CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209310Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review/ Division Director Summary

Date	December 8, 2017
From	Banu A. Karimi-Shah, MD Lydia Gilbert-McClain, MD
Subject	Cross-Discipline Team Leader Review Division Director Summary Review
NDA/BLA # Supplement#	NDA 209310
Applicant	Intersect ENT
Date of Submission	March 7, 2017
PDUFA Goal Date	January 7, 2018
Proprietary Name / Established (USAN) names	Sinuva (mometasone furoate) Sinus Implant
Dosage forms / Strength	Sinus Implant containing 1350 mcg of mometasone furoate
Proposed Indication(s)	Treatment of (b) (4) [redacted] (b) (4) [redacted] pol ethmoid sinus surgery
Approved Indication	Treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery
Recommended:	***Approval***

1. Introduction

Intersect ENT (the Applicant) submitted a 505(b)(2) New Drug Application (NDA) 209310 on March 7, 2017, for the Sinuva Sinus Implant for the treatment of nasal polyps in patients 18 years of age and older who have had ethmoid sinus surgery. Of note, the Applicant had initially proposed an indication (b) (4) [redacted]

The Sinuva Sinus Implant is a drug-device combination product comprised of a self-expanding, bioabsorbable, drug-eluting, sinus implant coated with 1350 mcg of mometasone furoate (MF). The implant is designed to gradually release 1350 mcg of MF over 90 days; it is also designed to physically open the middle meatus and ethmoid sinus, where it is placed under endoscopic visualization. The Sinuva Sinus Implant is to be inserted by physicians trained in otolaryngology. Given that the product is designed to be used in lieu of surgery, and the high dose of MF with which the implant is coated is exerting the primary effect of the product, the anti-inflammatory action of the corticosteroid was determined to be the primary mode of action;

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therefore, the jurisdiction of the product was determined to be within the Center for Drug Evaluation and Research (CDER).

To support the efficacy and safety of the Sinuva Sinus Implant, Intersect ENT conducted a development program which consisted of 2 studies, RESOLVE (also referred to as Study 1 in the package insert) and RESOLVE II (Study 2, package insert). This memorandum provides an overview of the application, summarizing the data which demonstrate the safety and efficacy of the Sinuva Sinus Implant, as well as the recommendations of each of the individual review disciplines/consultants.

2. Background

Nasal polyps are a chronic condition characterized by eosinophilic inflammatory outgrowths of the nasal mucosa, often occurring bilaterally along the middle and superior meatus. An estimated 4% of the general population develops nasal polyps. The disease primarily affects adults and while not life-threatening, nasal polyps can cause nasal obstruction, facial pain, hyposmia, and rhinorrhea, and have significant impact on quality of life. Treatment of nasal polyps can be difficult, and typically includes both medical and surgical therapy aimed at either complete elimination of the polyps or sufficient reduction in polyp size to alleviate nasal obstruction and associated symptoms. Medical therapy is largely limited to use of intranasal, and if refractory, systemic corticosteroids. If unsuccessful, surgical treatment is an alternative, but post-surgical recurrence occurs in up to 10% of patients. Currently, there are three corticosteroid-containing nasal spray products approved to treat or prevent recurrence of nasal polyps; beclomethasone dipropionate (Beconase AQ, NDA 19389), mometasone furoate (Nasonex, NDA 20762), and fluticasone propionate (Xhance, NDA 209022).

MF, the active ingredient in the Sinuva Sinus Implant, is available as inhaled (Asmanex Twisthaler/Asmanex HFA; in combination with formoterol fumarate in Dulera), intranasal (Nasonex), and topical formulations (Elocon, Elocom, and Elomet). MF is also used as the corticosteroid in three other marketed sinus implants: Propel, Propel-mini, and Propel Contour. In the case of the Propel implants, these are inserted post-sinus surgery to prevent adhesions and maintain patency. These implants contain a low dose of MF (370 μg) which plays a secondary anti-inflammatory role. The device function of these implants is the primary mode of action; therefore, the Propel family of implants is under the jurisdiction of the Center for Devices and Radiologic Health (CDRH).

