CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209310Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209310
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Division / Office	DPARP/ODEII/OND/CDER/FDA
Reviewer Name(s)	Miya Okada Paterniti, M.D.
Through CDTL	Banu Karimi-Shah, M.D.
Review Completion Date	November 13, 2017
Established Name	Mometasone Furoate (MF) Sinus Implant
(Proposed) Trade Name	Sinuva Sinus Implant
Therapeutic Class	Corticosteroid
Applicant	Intersect ENT
Formulation(s)	Sinus Implant containing 1350 mcg of MF
Dosing Regimen	One Sinus Implant placed bilaterally to gradually release MF over 90 days
Indication(s)	Treatment of nasal polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery
Intended Population(s)	Patients 18 years and older with nasal polyps who have had ethmoid sinus surgery

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on my review of the risk-benefit assessment, my recommendation is **Approva**l pending revisions to the label.

1.2 Risk Benefit Assessment

To frame the discussion regarding risk-benefit assessment, a summary of the efficacy and safety of the Mometasone Furoate (MF) Sinus Implant is provided below.

Introduction

Intersect ENT submitted a 505(b)(2) New Drug Application (NDA 209310) for the MF Sinus Implant for the treatment of (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery. (b) (4) From a regulatory standpoint, the development program was designed to evaluate treatment of nasal polyps, and thus the indication will be modified.

The MF Sinus Implant is a combination drug-device product comprised of a self-expanding, bioabsorbable, drug-eluting, sinus implant coated with 1350 mcg of mometasone furoate (MF). The intended design of the implant is to provide a physical opening in middle meatus and ethmoid sinus in addition to the mechanism of action of the corticosteroid. MF is gradually released (b) (4).

Summary of Clinical Findings

Summary of Efficacy

The MF Sinus Implant is a bioabsorbable, corticosteroid-eluting implant to be placed in the ethmoid sinus, indicated for the treatment of nasal polyps, in patients 18 years of age or older who have had ethmoid sinus surgery.

Efficacy for the MF Sinus Implant was supported by the RESOLVE and RESOLVE II studies. The RESOLVE study was a 6-month, randomized, single-blind, parallel group, concurrently controlled, study in 100 subjects aged 18 years and older with chronic sinusitis and prior bilateral total ethmoidectomy who presented with recurrent sinus obstruction due to sinus polyposis. The control group underwent a sham procedure, consisting of advancement of a delivery system with the MF Sinus Implant into the ethmoid sinus, followed by removal of the delivery system without deployment of the MF Sinus Implant. The co-primary endpoints were nasal congestion/obstruction score and polyp grade at Day 90. The RESOLVE II study was similar in

design, but was shorter (90 days), and included more subjects (201 for the MF Sinus Implant group and 99 for the control (sham) group). Additionally, the co-primary endpoint of nasal congestion/obstruction score was measured at Day 30. Of note, in RESOLVE II, patients had a higher polyposis grade, and the polyp grade score was changed from a 5-point scale (RESOLVE I) to an 8-point scale to include percent ethmoid sinus obstruction. This modification was made to account for post-surgical changes, specifically, the varied amount of obstruction by polypoid edema after endoscopic sinus surgery.

Baseline demographics were generally balanced across treatment groups. The mean age across both studies was 49-50 years, with a range of 19-86 years. For both studies, most patients were male (60-61%), and white (83-85%).

For both studies, most subjects had sinus symptoms despite intranasal steroid spray use, except for facial pain/pressure, which only occurred in about half of subjects. The endoscopic findings were slightly less severe in the control group in both studies. The numbers of sinus surgeries were generally balanced across treatment groups. About 40% of the subjects had one endoscopic sinus surgery, with only about 15% having 4 or more surgeries. The average time since the last surgery was about 4.7 years for both groups. Most subjects had asthma and allergic rhinitis, with about 25% having aspirin intolerance/allergy, which is consistent with what would be expected for this population.

For both studies, most subjects completed the study (98-99%). One subject in the RESOLVE II study discontinued for an adverse event of Parosmia (an olfactory dysfunction that is characterized by the inability of the brain to properly identify an odor's 'natural' smell, replacing it with unpleasant odor such as burning or a chemical smell). A total of 23-45% of subjects in the RESOLVE and 3% of subjects in the RESOLVE II study had their implants removed prior to the planned removal on Day 60.

The co-primary endpoints were change from baseline in nasal obstruction/congestion score to Day 90 (RESOLVE, based on a 0-5 score) or Day 30 (RESOLVE II, based on a 0-3 score) and change from baseline to Day 90 in bilateral polyp grade (0-4 score) as determined from video endoscopies reviewed by a blinded independent panel of sinus surgeons.

In the RESOLVE study, the co-primary endpoint of change from baseline to Day 90 in the nasal obstruction/congestion score (Scale 0-5) was -1.2 in the treatment group compared to -0.8 in the control group with a treatment difference of -0.4 (95% CI: -0.9, 0.1). The co-primary endpoint of change from baseline in polyp grade (scale 0-4) at Day 90 was -0.7 in the treatment group compared to -0.4 in the control, with a treatment difference of -0.3 (95% CI: -0.7, 0.1). Neither endpoint was statistically significantly different than the control group, although they were numerically lower in the MF Sinus Implant group for both endpoints.

In the RESOLVE II study, the co-primary endpoint of change from baseline in nasal congestion/obstruction score at Day 30 was statistically significantly lower than the control group (MF sinus implant -0.8 mean change vs. control -0.6 mean change; treatment difference: -0.2 (95% CI: -0.4, -0.1)). The RESOLVE II study also showed a statistically significant

improvement in the change from baseline in bilateral polyp grade at Day 90 for subjects treated with the MF Sinus Implant (mean change -0.6) compared to control (mean change -0.2) with a treatment difference of -0.4; 95% CI: -0.6, -0.1).

The RESOLVE II study likely showed a statistically significant benefit compared to control in both co-primary endpoints due to key changes in the study design. The RESOLVE II study had four times the number of subjects on treatment (n=53 in RESOLVE I vs. n=201 in RESOLVE II), subjects were required to have a minimum nasal congestion/obstruction score of 2 despite use of intranasal steroid (compared to no minimum in RESOLVE), the nasal congestion/obstruction score was assessed at Day 30 (instead of Day 90 in RESOLVE), when the MF Sinus Implant is still present and eluting steroids (implants were removed at Day 60), and the bilateral polyp score was modified to included ethmoid sinus obstruction, where the implant is expected to have the greatest effect given that the implant is placed in the ethmoid sinus. These changes allowed the RESOLVE II study to robustly and more accurately assess the efficacy of the MF Sinus Implant on nasal polyps.

In RESOLVE II, secondary endpoints, in hierarchical order were change from baseline in percent ethmoid sinus obstruction at Day 90, proportion of patients still indicated for repeat endoscopic sinus surgery at Day 90, change from baseline in decreased sense of smell at Day 90, and change from baseline to Day 90 in facial pain/pressure. Change from baseline in reflective nasal obstruction/congestion score and polyp grade at all timepoints for both studies was also included, but was not in the hierarchy. As the co-primary endpoints for RESOLVE were not statistically significant, analyses of the secondary endpoints are not statistically valid, but are included in this review as supportive information.

In RESOLVE II, the secondary endpoints supported the primary endpoints, except for facial/pain pressure at Day 90. Percent ethmoid sinus obstruction was significantly decreased in the treatment group compared to controls at Day 90 for both studies, as was the proportion of patients still indicated for repeat ESS at Day 90. Consistent with the primary endpoint, the reflective nasal congestion/obstruction score was statistically significant for the RESOLVE II study at Days 30 and 60. Of note, the reflective nasal congestion/obstruction score was not statistically significant at any time point in the RESOLVE study. For both studies, the bilateral polyp grade was statistically significant at all time points (Days 14, 30, 60 and 90); however, these results should be interpreted with caution as the assessment was made by unblinded clinical investigators.

In the RESOLVE study, less subjects received oral steroid therapy in the treatment group compared to the control (MF Sinus Implant, n=9 (17%); Control, n=17 (36%)) through Day 90. Two (4%) subjects in the treatment group underwent polypectomy or endoscopic sinus surgery compared to no subjects in the control group through Day 90. Similar results were seen in the RESOLVE II study. Although RESOLVE did not show statistically significant efficacy for the co-primary endpoints, the prednisone use pattern (decreased in treatment compared to control) does support efficacy for the MF Sinus Implant. The RESOLVE II rescue patterns, in favor of treatment, also support the primary endpoints.

Overall, efficacy for the MF Sinus Implant has been demonstrated in the RESOLVE II study for treatment of nasal polyps in patients ≥ 18 years of age, who have had ethmoid sinus surgery. The co-primary endpoints of change from baseline in nasal obstruction/congestion score at Day 30 and the bilateral polyp grade at Day 90 were statistically significantly lower than control. The efficacy was supported by both the RESOLVE and RESOLVE II studies showing significant decreases in percent ethmoid sinus obstruction at Day 90.

Summary of Safety

The safety evaluation for the MF Sinus Implant relies on data from the RESOLVE and RESOLVE II studies. Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these studies had similar study designs (randomized, sham-controlled, single bilateral implants placed at Day 0 and removed at Day 60, and intranasal steroid background therapy) and the patient population was comparable in terms of demographics and baseline characteristics.

The sponsor also conducted an open-label PK study and a pilot study in a total of 17 subjects, where all subjects received treatment. The safety results of these studies are included in Section 7.7.1 Open-label studies and were found to have a similar safety profile as the RESOLVE and RESOLVE II studies. These 17 patients are not included in the pooled data discussed below.

There was a total of 254 subjects treated with the MF Sinus Implant and 146 subjects who underwent a sham procedure. Each treated subject had one implant placed bilaterally in each ethmoid sinus with 1350 mcg of MF/implant for a total of 2700 mcg per patient. All subjects used Nasonex (MF nasal spray) 200 mcg (two 50 mcg sprays per nostril) daily.

The planned implant removal date was Day 60 for all subjects; however, 24 implants in RESOLVE (unknown number of subjects) and 11 implants in RESOLVE II (in 10 subjects) were removed. In RESOLVE II, 6 were removed for adverse events (acute sinusitis x 2, rhinalgia, epistaxis, parosmia). No data was provided for RESOLVE.

There were no deaths. The overall occurrence of serious adverse events (SAEs) was low and equally distributed across treatment groups (1%). A total of 3 (1%) SAEs (streptococcal asthmatic bronchitis, epistaxis, and pneumonia) were reported in 2 subjects in the MF Sinus Implant group and 2 (1%) SAEs (suicidal ideation and pneumonia) were reported in 2 subjects in the sham group. The SAE of epistaxis led to early implant removal at Day 40. Thirty-nine (39) days later, on Day 79, epistaxis recurred, requiring cautery. There was one subject with a reported adverse event of parosmia (abnormality in the sense of smell) which led to study discontinuation.

Ocular safety evaluations were included in the RESOLVE study. The intraocular pressures were consistent with variability seen in normal patients. Cataracts were not noted; however, it would be unlikely for cataract formation to occur within a 90-day study. Due to the findings in

RESOLVE and the limited duration and follow-up of the RESOLVE II study, no ocular safety assessments were deemed necessary in the RESOLVE II study.

The incidence of adverse events was reported similarly across treatment groups. Bronchitis, nasopharyngitis, otitis media, headache, presyncope, asthma, epistaxis, and nasal discomfort were the most frequent adverse events, occurring with a 1% incidence and more commonly than the control group.

Pediatric assessments were not included as nasal polyps are extremely rare (0.1%) in the pediatric population. In addition, the proposed indication for this product includes only those patients who have previously undergone endoscopic sinus surgery, which is also not routinely performed in children. The sponsor has included a full waiver for subjects < 18 years of age in this submission.

The safety database is adequate to assess the safety of the MF Sinus Implant. The safety findings should be factored into the risk-benefit assessment of MF Sinus Implant for treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery.

Risk-Benefit Assessment

The clinical development program demonstrated robust efficacy in the RESOLVE II study for the MF Sinus Implant in the treatment of nasal polyps, based on the co-primary endpoints of nasal congestion/obstruction score at Day 30 and the bilateral nasal polyp grade at Day 90. The safety profile is similar to the currently marketed topical intranasal steroids products/implants. The risk-benefit supports the approval of the MF Sinus Implant for the treatment of nasal polyps.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

A Postmarket Requirement for a repeat use study will be included to further understand the safety of the MF Sinus Implant with repeated use. As nasal polyps are a chronic condition and recur after both oral steroid use and surgery, the MF Sinus Implant will likely be used repetitively. After endoscopic sinus surgery, 40% of subjects show nasal polyp recurrence within 18 months (1). Both, RESOLVE and RESOLVE II were single-use studies. The sponsor proposed the ENCORE study, a prospective, non-randomized, open-label, 180-day study in 50 subjects with chronic sinusitis and nasal polyps who have had previous endoscopic sinus surgery.

(b) (4)

(b) (4)

The planned start date is October 2017, with an enrollment end date of January 2018 and a follow-up end in (b) (4).

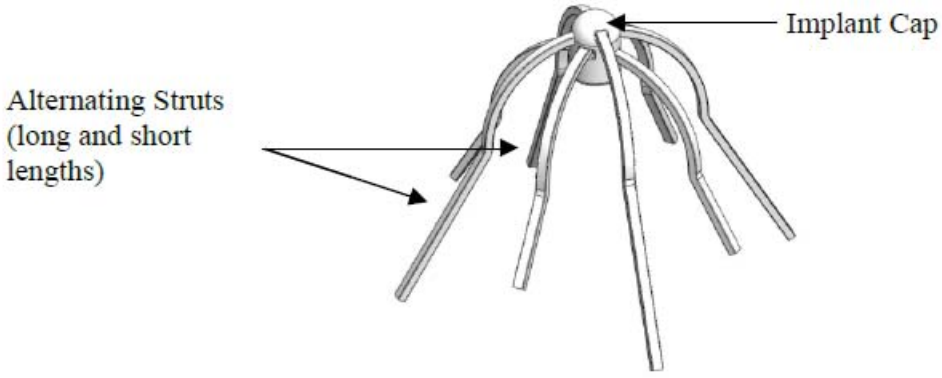
We noted to the sponsor that a 6-month follow up period, after Day 180 would be more appropriate to capture safety events that may develop over time, such as vision changes. An additional observational, event-driven study may also be included as a PMR. The details of the PMR studies are still being discussed at the time of the finalization of this primary review.

2 Introduction and Regulatory Background

2.1 Product Information

The MF Sinus Implant is a combination drug-device product comprised of a self-expanding, bioabsorbable, drug-eluting, sinus implant coated with 1350 mcg of MF, as displayed in Figure 1. The implant is 20 mm in length, with a 34 mm diameter.

Figure 1. MF Sinus Implant



Source: Description and Composition of the Drug Product, pg. 3, Figure 1

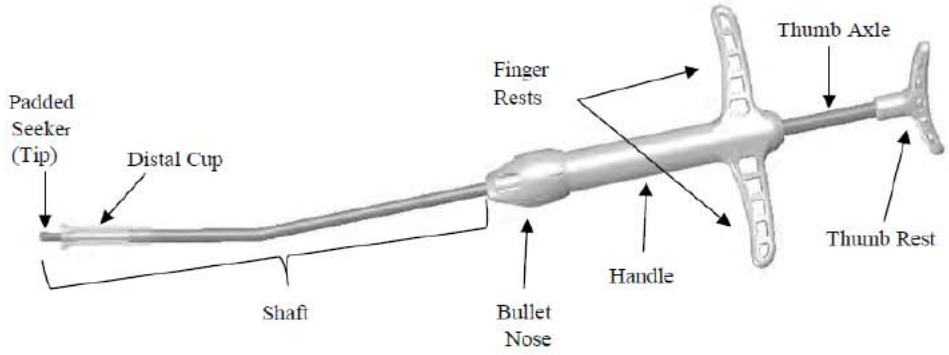
A crimper (Figure 2), which holds the MF Sinus Implant in the product packaging and compresses the implant for loading into the delivery system, and a single-use delivery system (Figure 3) is included with the implant. The shaft length of the delivery system is 117 mm to

deploy the implant in the ethmoid sinus. The MF is embedded in a bioabsorbable polymer matrix containing (b) (4) poly (DL-lactide-co-glycolide) and polyethylene glycol which provides for graduate release of the MF.

Figure 2. Crimper with Loaded Implant

Source: Description and Composition of the Drug Product, pg. 4, Figure 3

Figure 3. Delivery System



Source: Description and Composition of the Drug Product, pg. 3, Figure 2

The intended design of the implant is to provide a physical opening in the middle meatus and ethmoid sinus in addition to the steroid action. MF is gradually released over (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Available Therapies for the Treatment of Nasal Polyps

Generic Name	Indication	Brand Name	Approval Year
Mometasone Furoate (MF) monohydrate	Treatment of nasal polyps in patients ≥ 18 years of age	Nasonex	1997
Beclomethasone diproprionate monohydrate	Prevention of recurrence of nasal polyps following surgical removal	Beconase AQ	1987

2.3 Availability of Proposed Active Ingredient in the United States

MF, the active ingredient in the MF Sinus implant, is available as inhaled, intranasal, and topical formulations. Inhaled formulations include monotherapy (Asmanex) and combination therapy (Dulera: MF and formoterol fumarate (long-acting beta-agonist)). Intranasal formulations include Nasonex (intranasal spray), Propel (intrasinus implant), Propel mini, and Propel Contour. Topical formulations include ointment and creams. Topical formulations will not be discussed further.

The dosing of the available inhaled and intranasal products is summarized in **Table 2**.

Table 2. Summary of Available Inhaled and Intranasal Products with MF

Product	Formulation	Max daily dose	Indication	Approval year	Sponsor
Asmanex	Inhaled	880 mcg	Asthma	1987	Merck
Dulera	Inhaled	800 mcg	Asthma	2010	Merck
Nasonex	Intranasal	50 mcg	-Allergic Rhinitis -Nasal Congestion a/w SAR -Nasal Polyps	1997	Merck
Propel	Intranasal implant	370 ug	Following ethmoid sinus surgery to maintain patency	2011	Intersect ENT
Propel-mini	Intranasal implant	370 ug	Following ethmoid/frontal sinus surgery to maintain patency	2012	Intersect ENT
Propel Contour	Intranasal implant	370 ug	Following frontal/maxillary surgery to maintain patency	2017	Intersect ENT

2.4 Important Safety Issues with Consideration to Related Drugs

As reflected in the labeling for pharmacologically related products, the following issues are considered important:

1. Hypercorticism and adrenal suppression with systemic corticosteroids and the need for careful monitoring of such patients for acute adrenal insufficiency during periods of stress
2. Suppression of the immune system in patients on systemic corticosteroids and the unknown risk associated with intranasal corticosteroids
3. Rare localized infections of the nose or pharynx
4. Rare development of nasal septal perforation
5. Rare reports of glaucoma or cataracts
6. Inhibitory effects on wound healing after nasal surgery or trauma

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Prior to submission of this NDA, this product has been the subject of multiple regulatory interactions under IND 116042. Key regulatory milestones and meetings are summarized below in Table 3.

