October 7, 2024
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Medical Product 4, Orthopedic product
Term Name	Bioabsorbable drug-eluting stent for sinus (to be newly created)
Brand Name	Propel Sinus Implants
Applicant	Medtronic Japan Co., Ltd.
Date of Application	November 30, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on October 7, 2024, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved with no designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

Review Report

September 13, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Medical Product 4, Orthopedic product
Term Name	Bioabsorbable drug-eluting stent for sinus (to be newly created)
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Date of Application	November 30, 2023
Reviewing Office	Office of Medical Devices I

Review Results

September 13, 2024

Classification	Medical Product 4, Orthopedic product
Term Name	Bioabsorbable drug-eluting stent for sinus (to be newly created)
Brand Name	Propel Sinus Implants
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Date of Application	November 30, 2023

Results of Review

Propel Sinus Implants (hereinafter referred to as "Propel") is a bioabsorbable self-expanding drug-eluting stent for sinus used to maintain nasal patency following endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS). The Propel consists of a self-expanding, drug-eluting bioabsorbable stent and a delivery system for stent placement. The surface of the Propel stent is coated with an agent containing mometasone furoate, a corticosteroid, to alleviate inflammation at the site.

The applicant submitted non-clinical data supporting the physicochemical properties, biological safety, mechanical safety, stability, and durability, and performance of the Propel. There was no particular problem in the data submitted.

Also submitted were efficacy and safety evaluation data of the Propel, in the form of results from 5 foreign clinical studies in patients with CRS (hereinafter referred to as "US clinical studies") and a clinical evaluation report from published articles.

In the US clinical studies conducted as verification studies, i.e., the Advance II study, the Progress Mini study, and the Progress Nova study, the efficacy of the Propel was evaluated based on the primary endpoint, "need for postoperative interventions at Day 30." The percentage of subjects with a need for postoperative interventions at Day 30 in these studies was 33.3%, 38.8%, and 11.5% in the test groups, and 46.9%, 62.7%, and 32.8% in the control groups, respectively. The all studies demonstrated a significant reduction in the test groups compared to the control groups (McNemar's test, $P = 0.0280$, 0.0070, and 0.0023). The published articles submitted supported these US clinical study results.

No unknown adverse event was reported in the US clinical studies or the published articles submitted. One case of infection (fungus) reported in a published article was the only serious adverse event for which a causal relationship to the Propel could not be ruled out. In the US clinical studies, debris resembling mold or fungal elements was observed in both test and control groups, which however did not lead to infection or any adverse event. This suggests that it was not a Propel-specific adverse event but a common event that could occur after ESS even without the Propel. The published article submitted

reported no concerns in long-term safety of the Propel. The safety of the Propel is thus clinically acceptable.

PMDA comprehensively reviewed the data submitted taking into account the comments from the Expert Discussion, and has concluded that the efficacy and safety of the Propel are assured.

As a result of its review, PMDA has concluded that the Propel may be approved for marketing for the following intended use and that the results should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Propel Sinus Implants is intended for use to maintain nasal patency following sinus surgery in adult patients with chronic rhinosinusitis.

Review Report

September 13, 2024

Product for Review

Classification	Medical Product 4, Orthopedic product
Term Name	Bioabsorbable drug-eluting stent for sinus (to be newly created)
Brand Name	Propel Sinus Implants
Applicant	Medtronic Japan Co., Ltd.
Date of Application	November 30, 2023 (Application for marketing approval of a medical device)
Proposed Intended Use	Propel Sinus Implants is intended for use to maintain nasal patency following sinus surgery in patients aged ≥18 years with chronic sinusitis. Propel Sinus Stent provides stabilization of the turbinates, prevents obstruction by tissue adhesions, and reduces inflammation and edema thereby reducing the need for postoperative interventions.

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List of Abbreviations

CRS	Chronic Rhinosinusitis
ESS	Endoscopic Sinus Surgery
FIH	First in human
FSO	Opening of frontal sinus
ITT	Intention to treat
LM	Lund-Mackay
MF	Mometasone Furoate
PBS	Phosphate-buffered-saline
PEG	Polyethylene glycol
PGLA	Poly lactic-co-Glycolic Acid
PK	Pharmacokinetics
PLCL	ε-caprolactone-co-L-lactide
SALT	Serious adverse local tissue response
SNOT	Sino-Nasal Outcome Test
VAS	Visual Analogue Scale

I. Product Overview

Propel Sinus Implants (hereinafter referred to as "Propel") is a bioabsorbable self-expanding drug-eluting stent for sinus (hereinafter referred to as "Propel stent") to be used to maintain paranasal patency following endoscopic sinus surgery (ESS) for the treatment of chronic rhinosinusitis (CRS), with a delivery system (hereinafter referred to as "Propel delivery system") for stent placement (Figure 1). The compressed Propel stent is loaded into the tip of the Propel delivery system through the funnel. The Propel delivery system is then moved forward in the sinus endoscopically. When the delivery system reaches the intended placement site, pressing the pusher allows the stent to be deployed.

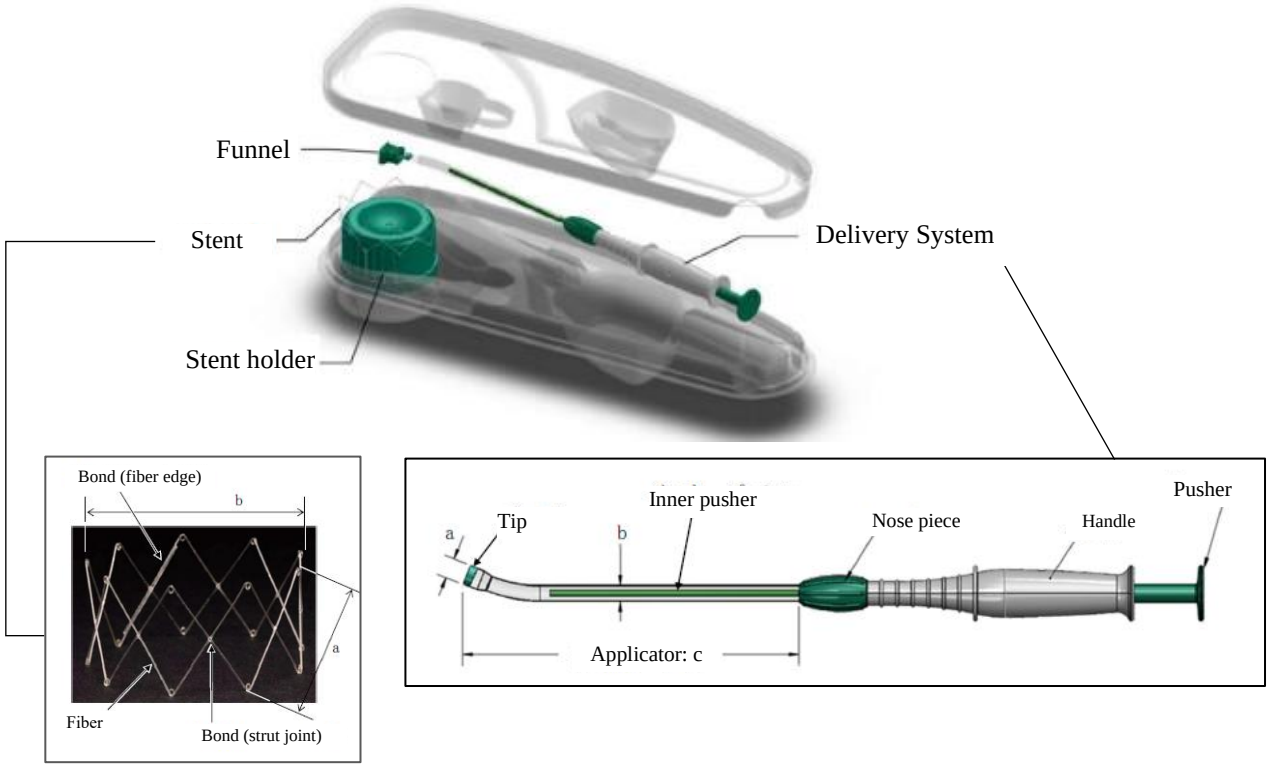
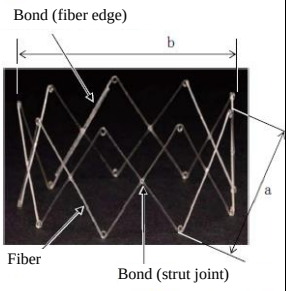
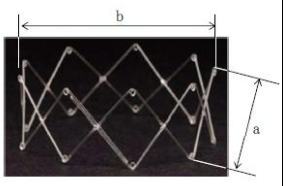
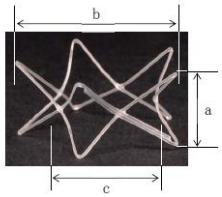


Figure 1. Appearance of the Propel

The Propel stent is available in 3 models for different sites (Table 1). While maintaining post-ESS paranasal patency for approximately 2 weeks, ≥90% of its structure is gradually absorbed by hydrolysis through the mucosal tissues over 30 to 45 days, becoming invisible after 60 days. The fibers of the Propel stent are made of a bioabsorbable polymer matrix containing poly lactic-co-glycolic acid (PGLA) The adhesive to glue the fiber edges to the struts is made from ε-caprolactone-co-L-lactide (PLCL). To alleviate inflammation and edema, the stent surface is coated with mometasone furoate (MF), a corticosteroid, and a mixture of poly DL-lactic-co-glycolic acid and polyethylene glycol (PEG) (hereinafter referred to as the drug coating). MF is the active ingredient of "Nasonex Nasal 50 µg 56 Sprays" and "Nasonex Nasal 50 µg 112 Sprays" (Organon K.K.) approved for allergic rhinitis (Approved Number 22000AMX01710000) (hereinafter referred to as "Nasonex") that have topical anti-inflammatory activity. The Propel is the first drug-eluting stent containing MF.