Relevant Regulatory History for the Sinuva Sinus Implant
The development of the Sinuva Sinus Implant was subject to the usual milestone meetings under IND 116,042. Key regulatory interactions included:

- Pre-IND Meeting: October 2012
- IND opened: December 2012
- End-of-Phase 2 (EOP2) Meeting: October 2014

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During these meetings, advice was provided regarding choice and evaluation of primary endpoints, as well as the need for appropriate background/rescue therapy throughout the conduct of the studies. Specifically, at the EOP2 meeting, the Division agreed with changing the evaluation of the nasal congestion score in RESOLVE II from Day 90 (in RESOLVE) to Day 30. In addition, it was agreed that, if successful, the RESOLVE II study could serve as a single efficacy study for this application, with support from the RESOLVE study. A Pediatric Study Plan (with a full waiver of studies in patients < 18 years of age) was also agreed upon and submitted in April 2015.

3. CMC/Device

The recommended action from a CMC/Device perspective is Approval. There are no outstanding issues at this time.

The Sinuva Sinus Implant is a drug-device combination product comprised of a self-expanding, bioabsorbable, drug-eluting, sinus implant coated with 1350 mcg of mometasone furoate (MF). The implant is 20 mm in length and 34 mm in diameter. A crimper which holds the implant in the product packaging and compresses the implant for loading into the delivery system, and a single-use delivery system, are included in product packaging. The shaft length of the delivery system is 117 mm to deploy the implant into the ethmoid sinus (see Figure 1). The MF is embedded in a bioabsorbable polymer matrix containing (b) (4) poly (DL-lactide-co-glycolide) and polyethylene glycol, which provides for gradual release of the MF. The Sinuva Sinus Implant is sterilely packaged in a tray, which is then sealed in a foil pouch and placed in the product carton.

Figure 1. Sinuva Sinus Implant (left panel), Crimper with Loaded Implant (middle panel), and Delivery System (right panel)

Mometasone furoate (MF), the drug component of the Sinuva Sinus Implant, is a well-known glucocorticoid compound that has been previously used as the active ingredient for several marketed inhaled, intranasal, and topical products. The drug substance, mometasone furoate (b) (4) is a white to off-white powder, which is soluble in acetone and dichloromethane, slightly soluble in ethanol, and practically insoluble in water. The drug substance is manufactured, tested, and packaged by (b) (4) Detailed information on the chemistry, manufac ferenced to (b) (4) Drug Master File (DMF) (b) (4) which was reviewed and found to be adequate.

The Sinuva Sinus Implant container closure system consists of the crimper, labeled foil pouch, tray/lid, (b) (4), and product carton/box. The

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registration stability data support the Applicant's proposed expiration date of 24 months for the finished product when stored in the commercial packaging (protected from light) at controlled room temperature.

- CDRH Review

CDRH was also consulted to evaluate the device aspects of the Sinuva Sinus Implant; the CDRH review evaluated design verification testing, biocompatibility, sterilization validation, manufacturing information, and quality management system documentation and found these components to be acceptable. The CDRH review concluded that from a device standpoint, the implant poses low risk in that it is not permanent; it is also composed of materials that are similar to the Applicant's own family of approved products, which have a well-characterized safety profile over several years of use on the market. CDRH also provided several labeling recommendations for the carton/container, which were conveyed to and incorporated by the Applicant.

- Facilities

All manufacturing and testing facilities associated with the drug product have acceptable establishment evaluation status.

(b) (4) is the proposed drug substance manufacturer for MF. The most recent inspection of (b) (4) was completed in (b) (4). Intersect ENT (Menlo Park, CA) is the proposed manufacturer of the Sinuva Sinus Implant. The majority of the sites (including the contract testing and sterilizing laboratories) were found to be acceptable based on their inspectional history. A pre-approval inspection (PAI) of Intersect ENT was conducted October 30 to November 3, 2017, focusing primarily on the drug coating process, since the firm had been previously inspected for similar products from a device perspective in April 2017. While there were several 483 observations noted regarding the (b) (4) coating process, location of lot history records, and the absence of a defect library to train operators to visually inspect the implant, subsequent responses from the Applicant have mitigated several of these concerns, and for the remaining observations, the Applicant has adequate corrective actions planned to be completed by February 2018. Therefore, from the facilities perspective, the application is also found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical issues at this time.

