

APPENDIX 6. FIG 1. Mean change in reflective AM symptoms of congestion, facial pain and pressure, rhinorrhea, and sense of smell at weeks 4, 8, 12, and 16.



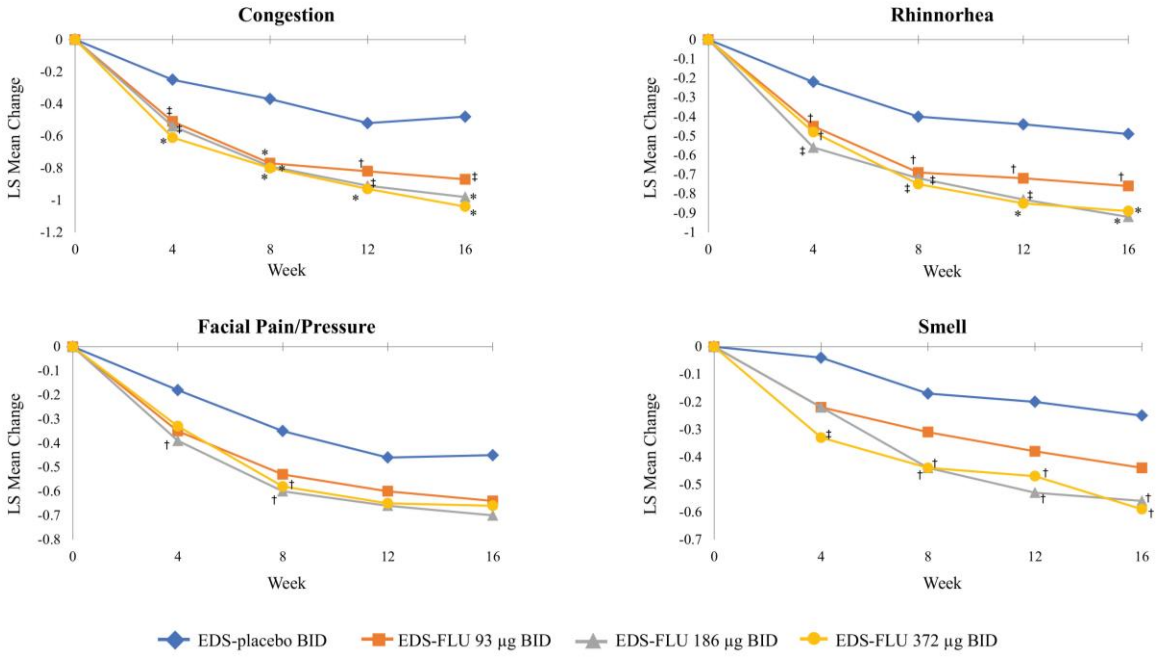
AM = morning; BID = twice daily; LS = least squares.

† $P \leq .05$ vs EDS-placebo

‡ $P \leq .01$ vs EDS-placebo

* $P \leq .001$ vs EDS-placebo

APPENDIX 6. FIG 2. Mean change in instantaneous PM symptoms of congestion, facial pain and pressure, rhinorrhea, and sense of smell at weeks 4, 8, 12, and 16.



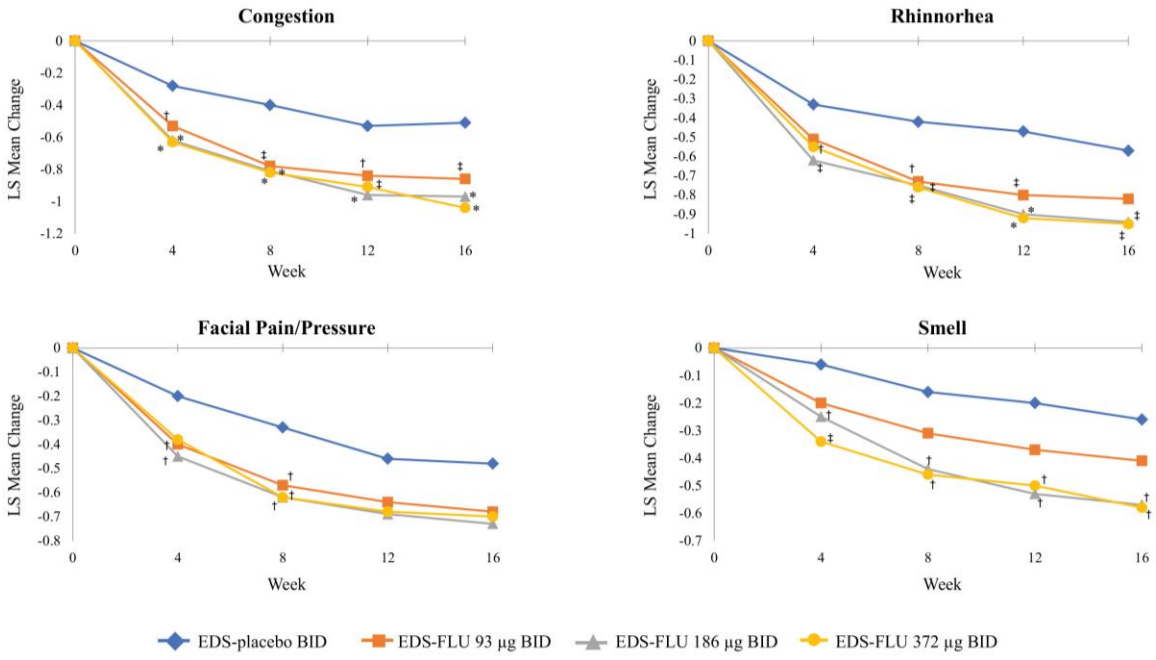
AM = morning; BID = twice daily; LS = least squares.

† $P \leq .05$ vs EDS-placebo

‡ $P \leq .01$ vs EDS-placebo

* $P \leq .001$ vs EDS-placebo

APPENDIX 6. FIG 3. Mean change in reflective PM symptoms of congestion, facial pain and pressure, rhinorrhea, and sense of smell at weeks 4, 8, 12, and 16.



AM = morning; BID = twice daily; LS = least squares.

† $P \leq .05$ vs EDS-placebo

‡ $P \leq .01$ vs EDS-placebo

* $P \leq .001$ vs EDS-placebo