Table 1. Appearance of the Propel stent

Model	**Propel**	**Propel Mini**	**Propel Contour**
Application site	Ethmoid sinus	Ethmoid sinus and frontal sinus	Frontal sinus
Stent			
Nominal size a × b (mm)	25 × 50	18 × 42.5	8 × 27
Waist diameter c (mm)	[redacted]		
Number of crowns			
Fiber diameter (mm)			
Maximum collapsed diameter-Maximum expanded diameter (mm)			
Surface area (mm²)			
Mometasone content per unit area (μg/mm²)			

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in support of the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the Propel declared that they did not fall under the Item 5 in Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Rhinosinusitis is an inflammation of the tissue in any of the 4 paranasal cavities called sinuses (maxillary sinuses, ethmoid sinuses, frontal sinuses, and sphenoid sinuses). It causes respiratory symptoms such as nasal congestion, rhinorrhea, postnasal drip, and cough, accompanied by headache, cheek pain, and olfactory dysfunction. Rhinosinusitis with those symptoms lasting for ≥12 weeks is diagnosed as CRS.[1] CRS is treated by intranasal irrigation or other topical therapies, or drug therapy (e.g., antimicrobials, airway mucolytics, and steroids). CRS that does not respond well to drug therapy is treated by ESS.[1]

ESS is intended to create a good airflow and drainage pathway by enlarging the natural opening of sinuses. ESS removes the walls of the 4 paranasal cavities to create a single cavity (Figure 2). ESS is associated with postoperative risks of the narrowing of the treated natural sinus opening due to the lateralization of the middle turbinate, or inflammation at the surgical site, or swelling and tissue adhesion at the surgical site in its healing process. To reduce these risks, ESS is followed by removal of intranasal scar tissue and blood clots, nasal irrigation, and hemostasis with an electric scalpel. In the surgically

enlarged ethmoid sinus, hydrolysable or non-hydrolysable packing materials, dressing materials, gauzes, or sponges (hereinafter referred to as "packing materials") are placed for approximately 1 to 2 weeks after ESS in order to stop bleeding and prevent tissue adhesion in the nose. After these interventions, patients receive follow-up with or without drug therapy (e.g., antimicrobials or steroids [nasal drop, spray, or oral]) according to their condition. The post-ESS frontal sinus, in which packing materials are not placed, is treated by personalized drug therapy and patients receive follow-up. Additional drug therapy with steroids, etc., or surgical intervention such as surgical tissue adhesiolysis is administered as necessary.

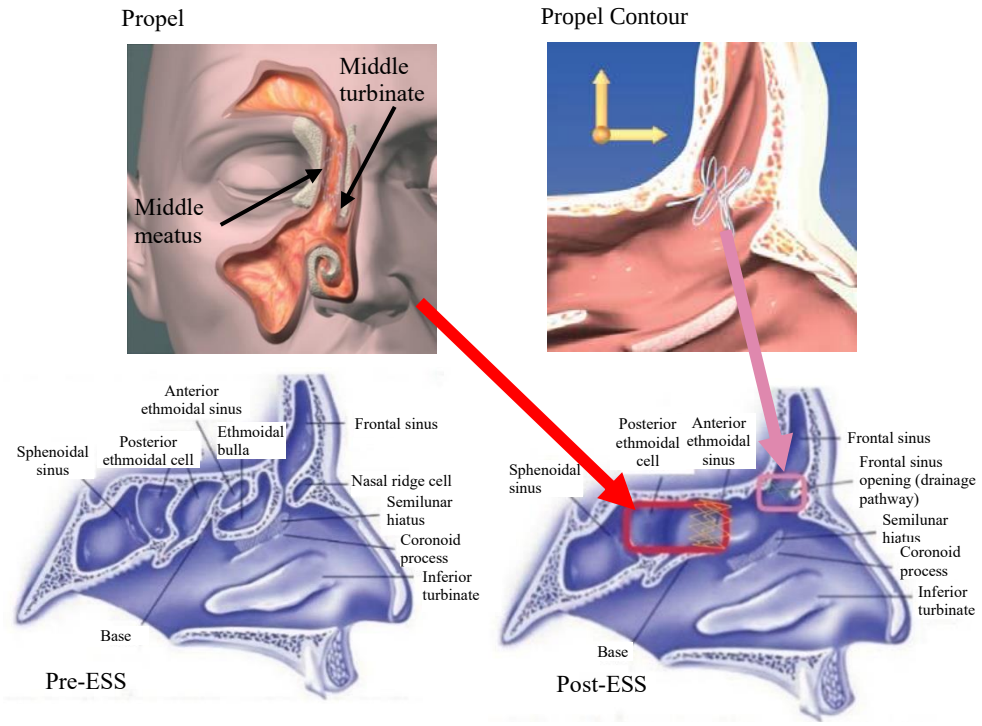


Figure 2. Placement sites of the Propel stent

The applicant raised the following issues with current post-ESS interventions:

(a) The duration of packing material placement is not long enough to achieve tissue separation at the surgical site.

(b) Removal of packing materials may cause pain or hemorrhage.

(c) Oral steroids may cause adverse drug reactions (e.g., susceptibility to infection, cataract, glaucoma, and osteoporosis[2]).

(d) Approximately 60% of steroids administered through nasal drops or sprays is removed by peristalsis of the nasal mucosa in approximately 15 minutes.[3]

To address these issues, the development of the Propel began in view of the following concepts:

(a) The self-expanding stent is designed so that the middle turbinate is stable after ESS and the ethmoid sinus opening and the frontal sinus opening (FSO) are supported, and thereby the paranasal patency is maintained.

(b) The stent is bio-decomposed and bio-absorbed so that it does not need to be removed.

(c) After ESS, the stent remains in the surgical site, gradually releasing the drug over a period during which inflammation-associated edema, etc. are likely to occur.

1.A.(2) Use in foreign countries

Table 2 presents the information regarding the approval status overseas. In the US and Europe, the number of shipments was [redacted] as of December 2022.

Table 2. Approvals in foreign countries

Country	Brand name	Intended use or indication	Date of approval
US	PROPEL SINUS IMPLANT	The Propel Sinus Implant is intended for use in patients ≥18 years of age following ethmoid sinus surgery to maintain patency, thereby reducing the need for postoperative interventions such as surgical adhesiolysis and/or use of oral steroids. The Propel Sinus Implant separates mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces edema.	August 2011
	PROPEL MINI SINUS IMPLANT	The Propel Mini Sinus Implant is intended for use in patients ≥18 years of age following ethmoid/frontal sinus surgery to maintain patency of the ethmoid sinus/frontal sinus opening. The Propel Mini Sinus Implant separates/dilates surrounding mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces inflammation. The implant reduces the need for postoperative interventions such as surgical adhesiolysis and/or use of oral steroids.	September 2012 (ethmoidal sinus) March 2016 (frontal sinus)
	PROPEL CONTOUR SINUS IMPLANT	The Propel Contour Sinus Implant is intended for use in patients ≥18 years of age to maintain patency of the frontal and maxillary sinus following sinus surgery and locally deliver steroids to the sinus mucosa. The Propel Contour Sinus Implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema. The implant reduces the need for postoperative interventions such as surgical adhesiolysis and/or use of oral steroids.	February 2017
Europe	PROPEL SINUS IMPLANT	The Propel Sinus Implant is intended for use in patients following sinus surgery to separate mucosal tissues, provide stabilization of the middle turbinate, prevent obstruction by adhesions, and minimize edema thereby maintaining patency of the ethmoid sinus opening. The implant reduces the need for postoperative interventions such as surgical adhesiolysis and/or use of oral steroids. The implant contains 370 µg of MF, which gradually elutes into the treated tissues over time to minimize edema.	July 2014
	PROPEL MINI SINUS IMPLANT	The Propel Mini Sinus Implant is intended for use in patients following sinus surgery to separate mucosal tissues, provide stabilization of the middle turbinate, prevent obstruction by adhesions, and minimize edema thereby maintaining patency of the ethmoid or frontal sinus opening. The implant reduces the need for postoperative interventions such as surgical adhesiolysis and/or use of oral steroids. The implant contains 370 µg of MF, which gradually elutes into the treated tissues over time to minimize edema.	May 2017
	PROPEL CONTOUR SINUS IMPLANT	The Propel Contour Sinus Implant is intended for use in patients following sinus surgery to maintain patency of the frontal sinus and locally deliver steroids to the sinus mucosa. The Propel Contour Sinus Implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema. The implant reduces the need for postoperative interventions such as surgical adhesiolysis and/or use of oral steroids.	May 2021

1.A.(3) Malfunctions and adverse events reported in foreign countries

Tables 3 to 6 show malfunctions and adverse events reported in foreign regulatory authorities as of December 2022.