The Applicant refers to the reference listed drug, Asmanex Twisthaler, (marketed under NDA 21-067, approval date March 30, 2005), which utilizes the same active pharmaceutical ingredient, MF. A complete nonclinical program was previously conducted for MF; therefore, no new nonclinical pharmacology or toxicology studies were conducted or required to directly

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support the safety of mometasone furoate in the Sinuva Sinus Implant. Based upon the Agency's previous findings of safety and efficacy for the reference listed drug, there is sufficient information from the nonclinical perspective to recommend approval. The nonclinical team evaluated and proposed edits to the pertinent sections of the label, recommending adoption of the nonclinical sections of the Asmanex HFA label, because it is compliant with the Pregnancy Lactation Labeling Rule (PLLR), and the nonclinical section of all MF product labels are based on the same set of nonclinical data.

5. Clinical Pharmacology/Biopharmaceutics

The recommended regulatory action from a Clinical Pharmacology perspective is Approval. There are no outstanding clinical pharmacology issues at this time.

To support this NDA submission, the Applicant provided information from one clinical pharmacology study, Study R500-0513, a single-center, open-label study treating five adult patients diagnosed with chronic sinusitis with prior bilateral total ethmoidectomy who presented with recurrent sinus obstruction due to sinus polyposis. All patients received bilateral Sinuva Sinus Implants and were followed for 3 months. In total, six blood samples for measuring MF plasma concentrations were collected from each subject during a 30-day period following the implantation.

A cross-study PK comparison of MF between the Sinuva Sinus Implant and Asmanex Twisthaler demonstrated that the systemic exposure ($AUC_{0\text{-}12h}$) of MF during the first 3 weeks following placement of the Sinuva Sinus Implants (the period that MF had the highest release rate) was generally comparable to the systemic exposure achieved with inhaled administration of Asmanex Twisthaler 440 µg twice daily BID (highest approved dosing regimen). As the MF release rate from the implant declines with time, the MF systemic exposure is also expected to decrease with time. Therefore, from a clinical pharmacology perspective, the systemic safety profile of the Sinuva Sinus Implant at the proposed dosing regimen [i.e., bilateral implantation in the ethmoid sinus (with each implant containing 1350 µg MF) is covered by the known systemic safety profile following Asmanex Twisthaler administration at the highest approved dose.

6. Clinical Microbiology

Non-applicable.

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7. Clinical/Statistical-Efficacy

Overview of the clinical program

The clinical program to support the Sinuva Sinus Implant for the treatment of nasal polyps in patients 18 years of age and older who have had ethmoid sinus surgery consisted primarily of two studies, a trial of 6 months' duration (RESOLVE, Study 1) and another trial of 90 days' duration (RESOLVE II, Study 2). The efficacy of SINUVA Sinus Implant is based primarily on Study 2 as described below in Table 1. This memorandum summarizes the main results from these studies.

Table 1. Sinuva Sinus Implant Clinical Development Program

Study ID Study Dates	Design	Study Duration[1]	Treatment Arms (mcg)[2]	N[3]	Co-Primary Endpoints
RESOLVE P500-1113 *(Study 1)** *Jan 2013 – May 2014*	SB, R, PG, CC	6 months	• Sinuva Sinus Implant • Sham†	53 47	Change in nasal obstruction/ congestion score @ Day 90 Change in polyp grade @ Day 90
RESOLVE II P500-1012 *(Study 2)** *Dec 2014 – Aug 2016*	SB, R, PG, CC	90 days	• Sinuva Sinus Implant • Sham†	201 99	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 (200 mcg/day) was administered at least through Day 90, [3]Intent-to-treat
† sham consisted of advancement of the delivery system with the implant into the ethmoid sinuses, followed by removal of the delivery system without deployment of the implant
Note: All study sites were in the US
*Study ID as referenced in the package insert