Table 3. Summary of Pre-submission Regulatory Activity

Interaction	Date	Highlights of Discussion
Pre-IDE DPARP Consult	December 2011	Require randomized control trial that drug and device contributes to effectiveness with clinically significant endpoints
PIND	October 2012	1. Modify primary endpoint from Sino-Nasal Outcome Test (SNOT-22) to nasal obstruction/congestion score used for Nasonex poly program. 2. Include pharmacokinetic assessments.
IND opened	December 2012	1. Include ocular and infection triggers for early implant removal 2. Refine ocular exclusion criteria
EOP2	October 2014	1. Agreed with changing the nasal congestion/obstruction score from (b) (4) to day 30 2. Recommended adjusting the polyp grade score (b) (4) 3. Noted rescue therapies, including medical and surgical therapies must be available to study subjects and a last observation carried forward analysis for rescued subjects is reasonable

2.6 Other Relevant Background Information

There is no further relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. The device inspections conducted by the Center for Devices and Radiological Health (CDRH) were completed and no major issues were identified. The drug product pre-approval inspection is scheduled to be completed in November.

Inspections of the two highest enrolled sites for RESOLVE II (Drs. Silver and Gould) were requested through the Office of Scientific Investigations and completed on August 30, 2017. While the final review is pending, preliminary reports indicate that there are no inspection issues which require action for either site.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in this submission were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 116042 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Details of the financial disclosure are outlined below:

Covered Clinical Studies: PK (0513), Pilot (9011), RESOLVE (1113) and RESOLVE II (1012)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of primary investigators identified: 264		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

(b) (6) was a clinical investigator for (b) (6) and received $87,264 for (b) (6) and $83,380 for (b) (6) in speaker fees and expenses. (b) (6) site contributed (b) (6) subjects for the (b) (6) study and (b) (6) subjects for the (b) (6) study.

(b) (6) was a clinical investigator for (b) (6) and received $114,580 in speaker fees and expenses (b) (6) contributed (b) (6) of subjects for (b) (6)

As this was a randomized, multi-center study and clinical investigators did not influence the primary endpoints (patient reported or assessed by an independent blinded panel of surgeons), no potentially conflicting financial interests are identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues were identified regarding the drug substance as this was the same drug substance used for the approved Propel implant.

For the drug product, two of the 5 lots (C41106001 and C50226004) used in the RESOLVE II study were manufactured prior to the implementation of tighter environmental controls which are used for commercial manufacturing. As the tighter environmental controls reduce in vitro release rate variability, there was a concern that efficacy and safety may be different for the commercial manufactured lots (C50428002, C50702001, and C51019001) compared to those lots manufactured prior to the implementation of tighter environmental controls.

The commercial lots were used in 137 treatment and 70 control subjects totaling 207 subjects, and the non-commercial lots were used in 62 treatment and 29 control subjects, totaling 91 subjects. The efficacy and safety analysis for the commercial lots were similar to the ITT population analysis, therefore this concern was resolved.

4.2 Clinical Microbiology

Dr. Jason God from the product quality microbiology review is pending at the time of this review.

4.3 Preclinical Pharmacology/Toxicology

While the final review is pending, preliminary reports indicate that the nonclinical program is adequate to support the approval of the MF Sinus Implant. For further details, refer to Dr. Luqi Pei's nonclinical review.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology finds the application acceptable to support the approval the MF Sinus Implant for treatment of nasal polyps.

4.4.1 Mechanism of Action

MF is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on inflammation is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

4.4.3 Pharmacokinetics

One open-label PK study in 5 subjects was conducted, as described in Table 4. The protocol is summarized in 6.1.10 Additional Efficacy Issues/Analyses7.7.1 Open-label studies.

Table 4. PK Study Summary

Study Identifier	Design	Duration	Treatment arms	N	Population
PK Study *R500-0513* *Jun 2013 – Oct 2013*	OL	90 days (90 day f/u)	MF Sinus Implant	5	Chronic sinusitis with bilateral ethmoidectomy w/recurrent sinus obstruction due to nasal polyps

Plasma MF concentrations measured at five time-points between Days 3 and 30. Plasma MF concentrations were quantifiable near the limit of quantitation in human plasma (i.e., LLOQ 30 pg/mL) in 6 out of the 30 samples. The remaining 24 samples were below LLOQ. The average cortisol concentrations at follow-up ranged from 3.87 to 5.65 mg/dL compared to 4.68 mg/dL at baseline and were within a normal daytime range.

The mean terminal half-life ($t_{1/2}$) of MF is about 5 hours based on a 400 mcg intravenous dose.

Based on the Asmanex Twisthaler studies, MF is primarily metabolized in the liver, with CYP3A4 as the primary metabolizer.

A cross-study PK comparison for MF between the MF Sinus Implant and the Asmanex Twisthaler indicates that the systemic exposure (AUC0-12h) of MF during the first 3 weeks following implantation of two MF Sinus Implants (the period that MF had the highest release rate) is generally comparable to Asmanex Twisthaler following 440 µg, BID treatment. The MF release rate from the implant declines with time and the MF systemic exposure is expected to reduce with time. Therefore, the systemic safety profile of the MF Sinus Implant at the proposed dosing regimen [i.e., bilateral implantation in the ethmoid sinus with one implant (containing 1350 µg MF per implant)] could be covered by the systemic safety profile following Asmanex Twisthaler at the highest approved dose (440 µg, BID) from clinical pharmacology perspective.

For further details, refer to Dr. Yunzhao Ren's clinical pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5. Sources of Clinical Data

Study ID Sites Study Dates	Design	Study Duration[1]	Treatment Arms (mcg)[2]	N[3]	Population	Primary Endpoint
RESOLVE P500-1113 US Jan 2013 – May 2014	SB, R, PG, CC	6 months	MF Sinus Implant Sham +Nasonex (MF) 200 mcg/day	53 47	CS with bilateral ethmoidectomy w/ recurrent sinus obstruction due to sinus polyps	Change in nasal obstruction/congestion score @ Day 90 Change in polyp grade @ Day 90

Table 5. Sources of Clinical Data

Study ID Sites Study Dates	Design	Study Duration[1]	Treatment Arms (mcg)[2]	N[3]	Population	Primary Endpoint
RESOLVE II P500-1012 US Dec 2014 – Aug 2016	SB, R, PG, CC	90 days	MF Sinus Implant Sham + Nasonex (MF) 200 mcg/day	20 1 99	CS with bilateral ethmoidectomy w/ recurrent sinus obstruction due to sinus polyps	Change in nasal obstruction/congestion score @ Day 30 Change in polyp grade @ Day 90

R=randomized, SB=single-blind, CC=concurrently-controlled, PG=parallel group, CS=chronic sinusitis
[1] MF Sinus Implant removed at 60 days, [2]Nasnoex background therapy was administered at least through Day 90, [3]Intent-to-treat
Source: Clinical overview, Table 1, pg. 16, Study CSRs, pp. 21 and 22

5.2 Review Strategy

The program to support the MF Sinus Implant for the treatment of nasal polyps in patients 18 years and older who have had ethmoid sinus surgery consists of 2 key studies: RESOLVE and RESOLVE II.

The protocols for the 2 studies are summarized and reviewed in Section 5. The individual efficacy results are provided in Section 6 and the pooled safety results are discussed in Section 7.

Two open-label studies (a PK study and a pilot study) were also conducted. As these studies were both open label, they are not included in the efficacy discussion, but will be mentioned in Section 6.1.10 Additional Efficacy Issues/Analyses, where applicable. Their protocols and safety results are summarized in Section 7.7.1 Open-label studies.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 RESOLVE (Study P500-1012)

Administrative Information

- **Study title:** A Clinical Evaluation of the Safety and Efficacy of the Steroid Releasing MF Sinus Implant Used in Post-Sinus Surgery Patients with Recurrent Sinus Obstruction
- **Study dates:** January 30, 2013 – May 6, 2014
- **Study sites:** 18 US sites
- **Study report date:** February 11, 2016

Objectives/Rationale

Primary Objectives

Assess the safety and efficacy of the steroid-releasing MF Sinus Implant when used in post-sinus surgery patients who present with recurrent sinus obstruction.

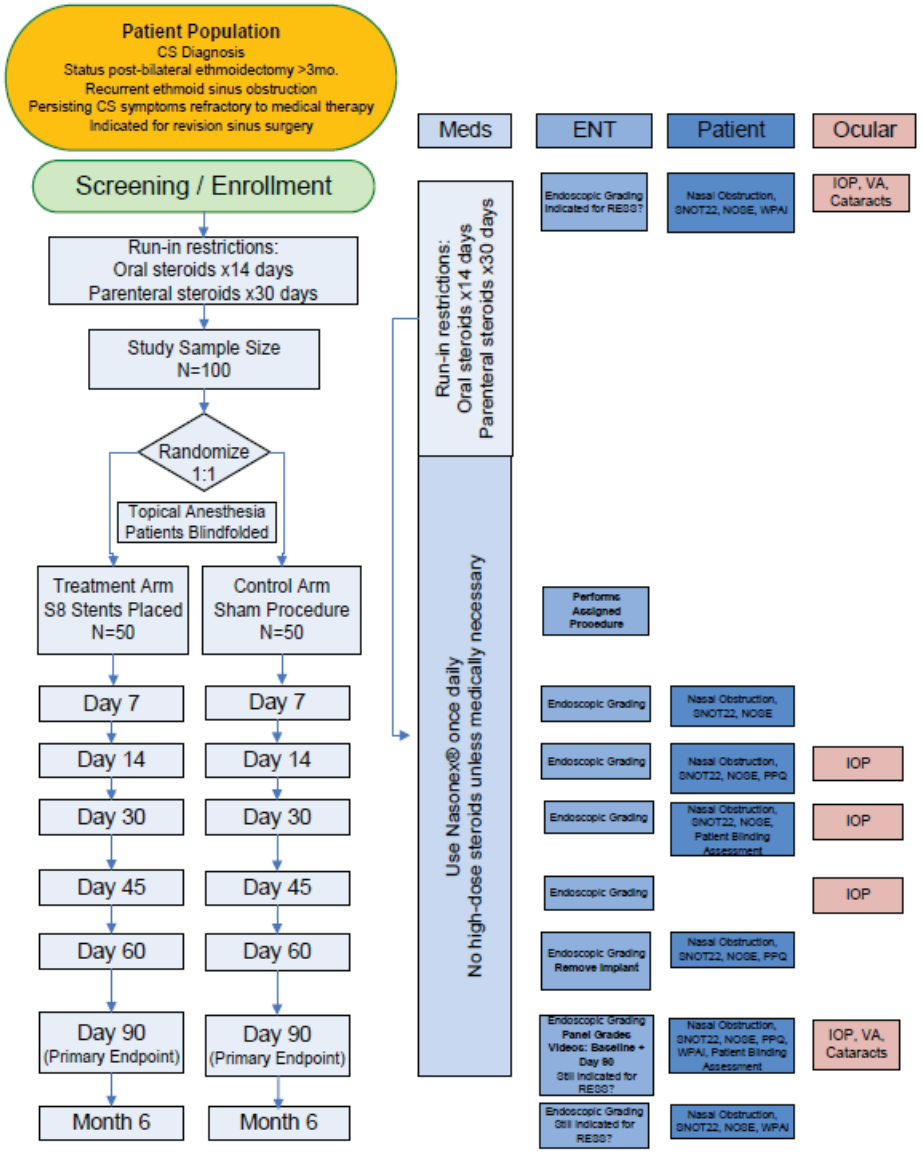
Study Design and Conduct

Overview

The RESOLVE study was a 6-month, prospective, randomized, single-blind, parallel group, concurrently controlled, multicenter study in 100 subjects aged 18 years and older with chronic sinusitis and prior bilateral total ethmoidectomy who presented with recurrent sinus obstruction due to sinus polyposis. Patients were screened for eligibility and then either had one MF Sinus Implant inserted bilaterally into each ethmoid sinus or underwent a sham procedure. An intranasal MF spray (Nasonex; 50 mcg, 2 sprays each nostril = 200 mcg daily) was used as background therapy through at least Day 90. The implants were removed on Day 60. The co-primary endpoints of change from baseline in nasal obstruction/congestion score and bilateral polyp grade was analyzed at Day 90.

The study design for the RESOLVE study is depicted in Figure 4.

Figure 4. RESOLVE Study Design



CS, chronic sinusitis; ENT = ear, nose throat; IOP, intraocular pressure; VA, visual acuity.

Source: RESOLVE CSR, pg. 24, Figure 1

Study visits occurred on Day 7, every 2 weeks through Day 60, and then on Day 90 and at 6 months. Endoscopic grading and symptom assessments were done at various timepoints throughout the study, including at Day 90 and at the end of the study. Ocular safety assessments (e.g., intraocular pressure, visual acuity, and cataract assessments) were also included.

The schedule of assessments is shown in Figure 5.

Figure 5. RESOLVE: Schedule of Assessments

Assessments	Screening	Baseline: Implant/ Sham Procedure	7 Day Follow-up (± 3 days)	14 Day Follow-up (± 3 days)	30 -Day Follow-up (± 3 days)	45-Day Follow-up (±3 days)	60-Day Follow-up (±3 days)	90-Day Follow-up (±7 days)	6- Month Follow-up (± 14 days)
Medical History & Physical, Informed Consent	X								
Females of child-bearing potential: documentation of birth control method/s employed	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Endoscopic Evaluation-feasibility of S8 Sinus Implant placement	X[b]								
Indication for Repeat ESS	X[b]							X	X
CT Scan[c]	X								
Pregnancy Test[d]	X								
Nasal Obstruction/Congestion Score	X		X	X	X		X	X	X
SNOT-22	X[b]		X	X	X		X	X	X
NOSE	X		X	X	X		X	X	X
Patient Preference Questionnaire (PPQ)				X				X	
WPAI	X							X	X
Patient Blinding Questionnaire					X			X	
Removal of Implants							X		
Endoscopic Evaluation *DVD record of endoscopy*	X	X	X	X	X	X	X	X	X
Endoscopic Grading by clinician		X	X	X	X	X	X	X	X
Ocular Examination	X[e]			X[f]	X[f]	X[f]		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X
Review of Adverse Events		X	X	X	X	X	X	X	X

CT, computed tomography; DVD, digital versatile disk; ESS, endoscopic sinus surgery; IOP, intraocular pressure; NOSE, Nasal Obstruction Symptom Evaluation; PPQ, Patient Preference Questionnaire; SNOT-22, WPAI, Work Productivity and Activity Impairment Questionnaire.

[a] Confirmation of birth control maintained.
[b] Part of initial eligibility; could be combined with baseline visit if all other eligibility criteria were met.
[c] CT scan was graded, if available; CT scan not required by protocol.
[d] Women of child-bearing potential only, prior to S8 Sinus Implant.
[e] Baseline ocular exam had to be performed within 30 days prior to baseline study procedure.
[f] Only IOP at Days 14, 30, and 45.

Source: RESOLVE CSR, Table 1, pg. 36

Population

Key Inclusion Criteria

1. ≥ 18 years of age
2. Chronic sinusitis – defined as inflammation of the mucosa of the paranasal sinuses
3. Undergone bilateral total ethmoidectomy (≥ 90 days before screening)
4. Recurrent bilateral sinus obstruction due to polyposis (Grades 1-3 only)
5. Grade 2 polyposis on ≥1 ethmoid side
6. Indicated for repeat endoscopic sinus surgery
    a. Minimum SNOT-22 symptom score of 2 on ≥ 2 of the 5 hallmark symptoms of chronic sinusitis (nasal blockage, post-nasal discharge, thick nasal discharge, fascial pain/pressure, and decreased sense of smell)
    b. Persistent chronic sinusitis symptoms despite intranasal steroids (≥ 2 weeks of therapy)
    c. Treated with high-dose steroids and/or sinus steroid irrigations within 2 years (or refused due to intolerance, etc) and a known history of repeated courses of treatment with aggressive steroid therapy for recurrent sinusitis
    d. Endoscopic evidence of polyp recurrence, scarring, and/or obstructive mucosal edema

Key Exclusion Criteria

1. Propel implanted ≤ 90 days
2. Adhesions/synechiae Grade 3 or 4
3. Severe scarring or Grade 4 adhesions within the ethmoid cavity
4. Grade 4 polyposis
5. Immune deficiency (including cystic fibrosis), active chemotherapy and/or immunotherapy
6. Oral steroid dependent condition (e.g., COPD or asthma)
7. Known history of resistance or poor response to oral steroids
8. Physical obstruction that would preclude access to either ethmoid sinus for device delivery
9. Acute bacterial sinusitis or invasive fungal sinusitis
10. Participation in another clinical trial within 30 days
11. CSF leak or compromised vision due to Endoscopic Sinus surgery
12. Resected middle turbinate
13. Known dehiscence of the lamina papyracea
14. Active viral disease (e.g. tuberculosis, ocular herpes simplex, chicken pox, measles, etc)
15. Glaucoma (closed-angle) or ocular hypertension (intraocular pressure > 21 mm Hg)
16. Posterior subcapsular cataract or nuclear sclerosis or cortical cataract of ≥ Grade +3
    a. Posterior subcapsular cataracts form faster than nuclear or cortical cataracts and affect the back of the lens. Nuclear sclerosis is a type of cataract that forms in the middle of the lens and causes the nucleus (or center) to become yellow or brown.

Cortical cataracts are wedge-shaped and form around the edges of the nucleus. Grading is on a scale of 1-4, with 4 being the most severe.

With respect to exclusion criteria 12 and 13 above, the reader should note that the middle turbinate and lamina papyracea are the anatomic boundaries of the ethmoid cavity (in addition to the ethmoid sinus roof and the anterior face of the sphenoid sinus). The anatomic boundaries are necessary to determine the percentage of ethmoid sinus obstruction present, a secondary efficacy endpoint.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate.

Concomitant medications/therapies permitted/prohibited

- 2-weeks for high dose steroids (oral steroids, budesonide respules, nebulized steroids or budesonide drops)
- 1 month for parenteral steroids
- High-dose steroids only allowed if medically necessary (clinically significant increase or persistence in ethmoid sinus polyposis coupled with sinusitis symptoms that cause patient to request intervention).
- Inhaled (oral) steroids allowed for control of asthma
- Stable sinus-related medications regimens (e.g. montelukast, leukotriene inhibitors, immunotherapy)
- Antibiotics were allowed
- Surgical intervention could be required in cases where a clinically significant increase or persistence in ethmoid sinus polyposis occurred, coupled with sinusitis symptoms that caused the patient to request surgery.

Treatment groups

<u>MF Sinus Implant</u>

1. Anesthetize
    a. Spraying the nasal cavity with 4% lidocaine with Afrin
    b. Lidocaine soaked cotton plegets applies
    c. Injection of sinus tissue and or polyps with lidocaine if necessary
2. Blindfold and earmuffs placed on patient
3. Debride
    a. Suction/debride to permit adequate endoscopic visualization
    b. Blunt dissection of focal (Grade 1 and 2) adhesions of the anterior middle turbinate
4. Assess space
    a. Insert rosebud-tipped stainless steel surgical probe into ethmoid sinus to judge space into while the implant will be placed, then remove
5. Insert MF Sinus Implant
    a. Advance MF implant under endoscopic visualization

   b. Deploy MF implant to the target location within the ethmoid sinus (endoscopic instruments may be used to manipulate implant into final position)
6. Post-implant
   a. Implant removed at Day 60 (to ensure that Day 90 primary endpoint endoscopy remains blinded to assessor)
   b. Implant may be removed earlier if it has moved out of place and could be expelled between study visit (to protect the blind)

Sham

- Steps 1 – 4 are identical
- Insert MF Sinus Implant
  - Advance MF implant under endoscopic visualization
  - Do not deploy implant, but remove implant + holding device

Nasonex background therapy

All patients were required to self-administer Nasonex, mometasone furoate intranasal spray, once daily, two sprays in each nostril (50 mcg per spray for a total of 100 mcg per nostril) for a total of 200 mcg per day.