Table 3. Malfunctions and adverse events reported overseas (Propel)

Adverse event	Number of events	Incidence*
Infection	[redacted]	0.0011%
Pain		0.0008%
Visual abnormality		0.0005%
Choking		0.0003%
Migration		0.0008%
Dysfunction		0.0003%

*Incidence based on the number of shipments of this model

Table 4. Malfunctions and adverse events reported overseas (Propel Mini)

Adverse event	Number of events	Incidence*
Cerebrospinal rhinorrhea	[redacted]	0.0006%
Infection		0.0003%
Inflammation		0.0003%
Migration		0.0006%

*Incidence based on the number of shipments of this model

Table 5. Malfunctions and adverse events reported overseas (Propel Contour)

Adverse event	Number of events	Incidence*
Cerebrospinal rhinorrhea	[redacted]	0.0009%

*Incidence based on the number of shipments of this model

Table 6. Malfunctions and adverse events reported overseas (model unknown)

Adverse event	Number of events
Infection	2
Inflammation	1
Hemorrhage	1
Granulation	1
Dysfunction	1
Migration	1

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

Among the performance and safety specifications of the Propel, the following performance specifications were proposed.

- Propel stent

Bond joint integrity, bond joint tensile strength, radial strength, retention capacity, coating integrity, and inherent viscosity

- Drug coating

Drug content, drug content uniformity, identification of drug, drug elution rate, degradation products/impurities, and residual solvents

- Propel delivery system

Maximum tensile strength of applicator and nosepiece bond joint, maximum tensile strength of handle, inner pusher, and tip bond joints, functional test, and fatigue test

The proposed quality and safety specifications of the Propel were sterility assurance and biological safety.

2.(1). B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the proposed performance and safety specifications to evaluate the appropriateness of the test parameters and specification limits taking into consideration the discussion described later in Section "2.(4) Mechanical safety," and concluded that there was no particular problem in the submitted data.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

To support the physicochemical properties of the Propel, the applicant submitted data on tests for drug content, drug content uniformity, identification of drug, drug elution rate, degradation products and impurities, residual solvents, intrinsic viscosity, and coating integrity. The test results met the predefined specifications, assuring the physicochemical properties of the Propel stent.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the physicochemical properties and concluded that there was no particular problem.

2.(3) Biological safety

2.(3).A Summary of the data submitted

To support the biological safety of the Propel, the applicant submitted the results of biological safety studies conducted in accordance with the "Revision of basic principles of biological safety evaluation required for marketing application for medical devices (in Japanese)" (PSEHB/MDED Notification No. 0106-1, dated January 6, 2020) and ISO 10993-1. The biological safety was tested separately for the Propel stent and Propel delivery system based on their contact risk levels. The Propel stent, for being categorized as long-term contact (>30 days) implant, requires tests for cytotoxicity, sensitization, irritation/intracutaneous reactivity, material-mediated pyrogenicity, acute systemic toxicity, sub-acute systemic toxicity, sub-chronic systemic toxicity, chronic systemic toxicity, implantation, genotoxicity, and carcinogenicity. The Propel delivery system, a limited-contact (≤24 hours) external communicating device, requires to be tested for cytotoxicity, sensitization, irritation/intracutaneous reactivity, material-mediated pyrogenicity, and acute systemic toxicity.

2.(3).A.1) Biological safety assessment of the Propel stent

The Propel is available in 3 models with different shapes. Since all of the models use the same raw materials, manufacturing process, sterilization conditions, and packaging conditions, the Propel was used in the following biological safety studies as sample: Cytotoxicity, sensitization, intracutaneous reactivity, sub-chronic systemic toxicity, and genotoxicity. The studies showed no findings of biological safety concerns.

No pyrogenicity, acute systemic toxicity, sub-acute systemic toxicity, chronic systemic toxicity, or carcinogenicity study of the Propel was newly conducted for the reasons shown below. Instead, the biological safety of the Propel was assessed based on its existing information.

The Propel stent uses no raw material listed in ISO 10993-11 Annex G and contains no pyrogenic substance.

The biological safety of the Propel can be assured without conducting an acute systemic toxicity, sub-acute systemic toxicity, chronic systemic toxicity, or carcinogenicity study for the following reasons: (1) The results of the biological safety studies and performance tests using the Propel stent as sample showed no safety issue; (2) the results of the drug elution and degradation tests described later showed that no harmful substance was released immediately after implantation or after the end of the sub-chronic test period, or that those substances, if any, were unlikely to cause any considerable clinical problems; and (3) comprehensive assessment of toxicity information from published articles on each raw material (based on their generic names) and toxicity test results of Propel-derived substances that may come into contact in clinical use raised no concerns.

2.(3).A.2) Biological safety assessment of the Propel delivery system

The cytotoxicity, sensitization, and intracutaneous reactivity studies were conducted using the Propel delivery system. None of the studies yielded any significant findings. The delivery systems of the Propel Mini and the Propel Contour have a tube and inner pusher made of stainless steel ([redacted]), which is not used in the Propel delivery system. [redacted] is used in approved medical devices with a risk level of contact with body fluids is comparable to or higher than that of the Propel delivery system. Thus, there is no safety issue in using this material.

The Propel comes into contact with a damaged surface for a short time, and the eluate in the delivery system does not flow into the body. A cytotoxicity study using extracts showed no toxicity, indicating that the Propel Delivery system is very unlikely to cause acute systemic toxicity. An acute systemic toxicity study of [redacted], the major raw material of the Propel Delivery system, also revealed no problems. The same explanation has been given about the pyrogenicity of the Propel Delivery system as that for the Propel stent.

2.(3).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the following issues since the Propel stent is a drug-coated bioabsorbable product:

(a) Degradation behavior, degradation products, and effects of interactions between degradation products and MF of the Propel stent on biological safety
(b) Toxicity of MF

The applicant's explanation:

(a) Degradation behavior, degradation products, and effects of interactions between degradation products and MF of the Propel stent on biological safety

Table 7 presents the degradation products of the raw materials of the Propel stent, other than MF.

Table 7. Degradation products of the raw materials of the Propel stent

Raw material	Degradation products
PGLA	PGLA undergoes hydrolysis to generate monomers of lactic acid and glycolic acid, which are subsequently metabolized *in vivo* to CO_2 and H_2O through the Krebs cycle.[4,5] • Lactic acid → Pyruvic acid → Tricarboxylic acid cycle (TCA) → CO_2, H_2O • Glycolic acid → Glyoxylate → Glycine → Serine →TCA → CO_2, H_2O
PLCL	PLCL undergoes hydrolysis to generate 6-hydroxycaproic acid, lactic acid, and oligomers.[6,7,8] • Lactic acid → Pyruvic acid → Tricarboxylic acid cycle (TCA) → CO_2, H_2O • 6-Hydroxycaproic acid is excreted from the body through phase 1 oxidation and phase 2 conjugation.
Poly DL-lactic-co-glycolic acid	The same as PGLA
PEG	PEG is oxidized naturally in the presence of air (oxygen), heat, humidity, and light. When administered orally or percutaneously, PEG (PEG6000), which is a biologically inactive material used in the Propel, is not absorbed from the gastrointestinal tract and therefore is not influenced by intestinal microorganisms. Studies show that 96% of the dose of PEG6000 administered was excreted into urine within 12 hours after intravenous administration to men at a dose of 14 mg/kg body weight.[9,10,11]

No data on the maximum daily exposure limits of these degradation products are available. The degradation products of each raw material of the Propel are known to be decomposed to CO_2 and H_2O, and then excreted from the body. The biological safety results have shown no toxic property of the Propel stent. These findings suggest that the raw materials of the Propel stent and their degradation products have a satisfactory safety profile.

Interactions between the degradation products and MF are unlikely to affect the biological safety of the Propel stent because its degradation products are decomposed to CO_2 and H_2O and then excreted from the body, and no raw material-related adverse events have been reported in the US clinical studies or the overseas post-marketing adverse event reports.

(b) Toxicity of MF

The MF used in the Propel stent conforms to the United States Pharmacopeia and the European Pharmacopoeia. Since the Propel MF has a comparable quality to that of the drug substance of Nasonex, the single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and antigenicity of the Propel MF were assessed based on the published information of Nasonex. The toxicological assessments showed that the amount of MF used in the Propel stent was too small to impose any clinical risk.

PMDA accepted the applicant's explanations, reviewed the data supporting the biological safety, and concluded that there was no particular problem.

2.(4) Mechanical safety

2.(4).A Summary of the data submitted

To support the mechanical safety of the Propel stent, the applicant submitted data on tests for deployment diameter, radial strength, joint integrity, joint tensile strength. To support the mechanical safety of the Propel Delivery system, the applicant submitted data on tests for maximum joint tensile strength, fatigue,

and load required for stent deployment. The test results met the predefined acceptance criteria, assuring the mechanical safety of the Propel.

2.(4).B Outline of the review conducted by PMDA

The Propel stent needs to be strong enough to support the middle turbinate or FSO in order to maintain sinus patency. PMDA asked the applicant to explain the justification of the acceptance criteria for the radial strength of the Propel stent. In this mechanical safety section, the radial strength tested using the Propel stent before the start of the degradation is discussed. The radial strength of the Propel stent in the degradation process is discussed later in Section "2.(6) Performance."

