

TITLE PAGE

Title: Rates of Middle Meatus (MM) synechiae formation post Endoscopic Sinus Surgery (ESS): a double-blind randomized controlled study comparing Silastic and Restora™ steroid eluting MM spacer

Study Design: Double blinded, placebo controlled, randomized

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1 PROTOCOL SYNOPSIS

Title: Rates of MM synechiae formation post ESS: a double-blind randomized controlled study comparing Silastic and the Restora™ steroid eluting MM spacer

Primary Objective:

This study is designed to evaluate basic device usability and confirm safety and effectiveness of the Restora™ Steroid eluting spacer as compared to a Silastic spacer.

Background/ Rationale:

Endoscopic sinus surgery (ESS) is the gold standard surgical intervention for chronic rhinosinusitis that is not adequately controlled with maximal medical therapy.

In some patients, underlying inflammation (discharge, edema and polyposis), compounded by inflammation caused by surgical trauma may lead to an uncontrolled healing response, which results in the synechiae formation in the middle meatus (MM).

Incidence of synechiae formation varies in literature and ranges between 4-35%. Presence of middle meatal synechiae can impair sinus drainage, promote sinusitis, and limit endoscopic visualization of the sinus cavities postoperatively. This may result in difficulty in performing postoperative routine endoscopic debridement and examination, which is paramount to a successful outcome from ESS. Spacers are often inserted during surgery between nasal mucosal surfaces to prevent synechiae.

The aim of this study is to see if a steroid-impregnated spacer is more effective at reducing inflammation after sinus surgery than a Silastic spacer.

Study Population: Patient suffering from chronic rhinosinusitis in need of ESS

Number of Centers: 2-3

Number of Subjects:

A total of 49 patients will be treated.

Test article:

Restora Spacer material loaded with Mometasone Furoate

Study Design:

This is a double-blind randomized controlled study of 49 patients with chronic rhinosinusitis that require ESS.

Screening

In the screening period, inclusion/exclusion criteria for the study participation will be checked. Subjects who satisfy these criteria will be invited to participate in the study. Their consent will be recorded. As a standard of

care, all patients will fill out the validated SNOT-22 quality of life outcome questionnaire at this pre-op visit.

Blinding

The study will be double-blinded. Each patient will be his or her own control. The Silastic spacer will be placed on one side and the steroid-eluting spacer will be placed on the other. Neither the patient nor the assessor will know on which side the respective spacer is placed. The PI at the primary site will be the blinded assessor.

Procedure and follow up

Patient will undergo ESS and the spacers will be placed in the operating room upon procedure completion. Subjects will return to clinic after 6-8 days to have the spacers removed. The removed spacer materials will be shipped to SinuSys for residual steroid content analysis. After the initial visit, patients are seen again in clinic at 35 and 90 days postoperatively. At each visit endoscopic videos will be collected to enable scoring, as detailed in the endpoint section below. As a standard of care all patients are treated with oral antibiotics (Clavulin or Clindamycin if allergic to Penicillin) while they have spacers inserted into their nose.

The detailed study schedule is provided in Appendix A.

Projected Study Timelines

Anticipated Total Study Duration: Enrollment – 1-2 months, Follow up 3 months.

Study Endpoints

- **Primary Endpoint**
 - 35 day sinonasal mucosal inflammation assessed by rigid endoscopy and graded on Lund-Kennedy sinus mucosal endoscopic staging system
- **Secondary Endpoints**
 - 90-day sinonasal mucosal inflammation assessed by rigid endoscopy and graded on Lund-Kennedy sinus mucosal endoscopic staging system
 - 35 and 90-day intraocular pressure (IOP) assessed using applanation tonometry and compared to baseline IOP obtained preoperatively
 - 35 and 90-day post ESS incidence of middle meatal synechiae
 - 90-day Sinonasal Outcomes Test-22 (SNOT- 22) scores
 - 35-day frequency of postoperative interventions, including lyses of adhesions and debridement.
 - 35-day frequency of oral steroid rescue
 - 35 days middle turbinate position

Inclusion Criteria

- 1) Age between 18 and 75 years
- 2) Diagnosis of chronic rhinosinusitis (CRS), per current guidelines
- 3) Patients who need to undergo primary bilateral complete endoscopic sinus surgery
- 4) Subject has the ability to follow the study instructions, is willing to be available on the specific required study visit days, and is willing to complete all study visit procedures and assessments

5) Subject must understand the research nature of this study and sign an informed consent prior to the performance of any study-specific procedure or assessment

