CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209310Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	209310 (Related IND 116042)
Submissions Date:	03/07/2017
Submission Type:	505(b)(2)
Proposed Brand Name:	Sinuva
Generic Name:	S8 Mometasone Furoate Sinus Implant
Sponsor:	Intersect Ent Inc.
Route of Administration:	Ethmoid sinusoid implantation
Dosage Form:	Drug-eluting implant
Dosage Strength:	Each implant contains 1350 µg mometasone furoate
Proposed Dosing Regimen:	(b) (4)
Proposed Indication(s):	Treatment of (b) (4) polyps, in patients who have had ethmoid sinus surgery.
Proposed Population(s):	Patients ≥ 18 years of age
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Bhawana Saluja, Ph.D.
Molecular Structure of Mometasone Furoate	

Note –

In this review, early development name S8 Sinus Implant sometimes was used to refer to Sinuva implant.

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1. EXECUTIVE SUMMARY

Intersect Ent Inc. has submitted NDA 209310 through the 505(b)(2) path seeking marketing approval for Sinuva implant [S8 sinus implant containing 1350 μg mometasone furoate (MF)] for the proposed indication of "treatment (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery". The implant is a self-expanding, bioabsorbable, drug eluting implant provided with a crimper and a single-use delivery system. MF ((b) (4) is embedded in a bio-absorbable polymer matrix coated on the implant. The proposed dosing regimen is bilateral implantation in the ethmoid sinus with one implant per each side. During the implantation, Sinuva implant is loaded into a delivery system and placed in the ethmoid sinus under endoscopic visualization. The implant may be left in the sinus to gradually release the corticosteroid over 90 days. The implant can be removed earlier at the physician's discretion, using standard surgical instruments.

In this NDA, the sponsor relies on FDA's previous findings for non-clinical safety and aspects of clinical pharmacology for the Asmanex Twisthaler® (NDA 021067), a MF dry powder inhaler, approved for the treatment of asthma (up to 440 μg, BID) on 3/30/2005.

In this device-drug combo development program, the sponsor only conducted one clinical pharmacology study (Study R500-0513). Study R500-0513 was 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 two Sinuva implants (bilateral)

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 for MF between Sinuva implant and Asmanex Twisthaler indicates that the systemic exposure ($AUC_{0\text{-}12h}$) of MF during the first 3 weeks following implantation of two Sinuva 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 Sinuva 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.

It should be noted that Sinuva implant Lot 30530001 was used in Study R500-513. According to the NDA submission, Lot 30530001 was manufactured prior to the Implementation of Tighter Environmental Controls requested by CMC in order to reduce MF release rate variability (*in vitro*). For details, refer to Product Quality Review by Drs. Cooper and Chen.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the original NDA 209310 submitted on March 07, 2017 and has found the application approvable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Sinuva implant was investigated under IND 116042 before the NDA submission. IND 116042 was opened on 11/19/2012 and the clinical pharmacology-related regulatory background is listed below in a chronological order:

- A pre-IND meeting with FDA was held on 10/03/2012. The summary of clinical pharmacology-related questions and comments are listed below:

  Question 4: Intersect has completed the Pilot study of the S8 stent and is proposing conducting two randomized, blinded, controlled clinical studies (Study 2 and Study 3) to generate the safety and efficacy data for the S8 NDA. The clinical studies are summarized in section 4.3. Does the FDA agree with our proposed clinical development plan?

  FDA Response: *We do not agree. We have the following general comments regarding your proposed development plan:* (b) (4) *You must include PK assessments of mometasone in your development program. This is essential to determine what additional safety measurements may be required. If*

the systemic PK of mometasone in your drug/device product is higher than that of your reference product, additional safety data may be required.