Blinding

The patients were blinded. To maintain the blind, subjects were blindfolded and ear-muffed during every visit through Day 90 in case pieces of the implant were removed during follow-up endoscopic exams.

Additionally, study patients and staff were masked regarding the impending treatment assignment until after a study patient was screened, enrolled, and completed the baseline endoscopic examination, symptom scoring questionnaires, and ocular examination.

Compliance

Compliance of Nasonex use through Day 90 was assessed.

Reviewer comment: Compliance with the MF Sinus implant was not needed as all patients had one MF Sinus Implant inserted bilaterally into each ethmoid sinus.

Efficacy Endpoints

Co-Primary Endpoint

- Change from baseline to Day 90 in Nasal Obstruction/Congestion score
- Change from baseline to Day 90 in the mean bilateral polyp grade

Secondary Endpoints

- Endoscopic Measures at all timepoints
    - Percent volume of ethmoid sinus obstruction
    - Polyp grade (bilateral score)
    - Adhesion/scarring (presence and severity)
    - Middle turbinate position
    - Appearance of the implant, including percent of implant remaining and percent apposition of the implant to cavity wall, over time up to Day 90
    - Need for oral steroids to resolve recurrent ethmoid sinus inflammation, edema, and/or polyposis
- Patient Reported Outcomes
    - Sino-Nasal Outcomes Test-22 (SNOT-22)
    - Nasal Obstruction Symptom Evaluation (NOSE)
    - Patient Preference Questionnaire (PPQ)
    - Work Productivity and Activity Impairment Questionnaire (WPAI)

Other endpoints

- Device delivery success
- Proportion of patient still judged to be indicated for repeat endoscopic sinus surgery at Day 90 and Month 6
- Concomitant medication use

Efficacy Endpoint Parameters

Primary Efficacy Parameter

Nasal Obstruction/Congestion Score
0: no problem
1: very mild problem
2: mild or slight problem
3: moderate problem
4: severe problem
5: problem as bad as it can be

The nasal obstruction/congestion score was an instantaneous score obtained via a daily diary.

Polyp Grading Scale

GRADE	DEFINITIONS:
0	No visible nasal polyps (NP)
1	Small amount NP confined in middle meatus (clinically insignificant, not requiring treatment)
2	Expanded amount of NP confined in middle meatus
3	NP extending beyond middle meatus, within the sphenoethmoid recess not totally obstructing, or both
4	NP completely obstructing the nasal cavity

Endoscopic polyp grading was determined by an independent panel of sinus surgeons who were blinded to treatment assignment. The polyp grade is a sum of the left and right polyp grades, resulting in a total bilateral polyp grade of 0 to 8, 8 being the largest polyps.

Secondary Efficacy Parameters

Adhesion Grading Scale
0: none
1: small but non-obstructing (no separation required)
2: obstructing, but easily separated
3: dense and obstructing, separation difficult
4: severe, complete adhesion of the middle turbinate to the lateral nasal wall

Middle Turbinate Position Grading Scale
0: medialized
1: normal
2: partially lateralized
3: lateralized

Percent ethmoid sinus obstruction
100 mm visual analogue scale, where 0 is defined as the absence of obstruction and 100 is defined as complete obstruction of the ethmoid cavity

Reflective nasal obstruction/congestion
The reflective score was over 1 week. This was assessed at all timepoints.

Polyp grade
Polyp grade at all timepoints was also assessed as a secondary endpoint, evaluated by unblinded clinical investigators.

Patient-Reported Outcomes

Nasal Obstruction Symptom Evaluation (NOSE) (2)
The NOSE is a validated instrument consisting of 5 questions evaluating nasal congestion/stuffiness, nasal blockage/obstruction, trouble breathing through nose, trouble

sleeping, getting enough air through nose during exercise or exertion. Each question is scored by the patient on a scale of 0 to 4, as follows:

0: Not a problem
1: Very mild problem
2: Moderate problem
3: Fairly bad problem
4: Severe problem

Patient Preference Questionnaire (PPQ)
The PPQ is a questionnaire regarding individual patient's perceptions about the procedure and outcomes.

Sino-Nasal Outcome Test 22 (SNOT-22)
SNOT-22 is a validated, disease-specific, symptom-scoring instrument consisting of 22 questions, each scored by the patient on a scale of 0 to 5, over the past 2-weeks, as follows:

0: No problem
1: Very mild problem
2: Mild or slight problem
3: Moderate problem
4: Severe problem
5: Problem as bad as it can be

The 22 questions are as follows:

1. Need to blow nose
2. Nasal blockage
3. Sneezing
4. Runny nose
5. Cough
6. Post-nasal discharge
7. Thick nasal discharge
8. Ear fullness
9. Dizziness
10. Ear pain
11. Facial pain/pressure
12. Decreased sense of smell/taste
13. Difficulty falling asleep
14. Wake up at night
15. Lack of a good night’s sleep
16. Wake up tired
17. Fatigue
18. Reduce productivity

19. Reduced concentration
20. Frustrated/restless/irritable
21. Sad
22. Embarrassed

Work Productivity and Activity Impairment (WPAI)
The WPAI assesses absenteeism (# hours missed/ # hours missed + # of hours worked), presenteeism, activity impairment, and overall work impairment/productivity loss.

Safety Parameters

Safety parameters included a physical exam, CT scan and pregnancy test at screening, Endoscopic evaluations and ocular exams were also included. No clinical labs were included.

Ocular safety
Ocular examinations (by blinded ophthalmologists, optometrists, or trained technicians) and intraocular pressure were assessed at baseline and Days 14, 30, 45, and 90. Visual acuity, intraocular pressure, and a dilated slit lamp examination for cataracts were assessed at baseline and Day 90.

Elevated intraocular pressure (≥ 10 mmHg greater than baseline or > 28 mm Hg) was treated with medications.

Ethics
An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Statistical Plan

Co-Primary endpoints:
All patients in the ITT population were included in the primary efficacy analysis. An Analysis of Covariance (ANCOVA) model was used. Site and treatment groups were included as fixed effects in the model. For the bilateral polyp grade, 3 panelists' results were averaged.

Surgery and high-dose steroid imputation
Subjects who required treatment with high-dose steroids (oral steroids, budesonide drops/irrigation, or nebulized steroids) or surgical intervention were analyzed to account for these confounding therapies and termed 'intervention-adjusted values." Last observation carried forward was used to impute missing data for these subjects, as follows:

- If a patient initiated high-dose steroids or required revision surgery for his or her CS conditions during the 90-day window, this represented treatment failure. The patient was asked to complete the Nasal Obstruction/Congestion, SNOT-22 and NOSE questionnaires and to have an additional video-endoscopy recorded (if not at a protocol-

required study visit) at the time of presentation with symptoms precipitating the subsequent intervention. These observations were used as the patient's Day 90 values for these objectives, meaning the latest video-endoscopy was presented to the independent panel for grading of the endoscopic outcome measures.

- If a patient initiated high-dose steroids for other reasons not involving the sinuses during the 90-day window, this did not represent treatment failure. The patient's most recent Nasal Obstruction/Congestion, SNOT-22, and NOSE observations were used as his/her Day 90 values for these objectives, and the patient's most recent video-endoscopy was presented to the independent panel for grading of the endoscopic outcome measures.

- The last available scores for Nasal Obstruction/Congestion, SNOT-22, and NOSE, as well as endoscopic measures prior to interventions, were carried forward to all time points through Month 6.

Analyses Population

Intent-to-Treat (ITT) Population
The ITT population was defined as all patients in whom placement of the MF Sinus Implant or sham procedure was attempted.

Protocol Amendments

A total of 2 amendments were made to the protocol. The protocol amendments that occurred after patients were enrolled are listed below.

Amendment 2 (January 17, 2013)

- Added criteria for implant removal prior to Day 60

Amendment 3 (July 19, 2013)

- Expanded prior high-dose steroid treatment period from 6 months to 2 years

Reviewer comment: The amendments were considered minor.

Protocol Deviations

Out of the 108 total protocol deviations, none were considered major. The most common (67%) were out of range visits.

5.3.2 RESOLVE II (Study R500-1012)

Administrative Information

- **Study title:** The RESOLVE II Study: A Clinical Evaluation of the Safety and Efficacy of the Steroid-Releasing MF Sinus Implant in Chronic Sinusitis Patients with Recurrent Sinus Obstruction
- **Study dates:** December 23, 2014 to August 29, 2016
- **Study sites:** 36 US sites
- **Study report date:** February 18, 2017

Objectives/Rationale

Primary Objectives

Assess the safety and efficacy of the steroid-releasing MF Sinus Implant when used in post-sinus surgery patients who present with recurrent sinus obstruction.

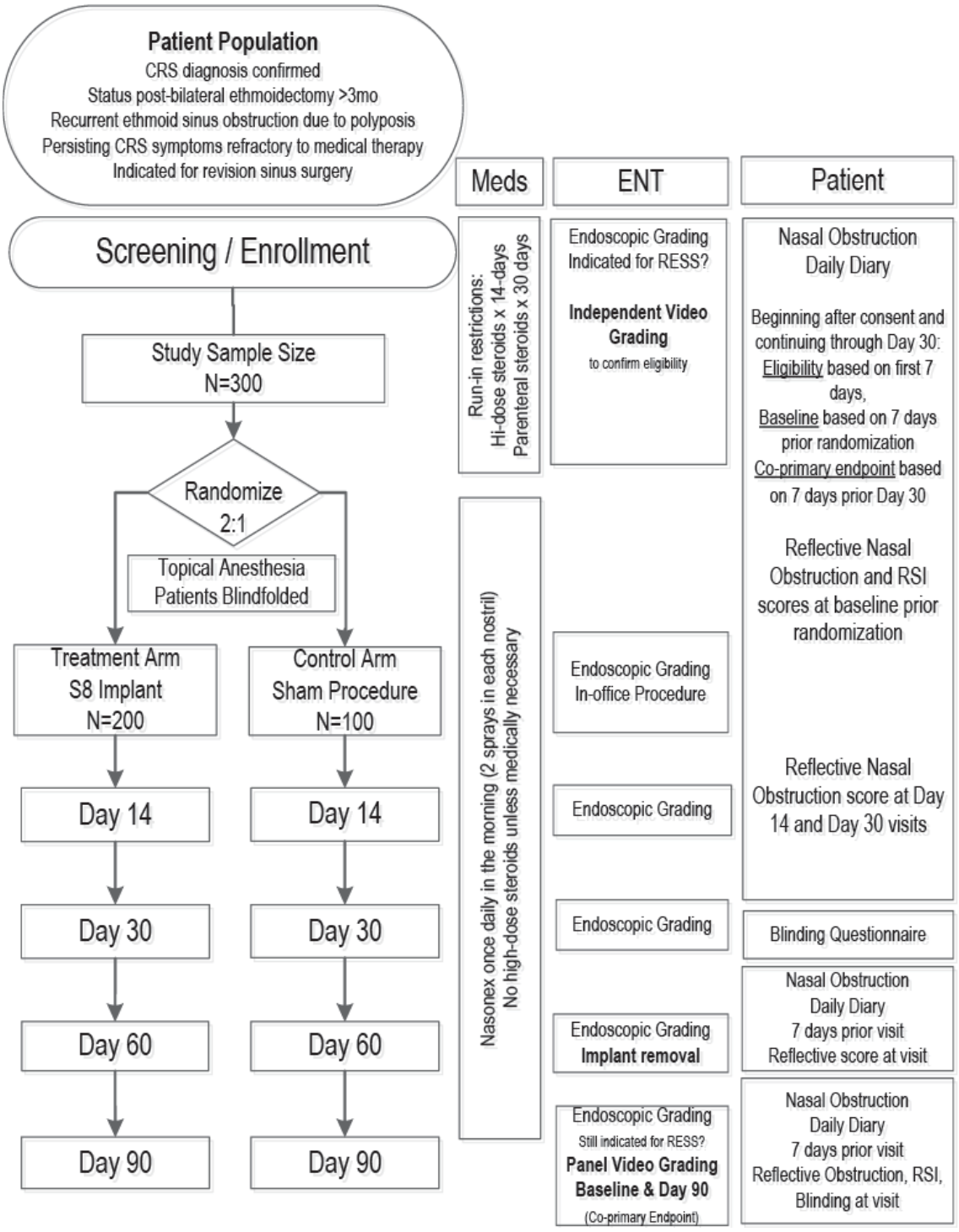
Study Design and Conduct

Overview

The RESOLVE II study was similar in design to the RESOLVE study, but was shorter in duration (90 days), and included more subjects (201 for the MF Sinus Implant group and 99 for the control (sham) group). Additionally, the time point for the analysis of the co-primary endpoint of nasal congestion/obstruction score was earlier (Day 30). In addition, patients had a higher-grade polyposis (grade 2 on both sides compared to grade 4 combined as in RESOLVE (could have had grade 1 + grade 3)), and the polyp grade score changed to include 0.5 increments, to include ethmoid sinus obstruction. This change was made to improve quantification of the burden of polyposis in patients after endoscopic sinus surgery and to account for post-surgical changes, specifically, the varied amount of obstruction by polypoid edema after endoscopic sinus surgery.

The study design for the RESOLVE II study is depicted in Figure 6.

Figure 6. RESOLVE II Study Design



Source: RESOLVE II CSR, pg. 26, Figure 1

Study visits occurred every 2 weeks through Day 30, and then monthly through Day 90. Endoscopic grading and symptoms assessments were done at various timepoints throughout the study, including at Day 90 and at the end of the study. All subjects were on Nasonex background therapy through Day 90.

The schedule of assessments is shown in Figure 7.

Figure 7. RESOLVE II: Schedule of Assessments

Assessments	Screening	Baseline/Procedure	Day 14 (±3 days)	Day 30 (±3 days)	Day 60 (±3 days)	Day 90 (±7 days)
Medical history, Informed Consent	X					
Females of child-bearing potential – *Documentation of birth control method/s employed*	X	X	X	X	X	X
Females of child-bearing potential – *Pregnancy test*	X	X				
Endoscopic evaluation – *Grading by clinician and recording*	X	X	X	X	X	X
Endoscopic evaluation – *Feasibility of S8 Sinus Implant placement*	X					
Video-endoscopy review – *Independent evaluator*	X					
Indication for revision ESS	X					X
Nasal Obstruction/Congestion score – *Daily diary (instantaneous)*	---------- X[a] ----------				-- X[a]	-- X[a]
Nasal Obstruction/Congestion score – *Questionnaire (reflective)*		X	X	X	X	X
Rhinosinusitis Symptom Inventory – *Questionnaire (reflective)*		X				X
Implant placement or sham procedure		X				
Implant removal					X	
Video-endoscopy review – *Independent panel*		X				X
Patient Blinding Questionnaire				X		X
Concomitant Medications	X	X	X	X	X	X
Adverse Events reporting		X	X	X	X	X

Source: RESOLVE II CSR, Table 1, pg. 37

Population

Key Inclusion Criteria

1. ≥ 18 years of age
2. Chronic sinusitis – defined as inflammation of the mucosa of the paranasal sinuses
3. Undergone bilateral total ethmoidectomy (≥ 90 days before screening)

4. Nasal obstruction/congestion score of at least 2 (scale 0 to 3) on ≥ 5 days out of 7 despite use of topical intranasal steroid irrigations or spray for at least 14 days preceding scoring
5. Grade 2 polyposis on ≥1 ethmoid side
6. Indicated for repeat endoscopic sinus surgery
    a. ≥ 2 of the 5 hallmark symptoms of chronic sinusitis (nasal blockage, post-nasal discharge, thick nasal discharge, fascial pain/pressure, and decreased sense of smell)
    b. Endoscopic evidence of bilateral sinus obstruction due to polyposis (minimum grade 2 on each side)
    c. Documented treatment of high-dose form of steroids and/or sinus steroid irrigations within the preceding 1 year or refused therapy due to side effects

Reviewer comment: Compared to RESOLVE, the study population for RESOLIVE II was required to have a minimum nasal obstruction/congestion score, increased polyp grade from Grades 1-3 on either side to a minimum of Grade 2 on each side. The criteria for sinusitis symptoms despite intranasal steroid use were more specific for RESOLVE II. The high-dose steroid use inclusion criteria were decreased from 2 years to 1 year.

Key Exclusion Criteria

The exclusion criteria was similar to those is RESOLVE with the exception of:

1. Grade 1, 1.5 or 4 polyposis (compared to Grade 4 only for RESOLVE)
2. Posterior subcapsular cataract (RESOLVE also included nuclear sclerosis or cortical cataracts)

Reviewer comment: The RESOLVE II did not exclude subjects with nuclear sclerosis or cortical cataract of ≥ Grade +3 as this was recommended by the ophthalmology consult from September 2014.

Concomitant medications

Same as RESOLVE

Treatment groups

Same as RESOLVE

Blinding

Same as RESOLVE

Compliance

Implant delivery success rate was assessed as a measure of compliance.

Efficacy Endpoints

Co-Primary Endpoint

- Change from baseline to Day 30 in instantaneous nasal obstruction/congestion score
- Change from baseline to Day 90 in the mean bilateral polyp grade

Reviewer comment: Compared to RESOLVE, the nasal obstruction/congestion score time point was changed from 90 to 30 days (i.e. a time point at which the implant was still in and eluting drug).

Secondary Endpoints

- Endoscopic Measures at all time points
    - Percent volume of ethmoid sinus obstruction by endoscopy
    - Polyp grade (bilateral score)
    - Need for oral steroids to resolve recurrent ethmoid sinus inflammation, edema, and/or polyposis
- Patient Reported Outcomes
    - Instantaneous nasal obstruction/congestion score at Day 60 and 90
    - Reflective nasal obstruction/congestion score at Day 14, 30, 60, and 90
    - Reflective Rhinosinusitis Symptom Inventory (RSI) score at baseline and Day 90

Other endpoints

- Proportion of patient still judged to be indicated for repeat endoscopic sinus surgery at Day 90
- Concomitant medication use
- Blinding Questionnaire at Day 30 and 90.

Reviewer comment: The following secondary endpoints from RESOLVE were not included in the RESOLVE II study:

- Adhesion/scarring (presence and severity)
- Middle turbinate position
- Appearance of the implant, including percent of implant remaining and percent apposition of the implant to cavity wall, over time up to Day 90
- Sino-Nasal Outcomes Test-22 (SNOT-22)
- Nasal Obstruction Symptom Evaluation (NOSE)
- Patient Preference Questionnaire (PPQ)
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Device delivery success
- Proportion of patient still judged to be indicated for repeat endoscopic sinus surgery at Month 6

Efficacy Endpoint Parameters

Primary Efficacy Parameter

Nasal Obstruction/Congestion Score
Assessed using a daily diary (instantaneous) or a paper questionnaire (reflective) on a scale of 0 to 3, as follows:
0: No symptoms
1: Mild symptoms, clearly present but minimal awareness and easily tolerated
2: Moderate symptoms, definite awareness of symptoms that is bothersome but tolerable
3: Severe symptoms, hard to tolerate, cause interference with activities or daily living

Reflective

Reviewer comment: Compared to RESOLVE, the nasal obstruction/congestion score was simplified and changed from 0 – 5 to 0 -3.