RESOLVE and RESOLVE II were similarly designed randomized, single-blind, parallel group concurrently-controlled, multicenter US studies in subjects 18 years of age and older with chronic sinusitis who had undergone prior bilateral total ethmoidectomy, but were indicated for revision endoscopic sinus surgery because they presented with recurrent nasal obstruction/ congestion symptoms and recurrent bilateral sinus obstruction due to sinonasal polyposis. Patients were screened for eligibility and then either had one Sinuva Sinus Implant inserted bilaterally into each ethmoid sinus or underwent a sham procedure, consisting of advancement of the delivery system with the implant into the ethmoid sinuses, followed by removal of the delivery system without deployment of the implant. Patients were also blindfolded and wore earmuffs to maintain adequate blinding during the studies. All patients were required to use MF nasal spray (Nasonex; 50 mcg, 2 sprays each nostril = 200 mcg daily) as background therapy through at least Day 90. Subjects were excluded for grade 3 or 4 adhesions/synechiae, grade 4 polyposis, known history of resistant or poor response to oral steroids, acute bacterial or invasive fungal sinusitis, and immune deficiency, including cystic fibrosis. Key differences in the study designs are noted below.

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RESOLVE

RESOLVE was a 6-month study in 100 subjects (~50 per group). 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. The co-primary efficacy endpoints were change from baseline nasal congestion/ obstruction score (based on a 0-5 score) and bilateral polyp grade (based on a 0-4 score) measured at Day 90. Ocular safety assessments (e.g., intraocular pressure, visual acuity, and cataract assessments) were also included.

RESOLVE II

RESOLVE II was similar in design to RESOLVE, but was shorter in duration (90 days), and included more subjects (201 for the Sinuva Sinus Implant group and 99 for the control (sham) group). Study visits occurred every 2 weeks through Day 30, and then monthly through Day 90. Endoscopic grading and symptoms assessments were done at every visit, with the independent, blinded panel assessments occurring at baseline and Day 90.

In RESOLVE II, patients had a higher polyposis grade, and the polyp grade score was changed from a 5-point scale (RESOLVE) to an 8-point scale (measured from 0 to 4 with 0.5 point increments) 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. In addition, subjects were required to have a minimum nasal congestion/obstruction score of 2 despite use of intranasal steroids (compared to no minimum score required in RESOLVE). The nasal obstruction/congestion score was also simplified to a 0 to 3 point scale.

The co-primary efficacy endpoints were: change from baseline to Day 30 in nasal obstruction/congestion score (based on a 0-3 score), as determined by patients using a daily diary; and change from baseline to Day 90 in bilateral polyp grade (based on a 0-4 score, with 0.5 point increments), as determined from video-endoscopies reviewed by an independent panel of 3 sinus surgeons who were masked to treatment assignment.

Efficacy Results

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%). In RESOLVE II, the treatment group had a higher proportion of asthma patients (74% vs. 62%) and a higher mean Percent Ethmoid Sinus Obstruction score [76 (SD 17.4) vs. 69 (SD 19.9)]. However, the random imbalances did not impact treatment effect. For both studies, with respect to subject disposition, 98-99% of subjects completed the studies. The results of the co-primary efficacy endpoints are shown in Table 2 below.

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Table 2. Co-primary Efficacy Endpoints: Change from Baseline in Nasal Obstruction/Congestion Score and Bilateral Polyp Grade -RESOLVE and RESOLVE II (ITT Population)

	RESOLVE		RESOLVE II	
	Sinuva Sinus Implant N=53	Sham Control N=47	Sinuva Sinus Implant N=201	Sham Control N=99
Instantaneous Nasal Obstruction/Congestion Score[a]				
Baseline, Mean (SD)	3.62 (1.18)	3.30 (1.16)	2.36 (0.49)	2.35 (0.48)
Change from Baseline†, Mean (SD)	-1.33 (1.47)	-0.67 (1.45)	-0.80 (0.73)	-0.56 (0.62)
Treatment Difference vs. Control (95% CI)[b]	-0.40 (-0.93,0.13)		-0.23 (-0.39, -0.06)	
2-sided p-value	0.14		0.0074	
Bilateral Polyp Grade[c]				
Baseline, Mean (SD)	4.90 (0.92)	4.39 (1.45)	5.48 (1.13)	5.43 (1.01)
Change from Baseline, Mean (SD)	-0.76 (0.88)	-0.38 (1.00)	-0.56 (1.06)	-0.15 (0.91)
Treatment Difference vs. Control (95% CI)[b]	-0.32 (-0.70, 0.06)		-0.35 (-0.60, -0.09)	
2-sided p-value	0.10		0.0073	