Discussion: FDA agreed with Intersect ENT's proposal to conduct a separate PK assessment in five subjects using the same approach as for the Propel product. Intersect ENT proposed to restrict patients from taking mometasone furoate (MF) within 14 days prior to treatment and 30 days post treatment. Intersect ENT plans to collect blood for AM sampling on Day 0, 7, 14, 21, and 30 to measure plasma MF levels and systemic plasma cortisol. Intersect ENT expects that the level of MF in plasma will be low. The Agency stated that five subjects is on the lower side but given the purpose of the PK evaluation is to show that plasma concentrations of mometasone from Intersect ENT are low or undetectable and not to characterize the systemic PK of mometasone, the proposed number of 5 subjects was acceptable. With respect to sampling time points, the Agency stated that although the proposed sampling appears adequate to capture the average mometasone systemic concentrations, it would be desirable to have at least one additional sample between day 0 and day 7, e.g., day 3, to capture systemic levels on early days after the stent is implanted. Intersect ENT agreed to take the recommendation into consideration.

- An end-of-Phase 2 meeting with FDA was held on 10/02/2014. The summary of clinical pharmacology-related questions and comments are listed below:

  Question 7: Does the FDA concur that results from the PK study warrant no additional PK studies?

  FDA Response: *Based on a preliminary review of PK data from 'The S8 PK Study', we agree that no additional PK characterization for your product is warranted assuming that a) the final to-be-marketed product was employed in the PK study and b) no foreseeable conditions arise in which higher than expected systemic drug concentrations of mometasone, other than as expected, may occur (e.g, drug-interactions).*

- Another type C meeting with FDA was held on 10/08/2015. No clinical pharmacology-related questions were raised.

- On 02/04/2015, FDA PeRC meeting agreed the full waiver of pediatric studies proposed by the sponsor. The agreement was issued on 05/22/2015.

1.3.2 Comparison of MF Systemic Exposure between Sinuva Implant and Asmanex Twisthaler

- MF systemic exposure following implantation of two Sinuva implants in patients with chronic sinusitis

Animal sinus implantation Study 18005 using a truncated version of Sinuva implants in rabbits indicated that the release rate of MF is faster during the early period following implantation (Table 1.1).

The same trend of MF release rate was observed in the clinical Study R500-0513 where none of the PK samples had measurable MF plasma concentration above the lower limit of quantitation (LLOQ) after Day 21 following the implantation (Table 1.2).

Table 1.1 Estimated Average Daily MF Released* per Human Implant from Animal Study#

Total Drug Dose : 1350µg	
Duration	**Estimated Average Daily MF Released (µg/day)**
0-1 week	72
0-2 weeks	51
0-4 weeks	30
0-6 weeks	25
0-8 weeks	21
2-8 weeks	12
4-8 weeks	12
4-10 weeks	10
4-14 weeks	7
8-14 weeks	4

* Estimated as released from each human-sized implant (each rabbit implant is a truncation of the human-sized implant with approximately a quarter of the original size. The rabbit implant was coated with only 173 µg MF, therefore the results from rabbits were proportionally converted into human-sized implant in this table).

From Arm 1 of rabbit GLP Study 18005, all 14 rabbits received implantation of two stents at maxillary sinuses (one per each side). At each time point of Day 5, Day 8, Day13, Day 28, Day 42, and Day 57 following implantation, implants from two rabbits were removed to assess the mean amount of MF released. In addition, there was only one rabbit data available on Day 70 and on Day 98.

Table 1.2 Summary of Mometasone Furoate Plasma Concentrations (pg/mL) from 30 PK Samples Collected in Study R500-0513

Patient.	Baseline	Day 3	Day 7	Day 14	Day 21	Day 30
(b) (6)	<LLOQ	58.1	42.0	45.3	<LLOQ	<LLOQ
	<LLOQ	64.9	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	<LLOQ	<LLOQ	<LLOQ	34.0	<LLOQ	<LLOQ
	<LLOQ	39.0	<LLOQ	<LLOQ	<LLOQ	<LLOQ

Source: from Table 4.1

The maximum MF plasma concentration recorded from this study was 64.9 pg/mL from Patient (b) (6) on Day 3. By applying a conservative estimate for estimation of total MF exposure following implantation, where all the "<LLOQ" MF plasma concentrations values on Day 3, 7, and 14 are imputed to the LLOQ value (i.e., 30.0 pg/mL), the mean MF plasma concentrations for the five subjects were 44.4, 32.4, and 33.9 pg/mL on Day 3, 7, and 14, respectively (Table 1.3). Assuming a steady release rate for MF over 12 hours on the day when the PK samples were collected, the estimated mean MF $AUC_{0\text{-}12h}$ was 533, 389, and 407 pg•h/mL on Day 3, 7, and 14, respectively.