Polyp Grading Scale

0: No visible sinonasal polyps
1: Small amount of sinonasal polyps confined in middle meatus
1.5: Small amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 25% of the ethmoid sinus cavity
2: Expanded amount of sinonasal polyps confined in middle meatus
2.5: Expanded amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 50% of the ethmoid sinus cavity
3: Sinonasal polyps extending beyond middle meatus but not totally obstructing the nasal cavity
3.5: Sinonasal polyps extending beyond middle meatus with expanded amount of polypoid edema obstructing ≥ 75% of the ethmoid sinus cavity
4: Sinonasal polyps completely obstructing the nasal cavity

Endoscopic polyp grading was determined by an independent panel of sinus surgeons who were blinded to treatment assignment. The polyp grade is a sum of the left and right polyp grades, resulting in a total bilateral polyp grade of 0 to 8, 8 being the largest polyps.

A comparison of the nasal obstruction/congestion score is summarized in Table 6.

Table 6. Comparison of the Nasal Obstruction Congestion Scores for RESOLVE and RESOLVE II

6-Point Scale (RESOLVE)	4-Point Scale (RESOLVE II)
0: No symptoms	0: No symptoms
1: Very mild 2: Mild or slight problem	1: Mild symptoms (symptoms clearly present, but minimal awareness, and easily tolerated)
3: Moderate problem	2: Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
4: Severe problem 5: Problem as bad as it can be	3: Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

A comparison of the polyp grade scales in summarized in Table 7.

Table 7. Comparison of the Polyp Grade Scales for RESOLVE and RESOLVE II

5-Point Scale (RESOLVE)	8-Point Scale (RESOLVE II)
0: No visible nasal polyps (NP)	0: No visible sinonasal polyps
1: Small amount NP confined in middle meatus (clinically insignificant, not requiring treatment)	1.0: Small amount of sinonasal polyps confined in middle meatus
NA	1.5: Small amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 25% of the ethmoid sinus cavity
2: Expanded amount of NP confined in middle meatus	2.0: Expanded amount of sinonasal polyps confined in middle meatus
NA	2.5: Expanded amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 50% of the ethmoid sinus cavity
3: NP extending beyond middle meatus, within the sphenoethmoid recess not totally obstructing, or both	3.0: Sinonasal polyps extending beyond middle meatus but not totally obstructing the nasal cavity
NA	3.5: Sinonasal polyps extending beyond middle meatus with expanded amount of polypoid edema obstructing ≥75% of the ethmoid sinus cavity
4: NP completely obstructing the nasal cavity	4.0: Sinonasal polyps completely obstructing the nasal cavity

Reviewer comment: Compared to RESOLVE the polyp grading scale was expanded to include 0.5 increments, with a focus on sinonasal polyps originating from the ethmoid sinus/middle meatus. This change was made to improve quantification of the burden of polyposis in patients after endoscopic sinus surgery and varied amount of obstruction by polypoid edema were modified to account for post-surgical changes.

Secondary Efficacy Parameters

Percent ethmoid sinus obstruction
100 mm visual analogue scale, where 0 is defined as the absence of obstruction and 100 is defined as complete obstruction of the ethmoid cavity

Rhinosinusitis Symptom Inventory (RSI)
RSI was administered using a paper (reflective) questionnaire to assess the CRS symptoms (5 key symptoms: facial pain/pressure, facial congestion/ fullness, nasal obstruction/blockage, nasal discharge or post-nasal drip, decreased sense of smell; 7 other symptoms: headache, halitosis, dental pain, cough, ear symptoms, fevers, and fatigue) on a 6-point scale of 0 to 5, as follows, as well as to assess lost productivity and medication use.

0: Absent
1: Very mild
2: Mild
3: Moderate
4: Severe
5: Very severe

The individual symptom scores were used to calculate 4 domain scores as follows:

Nasal = sum of scores for nasal obstruction, rhinorrhea, sense of smell
Facial = sum of scores for facial pain/pressure, facial congestion fullness, and headache
Oropharyngeal = sum of scores for halitosis, dental pain, cough, and ear symptoms
Systemic = sum of scores for fevers, and fatigue

Patient-Reported Outcomes

Other Endpoints

Blinding assessments were performed at Day 30 and 90. The 5 possible responses were:

- Strongly believe I received the new treatment (the implant procedure);
- Somewhat believe I received the new treatment (the implant procedure);
- Strongly believe I received the placebo (the sham procedure);
- Somewhat believe I received the placebo (the sham procedure); or
- Don’t know

A comparison of the endpoints for the RESOLVE and RESOLVE II studies are summarized in Table 8.

Table 8. Endpoint Comparison for the RESOLVE and RESOLVE II Studies

P500-1012 (RESOLVE)	P500-1113 (RESOLVE II)
Co-Primary Efficacy Endpoints	
Change in mean Nasal Obstruction/Congestion score from baseline to Day 90, as determined by patients using a reflective questionnaire; And Change in mean bilateral polyp grade from baseline to Day 90 based on video-endoscopy review by an independent panel of 3 sinus surgeons who were masked to treatment assignment.	Change in mean Nasal Obstruction/Congestion score from baseline to Day 30, as determined by patients using a daily diary; And Change in mean bilateral polyp grade from baseline to Day 90 based on video-endoscopy review by an independent panel of 3 sinus surgeons who were masked to treatment assignment.
Secondary Efficacy Endpoints	
Nasal Obstruction/Congestion scores at baseline and Days 7, 14, 30, 60, 90 and Month 6 as determined by patients during each visit using a reflective questionnaire	Nasal Obstruction/Congestion scores at baseline and Days 14, 30, 60, and 90 as determined by patients during each visit using a reflective questionnaire
NA	Nasal Obstruction/Congestion scores at Day 60 and Day 90 as determined by patients using an instantaneous daily diary
CRS hallmark symptoms as determined by patients using validated reflective SNOT-22 and NOSE on scale from 0 to 5 at all time-points	CRS hallmark symptoms as determined by patients using a validated reflective RSI on scale from 0 to 5 at baseline and Day 90
Patient Blinding Questionnaire at Days 30 and 90	Patient Blinding Questionnaire at Days 30 and 90
Percent Ethmoid Sinus Obstruction on a 100-mm VAS at baseline and Day 90, as determined from video-endoscopies reviewed by the independent panel, and at baseline and Days 7, 14, 30, 45, 60, 90 and Month 6, as determined by clinical investigators	Percent Ethmoid Sinus Obstruction on a 100-mm VAS at baseline and Day 90, as determined from video-endoscopies reviewed by the independent panel, and at baseline and Days 14, 30, 60 and 90, as determined by clinical investigators
Polyp grade at baseline, Days 7, 14, 30, 45, 60, 90 and Month 6, as determined by clinical investigators	Polyp grade at baseline and Days 14, 30, 60 and 90, as determined real-time by clinical investigators
The proportion of patients still indicated for repeat ESS at Day 90 and Month 6 by clinical investigators	The proportion of patients still indicated for repeat ESS at Day 90 by clinical investigators

Source: SCE, Table 2, pg. 17

Safety Parameters

Safety parameters included endoscopic evaluations, CT scan at screening, and pregnancy test at screening. No clinical labs were included.

Reviewer comment: Based on the September 2014 ophthalmology consult, in the absence of direct physical trauma or radiation, cataract changes are not expected to develop within this 90 day clinical trial even when the lens is exposed to products which have been well established to cause cataracts. Additionally, after review of the intraocular pressures from RESOLVE, these were consistent with the variability seen in normal patients, therefore, it was not deemed necessary to require ocular assessment in the RESOLVE II study.

Statistical Plan

Same as RESOLVE with the following exceptions

For patients who receive rescue therapy (surgery or oral steroids), regardless of whether the reason that the steroid is being used, the last-observation carried forward method will be used to impute data.

Multiplicity adjustments were included in the RESOLVE II Statistical Analysis Plan, but not in RESOLVE.

Reviewer comment: Multiplicity adjustments for secondary endpoints in the RESOLVE study would not be applicable given that the co-primary endpoints were not met.

Holm's step-down procedure was used to control the familywise type 1 error rate at a 2-sided significance level of 0.05. The order of hierarchy was as follows (if the co-primary efficacy endpoints were met):

1. Change from baseline to Day 90 in mean Percent Ethmoid Sinus Obstruction
2. Proportion of patients indicated for Repeat ESS at Day 90
3. Change from baseline to Day 90 in the Decrease of Sense of Smell score
4. Change from baseline to Day 90 in the Facial Pain/Pressure
5. Change from baseline to Day 90 in the Instantaneous Nasal Obstruction/Congestion score

Protocol Amendment

One protocol amendment was made on October 27, 2014

Several changes were included in this protocol amendment, but all were incorporated before any subjects were enrolled. The changes included the co-primary endpoints, secondary endpoints, SAP, safety assessments, and inclusion and exclusion criteria. The review above reflects this amendment.

Protocol Deviations

Out of the 500 total protocol deviations, none were considered major. Not completing the dairy diary made up 40% of the protocol deviations. Another 14% were related to unblinding 59

patients who experienced implant expulsion upon sneezing, coughing, or vigorous rinsing. All expulsions occurred after the subjective nasal congestion/obstructive score co-primary endpoint was measured on Day 30.

Reviewer comment: The Day 90 endpoint of nasal polyp score was measured using endoscopy and assessed by an independent blinded panel, and would not have been affected by the 14% of treatment subjects who were unblinded.

6 Review of Efficacy

Efficacy Summary

The MF Sinus Implant is a bioabsorbable, corticosteroid-eluting implant to be placed in the ethmoid sinus, indicated for the treatment of nasal polyps, in patients 18 years of age or older who have had ethmoid sinus surgery.

Efficacy for the MF Sinus Implant was supported by the RESOLVE and RESOLVE II studies. The RESOLVE study was a 6-month, randomized, single-blind, parallel group, concurrently controlled, study in 100 subjects aged 18 years and older with chronic sinusitis and prior bilateral total ethmoidectomy who presented with recurrent sinus obstruction due to sinus polyposis. The control group underwent a sham procedure, consisting of advancement of a delivery system with the MF Sinus Implant into the ethmoid sinus, followed by removal of the delivery system without deployment of the MF Sinus Implant. The co-primary endpoints were nasal congestion/obstruction score and polyp grade at Day 90. The RESOLVE II study was similar in design, but was shorter (90 days), and included more subjects (201 for the MF Sinus Implant group and 99 for the control (sham) group). Additionally, the co-primary endpoint of nasal congestion/obstruction score was measured at Day 30. Of note, in RESOLVE II, patients had a higher polyposis grade, and the polyp grade score was changed from a 5-point scale (RESOLVE I) to an 8-point scale to include percent ethmoid sinus obstruction. This modification was made to account for post-surgical changes, specifically, the varied amount of obstruction by polypoid edema after endoscopic sinus surgery.

Baseline demographics were generally balanced across treatment groups. The mean age across both studies was 49-50 years, with a range of 19-86 years. For both studies, most patients were male (60-61%), and white (83-85%).

For both studies, most subjects had sinus symptoms despite intranasal steroid spray use, except for facial pain/pressure, which only occurred in about half of subjects. The endoscopic findings were slightly less severe in the control group in both studies. The numbers of sinus surgeries were generally balanced across treatment groups. About 40% of the subjects had one endoscopic sinus surgery, with only about 15% having 4 or more surgeries. The average time since the last surgery was about 4.7 years for both groups. Most subjects had asthma and allergic rhinitis, with about 25% having aspirin intolerance/allergy, which is consistent with what would be expected for this population.

For both studies, most subjects completed the study (98-99%). One subject in the RESOLVE II study discontinued for an adverse event of Parosmia (an olfactory dysfunction that is characterized by the inability of the brain to properly identify an odor's 'natural' smell, replacing it with unpleasant odor such as burning or a chemical smell). A total of 23-45% of subjects in the RESOLVE and 3% of subjects in the RESOLVE II study had their implants removed prior to the planned removal on Day 60.

The co-primary endpoints were change from baseline in nasal obstruction/congestion score to Day 90 (RESOLVE, based on a 0-5 score) or Day 30 (RESOLVE II, based on a 0-3 score) and change from baseline to Day 90 in bilateral polyp grade (0-4 score) as determined from video endoscopies reviewed by a blinded independent panel of sinus surgeons.

In the RESOLVE study, the co-primary endpoint of change from baseline to Day 90 in the nasal obstruction/congestion score (Scale 0-5) was -1.2 in the treatment group compared to -0.8 in the control group with a treatment difference of -0.4 (95% CI: -0.9, 0.1). The co-primary endpoint of change from baseline in polyp grade (scale 0-4) at Day 90 was -0.7 in the treatment group compared to -0.4 in the control, with a treatment difference of -0.3 (95% CI: -0.7, 0.1). Neither endpoint was statistically significantly different than the control group, although they were numerically lower in the MF Sinus Implant group for both endpoints.

In the RESOLVE II study, the co-primary endpoint of change from baseline in nasal congestion/obstruction score at Day 30 was statistically significantly lower than the control group (MF sinus implant -0.8 mean change vs. control -0.6 mean change; treatment difference: -0.2 (95% CI: -0.4, -0.1)). The RESOLVE II study also showed a statistically significant improvement in the change from baseline in bilateral polyp grade at Day 90 for subjects treated with the MF Sinus Implant (mean change -0.6) compared to control (mean change -0.2) with a treatment difference of -0.4; 95% CI: -0.6, -0.1).

The RESOLVE II study likely showed a statistically significant benefit compared to control in both co-primary endpoints due to key changes in the study design. The RESOLVE II study had four times the number of subjects on treatment (n=53 in RESOLVE I vs. n=201 in RESOLVE II), subjects were required to have a minimum nasal congestion/obstruction score of 2 despite use of intranasal steroid (compared to no minimum in RESOLVE), the nasal congestion/obstruction score was assessed at Day 30 (instead of Day 90 in RESOLVE), when the MF Sinus Implant is still present and eluting steroids (implants were removed at Day 60), and the bilateral polyp score was modified to included ethmoid sinus obstruction, where the implant is expected to have the greatest effect given that the implant is placed in the ethmoid sinus. These changes allowed the RESOLVE II study to robustly and more accurately assess the efficacy of the MF Sinus Implant on nasal polyps.

In RESOLVE II, secondary endpoints, in hierarchical order were change from baseline in percent ethmoid sinus obstruction at Day 90, proportion of patients still indicated for repeat endoscopic sinus surgery at Day 90, change from baseline in decreased sense of smell at Day 90, and change from baseline to Day 90 in facial pain/pressure. Change from baseline in reflective nasal obstruction/congestion score and polyp grade at all timepoints for both studies was also

included, but was not in the hierarchy. As the co-primary endpoints for RESOLVE were not statistically significant, analyses of the secondary endpoints are not statistically valid, but are included in this review as supportive information.

In RESOLVE II, the secondary endpoints supported the primary endpoints, except for facial/pain pressure at Day 90. Percent ethmoid sinus obstruction was significantly decreased in the treatment group compared to controls at Day 90 for both studies, as was the proportion of patients still indicated for repeat ESS at Day 90. Consistent with the primary endpoint, the reflective nasal congestion/obstruction score was statistically significant for the RESOLVE II study at Days 30 and 60. Of note, the reflective nasal congestion/obstruction score was not statistically significant at any time point in the RESOLVE study. For both studies, the bilateral polyp grade was statistically significant at all time points (Days 14, 30, 60 and 90); however, these results should be interpreted with caution as the assessment was made by unblinded clinical investigators.

In the RESOLVE study, less subjects received oral steroid therapy in the treatment group compared to the control (MF Sinus Implant, n=9 (17%); Control, n=17 (36%)) through Day 90. Two (4%) subjects in the treatment group underwent polypectomy or endoscopic sinus surgery compared to no subjects in the control group through Day 90. Similar results were seen in the RESOLVE II study. Although RESOLVE did not show statistically significant efficacy for the co-primary endpoints, the prednisone use pattern (decreased in treatment compared to control) does support efficacy for the MF Sinus Implant. The RESOLVE II rescue patterns, in favor of treatment, also support the primary endpoints.

Overall, efficacy for the MF Sinus Implant has been demonstrated in the RESOLVE II study for treatment of nasal polyps in patients ≥ 18 years of age, who have had ethmoid sinus surgery. The co-primary endpoints of change from baseline in nasal obstruction/congestion score at Day 30 and the bilateral polyp grade at Day 90 were statistically significantly lower than control. The efficacy was supported by both the RESOLVE and RESOLVE II studies showing significant decreases in percent ethmoid sinus obstruction at Day 90.

6.1 Indication

MF Sinus Implant is a corticosteroid-eluting implant indicated for the treatment of nasal polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery.

Reviewer comment: The Applicant's proposed indication was ((b) (4) *polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery). The proposed indication is* (b) (4) *The*

revised indication will be included in labeling; the revised indication is used throughout this review.

6.1.1 Methods

The program to support the MF Sinus Implant consists of two efficacy studies, RESOLVE and RESOLVE II.

The RESOLVE study was a 6-month, randomized, single-blind, parallel group, concurrently controlled, study in 100 subjects aged 18 years and older with chronic sinusitis and prior bilateral total ethmoidectomy who presented with recurrent sinus obstruction due to sinus polyposis. The control group underwent a sham procedure, consisting of advancement of a delivery system with the MF Sinus Implant into the ethmoid sinus, followed by removal of the delivery system without deployment of the MF Sinus Implant. The co-primary endpoints were nasal congestion/obstruction score and polyp grade at Day 90.

The RESOLVE II study was similar in design, but was shorter (90 days), and included more subjects (201 for the MF Sinus Implant group and 99 for the control group). Additionally, the time point for the co-primary endpoint nasal congestion/obstruction score was changed from Day 90 to Day 30, patients had a higher-grade polyposis (grade 2 on both sides compared to grade 4 combined as in RESOLVE (could have had grade 1 + grade 3)), and the polyp grade score changed from a 5-point scale to an 8-point scale, to ethmoid sinus obstruction. This modification was made to account for post-surgical changes, specifically, the varied amount of obstruction by polypoid edema after endoscopic sinus surgery.

A pilot study (R500-9011) was also conducted from November 2011 to August 2012. This study was 60 days in duration and enrolled 12 subjects treated with MF Sinus implant on a background of daily Nasonex, similar to the RESOLVE and RESOLVE II studies. An open-label PK study in 5 subjects followed for 90 days was also conducted. As these studies were both open label, they are not included in the efficacy discussion, but will be mentioned in Section 6.1.10 Additional Efficacy Issues/Analyses, where applicable. Their protocols and safety results are summarized in Section 7.7.1 Open-label studies.

Efficacy results are based on the sponsor's submission, unless otherwise indicated. The Agency's statistical review of the efficacy is mentioned where applicable. For further details, see the complete statistical review of the efficacy by Dr. Kate Meaker.

6.1.2 Demographics

The demographics for the combined study population are displayed in Table 9.

Table 9. Baseline Demographics (RESOLVE and RESOLVE II; ITT Population)						
	RESOLVE		RESOLVE II		Combined	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99	MF Sinus Implant N=254	Sham N=146
Sex, n (%)						
Male	29 (55)	31 (66)	127 (63)	56 (57)	156 (61)	78 (60)
Race, n (%)						
White	47 (89)	44 (94)	164 (82)	80 (81)	211 (83)	124 (85)
Black	6 (11)	2 (4)	27 (13)	13 (13)	33 (13)	15 (10)
Asian	0	1 (2)	4 (2)	4 (4)	4 (2)	5 (3)
Other	0	0	6 (3)	2 (2)	6 (2)	2 (1)
Age in Years						
Mean (SD)	48 (13)	52 (13)	51 (13)	48 (13)	50 (13)	49 (13)
Min-Max	19-74	30-80	22-86	21-82	19-86	21-82
Source: SCE, Table 5, pg. 25						

Baseline demographics were generally balanced across treatment groups. The mean age across both studies was 49 years, with a range of 21-82 years. Most patients were male (60%), and white (85%).