Exclusion Criteria

- 1) Subject is pregnant or breast feeding
- 2) Patients with sino-nasal tumors
- 3) Patients solely undergoing nasal septal reconstruction
- 4) Patients with previous history of endoscopic sinus surgery
- 5) Cystic fibrosis or syndromic patients
- 6) Patients with autoimmune diseases
- 7) Patients who have taken oral steroids less than 30 days prior to surgery
- 8) Patients with a history or diagnosis of glaucoma or ocular hypertension
- 9) Any other circumstance or condition that in the Investigator's opinion causes the subject to be an inappropriate candidate for participating in this study

Statistical Consideration

This study is designed to evaluate basic device usability and confirm safety and effectiveness of Steroid Impregnated Spacer. There is no success criteria set based on statistical calculation.

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3 ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CRS	Chronic Rhinosinusitis
CFR	Code of Federal Regulations
FDA	Food and Drug Administration
ESS	Endoscopic Sinus Surgery
ICH	International Conference on Harmonization
ITT	Intent To Treat
MM	Middle Meatus
PP	Per Protocol
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

4 INTRODUCTION

4.1 Literature review

Endoscopic sinus surgery (ESS) is the gold standard surgical intervention for chronic rhinosinusitis that is not adequately controlled with medical therapy. Synechiae formation in the middle meatus is the most common complication of endoscopic sinus surgery (1). Synechiae describes the adhesion of two opposing mucosal surfaces in the nasal cavity that can cause scarring and obstruction of the nasal passage. Incidence of synechiae formation varies in literature and ranges between 4-35 % (2, 3, and 4). Presence of middle meatal synechiae can impair sinus drainage, promote sinusitis, and limit endoscopic visualization of the sinus cavities postoperatively. This may result in difficulty in performing postoperative routine endoscopic debridement and examination, which is paramount to a successful outcome from ESS (5).

To prevent synechiae formation, numerous studies have been published evaluating the effectiveness of absorbable and non-absorbable spacers placed in the middle meatus for 1-2 weeks postoperatively. The spacer is meant to prevent contact between the denuded surfaces of the middle turbinate and the lateral nasal wall during re-epithelialization. In general, non-resorbable spacers that have been used include sponges, cotton gauze and plastic sheets. Of these, Silastic Silicone sheets have been used in a number of hospitals across the US and Canada. Lee (6) and Baguley (7) have demonstrated the effectiveness of Silastic spacers in reducing the risk of synechiae formation to between 0-6 % (6, 7). There are also a number of resorbable spacers that are in use, which are preferred by some physicians because there is minimal need to remove the packing materials as they naturally are removed or resorbed during the healing period.

In a recent meta-analysis, Lee et al (8) has revealed that usage of middle meatal spacers (absorbable and non-absorbable) did not decrease the rate of synechiae formation to a statistically significant degree compared to not using any spacer. However, when subgroup analysis was performed, non-absorbable spacer usage demonstrated a statistically significant lower incidence of synechiae compared to no spacers (6). This can be explained in part by an inherent capability of the absorbable spacer material to degrade to smaller size particulates that, if caught in the healing tissue, could illicit local inflammatory response to slow down the healing and cause further synechiae formation. This mechanism was demonstrated by Maccabee et al (9) in a rabbit model, where fibers of the absorbable spacer became incorporated into healing mucosa and increased the extent of the inflammatory response and formation of fibrosis.

To improve outcomes, physicians have attempted to load steroids such as Triamcinolone (10, 15) and antibiotics such as Neosporin (11) into nasal packing and/or stents. However, residence of the drug in the intended treatment space is minimized as the drug, which is not bound to the spacer, quickly releases and may not remain long enough to impact inflammatory response. A Mometasone Furoate coated stent (Propel™), manufactured by Intersect ENT, is currently the only drug coated nasal stent that has a claim of longer sustained release. In a randomized, controlled, double-blind trial, Marple et al (12) found that this Mometasone Furoate steroid-eluting bio-absorbable stent could significantly improve postoperative outcomes compared to a non-steroid eluting placebo arm with the same stent. Zhao et al (13) conducted a systematic review of the efficacy of this steroid-eluting stent (Propel) vs inert (both resorbable and non-

resorbable) spacers and again confirmed that there are lower rates of synechiae formation in the steroid-eluting treatment groups. However, anecdotal evidence, based on discussion with a number of surgeons in the field, suggests that a drug-loaded resorbable spacer may be subject to the same issues as non-drug-loaded resorbable spacers, namely late stage degradation of the material that can cause a secondary spike of the inflammatory cascade, requiring additional surgical intervention to remove the remaining debris.