Table 1.3 Arithmetic Mean Mometasone Furoate Plasma Concentrations (pg/mL) up to Day 14 by Conservative Imputation of LLOQ Values Obtained from Study R500-0513

Patient	Day 3	Day 7	Day 14
(b) (6)	58.1	42.0	45.3
(b) (6)	64.9	30.0	30.0
(b) (6)	30.0	30.0	30.0
(b) (6)	30.0	30.0	34.0
(b) (6)	39.0	30.0	30.0
Mean (SD)	44.4 (16.2)	32.4 (5.4)	33.9 (6.6)

Source: Reviewer's analysis

- MF systemic exposure at steady state following Asmanex Twisthaler 440 µg, BID treatment in patients with moderate asthma

Since the applicant relies on FDA's previous findings for certain aspects of clinical pharmacology from NDA 021067 Asmanex Twisthaler, a MF (b) (4) dry powder inhaler approved for the treatment of asthma, the MF systemic exposure at steady state following the maximum approved dose (440 µg BID) is summarized here.

Study C97-049 was a multiple-dose safety and tolerability study of MF administered by dry powder inhaler (Twisthaler) in patients with symptoms of moderate asthma. The study was conducted by Schering-Plough and the study report was included in the original NDA 021067 package.

Following 440 µg BID oral inhalation of Asmanex Twisthaler, the mean MF $AUC_{0\text{-}12h,ss}$ for 15 patients was 375, 559, 523, and 634 pg•h/mL on Day 7, 14, 21, and 28, respectively (for details, refer to Clinical Pharmacology and Biopharmaceutics Review by Dr. Habet in 2004). The mean MF $C_{max,ss}$ value ranged from 88 to 114 pg/mL in 28-day period and the LLOQ value was 50 pg/mL in Study C97-049.

It should be noted that the absolute bioavailability of MF following inhalation via Asmanex Twisthaler is less than 1% (from approved label of NDA 021067).

- Effect of MF on HPA axis following Asmanex Twisthaler 440 µg, BID treatment in patients with moderate asthma:

In the same study (Study C97-049), the effect of MF on HPA axis was evaluated on Day 29 by cosyntropin stimulation assay. Reference is made to the approved label of NDA 021067 -

"The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dL for the ASMANEX 440 mcg twice daily group (n=16), compared to 14.5 mcg/dL for the oral prednisone 10 mg group (n=16) and 25 mcg/dL for the placebo group (n=16)."

There was no statistical significant difference between 440 µg BID group and placebo treatment group for the mean post-stimulation cortisol plasma concentrations. In addition, 2/16, 15/16, and 1/16 subjects in 440 µg BID group, 10 mg prednisone group, and placebo group had their plasma cortisone concentrations below 18 µg/dL 30 minutes after cosyntropin stimulation, respectively.

- MF systemic exposure comparison between two products:

  By a conservative estimate, $AUC_{0\text{-}12h}$ of MF in patients with chronic sinusitis who received two Sinuva implants (ranging from 389 to 533pg•h/mL from Day 3 to Day 14 post-implantation) are generally within the $AUC_{0\text{-}12h,ss}$ range observed in patients with asthma who received Asmanex Twisthaler 440 μg, BID treatment (ranging from 375 to 634pg•h/mL). The MF release rate from the implant declines with time, which was observed in both animal and human sinus implantation clinical studies. Therefore, MF systemic exposure is expected to decline with time after Day 14 with no measurable MF concentration at and after Day 21 post-implantation.

  In patients with chronic sinusitis who received two Sinuva implants, the C_{max} of MF is expected to be reached during the first couple days following sinus implantation. The estimated mean MF plasma concentration was 44.4 pg/mL on Day 3, which was approximately half to one-third of the mean $C_{max,ss}$ value observed in patients with asthma who received Asmanex Twisthaler 440 μg, BID treatment (ranging from 88 to 114 pg/mL).