Baseline disease characteristics

Baseline disease characteristics are summarized in Table 10.

Table 10. Baseline Disease Characteristics (RESOLVE and RESOLVE II; ITT Population)						
	RESOLVE		RESOLVE II		Combined	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99	MF Sinus Implant N=254	Sham N=146
Sinus Symptoms despite Intranasal steroids, n (%)						
Nasal obstruction/ congestion	48 (91)	40 (85)	185 (92)	90 (91)	233 (92)	130 (89)
Post-nasal discharge	48 (91)	44 (94)	182 (91)	83 (84)	230 (91)	127 (87)
Thick nasal discharge	50 (94)	41 (87)	144 (72)	74 (75)	194 (76)	115 (79)
Facial pain/pressure	42 (79)	32 (68)	77 (38)	44 (44)	119 (47)	76 (52)
Altered sense of smell/taste	42 (79)	39 (83)	174 (87)	89 (90)	216 (85)	128 (88)
Endoscopic findings						
Bilateral polyp grade, mean (SD)	4.8 (1.1)	4.4 (1.2)	5.5 (1.0)	5.3 (1.0)	5.4 (1.0)*	5.0 (1.1)
Polyp grade ≥2 on each side, n (%)	45 (85)*	30 (64)	201 (100)	99 (100)	246 (97)*	129 (88)
% ethmoid sinus obstruction, mean (SD)	69 (21)	63 (24)	76 (17)*	69 (20)	74 (18)*	67 (22)
# Of Endoscopic Sinus Surgeries, n (%)						

Table 10. Baseline Disease Characteristics (RESOLVE and RESOLVE II; ITT Population)						
1	22 (42)	16 (34)	83 (41)	41 (41)	105 (41)	57 (39)
2	12 (23)	15 (32)	57 (28)	36 (36)	69 (27)	51 (35)
3	9 (17)	8 (17)	32 (16)	7 (7)	41 (16)	15 (10)
≥4	10 (19)	8 (17)	29 (14)	15 (15)	39 (15)	23 (16)
Months since last surgery, mean (SD)	62 (63)	53 (65)	56 (57)	55 (51)	57 (59)	55 (56)
Concomitant medical diagnosis						
Asthma	33 (62)	31 (66)	148 (74)	61 (62)	181 (71)	92 (63)
Allergic Rhinitis	41 (77)	37 (79)	155 (77)	79 (80)	196 (77)	116 (80)
Aspirin intolerance/allergy	15 (28)	11 (23)	46 (23)	23 (23)	61 (24)	34 (23)
*p-value compare to the control group was < 0.05 Source: SCE, Table 6, pg. 28						

Most subjects had sinus symptoms despite intranasal steroid spray use, except for facial pain/pressure, which only occurred in about half of subjects. The endoscopic findings were slightly less severe in the control group in both studies. The numbers of sinus surgeries were generally balanced across treatment groups. About 40% of the subjects had one endoscopic sinus surgery, with only about 15% having 4 or more surgeries. The average time since the last surgery was about 4.7 years for both groups. Most subjects had asthma and allergic rhinitis, with about 25% having aspirin intolerance/allergy, which is implant consistent with what would be expected for this population.

Reviewer comment: The less severe endoscopic findings in the control group would tend to decrease the treatment effect (controls were less severe), and is therefore not a concern.

6.1.3 Subject Disposition

Study sites

All study sites were in the US.

Patients

Patient disposition for both studies is summarized in Table 11.

Table 11. Patient Disposition (RESOLVE and RESOLVE II)						
	RESOLVE		**RESOLVE II**		**Combined**	
n (%)	MF Sinus Implant	Sham	MF Sinus Implant	Sham	MF Sinus Implant	Sham
Randomized	53	47	201	100	254	147
ITT population[♣]	53 (100)	47 (100)	201 (100)	99 (99)	254 (100)	146 (99)
Subjects with successfully placed sinus implants	53 (100)	46 (99)	198 (99)	99 (99)	251 (99)	145 (100)

Table 11. Patient Disposition (RESOLVE and RESOLVE II)						
Completed	52 (98)	46 (98)	200 (99)	98 (98)	252 (99)	144 (98)
Reason for discontinuation						
Adverse event	0	0	1 (1)[λ]	0	1 (0.4)	0
Withdrew	1 (2)	1 (2)*	0	1 (1)	1 (0.4)	2 (1)
Implant removed prior to Day 60	12-24 (23-45)**	-	7 (3)	-	22-34 (9-13)	-
Rescued						
Sinus Surgery	2[$] (4)	0	2[α] (1)	0	4 (2)	0
Treated with oral steroids	9 (17)	17 (36)	27 (13)	16 (16)	36 (14)	33 (23)

♣ ITT population = number of subjects who had endoscopic delivery of the MF Sinus Implant attempted
*Withdrew to have endoscopic sinus surgery
**24 implants were removed prior to Day 60; however, the number of subjects was not given
λ Implant removed due to Parosmia at Day 48, then patient did not return for remaining study visits
$ Polypectomy occurred on Day 60 and endoscopic sinus surgery occurred on Day 90
α Polypectomies occurred on Day 60
Percentages are calculated based on randomized subjects per group as the denominator.
Source: SCE, Table 4, pg. 24; August 4, 2017 Information Request, Table 4.1 and Table 4.2, pp. 3-6; RESOLVE II CSR Table 20, pg. 81

In RESOLVE II, 1 subject in the control group was not randomized due to extensive adhesions. Most of subjects completed the study (98-99%). One subject discontinued in the RESOLVE II study due to the adverse event of parosmia (an olfactory dysfunction that is characterized by the inability of the brain to properly identify an odor's 'natural' smell, replacing it with unpleasant odor such as burning or a chemical smell). Implants were planned for removal in all subjects at Day 60. Subjects whose implants were removed prior to Day 60, or were rescued (with surgery or steroids) were not discontinued from the study. A total of 24 implants were removed in the RESOLVE study. The number of subjects involved was not given. The range of possible subjects with at least 1 implant removed given that 2 implants were implanted per subject is n=12-24. In the RESOLVE II study, 9 implants were removed in a total of 7 subjects prior to Day 60. In the combined treatment group, less treated subjects were treated with rescue steroids (14%) compared to control (23%). This trend was similar when looking at the individual studies. A total of 4 subjects (2%) in the combined (RESOLVE and RESOLVE II) treatment group received sinus surgery with none receiving surgery in the sham group.

In addition to implant removal, implants were also dislodged and expelled prior to Day 60. The status of the implants, which includes both removal and dislodgement, at various timepoints for both studies is displayed in Table 12 below.

Table 12. Implant Status (RESOLVE and RESOLVE II)		
	RESOLVE	**RESOLVE II**
	MF Sinus Implant Number of Implants=106	MF Sinus Implant Number of Implants=402
Implant Delivery Success	106 (100%)	398 (99%)
Present at*		
Day 14	n=106	n=390
	103 (98%)	377 (97%)

Table 12. Implant Status (RESOLVE and RESOLVE II)		
Day 30	n=106	n=398
	98 (93%)	384 (97%)
Day 60	n=106	n=396
	59 (57%)	276 (70%)
Day 90	-	n=396
	-	2 (1%)
*Otherwise either absent or unable to view Source: RESOLVE II CSR, Table 18, pg. 80; RESOLVE CSR, Table 4.1, pg. 179		

Generally, most of implants in both studies were present at Day 30, however this decreased down to 57% for the RESOLVE study and 70% for the RESOLVE II study at the time of scheduled removal at Day 60.

Reviewer comment: Given that 60% of the steroid (MF) is released over the first 30 days and the integrity of the implant is highest in the first 30 days, the efficacy of the implant at Days 30 and 90 was likely not affected by the lower number of implants present at Day 60.

Compliance of intranasal steroid background therapy was assessed. In the RESOLVE study, all subjects were compliant except one control subject who withdrew prior to Day 14 to have surgery. In the RESOLVE II study at Day 30, two subjects in the control group were not compliant. By Day 90, about 91-92% of subjects in each group were still compliant with daily Nasonex.

Reviewer comment: Given that compliance of Nasonex was similar between groups, the 10% of subjects who were noncompliant are not expected to affect the efficacy endpoint in favor of the MF Sinus Implant.

6.1.4 Analysis of Primary Endpoint

Primary Efficacy Results

The co-primary endpoints for the RESOLVE and RESOLVE II studies are as follows:

- Change from baseline to Day X in instantaneous **nasal obstruction/congestion** score.
  - RESOLVE: X= **Day 90** based on a 0-5 score.
  - RESOLVE II: X= **Day 30** based on a 0-3 score.

- Change from baseline to Day 90 in bilateral **polyp grade** as determined from video-endoscopies reviewed by a blinded independent panel of sinus surgeons.
  - RESOLVE: 0-5 polyp score
  - RESOLVE II: 0-8 polyp score, with **0.5 increments to include ethmoid sinus obstruction**.

The results for the primary endpoints are summarized in Table 13.

Table 13. Co-Primary Efficacy Endpoints (RESOLVE and RESOLVE II; ITT Population)

	RESOLVE		RESOLVE II	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99
Instantaneous Nasal obstruction/congestion score RESOLVE: 0-5 RESOLVE II: 0-3				
Change from baseline to Day 30				
N			199	97
Baseline, mean (SD)			2.4 (0.5)	2.4 (0.5)
Mean change (SD)			-0.8 (0.8)	-0.6 (0.6)
Treatment difference, mean			-0.2	
95% CI			-0.4, -0.1	
Change from baseline to Day 90				
N	52	45		
Baseline, mean (SD)	3.6 (1.2)	3.3 (1.1)		
LS Mean $^{\lambda}$ change (SD)	-1.2 (1.5)	-0.8 (1.4)		
Treatment difference, mean	-0.4			
95% CI	-0.9, 0.1			
Polyp grade* RESOLVE and RESOLVE II: 0-4¥				
Change from baseline to Day 90				
N	51	47	195	97
Baseline, mean (SD)	4.9 (0.9)	4.4 (1.4)	5.5 (1.1)	5.4 (1.0)
LS Mean $^{\lambda}$ change (SD)	-0.7 (0.9)	-0.4 (1.0)	-0.6 (1.1)	-0.2 (0.9)
Treatment difference, mean	-0.3		-0.4	
95% CI	-0.7, 0.1		-0.6, -0.1	

*Polyp grade determined by an independent blinded panel
¥ - The score of 0-4 was the same for RESOLVE and RESOLVE II, but RESOLVE II was on a 8-point scale (compared to a 5-point scale for RESOLVE) as the score included 0.5 increments
λ - LS mean adjusted for baseline
Last-observation carried forward imputation used for subjects that were rescued with oral steroids or surgery
Source: SCE, Table 9, pg. 34, RESOLVE CSR, Table 5, pg. 59, treatment difference, and LS mean change calculated by statistician, Dr. Kate Meaker

In the RESOLVE study, the co-primary endpoint of change from baseline to Day 90 in the nasal obstruction/congestion score (Scale 0-5) was -1.2 in the treatment group compared to -0.8 in the control group with a treatment difference of -0.4 (95% CI: -0.9, 0.1). The co-primary endpoint of change from baseline in polyp grade (scale 0-8) at Day 90 was -0.7 in the treatment group compared to -0.4 in the control, with a treatment difference of -0.3 (95% CI: -0.7, 0.1). Neither endpoint was statistically significantly different than the control group, although they were numerically lower in the MF Sinus Implant group for both endpoints.

In the RESOLVE II study, the co-primary endpoint of change from baseline in nasal congestion/obstruction score at Day 30 was statistically significantly lower than the control group (MF sinus implant -0.8 mean change vs. sham -0.6 mean change; treatment difference: -0.2 (95% CI: -0.4, -0.1).

The RESOLVE II study, also showed a statistically significant improvement in the change from baseline in bilateral polyp grade at Day 90 for subjects treated with the MF Sinus Implant (mean change -0.6) compared to control (mean change -0.2) with a treatment difference of -0.4; 95% CI: -0.6, -0.1).

For RESOLVE and RESOLVE II, the primary endpoint was evaluated using a last-observation carried forward (using assessments made at the time the subject presented for rescue therapy) to impute data for those subjects who were rescued either with steroids or surgery prior to the primary endpoint assessment day. We requested a sensitivity analysis using the worst-observation carried forward (WOCF) for the RESOLVE II study primary endpoints. A similar analysis was not requested for the RESOLVE study as neither co-primary endpoint was statistically different. The nasal polyp grade was not assessed with WOCF as the independent panel only assessed one video endoscopy (taken at the time of presentation for rescue or at Day 90) and therefore a WOCF vs. LOCF analysis would be the same. For the Day 30 nasal congestion/obstruction assessment, a total of 5 subjects on treatment and 5 subjects in the control group had imputed data. This altered the results for 3 treatment subjects and 2 control subjects. The results of the worst-observation carried analysis were similar to the last-observation carried forward analysis.

Further discussion of efficacy can be found in Dr. Kate Meaker's statistical review.

Reviewer comment: The RESOLVE II study likely showed a statistically significant benefit compared to placebo in both co-primary endpoints due to key changes in the study design compared to RESOLVE which did not show a statistically significant benefit in either co-primary endpoint. The RESOLVE II study had four times the number of subjects on treatment (53 vs 201), subjects were required to have a minimum nasal congestion/obstruction score of 2 despite use of intranasal steroid (compared to no minimum), the nasal congestion/obstruction score was assessed at 30 days (instead of 90 days), when the nasal implant is still present and eluding steroids (implants were removed at Day 60), and the bilateral polyp score was modified to included ethmoid sinus edema which is where the implant is expected to have the greatest effect given that the implant is placed in the ethmoid sinus. These changes allowed the RESOLVE II study to robustly and more accurately assess the efficacy of the MF Sinus Implant on nasal polyps.

1.1.5 Analysis of Secondary Endpoints(s)

Secondary Endpoint

The secondary endpoint results are listed in Table 14 through Table 19. They are generally presented in hierarchical order.

Reviewer comment: As the co-primary endpoints were not statistically significant for the RESOLVE study, the secondary endpoints cannot be analyzed with statistical validity, but are included here for informative purposes.

The results for the change from baseline in percent ethmoid sinus obstruction at all timepoints are shown in Table 14.

Table 14. Secondary Endpoint: Change from Baseline in % Ethmoid Sinus Obstruction (RESOLVE and RESOLVE II: ITT Population)

	RESOLVE		RESOLVE II	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99
Baseline				
N	53	47	201	99
Mean (SD)	70 (20)	61 (26)	75 (18)	70 (20)
Day 14				
N	53	45	195	99
Change from baseline, mean (SD)	-28 (21)	-0.4 (16)	-24 (20)	-3 (13)
Treatment difference, mean	-25		-20	
95% CI	-32, -18		-24, -15	
Day 30				
N	53	45	200	98
Change from baseline, mean (SD)	-27 (22)	1 (18)	-30 (22)	-5 (20)
Treatment difference, mean	-27		-23	
95% CI	-35, -19		-28, -17	
Day 60				
N	52	44	200	96
Change from baseline, mean (SD)	-23 (25)	3 (20)	-28 (24)	-8 (25)
Treatment difference, mean	-25		-18	
95% CI	-34, -15		-24, -12	
Day 90				
N	51	45	200	98
Change from baseline, mean (SD)	-21 (28)	1 (22)	-29 (26)	-9 (24)
Treatment difference, mean	-20		-18	
95% CI	-29, -10		-24, -11	
Source: SCE, Table 15, pg. 40				

Percent ethmoid sinus obstruction was significantly decreased in the MF Sinus group compared to the control (sham) group at all timepoints for both studies. Percent ethmoid sinus obstruction

was also evaluated by a blinded independent panel in both studies at Day 90 and was similar to the results from unblinded clinical investigators at Day 90, as shown in Table 14.

The results for the proportion of patients still indicated for repeat endoscopic sinus surgery (ESS) at Day 90 are shown in Table 15.

Table 15. Secondary Endpoint: Proportion of Patients Still Indicated for Repeat ESS at Day 90 (RESOLVE and RESOLVE II: ITT Population)

	RESOLVE		RESOLVE II	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99
N	52	46	200	98
Yes, n (%)	25 (48%)	36 (78%)	78 (39%)	62 (63%)
Treatment difference, 95% CI	-29% (-48%, -11%)		-24% (-36%, -12%)	

ESS = endoscopic sinus surgery
Source: SCE, Table 16, pg. 41, treatment difference calculated by statistician, Dr. Kate Meaker

In the RESOLVE study, about ½ of subjects treated with the MF Sinus Implant continued to be indicated for endoscopic sinus surgery at Day 90, compared to about ¾ of subjects not treated with the MF Sinus Implant. This difference was statistically significant. The criteria for indication of endoscopic sinus surgery are outlined in the study population section of the protocol description in Section 5. To be enrolled in either study, subjects had to be indicated for endoscopic sinus surgery.

A similar results was seen in the RESOLVE II study, where about 1/3 of subjects treated with the MF Sinus Implant continued to be indicated for endoscopic sinus surgery compared to about 2/3 not treated with the MF Sinus Implant.

Decreased sense of smell was included in the hierarchical listing for multiplicity adjustments in RESOLVE II as the sponsor intended for this secondary endpoint to support product labeling. Decreased sense of smell was not assessed in RESOLVE. Results for the change from baseline in Day 90 in decreased sense of smell was assessed as a parameter in the reflective rhinosinusitis symptom inventory symptom score is shown in Table 16.

Table 16. Secondary Endpoint: Change from Baseline to Day 90 in Decreased Sense of Smell (RESOLVE II: ITT Population)

	RESOLVE II	
	MF Sinus Implant N=201	Sham N=99
Baseline		
N	201	99
Mean (SD)	4.1 (1.4)	4.1 (1.4)
Day 90		
N	198	97

Table 16. Secondary Endpoint: Change from Baseline to Day 90 in Decreased Sense of Smell (RESOLVE II: ITT Population)		
Change from baseline, mean (SD)	-1.2 (1.7)	-0.8 (1.6)
p-value*	0.02	
*95% CI not provided Source: RESOLVE II CSR, Table 14.2.10, pg. 135		

Decreased sense of smell was significantly improved by Day 90 in subjects treated with the MF sinus implant (-1.2) compared to controls (-0.8, p=0.02). Sense of smell is more common in nasal congestion due to polyps than without polyps (3), therefore this endpoint supports the primary endpoint of decreased nasal polyp grade.

Reviewer's comment: While decreased sense of smell was significantly improved in RESOLVE II, it was not specifically assessed in RESOLVE I (except as a part of the SNOT-22 assessment). As such, we do not have replication of this secondary endpoint to support a labeling claim in Section 14.

Facial Pain/Pressure was also included in the hierarchical listing for multiplicity adjustments in RESOLVE II as the sponsor intended to support product labeling. Facial pain/pressure was not assessed in RESOLVE. Results for the change from baseline in Day 90 in facial pain/pressure assessed as a parameter in the reflective rhinosinusitis symptom inventory symptom score is shown in Table 17.