The applicant's explanation:

The attainment criteria for stent radial strength are [redacted] for the Propel and the Propel Mini, and [redacted] for the Propel Contour. These correspond to the stent compression rates determined taking into consideration the standard height and width of the post-ESS ethmoid sinus, and the diameter of the post-ESS FSO reported in published articles, etc. The reference values were determined from the results of tests of the prototypes in cadavers with these anatomical structures, which showed that the stent appropriately supported the sinus cavity.

PMDA accepted the applicant's explanations, taking into account the discussion about anatomical differences between Caucasian and Japanese subjects described later in Section 6.B.(1), reviewed the data supporting the mechanical safety, and concluded that there was no particular problem.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

Stability study of the Propel was conducted using a real-time degradation product (2 years of degradation). All of the tests in the performance and safety specifications, other than the tests for drug content uniformity and residual solvents specified for drug coating, showed the conformity of the Propel to the specifications. Drug content uniformity test was omitted as it is meant for manufacturing variation checking before batch release. Residual solvent test was also omitted because [redacted], a solvent, is not added after manufacturing and there is no concern about an increase in the residual solvent.

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the stability and durability, and concluded that there was no particular problem.

2.(6) Performance

2.(6).A Summary of the data submitted

To support the performance of the Propel stent, the applicant submitted the test results of retention capacity, degradation characteristics, drug release rate in rabbit maxillary sinus, and comparison with the packing materials. To support the performance of the Propel Delivery system, the applicant submitted the results of a function test. All test results met the specified acceptance criteria, assuring the performance of the Propel.

2.(6).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the following points on the performance data submitted.

(a) Justification of the ethmoid sinus model, sinus opening model, and paranasal sinus model used in the tests for retention capacity, degradation characteristics, and comparison with the packing materials of the Propel stent

(b) Differences in degradation behavior between the degradation characteristics test of the Propel stent and the drug release rate test in the rabbit maxillary sinus

(c) Justification of the dose of MF loaded on the Propel stent for the drug release rate test in the rabbit maxillary sinus and reasons for not assessing the optimal dose of MF in humans

The applicant's explanation:

(a) Justification of the ethmoid sinus model, sinus opening model, and paranasal sinus model used in the tests for retention capacity, degradation characteristics, and comparison with the packing materials of the Propel stent

The ethmoid sinus model is comprised of the main structure made of [redacted] and a [redacted] plate set in the main structure to mimic the middle turbinate. The sinus opening model is comprised of the main structure made of [redacted] and a [redacted] plate set in the main structure to mimic the sinus opening. The plate of the ethmoid sinus model weighs [redacted] and the plate of the sinus opening model weighs [redacted]. Those weights were determined based on the prototype tests using cadavers as for the attainment criteria for the radial strength test [see Section "2.(4).B Outline of the review conducted by PMDA"]. The models thus appropriately reproduced the expected pressure applied on the Propel stent. The ethmoid sinus model was designed assuming the post-ESS nasal cavity size of [redacted] based on a published article on the anatomical structure of the paranasal sinuses.[12] The paranasal sinus model was created based on the pictures of the anatomical structure, CT scans, and endoscopic anatomy videos of cadavers.[13]

A design verification test was conducted with test samples placed in the ethmoid sinus models by over time observation at each time point during storage at [redacted]. The repeatability of the moist condition was tested with [redacted]. In this condition, the Propel was expected to be dissolved faster than in the clinical environment, and this may result in faster time-course changes in stress. Therefore, the test appropriately simulated a severer moist condition.

(b) Differences in degradation behavior between the degradation characteristics test of the Propel stent and the drug release rate test in the rabbit maxillary sinus

The degradation characteristics test measured a percent decrease in intrinsic viscosity as a degradation characteristic index of the stent base material. The results were [redacted]% at Day 3, [redacted]% at Day 7, [redacted]% at Day 14, and [redacted]% at Day 30. The drug release rate test in the rabbit maxillary sinus measured a bioabsorption rate as a degradation characteristic index of the stent base material. The results were [redacted] at Days 3 and 7, [redacted]% at Day 14, and [redacted]% at Day 30. The results of these tests showed no consistent trend, which is likely explained by the following difference in the test system between the tests: The degradation characteristics test used the stent immersed in a phosphate-buffered-saline (PBS) solution

in a test tube without blood circulation and mechanical load. In both tests, however, the stent was degraded over time and the stent base material was degraded at approximately Day 30. The Propel is expected to be used in the clinical environment similar to that of the drug release rate test in the rabbit maxillary sinus. Thus, the biological reaction to the Propel was able to be assessed exhaustively through the test.

(c) Justification of the dose of MF loaded on the Propel stent for the drug release rate test in the rabbit maxillary sinus and reasons for not assessing the optimal dose of MF in humans

The dose of MF loaded on the Propel stent was determined with reference to the dose of Nasonex. The approved maximum dose of Nasonex is 200 µg/day in Japan and the US.[14] [redacted].

The drug release rate test using test samples containing a high dose ([redacted] mg) and a low dose ([redacted] µg) of MF in the rabbit maxillary sinus demonstrated that ≥[redacted]% of the total MF dose was released by Day 13 and almost all of the dose by Day 28 even at the low dose of [redacted] µg. The MF concentration in the maxillary sinus tissue met the early target threshold. On the basis of the MF dose per the unit area of the stent, the MF dose for the final product was determined to increase to 370 µg.

The results of the drug release rate test in the rabbit maxillary sinus and other relevant data show that the maximum daily amount of MF released from the Propel is [redacted] µg with the Propel placed in a sinus. The worst-case maximum daily amount of the eluate is estimated to be [redacted] µg when the maximum allowable number of the Propel (4 stents) are used. Multiple nasal spray administration of Nasonex, which is approved in Japan, at 800 µg/day for 7 days to adult Japanese men, caused no systemic transfer of MF. A study suggested no safety issue after multiple administration of Nasonex at the same dose as above for 2 weeks.[16] These results assure the clinical safety of the Propel. The optimal dose of MF was not discussed because the Consensus II study, which was the first in human (FIH) US clinical study of the Propel, demonstrated its intended efficacy and safety.

PMDA concluded that although the optimal MF dose for the Propel was not necessarily discussed, there was no considerable problem in the proposed dose of MF loaded on the Propel for the following reasons: The dose of MF can be estimated from the clinical data of Nasonex, which has the same mechanism of action at the same action site as the Propel MF; the safety of the daily amount of MF released from the Propel is explainable by comparing with Nasonex; and the contribution of MF to the efficacy of the Propel is explainable from the results of the US clinical studies later described. PMDA reviewed the other data supporting the performance and concluded that there was no particular problem.

2.(7) Directions for use

2.(7).A Summary of the data submitted

To support the directions for use of the Propel, the applicant conducted mock tests using cadavers for the Propel, and using a paranasal sinus model for the Propel Mini and Propel Contour. All of the test results met the specified acceptance criteria, indicating that the Propel has a clinically acceptable maneuverability.

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the directions for use, and concluded that there was no particular problem.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the Propel meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Propel to the Essential Principles as shown below.

(1) PMDA's view on the conformity of the Propel to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:

As described later in Section "6.B Outline of the review conducted by PMDA," the clinical evaluation submitted showed that the Propel maintained sinus patency after ESS, suggesting a reduction in the need for postoperative intervention. The Propel has been shown to have efficacy and safety when it is used in patients selected as eligible for the Propel therapy by physicians who understand that the Propel has no hemostatic property unlike the packing materials, which are used after ESS in clinical practice in Japan. The Propel conforms to Articles 3 and 6.

(2) PMDA's view on the conformity of the Propel to Article 17, which stipulates requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on Precautions, etc.):

As described later in Section "6.B Outline of the review conducted by PMDA," the following information should be provided through the Information on Precautions, etc.: The Propel has no hemostatic property unlike the packing materials; there is no clinical experience of using the Propel in combination with the packing materials; and the use of the Propel does not necessarily eliminate the need for post-ESS interventions, and post-ESS follow-up should be continued.

Based on the above, PMDA concluded that there was no particular problem with the conformity of the Propel to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971:2019 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA reviewed the document on risk management taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization methods for the Propel (results of sterilization validation). The applicant also submitted data on bacterial endotoxins from the manufacturing process. The test results met the specified acceptance criteria.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the manufacturing process, and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

For clinical evaluation of the Propel, the applicant submitted the results of the US clinical studies and a clinical evaluation report based on published articles.

6.A.(1) US clinical studies

The applicant submitted clinical study data of the Propel, in form of results from 5 US clinical studies listed in Table 8. The primary endpoint of the Advance II, the PROGRESS Mini, and the PROGRESS Nova studies, which were verification studies, was the need for postoperative interventions at Day 30. This was a composite endpoint that included surgical intervention and/or oral steroid intervention. Summaries of the 2 exploratory studies and details of the 3 verification studies are presented below.