Therefore, the systemic safety profile following Sinuva implantation could be adequately covered by the safety profile following Asmanex Twisthaler's highest approved dose (440 μg, BID) from a clinical pharmacology perspective.

2. QUESTION BASED REVIEW

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

In total, four clinical studies (Study R500-0513, Study R500-1113, Study R500-1012, and Study 500-0911) were submitted. Study R500-0513 was the only clinical pharmacology study conducted under NDA 021067.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

MF is a corticosteroid with the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione 17 (2-furoate). Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}C_{l2}O_6$, and molecular weight of 521.44 Daltons. MF is practically insoluble in water, freely soluble in both acetone and methylene chloride, and slightly soluble in alcohol.

According to the applicant, the MF coating on the Sinuva implant provides for controlled release of approximately (b) (4) during the manufacturing process. The final composition of the drug coating for each S8 Sinus Implant is summarized in Table 2.1.

Table 2.1 Drug Coating Composition

Material	Component Description [a]	Composition (w%) Per batch	Amount (mcg) per Implant
(b) (4)			

[a] (b) (4)

Source: section 2.7.1, 271-summary-biopharm.pdf, page 6, Table 1.

2.2.2 What are the highlights of the implant device?

The implant itself is manufactured from a synthetic bioabsorbable (b) (4) to achieve the desired geometry. The structural design features a rounded cap at the leading end and arched components that expand after placement (Figure 2.1).

Figure 2.1 Picture of Sinuva sinus implant

2.2.3 How is the proposed to-be-marketed formulation linked to the clinical development formulation?

The to-be marketed Sinuva implant (S8 sinus implant) was used in four clinical studies.

2.2.4 What are the proposed mechanism of action and therapeutic indications?

Refer to the approved label of NDA 021067,

"Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory 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 and in the asthmatic response.

Mometasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown."

The proposed indication is the treatment of [redacted] (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery.

2.2.5 What are the proposed dosage(s) and route(s) of administration?

The implants will be placed in the ethmoid sinus bilaterally with one per each side. Therefore, two implants contain 2700 µg of MF. The implant may be left in the sinus to gradually release the corticosteroid over 90 days.

2.2.6 What drugs (substances, products) indicated for the same indication are approved in the US?

Intersect Ent Inc. had another sinus implant product, Propel® mini sinus implant (each implant contains 370 µg MF), approved by CDRH (P100044) on 8/11/2011. Propel implant is intended for use in patients ≥ 18 years of age following ethmoid/frontal sinus surgery to maintain patency of the ethmoid sinus or frontal sinus opening. Propel® implant can be implanted in either ethmoid or frontal sinus.

2.3 General Clinical Pharmacology

2.3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

MF is the active moiety in the plasma and its plasma concentration was measured in Study R500-0513.

2.4 Exposure Response

No dose-response or exposure-response relationship was evaluated in this 505(b)(2) submission.

2.5 PK Characteristics of the Drug

2.5.1 What are the characteristics of drug absorption?

The absolute bioavailability of MF following Sinuva implantation in ethmoid sinus is unknown. In Study R500-0513, there were 25 post-implantation PK samples collected from 5 patients. Only 6/25 (24%) samples had MF plasma concentration above 30 pg/mL (LLOQ). In addition, all these 6 PK samples were collected no later than Day 14 post-implantation. The maximum MF plasma concentration recorded from this study was 64.9 pg/mL from Patient (b) (6) on Day 3.

2.5.2 What are the characteristics of drug distribution?

Refer to the approved label of NDA 021067-

"Based on the study employing a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder in humans, no appreciable accumulation of mometasone furoate in the red blood cells was found. The mean steady-state volume of distribution was 152 L. The in vitro protein binding for mometasone furoate was reported to be 98% to 99% (in a concentration range of 5-500 ng/mL)."

2.5.3 What are the characteristics of drug metabolism?

Refer to the approved label of NDA 021067-

"Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In vitro studies have confirmed the primary role of CYP 3A4 in the metabolism of this compound; however, no major metabolites were identified."