a) Nasal obstruction/congestion scores:
- RESOLVE (0-5 scale): 0-no problem, 1-very mild, 2-mild or slight, 3-moderate, 4-severe, 5-as bad as it can be
- RESOLVE II (0-3 scale): 0-no symptoms, 1-mild, 2-moderate, 3-severe
†Nasal obstruction/congestion scores measured at Day 90 in RESOLVE and Day 30 in RESOLVE II
b) Based on analysis of covariance (ANCOVA) model with baseline value as a covariate and site and treatment group as fixed effects.
c) Change from baseline to Day 90 in bilateral polyp grade was assessed based on grading of video-endoscopies by an independent panel of 3 sinus surgeons who were blinded to treatment assignment. Polyps were graded as follows: 0=no visible polyps, 1=Small amount of sinonasal polyps confined in middle meatus, 1.5= 1+ polypoid edema obstructing ≥ 25% of the ethmoid sinus cavity, 2=Expanded amount of sinonasal polyps confined in middle meatus, 2.5 = 2 + 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= 3 + polypoid edema obstructing ≥ 75% of the ethmoid sinus cavity, 4=Sinonasal polyps completely obstructing the nasal cavity. The score of 0-4 was the same for RESOLVE and RESOLVE II, but RESOLVE II was on an 8-point scale (compared to a 5-point scale for RESOLVE) as the score included 0.5 increments
Last-observation carried forward imputation used for subjects that were rescued with oral steroids or surgery
Source: FDA Analysis of data submitted with NDA 209310

In RESOLVE, neither of the co-primary efficacy endpoints was statistically significantly different than the sham control group, although they numerically favored the Sinuva Sinus Implant treatment group for both endpoints. In RESOLVE II, the co-primary efficacy endpoints showed a statistically significant improvement in both nasal obstruction/congestion score and bilateral polyp grade in patients treated with the Sinuva Sinus Implant as compared with the sham control group.

From a statistical standpoint, there was very little missing data due to few study discontinuations. For subjects who had one or both implants removed or who had rescue interventions (oral steroids or sinus surgery), video endoscopies from the visit prior to rescue were imputed at the Day 90 timepoint (Last Observation carried Forward (LOCF)). This approach was planned in the protocol as "intervention-adjusted" values. Because the treatment was administered at a single time, this methodology is acceptable. This also represents a Worst Observation Carried Forward (WOCF) scenario in that the need for intervention was determined by poor response on the efficacy assessments. For subjects who had the implants dislodge spontaneously between Day 30 and Day 60 no imputation was needed, as the implants were scheduled to be removed at the Day 60 visit by the clinician prior to video endoscopies at the Day 90 visit.

Secondary efficacy endpoints included percent ethmoid sinus obstruction, proportion of patients still indicated for repeat endoscopic sinus surgery (ESS), decreased sense of smell, facial pain/pressure, the reflective nasal obstruction/congestion score evaluated at additional time points, and the bilateral polyp grade evaluated at additional time points. In RESOLVE II, of the

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secondary endpoints listed above, percent ethmoid sinus obstruction, proportion of patients still indicated for repeat ESS, decreased sense of smell, and assessment of nasal obstruction/congestion at Days 30 and 60 and bilateral polyp grade at Days 30, 60, and 90 demonstrated statistically significant results in favor of the Sinuva Sinus Implant treatment group. While some of these secondary endpoints were also evaluated in RESOLVE (with the exception of decreased sense of smell and facial pain/pressure), the co-primary efficacy endpoints were not statistically significant in the RESOLVE study; therefore, conclusions from the secondary endpoints in RESOLVE are not statistically valid. As the results for secondary endpoints were not replicated in this clinical development program, labeling claims based on these endpoints are not supported. However, as percent ethmoid sinus obstruction is representative of the co-primary endpoint of nasal obstruction/congestion and polyp grade, this has been included in the package insert:

- Change from baseline to Day 90 in the mean Percent Ethmoid Sinus Obstruction score (100 mm VAS), as judged by the independent panel [Difference vs. control: -7.96%; 95% CI (-12.1, -3.8)], met statistical significance and supported the co-primary endpoints.