Table 8. Summaries of the US clinical studies

Study title (positioning of study)	Test	Control	Placement site	Follow-up period
Consensus II (exploratory, FIH)	PROPEL	Non-drug-eluting stent	Ethmoid sinus	Day 60
Advance (exploratory)	PROPEL	-		Month 6
Advance II (verification)	PROPEL	Non-drug-eluting stent		Day 90
PROGRESS Mini (verification)	Propel Mini	ESS alone	Frontal sinus	Day 90
PROGRESS Nova (verification)	Propel Contour	ESS alone		Day 90

6.A.(1).1) Consensus II study (study period, [redacted], 20[redacted] to [redacted], 20[redacted])

The Consensus II study was an exploratory clinical study to evaluate the steroid release performance, efficacy, and safety of the steroid-eluting Propel stents (stent length, [redacted] and [redacted] mm), the test device, after ESS in patients with CRS in comparison with a non-drug-eluting stent, the control device. This study was a randomized, double-blind, self-controlled study that enrolled 50 patients at 4 study sites in the US. Of 50 subjects, 45 (Cohort A) were randomized after ESS to the test group (Propel) or the control group (non-drug-eluting stent). The remaining 5 subjects (Cohort B) received the bilateral Propel stents for a pharmacokinetic study. Since the Consensus II study was a FIH study, the first 7 subjects in the Cohort A received the [redacted]-mm test device (Cohort A [[redacted] mm]). The subsequent 13 subjects received the [redacted]-mm test device (Cohort A [[redacted] mm]). On the basis of the results of an interim analysis in the 20 subjects, 25 subjects received the [redacted]-mm test device (Continuous Cohort A). A total of 49 subjects completed the final follow-up visit at Day 60. One subject was lost to follow-up.

The primary endpoints were delivery success rate (performance), ethmoid sinusitis assessment at Day 21 (efficacy), and the incidence of serious adverse local tissue responses (SALTs) (safety) through Day 30. In addition, systemic safety and adverse events were investigated in Cohort B.

The primary performance endpoint was delivery success rate, which was calculated by dividing the number of successful implant deliveries by the number of sinuses in which the study implant was attempted to be delivered. The performance goal was >75%. Stent placement was considered successful when the study implant was placed in the intended sinus with not more than 2 attempts. The delivery success rate was 100% (100 of 100 sinuses) in the whole subject population. The performance goal was met.

Ethmoid sinusitis at Day 21, which was the primary efficacy endpoint, was assessed by the investigator using a 100 mm visual analogue scale (VAS) during endoscopic examination. Continuous Cohort A was subject to the analyses. A negative difference in the bilateral mean VAS score (score in the test group – score in the control group) represents milder inflammation in the test group than the control group, while a positive difference represents more severe inflammation in the test group. The mean VAS score at Day 21 was 21.6 mm in the test group and 35.9 mm in the control group, showing a statistically significant difference between the groups (analysis using general estimation equation [GEE] model, $P = 0.0069$). A similar tendency of improvement in ethmoid sinusitis was observed through Day 60.

A SALT was defined as a serious adverse event in the implanted sinus tissue that required removal of the test device to resolve associated symptoms. The safety performance goal was the incidence of SALTs of <20% through Day 30. No SALT was seen in any of the implanted sinuses (n = 55) through Day 30, achieving the performance goal of the primary safety endpoint. No SALT was reported through Day 60.

In Cohort B, the systemic safety of the Propel was evaluated based on plasma MF concentration, plasma cortisol concentration, and ophthalmological findings. Plasma MF concentrations were below the quantitation limit at all time points. Plasma cortisol concentrations were measured at baseline, and Days 7, 14, 21, and 30. The mean plasma cortisol concentrations were within the reference range (2-23 µg/dL); 6.16 µg/dL at baseline, 5.78 µg/dL at Day 7, 5.38 µg/dL at Day 14, 4.13 µg/dL at Day 21, and 5.66 µg/dL at Day 30. There was no statistically significant difference between baseline and any of the post-implant time points. For ophthalmology, intraocular pressure was measured at baseline and Day 30. The mean intraocular pressure was 10.4 mmHg at baseline and 8.7 mmHg at Day 30, showing no clinically significant change.

Adverse events that occurred through Day 90 were analyzed. No test device-related serious adverse event was reported. For 1 adverse event of tension- or stress-related headache, its causal relationship to the test device could not be ruled out and was unknown. The event resolved.

6.A.(1).2) Advance study (study period, [redacted], 20[redacted] to [redacted], 20[redacted])

The Advance study was an exploratory clinical study to collect additional data on the performance and safety, including ophthalmological safety, of the steroid-eluting Propel stent (test device) after ESS in patients with CRS. This was a single-cohort, open-label clinical study that enrolled 50 patients at 7 study sites in the US. Of 50 subjects, 10 subjects received the unilateral test device and the remaining 40 subjects received the bilateral test devices, and a total of 90 sinuses were treated with the test device. A total of 45 subjects completed the final follow-up visit at Month 6. One subject was discontinued from the study after Day 30 because of a scheduling problem and 4 subjects were lost to follow-up.

The primary endpoints were implant delivery success rate (performance) and the incidence of SALTs through Day 30. All subjects who received the test device in the target sinuses were included in analyses. No subject was excluded from analyses.

The primary performance endpoint was delivery success rate, which was calculated by dividing the number of successful implant deliveries by the number of sinuses in which the study implant was attempted to be delivered. Implant delivery was considered successful when the study implant was placed in the intended sinus with not more than 2 attempts. The performance goal was >90%. The delivery success rate was 100% (90 of 90 sinuses) in the whole subject population. The performance goal was met.

A SALT was defined as a serious adverse event (hemorrhage, burning sensation, or infection) in the implanted sinus tissue that required removal of the test device to resolve associated symptoms. The safety performance goal was the incidence of SALTs of ≤15% through Day 30. SALTs were reported in

3 subjects (6 sinuses) through Day 30. Table 9 presents the detailed narratives of each event. The incidence of SALTs was 6.7%. The safety goal was met. No SALT was newly reported after Day 30.

Table 9. Detailed narratives of SALTs in 3 subjects

	Event	Severity	Narrative and outcome
1	Headache and nose burning sensation	Moderate	The subject experienced severe headache, as well as rhinalgia and burning sensation, which were exacerbated each time the subject blew their nose. The subject took either Aleve 880 mg or Tylenol 1800 mg as necessary depending on the severity of headache. In the investigator's opinion, these symptoms were caused by ESS, but the scarring on the stents might have contributed to the exacerbated symptoms. The bilateral stents were removed. The events were related to the test device (scarring on the stents) in the investigator's opinion. The events resolved without sequelae.
2	Headache with a feeling of pressure on the eyes and removal of bilateral stents	Moderate	The subject experienced persistent frontal headache and a feeling of pressure on the back of the eyes; more severe in the right eye than the left eye. The subjects returned to the study site with the exacerbated symptoms for the follow-up examination at Day 21. The investigator found scarring on the stents, which required removal of the stents so that dissoluble dressings remaining behind the stents in the backside of the ethmoid sinuses could easily be removed. The events resolved without sequelae.
3	Headache and removal of bilateral stents	Moderate	The subject experienced headache associated with right sinus, including frontal headache, for 3 days. After the investigator removed the bilateral stents during endoscopy, the subject experienced lightheadedness, which was resolving after the subject took a Trendelenburg position. The events resolved without sequelae.

One adverse event of SALT (headache and nose burning sensation) was related to the test device. For the following 5 adverse events, a causal relationship to the test device was unknown: 1 event each of acute bilateral sinusitis, unilateral intraocular pressure increased, headache with a feeling of pressure on the eyes and removal of bilateral stents, bilateral sinusitis, and headache and removal of bilateral stents. Of these, 2 events were reported as SALTs. All events resolved.

6.A.(1).3) Advance II study (study period, [redacted], 20[redacted] to [redacted], 20[redacted])

The Advance II study was conducted in patients with CRS at 11 study sites in the US to evaluate the safety and efficacy of the steroid-eluting Propel stent (test device) in comparison with a non-drug-eluting stent (control device). This was a randomized, double-blind, self-controlled study in which the test device was placed in one sinus and the control device in the other sinus after ESS for the treatment of the bilateral ethmoid sinuses. Table 10 presents an outline of the Advance II study.