2.5.4 What are the characteristics of drug elimination?

Refer to the approved label of NDA 021067-

"Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine."

2.6 Intrinsic Factors

2.6.1 Does age or gender affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Refer to the approved label of NDA 021067-

"Mometasone furoate pharmacokinetics have not been investigated in the pediatric population. The effects of gender on mometasone furoate pharmacokinetics have not been adequately investigated."

2.6.2 Renal Impairment

Refer to the approved label of NDA 021067-

"The effects of renal impairment on mometasone furoate pharmacokinetics have not been adequately investigated."

2.6.3 Hepatic Impairment

Refer to the approved label of NDA 021067-

"Administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few."

2.7 Drug-drug interactions (DDI)

Refer to the approved label of NDA 021067-

"In clinical studies, the concurrent administration of ASMANEX TWISTHALER and other drugs commonly used in the treatment of asthma was not associated with any unusual adverse reactions."

"In a drug interaction study, an inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/mL on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mL on Day 9 (211-324 pcg/mL)."

Based on the drug interaction study results, no dose-adjustment was recommended for Asmanex Twisthaler when co-administered with CYP 3A4 inhibitors.

2.8 PD Characteristics of the Drug

Refer to the approved label of NDA 021067; MF's effect on HPA axis is summarized as below:

"In a 29-day, randomized, double-blind, placebo-controlled, study in 64 adult and adolescent patients 18 years of age and older with asthma, ASMANEX TWISTHALER 440 mcg twice daily and 880 mcg twice daily (twice the highest recommended daily dose) were compared to both placebo and prednisone 10 mg once daily as a positive control. The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dL for the ASMANEX 440 mcg twice daily group (n=16) and 20.8 mcg/dL for the ASMANEX 880 mcg twice daily group (n=16), compared to 14.5 mcg/dL for the oral prednisone 10 mg group (n=16) and 25 mcg/dL for the placebo group (n=16). The difference between ASMANEX 880 mcg twice daily (twice the maximum recommended dose) and placebo was statistically significant."

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Only parent drug (MF) was measured in clinical pharmacology study R500-0513. MF plasma concentration was measured by a validated ultra-performance liquid chromatography tandem mass spectrometry (UPLC/MS/MS).

2.9.2 For all moieties measured, is free, bound, or total measured?

Due to the nature of the bioanalytical method, the total amount of MF was measured.

2.9.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

(b) (4) developed the UPLC/MS/MS assay for quantitation of MF in human plasma with K2EDTA as an anticoagulant. The assay was originally developed and qualified previously under (b) (4) Study SIE-2007-002 for the quantitation of MF in human plasma with K2EDTA as an anticoagulant. To enhance the performance of this method, the analogue internal standard (b) (4) was replaced with the stable isotope labeled internal standard d3-MF, and this change was partially revalidated in (b) (4) Study INR-2013-002. Assay validation parameters, acceptance criteria, results summary and brief conclusions of the data relating to each parameter are summarized in Table 2.2.

Table 2.2 Parameters of Bioanalytical Method Validation

Validation Parameters	Value	Validation Source
LLOQ	30 pg/mL	SIE-2007-002 and INR-2013-002
Linear Range	30 – 2000 pg/mL; R^2: 0.9908 to 0.9979	SIE-2007-002 and INR-2013-002
Between-batch Accuracy	Non-LLOQ QC: -0.1% to 8.0% LLOQ QC: -3.8%	INR-2013-002
Between-batch Precision (%CV)	Non-LLOQ QC: 6.2% to 12.7% LLOQ QC: 13.6%	INR-2013-002
Within-batch Accuracy	Non-LLOQ QC: -5.8% to 12.3% LLOQ QC: -7.6% to 0.7%	INR-2013-002
Within-batch Precision (%CV)	Non-LLOQ QC: ≤ 13.1% LLOQ QC: 8.0 to 17.3%	INR-2013-002
Matrix Selectivity/Specificity	All 6 lots of blank plasma <20% of assay	INR-2013-002

	LLOQ peak area;	
Stability	Room temperature 24 hour: bias ≤ ±11%	SIE-2007-002
	-20°C 4 weeks: bias ≤ ±13%	SIE-2007-002
	-80°C 4 weeks: bias ≤ ±10%	SIE-2007-002
	One freeze and thaw: bias ≤ ±10%	SIE-2007-002

Source: summary from sie-2007-002.pdf, page 11-13; and inr-2013-002.pdf, page 11-13.