Efficacy Conclusions

RESOLVE and RESOLVE II were similarly designed studies, enrolled the same population of patients, and included similar efficacy measurements. While the results of RESOLVE were supportive to the overall program, the study did not demonstrate a statistically significant difference between treatment and sham groups, although the results numerically favored the Sinuva Sinus Implant group. The Applicant used the RESOLVE study to inform the design of RESOLVE II; RESOLVE II 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 Sinuva Sinus Implant was 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 Sinuva Sinus Implant for the treatment of nasal polyps, using the co-primary endpoints of nasal obstruction/congestion and polyp grade. The supportive information provided from RESOLVE, along with the successful outcome of RESOLVE II, support the efficacy of the Sinuva Sinus Implant for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery.

8. Safety

The safety assessment of the Sinuva Sinus Implant is based on data from the RESOLVE and RESOLVE II studies, as well as the large breadth of clinical and historical experience with mometasone furoate. No new safety signals were noted in this development program. A summary of the safety evaluation is provided here.

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For this application, the safety evaluation included the pooled results of RESOLVE and RESOLVE II. Pooling of data across studies to examine the emergence of safety signals was deemed acceptable as these studies had similar 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 safety database consisted of 400 patients in the two controlled studies. In RESOLVE, one-hundred (100) subjects were followed for 6 months. In RESOLVE II, three-hundred (300) subjects were followed for 90 days. Of the 400 patients, 254 were assigned to the treatment group and underwent bilateral placement of Sinuva Sinus Implants in the ethmoid sinuses, totaling 2700 mcg of mometasone furoate, and 146 patients were assigned to the control group and underwent a sham procedure. All subjects used Nasonex (MF nasal spray) 200 mcg (two 50 mcg sprays per nostril) daily.

There were no deaths. The overall occurrence of serious adverse events[1] (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 Sinuva 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) in the treatment group which led to study discontinuation. A total of 24 implants were removed prior to Day 60 in RESOLVE, although the number of subjects and the reason for removal was not stated. In RESOLVE II, 9 implants (in 7 subjects) were removed prior to Day 60, 4 of whom who had implants removed due to adverse events (acute sinusitis, rhinalgia, epistaxis, and parosmia).

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.

Common adverse reactions (occurring in greater than 1% of subjects and more frequently in patients treated with Sinuva Sinus Implant compared to control, respectively) included asthma (4.7% vs. 4.1%), headache (3.5% vs. 3.4%), epistaxis (2.4% vs. 1.4%), presyncope (2.4% vs. 2.1%), bronchitis (2.0% vs. 1.4%), otitis media (2.0% vs. 1.4%), and nasopharyngitis (1.2% vs. 0.7%).

[1] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

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Safety Conclusions

In general, the submitted safety data are consistent with the well-known safety profile of mometasone furoate and other approved sinus implants. Evaluation of the deaths, serious adverse events, discontinuations due to adverse events, and common adverse events did not reveal any new safety signals. However, it is notable that the clinical program for the Sinuva Sinus Implant did not study repeat use. While there are other similar implants (with a lower dose of MF) currently marketed, they are indicated to be used after sinus surgery. Thus, the repeated use (e.g., multiple times in one year), is infrequent. The Sinuva Sinus Implant will be labeled to reflect that repeat use has not been studied. Given that the Sinuva Sinus Implant can be used in lieu of surgery, repeat use may occur more frequently with this product than with the previously approved products; therefore, repeat use will be evaluated in the post-marketing setting using the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System. See the Recommendation for Postmarketing Risk Evaluation and Management Strategies section at end of this memorandum for further details.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application. There were no unique findings in Sinuva Sinus Implant development program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatrics

The submitted clinical development program is conducted in adult patients, 18 years of age and older. The Applicant submitted an iPSP, proposing a full waiver of pediatric studies in November 2014, based on the rationale that nasal polyps are extremely rare (0.1%) in the pediatric population; further, the proposed indication for the Sinuva Sinus Implant includes only those patients with nasal polyps who have undergone previous ethmoid sinus surgery, which is also not routinely performed in children. The Division and PeRC agreed with the Applicant's rationale for a full waiver, and the PSP was agreed upon in February 2015, and submitted by the Applicant in April 2015. The request for a full waiver of pediatric studies was discussed again with the PeRC on November 15, 2017, as part of the NDA submission; both the Division and the PeRC consider the full waiver of pediatric studies to be acceptable.