Table 17. Secondary Endpoint: Change from Baseline to Day 90 in the Facial Pain/Pressure (RESOLVE II: ITT Population)		
	RESOLVE II	
	MF Sinus Implant N=201	Sham N=99
Baseline		
N	200	98
Mean (SD)	1.9 (1.4)	2.2 (1.4)
Day 90		
N	197	96
Change from baseline, mean (SD)	-0.77 (1.2)	-0.90 (1.3)
p-value*	0.91	
*95% CI not provided Source: RESOLVE II CSR, Table 14.2.10, pg. 131		

Facial pain and pressure was not significantly decreased by Day 90 in the RESOLVE II study.

The results for the change from baseline in reflective nasal obstruction/congestion score at all assessed time points are shown in Table 18.

Table 18. Secondary Endpoint: Change from Baseline in Reflective Nasal Obstruction/Congestion Score, All Time Points (RESOLVE and RESOLVE II: ITT Population)

	RESOLVE		RESOLVE II	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99
Baseline				
N	53	47	201	99
Mean (SD)	2.4 (0.8)	2.2 (0.8)	2.4 (0.5)	2.4 (0.5)
Day 14				
N	53	45	195	99
Change from baseline, mean (SD)	-0.8 (0.8)	-0.6 (0.8)	-0.6 (0.8)	-0.5 (0.8)
95% CI	-0.5, 0.1		-0.2, 0.1	
Day 30				
N	53	46	201	98
Change from baseline, mean (SD)	-0.9 (1.0)	-0.5 (1.0)	-0.9 (0.9)	-0.6 (0.8)
95% CI	-0.6, 0.1		-0.4, -0.04	
Day 60				
N	52	44	200	97
Change from baseline, mean (SD)	-0.9 (1.0)	-0.5 (1.0)	-0.9 (0.9)	-0.7 (0.9)
95% CI	-0.5, 0.2		-0.4, -0.03	
Day 90				
N	52	45	200	98
Change from baseline, mean (SD)	-0.9 (1.0)	-0.4 (1.0)	-1.0 (0.8)	-0.8 (0.9)
95% CI	-0.6, 0.1		-0.4, 0.01	
Source: SCE, Table 12, pg. 37				

The reflective nasal congestion/obstruction score was significant for the RESOLVE II study at Day 30 and 60. None of the endpoints in the RESOLVE study were statistically different for this secondary endpoint.

The results for the change in baseline in bilateral polyp grade (as determined by clinical investigators and not by a blinded independent panel as was done for the co-primary endpoint) at all assessed time points are shown in Table 19.

Table 19. Secondary Endpoint: Change from Baseline in Bilateral Polyp Grade as Determined by Clinical Investigators, All Time Points (RESOLVE and RESOLVE II: ITT Population)

	RESOLVE		RESOLVE II	
	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99
Baseline				
N	53	47	201	99
Mean (SD)	4.7 (1.0)	4.3 (1.1)	5.5 (1.0)	5.2 (1.1)
Day 14				
N	53	45	195	99
Change from baseline, mean (SD)	-1.3 (1.1)	-0.02 (0.8)	-1.5 (1.2)	-0.2 (1.0)
95% CI	-1.6, -0.8		-1.5, -1.0	
Day 30				
N	53	46	200	98
Change from baseline, mean (SD)	-1.43 (1.4)	-0.1 (1.0)	-1.8 (1.4)	-0.2 (1.1)
95% CI	-1.8, -0.8		-1.84, -1.2	
Day 60				
N	52	44	200	96
Change from baseline, mean (SD)	-1.1 (1.4)	0 (1.1)	-1.6 (1.4)	-0.4 (1.6)
95% CI	-1.5, -0.4		-1.5, -0.8	
Day 90				
N	52	45	200	98
Change from baseline, mean (SD)	-1.0 (1.7)	-0.1 (1.2)	-1.7 (1.5)	-0.4 (1.5)
95% CI	-1.3, -0.1		-1.6, -0.9	
Source: SCE, Table 13, pg. 38				

The change from baseline in the bilateral polyp grade assessed by unblinded clinical investigators (who inserted the MF Sinus implants) was statistically significant for both studies at all time points. This differs from the co-primary endpoint of bilateral polyp grade which was assessed by a blinded independent panel which was not significant for the RESOLVE study at Day 90.

Use of rescue therapy was considered a clinically meaningful secondary endpoint. In the RESOLVE study, less subjects received oral steroid therapy in the treatment group compared to the control (MF Sinus Implant, n=9 (17%); control, n=17 (36%)) through day 90. Two (4%) subjects in the treatment group underwent polypectomy or endoscopic sinus surgery compared to no subjects in the control group through day 90.

For the RESOLVE II study, prednisone use was similar in the control group (n=16 (16%)) compared to treatment (n=27 (13%)); however, more subjects were treated at or after implant removal on Day 60 in the treatment group (59%) compared to controls (31%). The frequency of polypectomy was higher in the treatment group (n=2 (4%)) compared to controls (0). No statistical comparison is available.

Reviewer comment: The prednisone use pattern (decreased in treatment compared to sham) in the RESOLVE study does support efficacy for the MF Sinus Implant. The RESOLVE II rescue patterns, after accounting for when the rescue was given, was also in favor of treatment.

6.1.7 Subpopulations

A subgroup analysis was performed by the sponsor by age, gender, race (white vs. non-white (Black or African American and Asian)), and polyp grade (patients with polyp grade ≥2 vs < 2 on each side at baseline as determined by the independent panel). The subgroups were either too small to make any conclusions or the differences were not statistically significant.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose exploration was included in this submission.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy was not evaluated past Day 90.

6.1.10 Additional Efficacy Issues/Analyses

Concomitant medication use

Concomitant medication use was considered an efficacy endpoint. All subjects used at least one concomitant medication, in addition to the protocol required Nasonex. The most frequently used medication was intranasal saline, other intranasal steroids, antibiotics, oral steroids, and anti-histamines. In RESOLVE, 14 (26%) treatment and 14 (30%) control subjects used other intranasal steroids up to 90 days. In RESOLVE II, 82 (41%) of treated subjects and 47 (47%) of control subjects used other intranasal steroids up to 90 days.

Reviewer comment: The use of other intranasal steroid use could be an efficacy issue; however, since the use was higher in the control group, this would bias the efficacy results to favor control and is therefore not a concern.

PK Study

The PK study was a single-center open-label study in 5 subjects. All subjects received a MF Sinus implant placed bilaterally and were monitored for 90 days. The protocol did not include a implant removal date. Nasonex topical steroid spray was used Day 30-90. The study population was similar to the RESOLVE study.

The efficacy endpoints of the PK study are summarized in Table 20.

Table 20. Efficacy Endpoints: PK Study

Mean	MF Sinus Implant N=5
Percent ethmoid sinus obstruction	
Baseline	59%
Day 30	29%
Day 90	56%
Bilateral polyp grade (0-8)	
Baseline	4.6
Day 14	2.6
Day 30	2.8
Day 60	3.6
Day 90	4.8
Nasal Obstruction/Congestion score (0-5)	
Baseline	2.2
Day 14	1.6
Day 30	1.2
Day 60	2.4
Day 90	2.8
Source: PK Study CSR, Figure 4 (p22), Table 7, (p23), Figure 6 (p24)	

The efficacy endpoint for the PK study did show numerical improvements at early timepoints for percent ethmoid obstruction (30% improvement from baseline by Day 30), bilateral polyp grade (2 point improvement on an 8 point scale by Day 14), and nasal obstruction/congestion score (1 point improvement by Day 30). All endpoints returned to baseline by Day 90.

One subject expelled both of their implants prior to Day 60. Another 3 subjects expelled their implants after Day 60. The fifth subject had their implant removed at Day 90. Notably future studies (RESOLVE and RESOLVE II) had all implants removed at Day 60.

Pilot Study

The pilot study was a 6-month single-arm, multi-center (4) study in 12 subjects who were treated with two MF Sinus Implants (one in each sinus). Implants were removed on Day 60. The demographic and baseline characteristics for the 12 subjects enrolled in the pilot study were similar to the RESOLVE and RESOLVE II studies.

The efficacy endpoints of the PK study are summarized in Table 24.

Table 21. Efficacy Endpoints: PK Study

Mean (SD)	MF Sinus Implant N=12
Percent ethmoid sinus obstruction	
Baseline	66%
Day 30	21%
Day 60	18%
Day 90	21%
Bilateral polyp grade (0-8)	
Baseline	4.5 (1.7)
Day 14	1.9 (1.6)
Day 30	2.3 (1.6)
Day 60	2.1 (1.3)
Day 90	2.0 (1.7)
Nasal Obstruction Symptom Evaluation (NOSE) score (0-100)	
Baseline	58 (20)
Day 14	32 (18)
Day 30	16 (15)
Day 60	23 (13)
Day 90	20 (16)
Source: Pilot Study CSR, Table 9, pg. 46, Table 10, pg. 47	

Percent ethmoid sinus obstruction decreased from 66% to 21% from baseline to Day 30 and the decrease was sustained through Day 90. Bilateral polyp grade also decreased from 4.5 out of 8 at baseline to 2.3 by Day 30. This decreased in polyp grade was also sustained through Day 90. Nasal obstruction symptom decreased from 58 (out of 100) at baseline to 16 at Day 30 and was sustained through Day 90.

One subject was treated with oral steroids on Day 21 for worsening nasal symptoms. Subjects were also assessed for meeting criteria for repeat endoscopic sinus surgery. At Day 30, 10 (91%) of the 11 evaluable subjects were no longer considered candidates. At Day 60 and 90, 73% and 82%, respectively, were no longer considered candidates for surgery.

Reviewer comment: The efficacy results in the 5 subjects included in this PK study and 12 subjects in the Pilot Study that were all treated with the MF Sinus Implant are generally implant consistent with the RESOLVE and RESOLVE II studies. However, given their open label nature, no definitive conclusions can be drawn from these two studies.

Review of Safety

Safety Summary

The safety evaluation for the MF Sinus Implant relies on data from the RESOLVE and RESOLVE II studies. Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these studies had similar study designs (randomized, sham-controlled, single bilateral implants placed at Day 0 and removed at Day 60, and intranasal steroid background therapy) and the patient population was comparable in terms of demographics and baseline characteristics.

The sponsor also conducted an open-label PK study and a pilot study in a total of 17 subjects, where all subjects received treatment. The safety results of these studies are included in Section 7.7.1 Open-label studies and were found to have a similar safety profile as the RESOLVE and RESOLVE II studies. These 17 patients are not included in the pooled data discussed below.

There was a total of 254 subjects treated with the MF Sinus Implant and 146 subjects who underwent a sham procedure. Each treated subject had one implant placed bilaterally in each ethmoid sinus with 1350 mcg of MF/implant for a total of 2700 mcg per patient. All subjects used Nasonex (MF nasal spray) 200 mcg (two 50 mcg sprays per nostril) daily.

The planned implant removal date was Day 60 for all subjects; however, 24 implants in RESOLVE (unknown number of subjects) and 11 implants in RESOLVE II (in 10 subjects) were removed. In RESOLVE II, 6 were removed for adverse events (acute sinusitis x 2, rhinalgia, epistaxis, parosmia). No data was provided for RESOLVE.

There were no deaths. The overall occurrence of serious adverse events (SAEs) was low and equally distributed across treatment groups (1%). A total of 3 (1%) SAEs (streptococcal asthmatic bronchitis, epistaxis, and pneumonia) were reported in 2 subjects in the MF Sinus Implant group and 2 (1%) SAEs (suicidal ideation and pneumonia) were reported in 2 subjects in the sham group. The SAE of epistaxis led to early implant removal at Day 40. Thirty-nine (39) days later, on Day 79, epistaxis recurred, requiring cautery. There was one subject with a reported adverse event of parosmia (abnormality in the sense of smell) which led to study discontinuation.

Ocular safety evaluations were included in the RESOLVE study. The intraocular pressures were consistent with variability seen in normal patients. Cataracts were not noted; however, it would be unlikely for cataract formation to occur within a 90-day study. Due to the findings in RESOLVE and the limited duration and follow-up of the RESOLVE II study, no ocular safety assessments were deemed necessary in the RESOLVE II study.

The incidence of adverse events was reported similarly across treatment groups. Bronchitis, nasopharyngitis, otitis media, headache, presyncope, asthma, epistaxis, and nasal discomfort were the most frequent adverse events, occurring with a 1% incidence and more commonly than the control group.

Pediatric assessments were not included as nasal polyps are extremely rare (0.1%) in the pediatric population. In addition, the proposed indication for this product includes only those patients who have previously undergone endoscopic sinus surgery, which is also not routinely performed in children. The sponsor has included a full waiver for subjects < 18 years of age in this submission.

The safety database is adequate to assess the safety of the MF Sinus Implant. The safety findings should be factored into the risk-benefit assessment of MF Sinus Implant for treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based primarily on the pooled results of the two pivotal studies, RESOLVE and RESOLVE II. The safety results for the open-label PK and Pilot studies are discussed briefly in Section 7.7.1 Open-label studies.

Implant dislodgements or removals were not listed as adverse events.

All analyses were based on the ITT population, unless otherwise specified. No safety population was defined in the statistical analysis plan for either study.

7.1.2 Categorization of Adverse Events

RESOLVE used MedDRA 16.0 and RESOLVE II used MedDRA 17.0. There were no relevant changes between the versions.

For all AE tables, a patient reporting the same AE more than once was counted once when calculating the number and percentage of patients with that event. If a patient reported the same AE more than once or had the same AE on multiple occasions, the maximum severity grade and the strongest relationship to the treatment recorded for the event was presented.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety was pooled for the two, randomized, sham-controlled, single-blinded pivotal studies, RESOLVE and RESOLVE II.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In RESOLVE and RESOLVE II, a total of 254 subjects had one MF Sinus implant placed in each ethmoid sinus with 1350 mcg of mometasone furoate in each implant for a total of 2700 mcg for per patient. An additional 146 subjects underwent a sham procedure. Implants were removed by Day 60. All subjects used background Nasonex 200 mcg (two 50 mcg sprays per nostril) daily.

The planned implant removal date was Day 60 for all subjects; however, 24 implants in RESOLVE (unknown number of subjects) and 11 implants in RESOLVE II (in 10 subjects) were removed. In RESOLVE II, 6 were removed for adverse events, as shown in Table 23. No data was provided for RESOLVE.

In addition to implant removal, implants were also dislodged and expelled prior to Day 60. Generally, the majority of implants in both studies were present at Day 30, however this decreased down to 57% for the RESOLVE study and 70% for the RESOLVE II study at the time of scheduled removed at Day 60. The status of the implants, which includes both removal and dislodgement, at various timepoints for both studies are displayed is summarized in Table 12.

7.2.2 Explorations for Dose Response

Dose response was not assessed in the MF Sinus implant program. The MF Sinus Implant sponsor also markets other sinus implants with lower (370 mcg) mometasone furoate content. These implants are used at the end of surgery. In contrast, the MF Sinus Implant is indicated in lieu of surgery, which makes comparisons difficult.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required to further explore the safety profile of nintedanib

7.2.4 Routine Clinical Testing

RESOLVE had study visits on Days 7, 14, 30, 45, 90, and 6 months. Endoscopic evaluations were performed on Days 14, 30, 60, and 90. Symptom scores and patient-reported outcomes were assessed at various timepoints. Ocular exams were conducted at screening, Day 14, 30, and 45. Adverse events were reported at all visits. At baseline, physical exam, sinus CT scan, and a pregnancy test were conducted. No other clinical testing was included.

RESOLVE II had study visits on Days 14, 30, 60, and 90. These visits included endoscopic evaluations, symptoms scores, blinding questionnaires at Days 30 and 90, and adverse event

reporting. A pregnancy test was conducted at screening and baseline. No other clinical testing was included.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Nasonex intranasal steroid spray is used for the treatment of nasal polyps. The prescribing information for Nasonex includes the following Warning and Precautions (revised 3/2013) include local nasal effects (epistaxis, candida infection, nasal septum perforation, impaired wound healing) glaucoma and cataracts, hypersensitivity reaction, immunosuppression, hypothalamic-pituitary-adrenal axis effects, and effect on growth. Adverse reactions include headache, viral infection, pharyngitis, epistaxis/blood-tinged mucous, coughing, upper respiratory tract infection, dysmenorrhea, musculoskeletal pain, and sinusitis. Other intranasal steroid products include similar safety labeling.

The sponsor did not specifically include these safety issues as adverse events of special interest. Ocular safety was evaluated in the RESOLVE study and will be discussed in Section 7.3.5 Submission Specific Primary Safety Concerns. HPA axis effects and effect on growth are included as class labeling for all corticosteroids, but were not specifically evaluated in this program. This is not concerning given the negligible systemic absorption based on PK assessments.

7.3 Major Safety Results

Safety Results

7.3.1 Deaths

No deaths were reported

7.3.2 Nonfatal Serious Adverse Events

An overview of SAEs for RESOLVE and RESOLVE II are provided in Table 22.

Table 22. Serious Adverse Events (RESOLVE and RESOLVE II; ITT population)

	RESOLVE		RESOLVE II	
PT	MF Sinus Implant N=53	Sham N=47	MF Sinus Implant N=201	Sham N=99
Total patients with adverse events, n (%)	0	1 (2%)	2 (1%)	1(1%)
Suicidal ideation		1		
Asthma			1*	
Streptococcal asthmatic bronchitis			1*	
Epistaxis			1	
Pneumonia				1

*Same patient
Source: CSR RESOLVE, pg. 87, and CSR RESOLVE II, pg. 95

The SAEs of asthma and streptococcal asthmatic bronchitis occurred in 42year-old male with a history of Samter triad (asthma, nasal polyps, and aspirin sensitivity). He was hospitalized on Day 4 with an acute asthma exacerbation and diagnosed with streptococcal asthmatic bronchitis. On Day 48, he was hospitalized for another asthma exacerbation.

The SAE of epistaxis occurred in a 50 year-old male with 4 prior endoscopic sinus surgeries. The epistaxis occurred on Day 40 requiring a visit to the emergency room. The implant was removed and the nose was packed with a hemostatic agent. Epistaxis recurred 39 days later (Day 79) requiring hospitalization and general anesthesia to cauterize the vessel.

The overall occurrence of SAEs was low and similar between groups.

Reviewer comment: Overall, these SAEs do not raise any additional safety concerns given the known safety profile of intranasal steroids. The SAE of epistaxis requiring a surgical procedure is notable. The sponsor proposes to include epistaxis as a Warning and Precautions.

7.3.3 Dropouts and/or Discontinuations

No AEs leading to discontinuation were reported in the RESOLVE or RESOLVE II studies.

The RESOLVE study reported 24 implants removed prior to Day 60 to prevent patient unblinding due to implant migration and risk of expulsion during study visits. No comment was included as to whether implants were removed for adverse events.

No adverse events in RESOLVE II were reported for the 59 subjects that had implant dislodgement. Additionally, 11 implants (in 10 subjects), 8 (in 5 subjects) for adverse events, were removed prior to the protocol assigned Day 60 as listed in Table 23.

Table 23. RESOLVE II Adverse Events in Subjects with Implant Removals			
Number of subjects N=201	**Number of implants N=402**	**Day**	**Adverse Event**
2	2	14	None
2	2	30	None
1	1	50	None
1	1	3	Acute sinusitis
1	1	21	Rhinalgia/nasal pain
1	1	38	Epistaxis
1	2	48	Acute sinusitis
1	1	48	Parosmia/cacosmia
Parosmia/cacosmia=olfactory dysfunction that is characterized by the inability of the brain to properly identify an odor's 'natural' smell. In its place is an unpleasant odor in their place such as burning or a chemical smell. Source: August 4, 2017 Information Request, page 7			

The adverse events that required early implant removal were acute sinusitis, rhinalgia/nasal pain, epistaxis, and parosmia/cacosmia, of which only epistaxis was considered an SAE.