The calibration curve of MF in human plasma ranged from 30 pg/mL to 2000 pg/mL. The LLOQ was 30 pg/ml. The non-LLOQ QC between-batch and within-batch bias were all within ±15%. The non-LLOQ QC between-batch and within-batch coefficient of variation were all within 15%. The LLOQ bias and coefficient of variation were all within 20%, and the relative error of accuracy were all at non-LLOQ concentrations and within 20% at LLOQ concentrations. There was no obvious interference from the blank plasma, or among the analyte and internal standard. MF in human plasma (K2EDTA) was stable at room temperature for 24 hours, at -20°C for up to 4 weeks, at -80°C for up to 4 week, and after 1 cycle of freezing/thawing.

2.9.4 How is the PD marker, cortisone plasma concentration measured in the study?

Plasma cortisol concentrations were analyzed by a research enzyme-linked immunosorbent assay (ELISA) method that was not validated. Therefore, Intersect ENT has not included any data with respect to levels of plasma cortisol and does not rely on the cortisol data to support safety of the S8 Sinus Implant.

3.0 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- Although this is a 505(b)(2) submission, some PK parameters and characteristics of MF described in the proposed label [redacted] (b) (4) These contents should be removed.

- In section 8.1 Pregnancy and 8.2 Lactation, the applicant stated that [redacted] (b) (4) and therefore should be deleted.

4.0 Appendix – Individual Study Review

Study R500-0513

Study Type: Phase 1 single dose bioavailability PK study in patients
Study Dates: 6/28/2013 to 10/22/2013

Title:
A Clinical Evaluation of the Safety and Performance of the Steroid-Releasing S8 Sinus Implant When Used in Post-Sinus Surgery Patients with Recurrent Sinus Polyps

Objective:
The objective of the S8 PK study was to assess the safety and performance of the steroid-releasing S8 sinus implant when used in post-sinus surgery patients who present with recurrent sinus obstruction.

Study Design and Method:
This was a single-center open label study treating up to 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 two S8 sinus implants and were followed for 3 months. Patients returned for periodic follow-up visits at Days 3, 7, 14, 21, 30, 60 and 90. Follow-up examinations included recorded endoscopic evaluation and grading performed by clinical investigators and patient reported outcomes. Blood samples were taken by an authorized phlebotomist at baseline and through first 30 days for measurement of plasma MF and morning plasma cortisol concentrations to assess whether there was systemic exposure to MF using this route of administration.

Study Endpoints:
- Primary endpoint: Implant delivery success rate, defined as successful access and deployment of an S8 sinus implant to the target site (ethmoid sinus). The study was considered successful if at least 80% of the ethmoid sinuses could be implanted successfully.

- PK endpoint: Plasma concentrations of MF and morning plasma cortisol concentrations were measured through 30 days post-procedure

- Safety endpoint: Adverse Events and Serious Adverse Events were recorded and tabulated through Day 90.

Noteworthy Inclusion Criteria:
- Patient is ≥ 18 years of age
- Patient has a previous confirmed diagnosis of chronic sinusitis defined as inflammation of the mucosa of the paranasal sinuses
- Patient has undergone bilateral total ethmoidectomy (must be at least 90 days beyond the date of last sinus surgery)
- Patient has recurrent bilateral sinus obstruction due to polyposis
- Patient must have Grade 2 polyposis on at least one ethmoid side

Noteworthy Exclusion Criteria:
- Use of mometasone furoate, in any form, within 2 weeks prior to the implant procedure