11. Other Relevant Regulatory Issues

- Financial Disclosure: Appropriate financial disclosure information was provided by the Applicant. Two investigators reported disclosable financial interests/agreements in the form of speaker fees and expenses. However, the number of subjects enrolled at each investigator site was not large enough to alter the outcome of either study. Further, as this was a randomized, multi-center, clinical development program in which the efficacy outcomes were determined by patient-reported outcomes or a panel of blinded

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investigators, the financial interests of these two investigators were unlikely to influence or bias the results.

- OSI audits information: The Division requested an inspection of two clinical sites with the highest enrollment. The inspections took place in June and July 2017. In general, both clinical sites were noted to be in compliance with Good Clinical Practices, and the data submitted by the clinical sites appeared acceptable. The Office of Scientific Investigations determined that no action was indicated (NAI) for either site.

11. Labeling

A revised label was sent to the Applicant on November 27, 2017. Major revisions to the package insert included changes in the indication statement, removal of non-replicated secondary endpoints, and removal of data from the RESOLVE study from Section 14, given that the data did not show statistically significant results. The proposed label and carton/container labeling were reviewed by the appropriate disciplines within the Division as well as OPDP, DMPP, OSE, DMEPA, and CDRH. The label has been agreed upon by both the Division and the Applicant.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is ***Approval*** for the Sinuva Sinus Implant for the treatment of patients 18 years of age and older with nasal polyps who have had ethmoid sinus surgery.

- **Risk Benefit Assessment**

The overall risk benefit assessment supports the approval of the Sinuva Sinus Implant for the treatment of patients 18 years of age and older with nasal polyps who have had ethmoid sinus surgery. The efficacy findings in the clinical development program were robust, demonstrating an improvement in both nasal obstruction/congestion and polyp grade. The risks with use of intranasal corticosteroids and previously approved sinus implants are well-known, and no new safety signals were identified during this clinical development program.

Notably, this development program did not evaluate the safety of repeat use of the Sinuva Sinus Implant. While there are other similar implants (with a lower dose of MF) currently marketed, they are inserted post-operatively following sinus surgery. Thus, the repeated use of the previously approved implants (e.g., multiple times in one year) is infrequent, and does not provide safety data that can be relied upon to support the repeated use of the Sinuva Sinus Implant. The package insert will reflect that repeat use has not been studied. Given that the Sinuva Sinus Implant is indicated to be used in lieu of surgery, repeat use may occur more frequently with this product than with the previously approved products; while the absence of data regarding repeat use does not preclude approval of the drug product at the current time,

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collecting data regarding repeat use of the Sinuva Sinus Implant in the post-market setting will provide important information on this issue.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Gathering data regarding potential adverse events with repeat use of the Sinuva Sinus Implant will be important in the post-market setting. The potential adverse events of concern include nasal septal perforation, cataracts, and glaucoma. Although the clinical development program did not reveal a safety signal, long-term use of oral or intranasal steroids has been linked to these adverse events. As a part of the review of this application, the Division consulted with the Office of Surveillance and Epidemiology (OSE) to determine the best way to assess the crude rates of these adverse events among patients who received a single implant as compared with those patients who had repeat implants in the post-market setting.

As a part of their review, OSE conducted an assessment of whether the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under Section 505(k)(3) of the Food Drug and Cosmetic Act (FDCA), would be sufficient to assess the potential adverse events. In their assessment, OSE concluded that ARIA is sufficient to assess the risk of cataracts, glaucoma, and nasal septal perforation because the outcomes are either well-validated in the claims data or qualified to improve accuracy of the codes, and the target population can be identified.

After approval, OSE will conduct a feasibility study to specifically examine the market uptake and numbers of patients with single and repeat Sinuva Sinus Implant use. The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org/ drugs/ongoing-aria-assessments. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website.

- **Recommendation for other Postmarketing Requirements and Commitments**

As ARIA has been deemed sufficient to assess the potential adverse events of concern with use of the Sinuva Sinus Implant, no other post-marketing requirements/commitments are necessary.

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/s/

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12/05/2017

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12/08/2017