Therefore, it has been hypothesized that a steroid eluting non-absorbable spacer may provide optimal benefit for the patient's outcome. The Restora™ spacer is made of a biocompatible non-resorbable material that is expected to deliver up to 370 µg of Mometasone Furoate. The steroid elutes out of the spacer and onto the surrounding mucosal tissue during the 6-8 day period during which it is retained.

This study is designed to evaluate basic device usability and confirm safety and effectiveness of the Restora™ Steroid eluting spacer as compared to the standard of care Silastic Silicone spacer.

5 RISK ASSESSMENT

The Restora Nasal Spacer has the primary mode of action of being a mechanical support to physically separate opposing mucosal surfaces and thereby reduce the potential for synechiae formation. The addition of Mometasone Furoate, a well-known and well characterized anti-inflammatory with a long history of use in the nasal cavity, is intended to reduce post-surgical inflammation during the natural healing process.

There are two potential sources of risks that can be derived from the use of the Restora spacer: 1) due to the spacer material and shape and 2) due to the drug loaded onto the spacer.

The risks associated with the spacer material itself is considered minimal as the material is biocompatible for its intended use and the material shape (thickness, and area) is similar to that of the standard Silastic Silicone sheet that is used surgically.

The risk associated with the drug is comparable to that with the use of the commercially available Intersect Propel Stent as the amount of drug that is expected to be released from Restora™ is similar to that released from Propel, 370µg. In addition, the anti-inflammatory steroid, Mometasone Furoate (active ingredient in Nasonex) has been approved for intra-nasal delivery since 1997. The recommended daily dose delivered for treatment of nasal allergies is 2 sprays per nostril per day and for polyposis is 2 sprays per nostril twice a day. Each spray dose is 50 µg. Therefore, the total maximum recommended dose for the patient is 400 µg per day, and total of 2,800 µg over a 7 day period. Topical Mometasone Furoate spray has also been administered post ESS to help reduce post surgical inflammation at the same dose prescribed for allergies, namely 400 µg/day (14). Compared with this spray dose, the dose of Mometasone Furoate delivered by Restora is at least 7 fold less than that for the Nasonex.

The Restora Nasal Spacer is considered a non-significant risk device because it does not meet the criteria specified by FDA for a significant risk device. Reference FDA Guidance "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Non-Significant Risk Medical Device Studies" dated January 2006:

- Restora is not intended as a permanent implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- Restora is not purported or represented to be for use supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- Restora is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject; and
- Does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject

This study will be conducted in accordance with requirements specified in 21 CFR 812.2(b).

Risks associated with the use of the SinuSys Restora Spacer are anticipated to be similar to those experienced by patients undergoing placement of other non-resorbable spacers and less than that of Propel due to its non-resorbable nature. The potential clinical benefits of the Restora Spacer are believed to exceed any residual risks associated with the use of the Restora Spacer.

6 STUDY OBJECTIVE

The main objective of the trial is to evaluate basic device usability and confirm safety and effectiveness of Restora™ Mometasone Furoate eluting spacer as compared to a Silastic spacer.

7 RESTORA AND SILASTIC SPACERS DESCRIPTION

Silastic spacer is an inert plastic that can be shaped to fit the operative field. A soft, pliable, 0.04 -inch-thick polymeric Silastic sheet, shaped into an inverted U by suturing the middle of the spacer to keep the shape, will be placed between the middle turbinate and lateral nasal wall. Image of Silastic spacer placed in the Middle Meatus is shown in figure 1.



Figure 1: Silastic Nasal Spacer placed in the Middle Meatus of the nose.

Restora spacer is composed of Tecophilic HP-93A-100 resin (Lubrizol Inc) that has been extruded, cut to the desired shape, shaped, packaged, and finally exposed to a terminal gamma irradiation (25-40 kGy) sterilization process to reduce bioburden. The material is provided in a boot shape geometry and has

thickness of approximately 0.84mm (Figure 1). The Restora spacer is pre-shaped into an inverted U to keep the shape before placement between middle turbinate and lateral nasal wall.



Figure 2: Restora Nasal Spacer placed in the Middle Meatus of the nose.

Mometasone Furoate will be loaded into the spacer using proprietary SinuSys protocol to target up to 370 μgm delivery in-vivo. Once loaded, the spacer is capable of eluting drug over its residency time in the middle meatus.