Table 10. Outline of the Advance II study

Item	Outline
Study objective	To evaluate the safety and efficacy of the drug (steroid)-eluting stent after ESS in patients with CRS
Type of study	Prospective, multicenter, randomized, double-blind, self-controlled study
Study population	Patients who met all of the inclusion criteria and none of the exclusion criteria
Inclusion criteria	<u>General inclusion criteria</u> a. Written informed consent obtained using a written information sheet approved by an IRB b. ≥18 years of age c. Willing and able to comply with protocol requirements d. Diagnosis of CRS defined as inflammation of the mucosa of the paranasal sinuses lasting for ≥8 consecutive weeks e. Has a clinical indication and has consented for ESS f. Ability to tolerate general anesthesia and ESS g. Treatment with the ESS procedure and the study device is technically feasible and clinically indicated in the ethmoid sinuses in the investigator's opinion h. ESS has been successfully completed without significant complication that would confound study results, and the patient's anatomy remains amenable to placement of the study device. i. Women of childbearing potential must not be pregnant and must agree to not become pregnant during the course of the study. <u>CT imaging inclusion criteria</u> j. CRS diagnosis confirmed by CT scan within 6 months of the ESS procedure k. Lund-Mackay (LC) score of ≥6 (including bilateral ethmoid sinus disease) l. Bilateral ethmoid sinus disease confirmed by CT scan <u>Surgical inclusion criteria</u> m. Planned ESS includes bilateral ethmoid sinus surgery. n. Septoplasty for access to the ostiomeatal complex is permitted.
Exclusion criteria	<u>General exclusion criteria</u> a. Known history of immune deficiency (IgG or IgA subclass deficiency) b. Oral steroid dependent conditions such as chronic obstructive pulmonary disease, asthma, or other conditions. c. Known history of allergy or hypersensitivity to steroids d. Clinical evidence of acute bacterial sinusitis (e.g. acute increase in purulent discharge, pyrexia, and facial pain). e. Eyes: Documented glaucoma or ocular hypertension (intraocular pressure >21 mmHg at baseline or in the past ophthalmological examination) f. Eyes: Closed angle (regardless of peripheral anterior synechia as diagnosed by gonioscopy) g. Eyes: Posterior subcapsular cataract, Grade ≥3 nuclear cataract, or Grade ≥3 cortical cataract in either eye h. Eyes: Artificial eyes i. Clinical evidence or suspicion of invasive fungal sinusitis (e.g. bone erosion on CT scan and necrotic sinus tissue) j. Clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day follow-up period k. Current or recent (within 30 days) participation in another clinical study l. History of insulin dependent diabetes mellitus m. Previously undergone ESS and experienced a cerebrospinal fluid leakage or has compromised vision as a result of a complication in a prior ESS procedure n. The middle turbinate was removed in a previous ESS. <u>Surgical exclusion criteria</u> o. Significant complication during the on-study ESS (e.g., excessive blood loss, cerebrospinal fluid leakage, and punctured lamina papyracea) p. The on-study ESS is aborted for any reason. q. The middle turbinate was removed in the on-study ESS. r. The middle turbinate required steroid injection.
Number of subjects (number of study sites)	105 subjects (11 study sites)
Follow-up period	90 days after surgery

Item	Outline
Concomitant therapy	• Steroids: The use of oral steroids and local intranasal steroid sprays was prohibited during the follow-up period up to Day 30. Continued oral steroid inhalation for asthma management was permitted during the study, but a new start or discontinuation of the existing steroid therapy was prohibited during the follow-up period. Postoperative interventions (in the sinuses) with oral steroids were permitted after Day 30 for the treatment of sinusitis if required. When the ethmoid sinus required a postoperative oral steroid intervention, it was recorded on the Endoscopic Examination page of the CRF. • Antibiotics: Antibiotic therapy was required for 14 days from the day before the surgery. Since antibiotics are commonly used after surgery, postoperative antibiotic use was included in the study design as a standard study therapy. The type of antibiotics was not specified. The study sites were allowed to adjust the dosage regimens of antibiotics provided that they were started on the day before surgery and continued as long as necessary. For the treatment of suspected infection, antibiotic therapy was allowed at any time point during the study. • Physiological saline: Spraying or irrigating the sinuses with physiological saline was permitted as necessary before surgery or during the follow-up period.
Primary endpoints	Efficacy Reduction in need for postoperative interventions at Day 30 in the test group in comparison with the control group, as determined based on endoscopic videos reviewed by the blinded independent data review committee. *Need for postoperative interventions was a composite endpoint that included surgical intervention required to resolve adhesions and oral steroid intervention required to resolve recurrent ethmoid sinusitis, and recurrent edema and/or nasal polyps. *Need for postoperative interventions was determined based on endoscopic videos reviewed by the blinded independent data review committee. Each of the 3 physicians reviewed video images. When the sinus required a postoperative intervention as determined by 2 or 3 of the 3 physicians, the sinus was assessed as "Need for postoperative intervention." Safety Ophthalmological safety through Day 90, which was defined as no clinically significant increase in intraocular pressure *A clinically significant increase in intraocular pressure was defined as a ≥10 mmHg increase in intraocular pressure of the eye on the same side as the study sinus but not in the control eye, lasting for 2 weeks. *The performance goal was the percentage of subjects with a clinically significant increase in intraocular pressure of <10%.
Secondary endpoints	Efficacy • "Incidence of polyp-like tissue formation at Day 30" as determined by the independent data review committee • Postoperative intervention, polyp-like tissue formation, lateralization of the middle turbinate, and significant adhesion at Day 30 as assessed by the investigator Safety • Ophthalmological safety, adverse events, and serious adverse events
Additional endpoint	• Scarring in the ethmoidal sinus

The Advance II study enrolled and randomized 105 subjects after ESS to the test group (Propel) or the control group (non-drug-eluting stent). A total of 102 subjects completed the final follow-up visit at Day 90, and 3 subjects were lost to follow-up (Figure 3). All subjects who received the test device (Intention to treat [ITT] population) were included in efficacy and safety analyses. Table 11 presents the patient characteristics of the ITT population (N = 105).

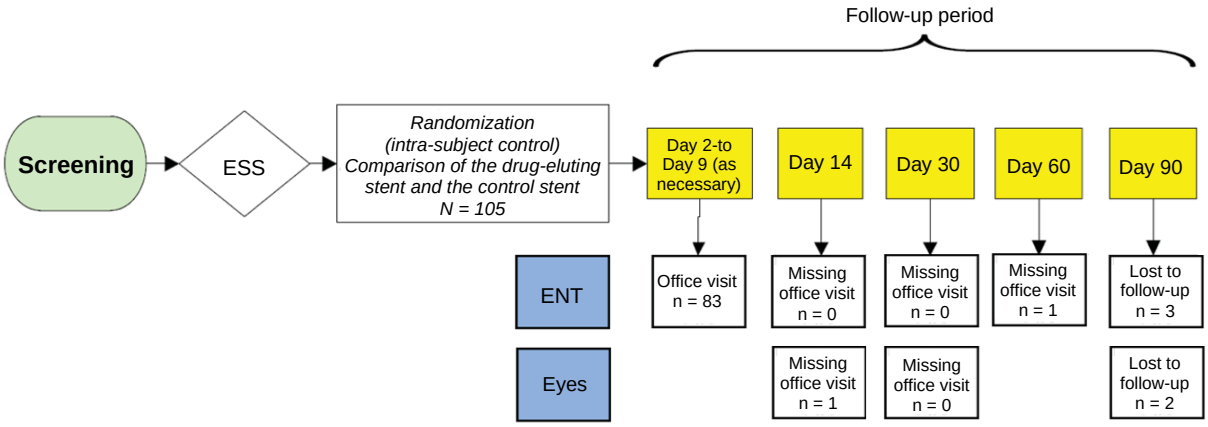


Figure 3. Disposition of subjects by follow-up visit

Table 11. Patient characteristics

	All subjects (N = 105)
Sex	N (%)
Man	60 (57.1%)
Woman	45 (42.9%)
Age (mean [SD])	46.5 (12.9)
Reported preoperative symptoms	N (%)
Nasal congestion/obstruction	95 (90.5%)
Nasal discharge discoloration	57 (54.3%)
Cough	42 (40.0%)
Toothache	18 (17.1%)
Headache	68 (64.8%)
Fatigue	50 (47.6%)
Mouth odor	15 (14.3%)
Ear pain, feeling of pressure on ear, and feeling of ear congestion	39 (37.1%)
Hyposmia or anosmia	53 (50.5%)
Facial pain and feeling of pressure on face	64 (61.0%)
Others	49 (46.7%)
History of smoking	
Never smoker	67 (63.8%)
Previous smoker, smokeless for >1 year	20 (19.0%)
Current smoker	18 (17.1%)
History of aspirin intolerance or allergy	3 (2.9%)
History of asthma as diagnosed by physician	29 (27.6%)
History of allergy	76 (72.4%)
Number of previous sinus surgeries	
None	74 (70.5%)
1	20 (19.0%)
2	6 (5.7%)
3	5 (4.8%)
≥4	0 (0.0%)

	All subjects (N = 105)
Previous sinus surgery (n = 31)	
ESS	24 (77.4%)
Sinuplasty	1 (3.2%)
Rhinoplasty	3 (9.7%)
Septoplasty	15 (48.4%)
Others	9 (29.0%)
LM CT scale	Mean (SD)
Right sinus	6.5 (2.4)
Left nasal cavity side	6.4 (2.4)
Total	12.8 (4.4)
Study sinus	6.4 (2.3)
Control sinus	6.4 (2.3)
Number of subjects with nasal polyps at baseline*	62 (59.0%)

* Nasal polyps at baseline are defined as Grade >0 nasal polyps in either right or left sinus at baseline.

In the Advance II study, 100% (105 of 105) of subjects underwent bilateral ethmoid sinus surgery. Table 12 presents concurrent surgical procedures. No restriction was imposed on the use and dose of oral or local intranasal steroids before the conduct of ESS. A total of 15 subjects received oral steroids for 2 weeks from approximately 3 days before ESS. All subjects received physiological saline sprays or nasal irrigation during the postoperative follow-up period.