7.3.4 Significant Adverse Events

No specific adverse events of special interest were identified. Ocular safety was assessed in the RESOLVE study and discussed in Section 7.3.5 Submission Specific Primary Safety Concerns below.

7.3.5 Submission Specific Primary Safety Concerns

Ocular

Intraocular pressure and cataract grades were assessed in the RESOLVE study.

Intraocular pressure (IOP)

There were no clinically significant elevations of IOP, defined as an increase of ≥ 10 mm Hg from baseline in either eye, through the Day 90 visit. The mean IOP pressure change from baseline to Day 90 was 0.1 (2.6 SD) in the MF Sinus Implant group compared to -0.6 (2.7 SD) in the sham group.

Lens Opacity

Lens opacity, as measured by change in cataract grade from baseline to Day 90, was similar between treatment arms. Types of cataracts assessed included nuclear sclerosis, cortical cataract, and posterior subscapular cataract.

Reviewer comment: An ophthalmology consult was obtained in 2014. The ophthalmology reviewer reviewed the intraocular pressures from RESOLVE and agreed that they were consistent with the variability seen in normal patients. In the absence of topical application of corticosteroids, elevations of intraocular pressure occur in genetically susceptible subjects after 4-8 weeks of systemically administered corticosteroids. The consult stated that if IOP elevations where going to occur following the use of the MF sinus implant, they should have been observed in the RESOLVE study.

In terms of cataracts, the ophthalmology reviewer noted that while corticosteroids are well known to accelerate the development of cataract formation, the effect is rarely seen in the first nine months following use, even with higher, direct ocular corticosteroid use. Even if the MF Sinus implant were to accelerate cataract development in this patient population, the acceleration would not be observed during the clinical trial. Considering the high likelihood of corticosteroid use in this population sometime during their life, the ophthalmology reviewer noted that it is unlikely that the effect of this product will be able to be separated from the natural history of cataract development in this population. It was recommended to include a warning in the prescribing information of the potential to accelerate cataract development similar to other corticosteroid products.

Based on these findings, the ophthalmology reviewer also agreed that including ocular safety in the RESOLVE II study was unnecessary.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse events with an incidence of >1% and greater than control in the RESOLVE and RESOLVE II studies through Day 90 are listed in Table 24.

Table 24. Common Adverse Events >1% Incidence and More Common than Control (RESOLVE and RESOLVE II; ITT population)

	COMBINED	
Preferred Term	MF Sinus Implant N=254 n (%)	Sham N=146 n (%)
Total patients with adverse events	124 (49)	70 (48)
Asthma	12 (4.7)	6 (4.1)
Headache	9 (3.5)	5 (3.4)
Epistaxis	6 (2.4)	2 (1.4)
Presyncope	6 (2.4)	3 (2.1)
Bronchitis	5 (2.0)	2 (1.4)
Otitis media	5 (2.0)	2 (1.4)
Nasal discomfort	4 (1.6)	0
Nasopharyngitis	3 (1.2)	1 (0.7)

Table 24. Common Adverse Events >1% Incidence and More Common than Control (RESOLVE and RESOLVE II; ITT population)

Source: ISS table 6.1, pg. 45

The incidence of adverse events was reported similarly across treatment groups. Bronchitis, nasopharyngitis, otitis media, headache, presyncope, asthma, epistaxis, and nasal discomfort were the most frequent adverse events, occurring with a 1% incidence and more commonly than the sham control group.

There were 2 (0.8%) AEs of hypersensitivity in the treatment group compared to 1 (0.7%) in the sham group. Two moderate events with the verbatim terms of allergic reaction and bronchitis in the treatment group and a mild allergic reaction in the control group. No other details for these AEs were provided.

In addition, the RESOLVE Study monitored subjects from Day 90 to 6 months. The adverse events reported during this period are summarized in Table 25.

Table 25. Common Adverse Events with an Incidence ≥4% and More Common than Control from Day 90 to 6 months (RESOLVE; ITT population)

	RESOLVE	
System Organ Class/Preferred Term	MF Sinus Implant N=53 n (%)	Sham N=47 n (%)
Total patients with adverse events	16 (30)	16 (34%)
Immune system disorders		
Hypersensitivity	2 (4)	0
Infections and infestations		
Chronic Sinusitis	6 (11)	4 (9)
Upper Respiratory Tract Infection	4 (8)	1 (2)

Source: ISS, Table 7.2, pg. 69-74

The number of adverse events in each group for the Day 90 to 6 month time period was similar. The adverse events were hypersensitivity, chronic sinusitis, and upper respiratory tract infections. Given that the implant was removed at Day 60, it is unlikely that the 2 events of hypersensitivity were directly related to the MF implant.

Reviewer comment: The largest discrepancy between treatment and control was with epistaxis. As epistaxis was also reported as an SAE, this will be included as a Warnings and Precautions in the prescribing information. Epistaxis is a known adverse event with intranasal steroids. Intranasal steroids sprays are also labeled for epistaxis.

7.4.2 Laboratory Findings

As the MF Sinus Implant is a localized therapy and after 30 days of two MF Sinus Implants (one in each side), the plasma concentration of mometasone furoate was negligible, no clinical labs were measured in either the RESOLVE or the RESOLVE II studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were not measured in either the RESOLVE or the RESOLVE II studies.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted with this application.

7.4.6 Immunogenicity

Immunogenicity is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose exploration was conducted.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not evaluated in this clinical development program with the exception of the Day 90 to 6 month adverse event summary provided in Table 25.

7.5.3 Drug-Demographic Interactions

Subgroup analyses for the RESOLVE and RESOLVE II studies were performed through Day 90 for AEs by age, gender, race, and polyp burden.

Several subgroup categories were small. No concerning differences between subgroups were noted.

7.5.4 Drug-Disease Interactions

No drug disease interactions were assessed in this submission.

7.5.5 Drug-Drug Interactions

Formal drug interactions studies were not conducted with the MF Sinus Implant. Due to historical data with mometasone furoate, in vitro studies have confirmed the primary role of CYP3A4 as the primary metabolizer. Therefore, co-administration with ketoconazole, a potent CYP3A4 inhibitor, may increase the plasma concentrations of mometasone furoate.

Additionally, it is unlikely for other drugs likely to be used concomitantly with the MF Sinus Implant, such as steroid nasal sprays, antihistamine nasal sprays, etc., to alter the release rate of MF as the sponsor notes these drugs are delivered to the nasal atrium and not the ethmoid sinus where the implant is placed. These drugs may reach the ethmoid through mucociliary clearance, however the implant is coated with a layer of mucous that will likely minimalize any effects of these concomitant medications.

Further details regarding drug-drug interactions can be found in the clinical pharmacology review by Dr. Yunzhao Ren.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant or lactating women were excluded from the study and no pregnancies were reported.

For further details regarding human reproduction and pregnancy data, including lactation, see the pharmacology-toxicology review from Dr. Luqi Pei.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatrics assessments were excluded from these studies as nasal polyps are extremely rare (0.1%) in the pediatric population. In addition, the proposed indication for this product includes only those patients who have previously undergone endoscopic sinus surgery, which is also not routinely performed in children. The sponsor has included a full waiver for subjects < 18 years of age in this submission.

The sponsor submitted an initial Pediatric Study Plan (iPSP), containing the plans for a full waiver request, in November 2014. After discussions with the Pediatric Review Committee, it was agreed to in February 2015. The Agreed iPSP was submitted in April 2015.

The Division considers the waiver acceptable. The Pediatric Review Committee (PeRC) plans to discuss this NDA on November 15, 2017.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose and drug abuse are not applicable to this submission as the implant will be inserted by a physician and patients will not have direct access to the MF Sinus Implant.

Assessment of withdrawal and rebound were not conducted by the sponsor, as these were all single-use studies.

7.7 Additional Submissions / Safety Issues

7.7.1 Open-label studies

PK Study

Administrative Information

- **Study title:** A Clinical Evaluation of the Steroid-Releasing MF Sinus Implant Used in Post-Sinus Surgery Patients with Recurrent Sinus Obstruction
- **Study dates:** November 4, 2011 to August 6, 2012
- **Study sites:** Single US site

Description

The PK study was a single-center, open-label study in 5 subjects diagnosed with chronic sinusitis who had undergone prior bilateral total ethmoidectomy and who later presented with recurrent sinus obstruction due to sinus polyposis. Subjects were followed for 90 days with visits at Day 3, 7, 14, 21, 30, 60, and 90. Plasma MF concentrations and morning cortisol was measured through Day 30. Bilateral implants were successfully places in all 5 subjects and all subjects completed the study. Subjects were on a 14-day restriction for high-dose steroids (oral steroids, budesonide irrigation, nebulized steroids or budesonide drops) and a 30-day restriction for parenteral steroids. High-dose and parenteral steroids were also prohibited through Day 30. Intranasal steroids were allowed, except Nasonex, which was restricted for the first 30 days. The implants were not removed at any specific date.

Pilot Study

Administrative Information

- **Study title:** A Clinical Evaluation of the Safety and Performance of the Steroid-Releasing MF Sinus Implant When Used in Post-Sinus Surgery Patients with Recurrent Sinus Polyps
- **Study dates:** June 28, 2013 to October 22, 2013
- **Study sites:** 4 US sites

Description

The pilot study was an open-label, multi-center study in 12 subjects with chronic sinusitis who had previously undergone endoscopic sinus surgery that included bilateral total ethmoidectomy and who had presented with recurrent sinus obstruction by nasal polyposis or obstructive mucosal edema and were indicated for repeat endoscopic sinus surgery. Subjects were on a 14-day restriction for high-dose steroids (oral steroids, budesonide irrigation, nebulized steroids or budesonide drops) and a 30-day restriction for parenteral steroids. High-dose and parenteral steroids were also prohibited through Day 30. Subjects continued to use a stabilized regiment of topical intranasal steroid spray for at least 90 days. Implants were removed at Day 60.

Safety results

No deaths, SAEs or AEs leading to discontinuation were reported in the PK or Pilot studies.

Common adverse events were low in frequency (9 total out of the 17 subjects in the PK and Pilot studies) and generally similar to RESOLVE and RESOLVE II.

Clinical labs and ECGS were not included in either of the open-label studies.

Reviewer comment: These open label studies did not reveal any new safety signals.

7.7.2 120-day Safety Update

All study reports were completed at the time of submission. No new information was submitted for the 120-day safety update.

7.7.3 Long-term safety

No long-term safety studies were included in this development program.

7.7.4 Other indications

No other indications for the MF Sinus Implant are planned at this time.

8 Postmarketing Experience

The MF Sinus Implant has never been marketed. Three other implants (Propel, Propel Mini, and Propel Contour) are marketed in the United States by Intersect ENT since August 2011. All 3 Propel sinus implants are indicated for use immediately after sinus surgery. The MF content in the Propel products is also lower (370 ug vs. 1350 ug for MF Sinus Implant).

Acknowledging that the applicability of post-marketing safety findings for the Propel family of sinus implants is limited due to the differing indications of use, as this was the only available

post-marketing safety data for a similar product, we requested the available data, which the sponsor submitted on September 22, 2017.

During the reporting period from August 19, 2011 through June 30, 2017, a total of (b) (4) commercial complaints (US and Ex-US) were reported for the Propel, Propel Mini, and Propel Contour Sinus Implants. During the same period, Intersect ENT shipped a total of (b) (4) units worldwide, which resulted in a worldwide complaint rate of 0.09%. The top 5 complaints reported were: infection, delivery system malfunction, discomfort, implant damage, and crusting.

Intersect ENT has submitted 33 Medical Device Reports (MDRs) from 21 patient events since commercialization in August 2011 through June 30, 2017 for Propel drug-eluting implants. Of the reports submitted by Intersect, 24 were related to Propel, 5 were related to Propel Mini, 4 were unknown product and there were none related to Propel Contour. The summary of the 21 patient events are as follows: 5 reports of infections (4 fungal, 1 bacteremia), 4 reports of implant migration to the throat, 3 scaring/middle turbinate lateralization, 2 periorbital cellulitis, 1 headache, visual acuity and ocular pain, 1 increase in IOP, 1 report of herpes zoster, 1 report of posterior septal perforation, 1 cerebral spinal fluid (CSF) leak, 1 granulomatous (delayed foreign body/allergen-mediated reaction), 1 periorbital edema, pain and blurred vision suspected allergic reaction to implant.

Reviewer comment: The safety information available for the MF Sinus Implant is only for one implant followed for 90 days, and a smaller subset followed for 6 months. It is unlikely that we would see the breadth of these adverse events; however, a post-marketing study will be required to assess the safety of repeated use for the MF Sinus implant. The details of this study are pending at the time of this review.

9 Appendices

9.1 Literature Review/References

1. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 2017; 127: 550-555.
2. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. *Otolaryngol Head Neck Surg* 2004; 130: 157-163.
3. Peters AT, Spector S, Hsu J, Hamilos DL, Baroody FM, Chandra RK, Grammer LC, Kennedy DW, Cohen NA, Kaliner MA, Wald ER, Karagianis A, Slavin RG, Joint Task Force on Practice Parameters rtAAoAA, Immunology tACoAA, Immunology, the Joint Council of Allergy A, Immunology. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol* 2014; 113: 347-385.

9.2 Labeling Recommendations

Trade Name:

The trade name SINUVA was initially found unacceptable due to the orthographic similarity to the currently marketed product, Januvia. The applicant was informed of this decision on December 2, 2016. On January 23, 2017, the applicant submitted a request for reconsideration of the proposed proprietary name as Sinuva and Januvia have different strengths (25 mg, 50 mg, 100 mg vs. 1350 mcg), dose (25 mg, 50 mg, or 100 mg vs. 1350 mcg delivered over 3 months), dosage form (tablets vs. sinus implant), route of administration (oral vs. intranasal), and frequency of administration (once daily vs. single administration). The Division of Medication Error Prevention and Analysis found this to be acceptable on November 8, 2017.

Discussions with the Office of Policy for Pharmaceutical Quality (OPPQ) were held regarding the product name of Sinuva (mometasone furoate) Sinus Implant. The Propel products by Intersect ENT are named Propel (mometasone furoate implant, 370 mcg). For the MF Sinus Implant, the proprietary name, Sinuva, refers to the drug, MF, therefore the decision was made to enclose MF in parenthesis to specify MF as the established name of the drug. The term 'implant' was consistent with the approved Propel implants. The Propel was termed an implant based on the definition of an implant for devices (21 CFR 860.3 (2017): a device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain implanted continuously for 30 days or more). This definition also applies to the MF Sinus Implant.

Suggested Revisions to Proposed Labeling

While the labeling has not been finalized at the time this review is being completed, we have proposed the following general recommendations as summarized in Table 26.

Table 26. Labeling Recommendations

Label Section	General Recommendations
Section 1 Indications and Usage	• Changed indication from (b) (4) to 'treatment of nasal polyps' • Added that there are no studies evaluating repeat administration
Section 2 Dosage and Administration	• Added to be inserted by physicians trained in otolaryngology in the highlights • Noted patients with cystic fibrosis were excluded from the clinical studies • Removed (b) (4)
Section 4 Contraindications	• Simplified to patients with known hypersensitivity to MF or any of the ingredients in the MF Sinus Implant
Section 5	• Moved the ocular W&Ps up to below the local effects, and ocular

Warnings and Precautions	effects are also likely to be local effects • Removed [redacted]
Section 6 Adverse Reactions	• Removed [redacted] • Modified the AE table for incidence >1% (from [redacted]) • Removed [redacted] • Removed [redacted]

Section 14	• Changes to primary efficacy endpoint table
	  • Removed [redacted]
	  • Removed [redacted]
	  • Added the treatment difference and removed [redacted]
	• Removed [redacted] except for percent ethmoid sinus obstruction which is similar to the primary endpoint assessment of polyp grade (which included ethmoid sinus obstruction evaluation in RESOLVE II).

9.3 Advisory Committee Meeting

Other steroid-eluting sinus implants are approved and no specific safety or efficacy concerns were identified; therefore, an Advisory Committee Meeting was not warranted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIYA O PATERNITI
11/13/2017

BANU A KARIMI SHAH
11/13/2017

MEDICAL OFFICER FILING REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 209310	**TRADE NAME:**	S8 Sinus Stent
APPLICANT/SPONSOR:	Intersect ENT	**CATEGORY:**	Corticosteroid
MEDICAL OFFICER:	Miya O. Paterniti, M.D.	**ROUTE:**	Sinus Stent
TEAM LEADER:	Banu Karimi-Shah, M.D.	**FILING DUE DATE:**	May 5, 2017

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
March 7, 2017	March 7, 2017	Original NDA	SD 1, eCTD 0001

REVIEW SUMMARY: This is a medical officer 45-day Filing Review of a 505(b)(2) NDA for the S8 Sinus Stent, which contains 1350 mcg of mometasone furoate, submitted by Intersect ENT, for the treatment of (b) (4) (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery. The reference listed drug (RLD) for this NDA is Asmanex Twisthaler (NDA 021067), a dry-power inhaler for asthma, which contains the (b) (4) form of mometasone furoate. We agreed to a full waiver for pediatric studies in the Agree iPSP, as nasal polyps are extremely rare in children and endoscopic sinus surgery is not routinely performed in children.

This NDA includes two pivotal studies (RESOLVE R500-1113 and RESOLVE II R500-1012) and two supportive studies (pilot study R500-9011-v2, and a PK study R500-0513). RESOLVE is a single-blind, randomized, sham controlled study in 100 subjects randomized 1:1 to bilateral S8 Sinus stents or a sham procedure. All subjects were treated with Nasonex (mometasone furoate) 200 mcg/day. The primary endpoint is change in nasal obstruction/congestion score at Day 90 and change in polyp grade at Day 90. RESOLVE II differs as it enrolled 2x the subjects in the treatment group, the change in nasal congestion/obstruction score was assessed earlier (day 30) to be more consistent with the Nasonex nasal polyp program, the nasal congestion/obstruction score was simplified, the polyp grading was refined to include ethmoid sinus obstruction, and subjects had to have a slightly larger polyp burden at baseline. The submission is provided in eCTD format.

The Applicant has included the necessary elements (21 CFR 314.50) in this NDA, and therefore the submission is fileable.

The filing meeting was held on April 27, 2017. The Division has several issues with this submission. The proposed indication is broad, (b) (4) The Division may also consider a limitation of use for those specialties which perform nasal endoscopy as the S8 Sinus stent is an endoscopically placed device. Additionally, nasal polyps are a chronic condition; however the current submission does include safety for recurrent use. Additional studies may be required to study the safety of recurrent use. These issues will be communicated in the sponsor in the 74-day filing letter.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILEABLE** X	**NOT FILEABLE**	
	APPROVAL	**APPROVABLE**	**NOT APPROVABLE**
OTHER ACTION:	**COMMENTS FOR SPONSOR** X		

Comments for the 74-day letter

These are draft comments and further edits may be made when the 74-day letter is reviewed.

1. (b) (4) and nasal polyps). The indications statement will require revision to include (b) (4), "treatment of nasal polyps".