7.1 Preclinical data

The Restora spacer has been tested in the USP dissolution apparatus in comparison to Intersect Propel stent. In order to do the side by side comparison, Restora spacer was loaded with the same amount of MF as Propel, 370 μgm . Figure 3 below demonstrates controlled sustained release of Mometasone Furoate as % of total drug loading.

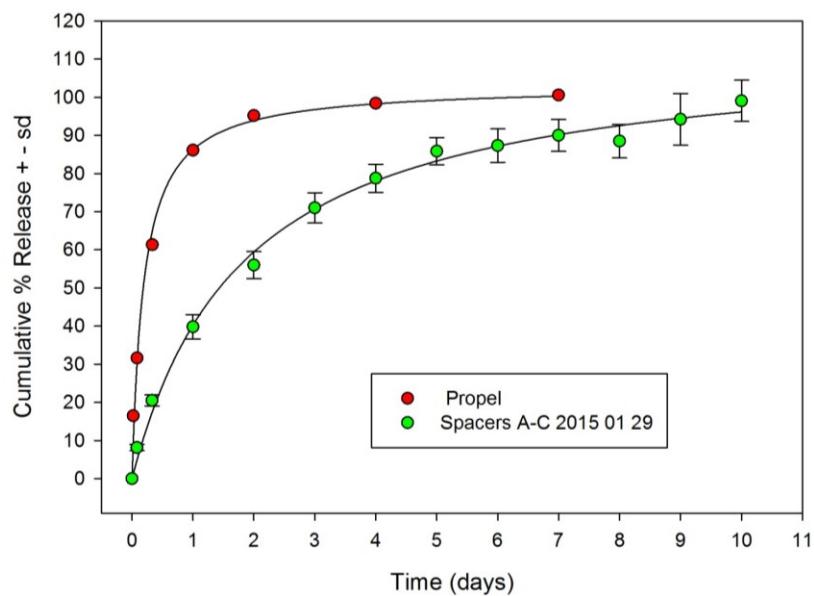


Figure 3: Cumulative Mometasone Furoate Release from Propel Mini compared to Restora Nasal spacer

This graph demonstrates that Restora platform has capacity to provide longer sustained release than the Propel product under same test conditions.

7.2 Clinical data

Initial experience with Restora Spacer has been completed on 23 patients, as part of on-going study by Dr. Amin Javer at University of British Columbia (Amin Javer MD, Principal Investigator), under similar protocol. In this study, patients undergoing ESS procedure received one Restora Spacer and one Silastic spacer, placed bi-laterally, post ESS. The spacers were removed at day 6 post surgery. There were no adverse events reported.

Spacers were sent to SinuSys for MF content analysis. The average amount of MF loaded on the spacers was 483.64 ± 25.62 μgm . Average amount of drug remaining on the spacers was 418.83 ± 25.65 μgm . Total amount of drug released was 64.81 μgm , 13% of the dose loaded.

Based on this information, loading protocol used in this study is adjusted to provide target dose of up to 370 μgm in vivo.

8 STUDY DESIGN AND ENDPOINTS

Approximately 50 patients will receive spacers during their ESS procedures and be followed for 90 days. This will require enrolling approximately 60 patients between all of the participating centers to account for possible loss-to-follow-up (LTf).

- **Primary Endpoint**
 - 35-day sinonasal mucosal inflammation assessed by rigid endoscopy and graded on Lund-Kennedy sinus mucosal endoscopic staging system
- **Secondary Endpoints**
 - 90-day post ESS incidence of middle meatal synechiae
 - 35 and 90-day sinonasal mucosal inflammation assessed by rigid endoscopy and graded on Lund-Kennedy sinus mucosal endoscopic staging system
 - 35 and 90-day intraocular pressure (IOP) assessed using applanation tonometry and compared to baseline IOP obtained preoperatively
 - 35 and 90-day post-ESS incidence of middle meatal synechiae
 - 90-day validated Sinonasal Outcomes Test-22 (SNOT- 22) scores
 - 35-day frequency of postoperative interventions, including lyses of adhesions and debridement.
 - 35-day frequency of oral steroid rescue
 - 35 days middle turbinate position