Table 12. Surgical information

	All subjects (N = 105)
ESS performed	N (%)
Bilateral ethmoidal sinus surgery	105 (100%)
Sphenoidal sinusotomy	66 (62.9%)
Frontal sinusotomy	72 (68.6%)
Middle meatal antrostomy	99 (94.3%)
Inferior turbinectomy	34 (32.4%)
Middle turbinectomy	4 (3.8%)
Concha bullosa resection	11 (10.5%)
Submucosal resection	11 (10.5%)
Septoplasty	59 (56.2%)
Others	18 (17.1%)

6.A.(1).3).(a) Efficacy evaluation

The primary efficacy endpoint was a need for postoperative interventions at Day 30. The secondary efficacy endpoints were polyp-like tissue formation, investigator's assessments, ethmoid sinusitis assessment, and performance of the study devices.

Primary endpoint

The primary endpoint "need for postoperative interventions" was a composite endpoint that included (1) surgical intervention required to resolve adhesions (hereinafter referred to as "surgical intervention") and (2) postoperative oral steroid intervention required to resolve recurrent ethmoid sinusitis, and recurrent edema and/or nasal polyps (hereinafter referred to as "oral steroid intervention"). Need for these postoperative interventions was determined based on endoscopic videos reviewed by the blinded independent data review committee. Each of the 3 physicians reviewed video images. When the sinus required a postoperative intervention as determined by 2 or 3 of the 3 physicians, the sinus was assessed as "need for postoperative intervention." To assess the need for (1) surgical intervention, an element constituting the primary endpoint, the severity of tissue adhesion was graded using the 5-point scale presented in Table 13. Grade ≥2 represents "need for surgical intervention." Need for (2) oral steroid intervention was assessed based on endoscopic findings and need for medical intervention was determined. Endoscopic videos of 8.6% (9 of 105) of subjects in the whole study population were not evaluable because of inadequate imaging of the relevant site or sub-optimal video quality and were handled as missing data. A total of 96 subjects were included in the analysis.

Table 13. Adhesion assessment criteria

Grade	Assessment criteria
0	None
1	Small and non-obstructive adhesion (no separation required)
2	Obstructive adhesion which can be separated easily
3	Dense adhesion which cannot be separated easily
4	Severe complete adhesion of the middle turbinate and the nasal cavity sidewall

Grade ≥3 represents "significant adhesion."

The percentage of sinuses with a need for postoperative interventions at Day 30 was 33.3% (32 of 96 sinuses) in the test group and 46.9% (45 of 96 sinuses) in the control group, showing a statistically significant difference between the 2 groups (McNemar's test, $P = 0.0280$). The percentage of sinuses with a need for (1) surgical intervention, an element constituting the primary endpoint, was 14.0% (14 of 100 sinuses) in the test group and 29.0% (20 of 100 sinuses) in the control group, showing a

statistically significant difference between the 2 groups (McNemar's test, $P = 0.0053$). The percentage of sinuses with a need for (2) oral steroid intervention was 23.3% (20 of 86 sinuses) in the test group and 32.6% (28 of 86 sinuses) in the control group, showing a reduction in the test group compared with the control group. However, the difference was not statistically significant (McNemar's test, $P = 0.0881$). Table 14 presents the results regarding the need for postoperative interventions and its constituting elements.

Table 14. Need for postoperative interventions at Day 30 (independent data review committee)

		Test	**Control**
Number of subjects in the ITT population	N	105	105
Number of subjects with bilateral sinuses evaluable for postoperative intervention	N	96	96
Number of sinuses needing for postoperative intervention*	N (%)	**32 (33.3%)**	**45 (46.9%)**
	95% CI**	0.2404, 0.4369	0.3661, 0.5734
	P-value*	**0.0280**	
Number of subjects with bilateral sinuses evaluable for surgical intervention	N	100	100
• **Number of sinuses needing for surgical intervention to treat adhesion**	N (%)	14 (14.0%)	29 (29.0%)
	95% CI**	0.0787, 0.2237	0.2036, 0.3893
	P-value*	0.0053	
Number of subjects with bilateral sinuses evaluable for oral steroid intervention	N	86	86
• **Number of sinuses needing for oral steroid intervention**	N (%)	20 (23.3%)	28 (32.6%)
	95% CI**	0.1482, 0.3361	0.2284, 0.4352
	P-value*	0.0881	

* Postoperative interventions is a composite endpoint that includes surgical intervention required to resolve adhesions (Grade 2, 3, or 4 adhesions) and oral steroid intervention required to resolve recurrent ethmoid sinusitis, and recurrent edema and/or nasal polyps. The 2-sided *P*-values of the primary efficacy endpoint and its constituent were calculated using McNemar's test at a significance level of 0.05.
** The 95% confidence interval (CI) for each group was calculated using Clopper-Pearson's method.

Missing data resulting from no availability of evaluable endoscopic videos were imputed using the 5-step approach shown in Table 15. The sensitivity of the results to the different imputation methods was assessed (Table 15). All of the methods, except for the most conservative one ([redacted]), led to the conclusion that the test device statistically significantly reduced the frequency of postoperative interventions compared to the control device. The most conservative imputation [redacted] did not retain a statistically significant difference between the groups (McNemar's test, $P = 0.2743$). However, the results did not deny the efficacy of the Propel. The results were consistent across all of the imputation approaches, indicating no effect of missing data on the interpretation of the study results.

Table 15. Methods and results of data imputation

Imputation method	Test	Control	*P*-value (McNemar's test)
[redacted]	31.4% (33/105 sinuses)	44.8% (47/105 sinuses)	0.0231
	31.4% (33/105 sinuses)	43.8% (46/105 sinuses)	0.0326
	37.1% (39/105 sinuses)	49.5% (52/105 sinuses)	0.0374
	31.4% (33/105 sinuses)	49.5% (52/105 sinuses)	0.0030
	37.1% (39/105 sinuses)	43.8% (46/105 sinuses)	0.2743

Secondary endpoints

- Polyp-like tissue formation

Polyp-like tissue formation at Day 30 was assessed by the independent data review committee. Endoscopic videos of 23 sinuses of 20 subjects (7 sinuses in the test group, 16 sinuses in the control group) among 210 sinuses of 105 subjects were not evaluable mainly because tissue adhesion interfered with filming the inside of the ethmoid sinus and was handled as missing data. A total of 85 subjects were included in analyses. Polyp-like tissue formation was graded using the 4-point scale presented in Table 16. Grade ≥1 represents "polyp-like tissue formation." Grade ≥2 represents "definite nasal polyps."

Table 16. Assessment criteria for polyp-like tissue formation

Grade	Assessment criteria
0	None
1	Small amount of polyps or polypoid edema confined within the middle meatus
2	Multiple polyps occupying the middle meatus
3	Polyps extending beyond the middle meatus

Grade ≥2 represents "definite nasal polyps."

The incidence of polyp-like tissue formation was 61.2% (52 of 85 sinuses) in the test group and 71.8% (61 of 85 sinuses) in the control group, showing a reduction in the test group compared with the control group. However, the difference was not statistically significant (McNemar's test, $P = 0.0947$). The incidence of definite nasal polyps (Grade ≥2) was 18.8% (16 of 85 sinuses) in the test group and 34.1% (29 of 85 sinuses) in the control group, showing a statistically significant difference between the 2 groups (McNemar's test, $P = 0.0023$) (Table 17).

Table 17. Incidence of polyp-like tissue formation at Day 30 (assessed by independent data review committee)

		Test	Control
Number of subjects in the ITT population	N	105	105
Number of subjects with bilateral sinuses evaluable for polyp-like tissue formation	N	85	85
Number of sinuses **with** any **polyp-like tissue formation**	N (%) 95% CI* *P*-value**	52 (61.2%) 0.4999, 0.7156 0.0947	61 (71.8%) 0.6096, 0.8100
Number of sinuses **with definite nasal polyps (Grade 2 or 3 polyp formation)**	N (%) 95% CI* *P*-value**	16 (18.8%) 0.1116, 0.2876 0.0023	29 (34.1%) 0.2418, 0.4520

* The 95% CI for each group was calculated using Clopper-Pearson's method.
**The 2-sided *P*-values were calculated using McNemar's test at a significance level of 0.05. An exact test was performed for sinuses with Grade ≥2 polyps because there were fewer than 20 unmatched pairs.

- Investigator's assessment

Need for postoperative intervention, polyp-like tissue formation, lateralization of the middle turbinate, and significant adhesion at Day 30 were assessed by the investigator. Polyp-like tissue formation and adhesion were not evaluable in 1 subject because the partial lateralization of the middle turbinate, edematous middle turbinate, and severe edema of the middle meatus in the left sinus interfered with assessment of the inside of the ethmoid sinus, and was handled as missing data. A total 104 subjects were included in analyses. Table 18 presents the results.