2. (b) (4)

3. (b) (4) (b) (4) This statement is vague and does not identify the intended user-group. Provide clarification regarding the intended user-group, the limitations to be placed on potential users, and how this information will be conveyed to ensure safe use. If this is already included in the submission, provide its location.

4. Nasal polyps are a chronic condition. Provide clarification as to whether you propose the S8 Sinus Stent for recurrent use. If this information is included in the submission, provide its location. Whether additional studies will be required to study the safety of recurrent use will be a review issue.

Filing Checklist

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			

	Content Parameter	Yes	No	NA	Comment
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	
10	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	
11	Has the applicant submitted a benefit-risk analysis for the product?	x			
12	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505 (b)(2)
DOSE					
13	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			x	
EFFICACY					
14	Do there appear to be the requisite number of adequate and well-controlled studies in the application? RESOLVE and RESOLVE II Indication: Treatment of (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery.	x			
15	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or	x			

	Content Parameter	Yes	No	NA	Comment
	in a manner previously requested by the Division?				
19	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?		x		
23	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28	Has the applicant submitted the pediatric	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	assessment, or provided documentation for a waiver and/or deferral?				
ABUSE LIABILITY					
29	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS – per stats					
31	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34	Are all datasets to support the critical safety analyses available and complete?	x			
35	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

Filing meeting slides

Summary

- Recommendation: Fileable
- 505(b)(2)
  - Asmanex Twisthaler (NDA 021067), DPI for asthma
    (b) (4)
    - Non-clinical safety
    - Clinical pharmacology
- Dose:
  - 1350 mcg mometasone furoate/stent/ethmoid sinus
  - 2700 mcg per patient
- PDUFA date: January 7, 2017

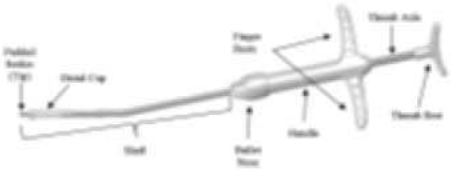
Indication

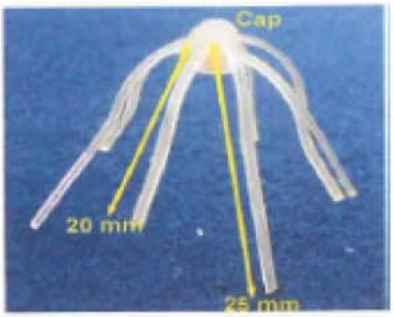
- Current Indication:
  - Treatment of (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery
- Previous Indications:

(b) (4)

S8 Sinus Stent

Delivery System





Contains 1350ug of Mometasone Furoate

(b) (4)

[redacted]

Stent Insertion Procedure

(b) (4)

[redacted]

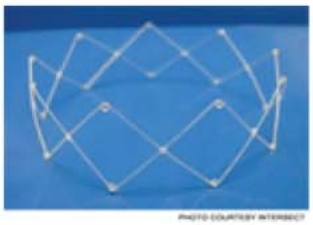
5

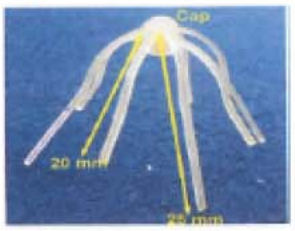
Stent Lifecycle

(b) (4)

6

Comparison to Propel





Parameter	Propel Sinus Implant	S8 Sinus Stent
Indication	At the completion of sinus surgery to maintain sinus patency	Treatment of (b) (4) (b) (4) polyps, who have had ethmoid sinus surgery
MF Content	370ug (b) (4) ug release in first week)	1350ug ((b) (4) ug release in first week) (b) (4)
Length of treatment	(b) (4)	(b) (4)
Polymer	(b) (4)	

7

Nasonex for Nasal Polyps

- Approved to treat nasal polyps in adults
- Mometasone Furoate 400 mcg/nostril daily
- 2 studies in 664 patients with nasal polyps tx x 4 months
  - R, DG, PC, PG
  - 200 mcg daily and 200 mcg BID
- Co-primary endpoints
  - Change from baseline in nasal congestion/obstruction averaged over the **first month** of treatment
    - Study 1 (win both doses), Study 2 (win both doses)
  - Change from baseline to last assessment in bilateral polyp grade during the **entire 4 months** of treatment assessed by endoscopy
    - Study 2 (win both doses), Study 2 (200 mcg daily loss, 200 mcg BID win)

8

Background Regulatory History

- Nasonex (NDA 020762)
  - Approved Oct 1, 1997 for tx nasal polyps
  - Two 50ug sprays per nostril twice daily
- Propel – ethmoid sinus
  - Approved August 11, 2011 (P10044)
  - DPARP consulted

(b) (4)

- Propel Mini (smaller w/same MF content)
  - Approved Sept 2012 (ethmoid sinus) and March 2016 (front sinus)

9

Regulatory History
(IND 116042)

Meeting	Interaction Date	Outcome
Pre-IDE DPARP Consult	Dec 2011	Require RCT which demonstrate that drug and device contribute to effectiveness w/clinically significant endpoints Clarify SAP for oral steroid use Discontinue INS during study due to confounding
Office of Combo Products	June 2012	Consider broader population Interim study could be confirmatory to pivotal study
PIND	Oct 2012	-Modify primary endpoint from (b) (4) to nasal obstruction/congestion score used for nasonex polyp program -Include PK assessment
IND	Dec 2012	-Ocular and infection triggers for early stent removal -Refined ocular exclusion criteria
EOP2	Oct 2014	-evaluate dose dumping potential -prefer nasal polyp score (b) (4) as primary (acknow post surgical changes) -allow rescue OCS or surgery per SOC (b) (4) -INS background (b) (4) -RESOLVE II can be single study (PK, Pilot, RESOLVE as support)

10

Development Program

Study	Design	Duration	Treatment Arms*	N	Population	Efficacy Endpoints
Pilot Study R500-9011 v2 Nov 2011 – Aug 2012	OL	60 days (6 month f/u)	S8 Sinus Stent + stable intranasal steroid spray	12	CS and recurrent sinus obstruction following ESS	Device placement success Safety
PK Study *R500-0513 Jun 2013 – Oct 2013*	OL	90 days (90 day f/u)	S8 Sinus Stent	5	CS with bilateral ethmoidectomy w/ recurrent sinus obstruction due to sinus polyps	PK, safety
RESOLVE R500-1113 Jan 2013 - May 2014	SB, R, PG, CC	60 days (6 month f/u)	S8 Sinus Stent Sham + nasonex (MF) 200 mcg/day	53 47	CS with bilateral ethmoidectomy w/ recurrent sinus obstruction due to sinus polyps	Change in nasal obstruction/congestion score @ Day 90 Change in polyp grade @ day 90
RESOLVE II R500-1012 Dec 2014 – Aug 2016	SB, R, PG, CC	60 days (6 month f/u)	S8 Sinus Stent Sham + nasonex (MF) 200 mcg/day	201 99	CS with bilateral ethmoidectomy w/ recurrent sinus obstruction due to sinus polyps	Change in nasal obstruction/congestion score @ Day 30 Change in polyp grade @ day 90

*S9® Sinus Stent with 1350 mcg mometasone furoate (MF); intranasal steroid spray administered for 90 days
Source: Table of clinical studies

11

Secondary Endpoints

RESOLVE	RESOLVE II
%ethmoid sinus obstruction (Day 90 and all time pts)	%ethmoid sinus obstruction (Day 90 and all time pts)
Bilateral polyp grade (all time pts)	Bilateral polyp grade (all time pts)
Middle turbinate position (all time pts)	
Adhesion/scarring presence and severity (all time pts)	
SNOT-22, NOSE, PPQ, WPAI (all time pts)	Instant Nasal Obstruction/Congestion score (Day 60/90)
	Reflective Nasal Obstruction/Congestion score (Days 14, 30, 60, and 90)
	Reflective Rhinosinusitis Symptom Inventory (bsl/day 90)
	Need for OCS (bsl, day 90, all time pts)
Patient blinding questionnaire (Day 30/90)	Patient blinding questionnaire (Day 30/90)*
Implant delivery success*	Implant delivery success*
Reduction in the proportion of pts indicted for ESS(Day 90/6m)*	Proportion of pts still indicated for ESS (Day 90)
*Additional endpoints	

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Polyp Grading Scale

5-Point Scale (RESOLVE)	8-Point Scale (RESOLVE II)
0: No visible nasal polyps (NP)	0: No visible sinonasal polyps
1: Small amount NP confined in middle meatus (clinically insignificant, not requiring treatment)	1.0: Small amount of sinonasal polyps confined in middle meatus
NA	1.5: Small amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 25% of the ethmoid sinus cavity
2: Expanded amount of NP confined in middle meatus	2.0: Expanded amount of sinonasal polyps confined in middle meatus
NA	2.5: Expanded amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 50% of the ethmoid sinus cavity
3: NP extending beyond middle meatus, within the sphenoethmoid recess not totally obstructing, or both	3.0: Sinonasal polyps extending beyond middle meatus but not totally obstructing the nasal cavity
NA	3.5: Sinonasal polyps extending beyond middle meatus with expanded amount of polypoid edema obstructing ≥75% of the ethmoid sinus cavity
4: NP completely obstructing the nasal cavity	4.0: Sinonasal polyps completely obstructing the nasal cavity

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Nasal Obstruction/Congestion Score

6-Point Scale (RESOLVE)	4-Point Scale (RESOLVE II)
0: No symptoms	0: No symptoms
1: Very mild 2: Mild or slight problem	1: Mild symptoms (symptoms clearly present, but minimal awareness, and easily tolerated)
3: Moderate problem	2: Moderate symptoms (definite awareness of symptoms that is bothersome but tolerable)
4: Severe problem 5: Problem as bad as it can be	3: Severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living)

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Chronic Rhinosinusitis Diagnosis

- The 2007 Multi-disciplinary Adult Sinusitis Guidelines define CRS as follows:
- 12 weeks or longer of two or more of the following signs and symptoms:
  - Mucopurulent drainage (anterior, posterior, or both)
  - Nasal obstruction/congestion
  - Facial pain-pressure-fullness
  - Decreased sense of smell
- And inflammation is documented by one or more of the following findings:
  - Purulent (not clear) mucus or edema in the middle meatus or ethmoid region,
  - Polyps in nasal cavity or the middle meatus and/or,
  - Radiographic imaging showing inflammation of the paranasal sinuses

Rosenfeld RM, Andes D, Bhattacharyya N, et al. 2007 Clinical practice guideline: Adult sinusitis. Otolaryngol Head Neck Surg; 137: S1-S31

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Study Population: Inclusion

P500-1012 (RESOLVE)	P500-1113 (RESOLVE II)
Key Inclusion Criteria	
Confirmed diagnosis of CRS	Confirmed diagnosis of CRS
Bilateral total ethmoidectomy ≥ 90 days prior to screening	Bilateral total ethmoidectomy ≥ 90 days prior to screening
(b) (4)	Nasal Obstruction/Congestion score by daily diary, with min 2 on at least 5 of 7 days, despite use of INS irrigations or sprays for at least 14 days preceding scoring (b) (4)
Indicated for a repeat ESS. Per the study definition, patient must have: • Min score 2 on at least 2 of the 5 hallmark symptoms of CRS on SNOT-22; • Persistent symptoms of CRS despite ongoing treatment with INS irrigations or sprays for at least 2 weeks preceding enrollment; • Had treatment with a high-dose form of steroids and/or sinus steroid irrigations within the preceding 2 years, or refused such therapy; • A known history of repeated courses of treatment with high-dose steroid therapy; and • Endoscopic evidence of polyp recurrence, scarring and/or obstructive mucosal edema.	Indicated for repeat ESS. Per the study definition, patient must have: • Complaints of at least 2 of the 5 hallmark symptoms of CRS; • Endoscopic evidence of bilateral sinus obstruction due to polyposis (min grade 2 on each side, as determined by an independent reviewer); and • Had a documented treatment with a high-dose form of steroids (e.g., oral, parenteral, injection into polyps) and/or sinus steroid irrigations within the preceding 1 year, or refused such therapy due to side effects.
Able to tolerate the use of Nasonex topical intranasal steroid spray once daily	Able to tolerate the use of Nasonex intranasal steroid spray once daily

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Study Population: Exclusion

Key Exclusion Criteria	
Adhesions/synechiae grades 3 or 4	Adhesions/synechiae grades 3 or 4
Polyp grade 4	Polyposis grade 1, 1.5 or 4 on either side ★
Completely resected middle turbinate	NA (resected middle turbinate wasn't exclusionary based on clinician feedback from RESOLVE) ★
Oral-steroid dependent condition	Oral-steroid dependent condition
History of allergy or intolerance to corticosteroids or mometasone furoate	History of allergy or intolerance to corticosteroids or mometasone furoate
History or diagnosis of glaucoma, ocular hypertension (baseline or a known prior ocular exam indicating IOP >21 mmHg), closed angle, or cataract (grade 3 or higher)	History or diagnosis of glaucoma or ocular hypertension (prior ocular exam with IOP >21 mmHg and pressure lowering medication given) or posterior subcapsular cataract

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Demographics

RESOLVE and RESOLVE II (ITT population)		
	Treatment N=254	**Control N=146**
Sex, n (%)		
Male	156 (61.4%)	87 (59.6%)
Female	98 (38.6%)	59 (40.4%)
Race, n (%)		
White	211 (83.1%)	124 (84.9%)
African American	33 (13.0%)	15 (10.3%)
Asian	4 (1.6%)	5 (3.4%)
Other	2 (2.0%)	6 (2.4%)
Age in Years		
Mean (SD)	49.9 (12.84)	49.1 (12.69)
Min-Max	19-86	21-82
Source: SCS, Table 5, pg 15		

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Baseline Clinical Characteristics

RESOLVE and RESOLVE II (ITT population)		
	Treatment N=254	**Control N=146**
Number of prior ESS procedures		
1	105 (41.3%)	57 (39.0%)
2	69 (27.2%)	51 (34.9%)
3	41 (16.1%)	15 (10.3%)
≥4	39 (15.4%)	23 (15.8%)
Bilateral polyp grade Mean (SD)	5.4 (1.02)	5.0 (1.14)
%Ethmoid Sinus Obstruction Mean (SD)	74 (18)	67 (22)
Source: SCS, Table 5, pg 15		

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Disposition

RESOLVE and RESOLVE II						
	RESOLVE		RESOLVE II		Combined	
	Treatment	Control	Treatment	Control	Treatment	Control
Randomized population	53	47	201	99	254	146
ITT Population	53	47	201	99	254	146
Number of unsuccessful sinus implant attempts (2 per person)	0	1 (1.1%)	4 (1%)	0	4 (0.8%)	1 (0.3%)
Completers	52 (98%)	46 (98%)	200 (99%)	98 (99%)	252 (99%)	144 (9%)
Prematurely discontinued **from study**	1 (2%)	1 (2%)	1 (1%)	1 (1%)	2 (1%)	2 (1%)
Adverse Event	0	0	0	0	0	0
Withdrew from study	1 (2%)	1 (2%)	0	1 (1%)	1 (0.4%)	2 (1.4%)
Lost to follow-up	0	0	1 (1%)	0	1 (0.4%)	0
Source: SCS						

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Blinding Questionnaire

RESOLVE **Table 15: Patient Blinding Questionnaire (N = 100)**

Assignment	Patient Believed He/She was in: Treatment	Control	Don't Know	BI (95% CI)
Day 30				
Treatment (N=53)	33 (62.3%)	5 (9.4%)	15 (28.3%)	0.53 (0.35, 0.71)
Control (N=47)	15 (31.9%)	12 (25.5%)	20 (42.6%)	-0.06 (-0.28, 0.16)
Day 90				
Treatment (N=52)	42 (80.8%)	5 (9.6%)	5 (9.6%)	0.71 (0.54, 0.88)
Control (N=46)	16 (34.8%)	15 (32.6%)	15 (32.6%)	-0.02 (-0.26, 0.22)

RESOLVEII **Table 21: Patient Blinding Questionnaire – ITT Population**

	Patient believes he/she was in: Treatment		Control			
Assignment	Strongly Believe	Somewhat Believe	Strongly Believe	Somewhat Believe	Don't Know	BI (95% CI)
Day 30						
Treatment	74 (36.8%)	59 (29.4%)	8 (4.0%)	24 (11.9%)	36 (17.9%)	0.50 (0.40, 0.60)
Control	25 (25.3%)	22 (22.2%)	15 (15.2%)	19 (19.2%)	17 (17.2%)	-0.13 (-0.31, 0.05)
Day 90						
Treatment	117 (58.5%)	38 (19.0%)	12 (6.0%)	12 (6.0%)	20 (10.0%)	0.66 (0.57, 0.75)
Control	24 (24.5%)	25 (25.5%)	20 (20.4%)	15 (15.3%)	14 (14.3%)	-0.14 (-0.32, 0.04)

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Primary Endpoint

Change from Baseline	P500-1113 (RESOLVE II)		P500-1012 (RESOLVE)	
	Treatment (N = 201)	Control (N = 99)	Treatment (N = 53)	Control (N = 47)
Nasal Obstruction/Congestion Score[a]				
N	199	97	52	45
Mean (SD)	-0.80 (0.729)	-0.56 (0.619)	-0.85 (0.998)	-0.44 (0.967)
95% CI[b]	-0.39, -0.06		-0.57, 0.13	
P-value[b]	**0.0074** ✓		0.2217 ✗	
Bilateral Polyp Grade[c]				
N	195	97	51	47
Mean (SD)	-0.56 (1.059)	-0.15 (0.907)	-0.76 (0.875)	-0.38 (0.998)
95% CI[b]	-0.60, -0.09		-0.70, 0.06	
P-value[b]	**0.0073** ✓		0.0985 ✗	

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Safety

- No deaths
- 2 SAEs in treatment (asthma and streptococcal asthmatic bronchitis) and 2 SAEs in placebo (pneumonia and suicidal ideation)
- No discontinuations due to AEs

Common AEs reported in ≥ 1% greater in Treatment than control (ITT population)		
	n (%)	
SOC/PIs	Treatment N=254	Control N=146
Patients with AEs	124 (49%)	70 (48%)
Respiratory, thoracic, and mediastinal disorders	31 (12%)	14 (9.6%)
Epistaxis	6 (2.4%)	2 (1.4%)
Nasal discomfort	4 (1.6%)	0
Ear infection	5 (2%)	0

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Optho Safety

- RESOLVE study included IOP and cataract assessment – no findings
- Optho Device consult
  - If IOP elevations were going to occur, RESOLVE study would show this.
  - No need to monitor in RESOLVE II as cataract would occur outside of clinical trial time
  - Include warning of the potential to accelerate cataract development in label

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PeRC

- Agreed iPSP for full waiver
  - Nasal polyps are extremely rare in children
  - Endoscopic sinus surgery not routinely performed in children

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Label

- Needs PLLR updating
- Section 2: Limitations of use?
- Section 6: Need to add common AE table
- Section 14: RESOLVE and RESOLVE II (includes combined data)

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Planning

- Unireview vs. Traditional
- CDRH engineering consult
- CDRH clinical consult not needed
- Inspection
  - RESOLVE 18 sites (n=100)
    - Max 20 patients enrolled at each site
  - RESOLVE II 36 sites (n=300)
    - One site (#31) n=33 (largest)
    - 11 (30%) sites ≥ 10 subjects

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIYA O PATERNITI
05/04/2017

BANU A KARIMI SHAH
05/05/2017