8.1 Inclusion Criteria

- 1) Age between 18 and 75 years

- 2) Diagnosis of chronic rhinosinusitis (CRS), per current guidelines
- 3) Patients who need to undergo primary bilateral complete endoscopic sinus surgery
- 4) Subject has the ability to follow the study instructions, is willing to be available on the specific required study visit days, and is willing to complete all study visit procedures and assessments
- 5) Subject must understand the research nature of this study and sign an informed consent prior to the performance of any study-specific procedure or assessment

8.2 **Exclusion Criteria**

- 1) Subject is pregnant or breast feeding
- 2) Patients with sino-nasal tumors
- 3) Patients solely undergoing nasal septal reconstruction
- 4) Patients with previous history of endoscopic sinus surgery
- 5) Cystic fibrosis or syndromic patients
- 6) Patients with autoimmune diseases
- 7) Patients who have taken oral steroids less than 30 days prior to surgery
- 8) Patients with a history or diagnosis of glaucoma or ocular hypertension
- 9) Any other circumstance or condition that in the Investigator's opinion causes the subject to be an inappropriate candidate for participating in this study

8.3 **Blinding**

The study is double-blinded. Each patient is his or her own control. Neither the patient nor the assessor will know on which side the respective spacer is placed. The Principal Investigator will be the blinded assessor. The choice of spacer for each side will be randomized using the sealed envelope system.

8.4 **Study Procedures**

A table of study assessments is presented in Appendix A.

8.5 **Screening/Enrollment Visit**

All consented subjects will be assigned a unique subject number. Screening procedures can occur only after consent is signed. Screening and device placement may occur on the same day. If the placement procedure occurs on a different day than the screening/enrollment visit the inclusion/exclusion criteria have to be reevaluated. The device placement attempt must occur within 30 days of initiating screening procedures.

As a standard of care, all patients will fill out the SNOT-22 quality of life questionnaire at this visit.

8.6 **Screening Procedures**

The following screening procedures will be performed before the device placement attempt is initiated:

1. Written informed consent prior to conducting any study-specific procedures
2. Demographic information
3. Targeted medical history
4. Medication history including medications for 7 days prior to enrollment
5. Pregnancy test
6. Nasal Endoscopy
7. Any other screening procedures for dilation of intended treatment spaces that are standard of care to the investigation site
8. Review of eligibility criteria (subject failing to meet all inclusion/exclusion criteria are to be recorded as Screen Failures)

8.7 Treatment visit

Patients will undergo bilateral ESS procedure. Each patient will receive one Silastic and one Restora spacer, placed bilaterally.

As a standard of care all patients are treated with oral antibiotics (clavulin or clindamycin if allergic to penicillin) while they have spacers inserted into their nose.

The device(s) can be removed anytime upon the subjects' request or if the Investigator deems it necessary.

8.8 Follow-up visits

There will be a total of 3 follow up visits: 6-8 days, 35 days, and 90 days after ESS. Follow-up visits will consist of appropriate standard of care treatment for subjects. At each follow-up visits a nasal endoscopy will be performed and endoscopic videos will be obtained. Any potentially device related complications will be assessed, concomitant medication will be recorded. During the follow up period, subjects may receive any medication the Investigator deems necessary. Prescription of a new medication will not exclude further participation.

As a standard of care, all patients will fill out the SNOT-22 quality of life questionnaire at their 90 day visit.

8.9 Unscheduled Visits

It is at the discretion of the Investigator to have the subject return to the study site prior to any regular scheduled visit if, for example, the subject experienced an adverse event and/or it is in the best interest of the subject for whatever reason. Evaluation of subjects during an unscheduled visit should include a nasal endoscopy if possible. All other evaluation and testing will be decided by the investigator based on the presenting issue(s) and should be documented.

9 SUBJECT DISCONTINUATION

Subjects may be discontinued from the study for any of the following reasons (but are not limited to):

- Adverse event
- Significant protocol deviation
- Subject noncompliance
- Subject voluntary withdrawal
- Investigator judgment (e.g., inter-current medical problem)
- Lost to Follow-up – for a subject to be considered lost to follow-up 3 documented attempts to contact the subject shall be made by phone and a certified letter shall be sent.

A subject may discontinue voluntarily at any time, for any reason during their participation in the study. If a subject decides to discontinue participation and withdraw from the study, an attempt shall be made to obtain information about any adverse events or reasons for discontinuation. The investigator may withdraw a subject from treatment if, in his/her judgment, it is in the subject's best interest to do so. The investigator shall record the reason for subject discontinuation on the appropriate CRF. Discontinued subjects may be replaced with another enrolled subject.