- Patient requires use of mometasone furoate, in any form, during the first 30 days post-implant procedure
- Patient had bilateral total ethmoidectomy less than 90 days previously
- Patient has presence of adhesions/synechiae Grades 3 or 4 at time of implant procedure
- Patient has presence of severe scarring or adhesions within the ethmoid cavity itself
- Patient has known history of immune deficiency
- Patient has concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease
- Patient has oral-steroid dependent condition such as COPD, asthma or other condition
- Patient has known history of allergy or intolerance to corticosteroids or mometasone furoate
- Patient has presence of physical obstruction that would preclude access to either ethmoid sinus for device delivery
- Patient has clinical evidence of acute bacterial sinusitis
- Patient has clinical evidence or suspicion of invasive fungal sinusitis
- Patient has completely resected middle turbinate
- Patient has known dehiscence of the lamina papyracea

Analytical Method:
MF plasma samples were sent to (b) (4) for determination of MF plasma concentrations. Samples were assayed with UPLC/MS/MS method that was originally developed and validated in (b) (4) study SIE-2007-002, and subsequently partially re-validated for the change of the internal standard in (b) (4) study INR-2013-002. The LLOQ of this bioanalytical method was 30 pg/mL.

Plasma cortisol levels were analyzed by a research enzyme-linked immunosorbent assay (ELISA) method that was not validated. Therefore, Intersect ENT has not included any data with respect to levels of plasma cortisol and does not rely on the cortisol data to support safety of the S8 Sinus Implant.

Patient Disposition
A total of six patients were enrolled (consented) between July 9, 2013 and July 17, 2013. One patient did not have the required grade 2 polyposis on at least one ethmoid side and was excluded. The remaining five patients meeting all eligibility criteria underwent an in-office bilateral placement of two S8 sinus implants. All five patients completed follow-up through the Day 90 visit.

The average age of the study patients was 46.2 years (range 37 to 58). Three out of five patients were male and four were White. Medical history revealed that four patients had allergies, mostly environmental, two had asthma, and one had intolerance or allergy to aspirin.

Study Results:
- Primary endpoint
  The implant placement was performed after initiation of topical and local anesthesia, except in one patient ((b) (6) who preferred not to use any anesthesia. Ten out of the 10 target ethmoid sinuses were successfully implanted, resulting in 100% delivery success.

  Among 10 placed S8 sinus implants, 9 remained at Day 30, 5 remained at Day 60, and only 2 remained at Day 90. Eight implants were expelled. The remaining two implants (patient (b) (6) - right & left) were removed by the clinician at Day 90.

- MF plasma concentrations
  In total, 25 post-implantation PK samples were collected in 5 patients from Day 3 to Day 30. Only 6/25 (24%) samples had MF plasma concentration above 30 pg/mL (LLOQ). All these 6 PK samples were collected no later than Day 14 post-implantation and there was only one patient ([(b) (6)] with multiple MF-quantifiable PK samples (Table 4.1).

Table 4.1 MF Plasma concentration (pg/mL) over time in Patients with Chronic Sinusitis

Patient.	Baseline	Day 3	Day 7	Day 14	Day 21	Day 30
[(b) (6)]	<LLOQ	58.1	42.0	45.3	<LLOQ	<LLOQ
	<LLOQ	64.9	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	<LLOQ	<LLOQ	<LLOQ	34.0	<LLOQ	<LLOQ
	<LLOQ	39.0	<LLOQ	<LLOQ	<LLOQ	<LLOQ

Source: CSR R500-0513, page 20, Table 5

- Cortisol plasma concentrations
  Since cortisol plasma concentrations from this study were analyzed by a research ELISA method that was not validated, the results of cortisol plasma concentration-time profile are not discussed in this review.

- Safety
  There were no serious adverse events reported in the study. Two adverse events—mild headache ([(b) (6)] and mild maxillary sinus infection ([(b) (6)] were unrelated to the study device or drug.

Conclusions:

- The implant delivery success rate of 100% supported technical feasibility of the in-office placement of the S8 Sinus Implant.

- Most (76%) of the post-implantation PK samples had MF plasma concentration BLQ. No PK sample was above LLOQ on or after Day 21 post-implantation.

- There was no serious adverse events observed in this study.

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/s/

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11/08/2017

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