Intent to treat occurs once all eligibility criteria have been met and informed consent has been signed and an attempt is made to place the device into the treatment space. Any discontinued subject will be followed for as long as possible and any safety and effectiveness results will be included in the final analysis and report.

10 RISK/BENEFIT ASSESSMENT

10.1 Potential Risks

There are two potential sources of risks that can be derived from the use of the Restora spacer: 1) due to the spacer material and shape and 2) due to the drug loaded onto the spacer.

The risks associated with the spacer material itself is considered minimal as the material is biocompatible for its intended use and the material shape (thickness, and area) is similar to that of the standard Silastic Silicone sheet that is used surgically.

The risk associated with the drug is comparable to that with the use of the commercially available Intersect Propel stent, as the amount of drug loaded on Restora™ is equivalent to that loaded onto Propel Stent, 370 μ gm. In addition, the anti-inflammatory steroid, Mometasone Furoate (active ingredient in Nasonex) has been approved for intra-nasal delivery since 1997. The recommended daily dose delivered for treatment of allergies is 2 sprays per nostril per day and for polyposis is 2 sprays per nostril twice a day. Each spray dose is 50 μ g. Therefore, the total maximum recommended dose for the spray user is 400 μ g per day and total of 2,800 μ g over a 7 day period. Compared with this recommended dose, the dose of Mometasone Furoate delivered by Restora is at least 7 fold less than that for the Nasonex.

The potential risks of study participation fall into the following categories:

Frequent: expected to occur in more than 25% of people (more than 25 out of 100 people)

Probable: expected to occur in 10-25% of people (10-25 out of 100 people)

Occasional: expected to occur in 1-10% of people (1-10 out of 100 people)

Remote: expected to occur in less than 1% of people (less than 1 out of 100 people)

Incredible: expected to occur in less than 0.1% of people (less than 1 out of 1000 people).

The risks and possible side effects may include the following:

1. Device Risks

- Premature Displacement of spacer post placement – Remote
- Swallowing of spacer – Incredible
- Adherence of crusting to the implant, resulting in or contributing to sensation of pain/pressure/headache - Occasional
- Foreign body response, including formation of granulation tissue - Remote
- Choking- Incredible

2. Drug Risks

- Nasal irritation and burning - Remote
- Intranasal bleeding - Remote
- Localized infection (bacterial, fungal, or viral) in the nose or pharynx – Occasional
- Nasal Dryness - Incredible
- Glaucoma/elevation of intraocular pressure - Incredible
- Cataracts/change in lens opacities - Incredible

3. General Side Effects with Steroids

- Alteration of the HPA axis including growth suppression (steroid modulation) - Incredible
- Immunosuppression - Incredible
- Headache - Incredible
- Epistaxis - Incredible
- Coughing - Incredible
- Arthralgia - Incredible
- Myalgia – Incredible
- Fatigue - Occasional

4. Nasal Endoscopy is part of routine care associated with rhinosinusitis. These risks may include mild discomfort or light bleeding.

5. The standard risks associated with general anesthesia.

6. An unexpected risk could emerge.

Risks associated with the use of the SinuSys Restora Spacer are anticipated to be similar to those experienced by patients undergoing placement of other non-resorbable spacers and less than that of Propel stent due to its non-resorbable nature. The potential clinical benefits of the Restora Spacer are believed to exceed any residual risks associated with the use of the Restora Spacer.

10.2 Potential Benefits of Study Participation

There may be no direct benefits of study participation. However, subjects will undergo an enhanced level of clinical scrutiny compared to routine clinical care, which may provide some indirect health benefits.

In addition, there could be a benefit of using a drug-eluting spacer post ESS to decrease rate of synechiae formation, and frequency of postoperative interventions, including lyses of adhesions and debridement.

This study is intended to confirm the feasibility of the use of the Restora Nasal Spacer for this purpose.

10.3 Risk/Benefit Conclusions

Based upon the Risk/Benefit analysis performed, the benefits associated with the Restora Nasal Spacer is expected to outweigh the potential risks to the patient.

11 ADVERSE EVENTS / COMPLICATIONS

11.1 Serious Adverse Event (SAE)/Unanticipated Adverse Device Effect (UADE) Definition

Serious Adverse Event (SAE): A SAE is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in medical or surgical intervention to prevent life threatening illness
- Results in injury or permanent impairment to a body structure or a body function
- Results in persistent or significant disability/incapacity

Also in the category of SAE is:

- Any other unanticipated serious problem caused by or associated with the device that relates to the rights, safety, or welfare of subjects [21 CFR 812.3(s)]

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Elective hospital admission will not be considered an SAE for this study.

Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

All SAE/UADEs will be collected from first application of the treatment product at the baseline visit until study exit.

11.2 Adverse Event/Adverse Device Effect Relationship to Study Device

The relationship of an event to study device will be documented by the investigator as follows:

Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant drugs administered to the subject. Note, it is not necessary to record in the CRFs these unrelated events.

Possible: The event follows a reasonable temporal sequence from the time of treatment product administration, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs.

Probable: The event follows a reasonable temporal sequence from the time of treatment product administration, and follows a known response pattern to the treatment product. The event cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs.

Definite: The event follows a reasonable temporal sequence from the time of treatment product/device administration, follows a known response pattern to the treatment product/device, cannot be reasonably explained by other factors such as the subject's condition, concomitant drugs or therapeutic interventions, AND either occurs immediately following treatment product administration, improves on stopping the treatment product, or reappears on re-exposure of the treatment product/device.

11.3 Procedure for Recording and Reporting Adverse Device Effects

All SAEs and all possibly device related AE/ADEs will be collected from first application of the study treatment products at the baseline visit until study exit.

Beginning with the first study treatment, the investigator will determine whether any SAEs or possibly device related adverse experiences have occurred by evaluating the subject's signs, symptoms, and other test results or assessments.

All SAEs and possibly device related AEs / complications and ADEs (expected or unexpected) which occur during the specified study period, whether observed by the investigator or by the subject, and whether or not thought to be related to treatment product or to study procedures, will be reported in detail on the appropriate CRF and followed until resolution, stabilization, or death, according to Good Clinical Practice (GCP). The record of the SAE/ADE will include a description of the event, start date, stop date, duration, outcome, intensity, if it was serious, relationship to treatment product or study procedure (i.e., causality), change in dosage or discontinuation of treatment product, if treatment was required and if the subject died. The investigator must verify this information.

11.4 Procedures for Reporting a Serious Adverse Event/Unanticipated Adverse Device Effect

It is the responsibility of the Investigators to inform their IRB about serious adverse events or other events as required by their IRB procedures and in compliance with the applicable regulations.

The investigator should inform SinuSys either by phone or email, within 24 hours of the investigator becoming aware of the event. SAE/UADEs shall be initially reported to:

Name: Janie Mandrusov
Title: Director, Preclinical and Clinical Development
Address: SinuSys Corp, 2468 Embarcadero Way, Palo Alto, Ca 94303
Telephone: 1-408-410-4411
Email: emandrusov@sinusys.com

A full investigation of any SAE/UADE will be conducted by the Investigator in collaboration with SinuSys Corporation. The Investigator shall report the results of such evaluation to the IRB within 10 working days after notice of the effect. Only Unanticipated possibly device related complications will need to be considered for possible reporting to the FDA. Please consult with regulatory counsel for guidance.

If principal investigator determines that an SAE/UADE presents an unreasonable risk to subjects, the investigation must be terminated as soon as possible, but no later than 5 working days after the investigator makes this determination.

All subjects with an SAE/UADE must be followed up and the outcomes reported. The Investigator should supply SinuSys Corporation and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy report, pathology report, operative report, terminal medical report, etc).

12 STATISTICAL PLAN

12.1 Sample Size

Up to approximately 50 subjects will be enrolled into the study. This study is designed to evaluate basic device usability and confirm safety and effectiveness of Restora Nasal Spacer.

There is no success criteria set based on statistical calculation.

12.2 Analysis Populations

The following subject populations will be created:

Safety (Safety): All subjects enrolled who underwent the device placement procedure, regardless of outcome.

Intent To Treat (ITT): All subjects enrolled who underwent the device placement attempt, regardless of outcome.

Per Protocol (PP): A subset of the ITT population that excludes subjects with major protocol deviations (to be identified prior to data lock).

The primary efficacy analysis will be carried out on both ITT and PP populations.

No effort will be made to impute or extrapolate data to replace missing values.

12.3 Statistical Analyses

Appropriate statistical methods will be used to analyze the data. Descriptive statistics for continuous variables will consist of the mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percentage of each category will be displayed.

For the primary endpoints the following acceptance criteria had been defined:

- Safety: The study will be considered successful if no Unanticipated Device Adverse Effect occurs during device residence time and the overall rate of device related complications is clinically acceptable.
- Performance: The study will be considered successful if there is a trend or significant difference in primary end point between Restora and Silastic spacer

13 ADMINISTRATIVE CONSIDERATIONS

13.1 APPLICABLE REGULATIONS/STANDARDS/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the “World Medical Association Declaration of Helsinki” (as amended in Tokyo, Venice, Hong Kong, South Africa and Scotland and Note of Clarification Washington, 2002).

The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” International Committee on Harmonization (ICH) Tripartite Guideline (January 1997) and to ISO14155:2011 requirements. The investigator will additionally ensure that the basic principles of “Good Clinical Practices” as outlined in the current version of FDA 21 Code of Federal Regulations (CFR) Subchapter D, Part 312, “Responsibilities of Sponsors and Investigators”, Part 50, “Protection of Human Subjects” and Part 56, “Institutional Review Boards” are adhered to.

14 IRB REVIEW

The protocol and any accompanying material provided to the subject will be submitted by the investigator to an IRB committee. Approval from the IRB must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted approval.

Any modifications made to the protocol after receipt of the IRB or EC approval must also be submitted by the investigator to the board in accordance with the local procedures.

Copies of all IRB correspondence with the investigator shall be provided to SinuSys Corporation.

15 INFORMED CONSENT

Voluntary informed consent will be obtained from all subjects, or the legally authorized representative of the subject participating in this study, in accordance with FDA regulations. The subject's informed consent must be obtained in writing prior to performance of any study-specific activity. The informed consent form used to consent the subject must be approved by the reviewing IRB. The original signed consent form shall be maintained in the subject's study file.

All subjects must be consented utilizing the most current approved version of the informed consent form, and re-consented if required by the IRB for any protocol amendments.

The principles of informed consent must be followed to be in compliance with health authorities' regulations for the conduct and monitoring of clinical investigations.

16 SUBJECT CONFIDENTIALITY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the treatment product may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to, SinuSys Corp, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records.

Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written authorization is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information ["HIPAA"]) and any other state privacy requirements, as required by the study site.

17 STUDY DOCUMENTATION, CRF'S AND RECORD KEEPING

17.1 Investigator Files/Retention of Documents

Principal investigator shall maintain clinical investigation documents, including study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of device, and copies of case report forms as required by the local or other applicable regulatory requirements. They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator may transfer custody of records to another person/party and document the transfer at the investigation site or to provide these to SinuSys Corporation.

18 STUDY MATERIALS ACCOUNTABILITY

Study materials accountability, reconciliation and record maintenance are responsibilities that must be performed in accordance with all applicable regulatory requirements. SinuSys will provide requested materials accountability records for this study for use by the investigative sites. The recipient will acknowledge receipt of all study material shipments, indicating content and condition. Damaged supplies will be replaced.

Accurate records of all study materials received, used to treat subjects, returned to the SinuSys, or designee, or destroyed at the study site, shall be maintained by the Investigator.

The investigator will not supply the study treatment materials to a third party, nor will he/she allow administration of the study material, other than as directed by this protocol to subjects properly enrolled into the study.

The SinuSys Restora Spacer material will be stored appropriately at the study site until the end of the study. All unused inventory will be stored for accountability and return. All used spacers will be retained

and stored in a designated closed vial. Storage and shipping procedures to return used and unused inventory will be provided by SinuSys.

If the spacer material does not perform as intended, the study site will return the device to SinuSys and will document the performance issue.

19 QUALITY CONTROL AND ASSURANCE

Case Report Forms (CRFs) for this study will be designed and provided by the investigator. A complete audit trail of changes to the data will be maintained and available upon request.

20 REFERENCES

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21 APPENDIX A

SCHEDULE OF EVENTS

Assessment	Screening/ Enrolment	Treatment	Spacer Removal 6+2 days	Follow up 5± 1 weeks	Follow up 13±2 weeks
Informed Consent	X				
Eligibility Criteria	X	X*			
Demographics	X				
Pregnancy Assessment	X				
Medical History	X				
CT Scan	X				
Nasal Endoscopy	X	X	X	X	X
Endoscopic Videos Acquisition/LK score		X	X	X	X
ESS procedure and spacer placement		X			
Adverse Events/UADE		X	X	X	X
Concomitant Medications	X	X	X	X	X
SNOT-22	X				X
Frequency of events**				X	
IOP (Intra-Ocular Pressure)	X			X	X

*If treatment performed on a different day than the Screening/enrollment visit

** Data collection for frequency of post op interventions, oral steroid use and turbinate position