Table 18. Need for postoperative interventions at Day 30 (assessed by investigator)

		Test	Control
Number of subjects in the ITT population	N	105	105
Number of subjects with bilateral sinuses evaluable for postoperative intervention	N	105	105
Number of sinuses needing for postoperative intervention*	N (%) 95% CI** *P*-value◊	23 (21.9%) 0.1442, 0.3103 0.0679	33 (31.4%) 0.2272, 0.4122
Number of subjects with bilateral sinuses evaluable for surgical intervention	N	104	104
• **Number of sinuses needing for surgical intervention to treat adhesion**	N (%) 95% CI** *P*-value◊	13 (12.5%) 0.0683, 0.2043 0.0330	23 (22.1%) 0.1457, 0.3131
Number of subjects with bilateral sinuses evaluable for oral steroid intervention	N	105	105
• **Number of sinuses needing for oral steroid intervention**	N (%) 95% CI** *P*-value◊	12 (11.4%) 0.0605, 0.1911 0.3877	16 (15.2%) 0.0897, 0.2356
Number of subjects with bilateral sinuses evaluable for polyp-like tissue formation	N	104	104
Number of sinuses with any **polyp-like tissue formation**	N (%) 95% CI** *P*-value◊	34 (32.7%) 0.2381, 0.4259 0.1701	42 (40.4%) 0.3087, 0.5046
Number of sinuses **with definite nasal polyps (Grade 2 or 3 polyp formation)**	N (%) 95% CI** *P*-value◊	4 (3.8%) 0.0106, 0.0956 0.3437	8 (7.7%) 0.0338, 0.1460
Number of subjects with bilateral sinuses evaluable for the position of the middle turbinate	N	105	105
Number of sinuses with **lateralization of the middle turbinat**e before Day 30	N (%) 95% CI** *P*-value◊	5 (4.8%) 0.0156, 0.1076 0.1797	10 (9.5%) 0.0466, 0.1682
Number of sinuses with **lateralization of the middle turbinate** at Day 30	N (%) 95% CI** *P*-value◊	2 (1.9%) 0.0023, 0.0671 0.1250	7 (6.7%) 0.0272, 0.1325
Number of subjects with bilateral sinuses evaluable for significant adhesion	N	104	104
Number of sinuses with **significant adhesion** before Day 30	N (%) 95% CI** *P*-value◊	8 (7.7%) 0.0338, 0.1460 0.0768	16 (15.4%) 0.0906, 0.2378
Number of sinuses with **significant adhesion** at Day 30	N (%) 95% CI** *P*-value◊	5 (4.8%) 0.0158, 0.1086 0.0386	13 (12.5%) 0.0683, 0.2043

* Postoperative interventions is a composite endpoint that includes surgical intervention required to resolve adhesions (Grade 2, 3, or 4 adhesions) and oral steroid intervention required to resolve recurrent ethmoid sinusitis, and recurrent edema and/or nasal polyps.
** The 95% CI for each group was calculated using Clopper-Pearson's method.
◊ The 2-sided *P*-values were calculated using McNemar's test at a significance level of 0.05. An exact test was performed when there were fewer than 20 unmatched pairs (oral steroid intervention, Grade ≥2 polyps, lateralization of the middle turbinate, and significant adhesion). Postoperative interventions and polyp-like tissue formation were counted based only on the assessments at Day 30. The lateralization of the middle turbinate and significant adhesion before Day 30 were counted as 1 event when these events occurred at either Day 14 or 30. Significant adhesion was defined as dense or severe adhesion.

The percentage of sinuses with a need for postoperative interventions at Day 30 as assessed by the investigator was 21.9% in the test group and 31.4% in the control group, showing no statistically significant difference. However, the test device was associated with a low frequency of postoperative interventions, showing a consistent tendency to the primary endpoint.

● Ethmoid sinusitis assessment

Ethmoid sinusitis at Days 14 and 30 was assessed by the investigator. Ethmoid sinusitis was defined as comprehensive symptoms including mucosal edema, erythema, thickening, and polyp-like change, and assessed using VAS during endoscopy; 0 mm represents "No inflammation," and 100 mm represents "Severe."

Table 19 presents the results of ethmoid sinusitis assessment. The difference between the test and control groups was −3.2 mm at Day 14 and −5.5 mm at Day 30. The difference at Day 30 was statistically significant between the 2 groups (t test, $P = 0.1005$ and 0.0141, respectively).

Table 19. Ethmoid sinusitis assessment (assessed by investigator)

		Test	Control	Difference (Tx – C)
Number of subjects in the ITT population	N	105	105	
Ethmoid sinusitis at Day 14 (mm)	N	105	105	105
	Mean (SD)	29.5 (23.2)	32.7 (22.4)	-3.2 (19.5)
	95% CI*	25.02, 34.00	28.34, 37.00	-6.94, 0.62
	P-value**			0.1005
Ethmoid sinusitis at Day 30 (mm)	N	103	100	98
	Mean (SD)	22.2 (20.1)	28.4 (23.1)	-5.4 (21.6)
	95% CI*	18.25, 26.12	23.82, 32.97	-9.77, -1.12
	P-value**			0.0141

Note: Inflammation was graded using the Visual analogue scale.
* The 95% CI of mean was calculated assuming a normal distribution.
** The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.

● Performance of study devices

The delivery success rate, short-term success rate (success defined as the fixation of the middle turbinate to the median nasal septum immediately after implantation or placement of the stent so that its strut reaches the anterior edge of the middle turbinate without any problem), and malfunctions were assessed by the investigator on the day of ESS.

The delivery success rate of the study devices was 100% (210 of 210 sinuses). The short-term success rate based on the fixation of the middle turbinate to the median nasal septum immediately after implantation was 99.0% (208 of 210 sinuses). The short-term success rate based on the placement of the stent so that its strut reached the anterior edge of the middle turbinate without any problem was 95.2% (200 of 210 sinuses). A total of 13 malfunctions of the study devices were reported during the procedure; including 4 cases of improper placement (replacement), 5 cases of crimping problems, and 4 cases of partial crossover of the strut. These malfunctions did not lead to health injury and resolved after replacement. The following events also occurred but not reported as malfunctions; early ejection from the nose in 2 subjects, and debris that resembled mold or fungal elements in 3 subjects (1 unit in the test group, 2 units in the control group) as assessed by the investigator and in 4 subjects (2 units in the test group, 4 units in the control group) as assessed by the independent data review committee. All of the events, except for those in 2 subjects who did not return to the study sites, resolved as confirmed by additional tests at office visits within 2 to 3 months after the events.

6.A.(1).3).(b) Safety evaluation

The primary safety endpoint was a clinically significant increase in intraocular pressure, which was defined as a ≥10 mmHg increase in intraocular pressure of the eye on the same side as the test sinus but not in the control eye, lasting for 2 weeks. The performance goal was the percentage of subjects with this event of <10%. The secondary endpoints were ophthalmological safety (intraocular pressure and lenticular opacities as confirmed by cataract test) and adverse events.

No clinically significant increase in intraocular pressure was reported through Day 90. Lenticular opacity test (nuclear opacity, cortical opacity, and posterior subcapsular opacity) revealed Grade +2 nuclear opacity in 1 adjacent eye and Grade +1 cortical opacity in 1 non-adjacent eye. No increase in posterior subcapsular opacity was observed in any eye. The test confirmed no clinically significant change.

No test device-related serious adverse event was reported. For the following adverse events, a causal relationship to the test device could not be ruled out: 2 events (2 events of acute sinusitis, 1.9%) in 2 subjects that were related to the test device, and 4 events (1 event of acute sinusitis, 1.0%; 1 event of headache, 1.0%; and 2 events of acute bilateral ethmoid sinusitis, 1.0%) in 3 subjects for which a causal relationship to the test device was unknown. All of the events resolved without sequelae.

6.A.(1).4) PROGRESS Mini study (study period, [redacted], 20[redacted] to [redacted], 20[redacted])

The PROGRESS Mini study was conducted at 11 study sites in the US to evaluate the safety and efficacy of the steroid-eluting Propel Mini stent (FSO implant) (test device), in patients with CRS in comparison with ESS alone (control). This was a randomized, single-blind, self-controlled study in which the test device was placed in one sinus and none in the other sinus after ESS for the treatment of the bilateral frontal sinuses. Table 20 presents an outline of the PROGRESS Mini study.

Table 20. Outline of the PROGRESS Mini study

Item	Outline
Study objective	To evaluate the safety and efficacy of the Propel Mini steroid-eluting stent placed in the FSO after frontal sinus surgery in patients with CRS
Type of study	Prospective, multicenter, randomized, blind, self-controlled study
Study population	Patients who met all of the inclusion criteria and none of the exclusion criteria
Inclusion criteria	General inclusion criteria a. Written informed consent obtained using a written information sheet approved by an IRB b. ≥18 years of age c. Willing and able to comply with protocol requirements d. CRS diagnosis confirmed by CT scan with symptoms lasting ≥12 consecutive weeks, accompanied by inflammation of the mucosa of the nose and paranasal sinuses. e. Has a clinical indication and has consented for ESS including bilateral frontal sinus surgery f. Ability to tolerate general anesthesia g. Treatment with the ESS procedure and placement of the Propel Mini in the FSO is technically feasible and clinically indicated in the investigator's opinion h. Women of childbearing potential must not be pregnant and must agree to not become pregnant during the course of the study. i. Women of child-bearing potential must agree to use consistent and acceptable method(s) of birth control during the course of the study. CT imaging inclusion criteria j. Documented CRS diagnosis confirmed by CT scan within 6 months of the ESS procedure k. Bilateral disease in both frontal sinuses confirmed by LM score of ≥1 on each side Surgical inclusion criteria l. Planned ESS includes bilateral ethmoidectomy (if judged necessary) and frontal sinus surgery using Draf II (A or B) dissection and/or balloon dilation, with minimum of 5-mm diameter opening created. m. Technique used for frontal sinus surgery was the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or surgical dissection and balloon dilation bilaterally). n. Septoplasty for access to the ostiomeatal complex is permitted. o. ESS including bilateral frontal sinus surgery has been successfully completed without significant complication that, in the investigator's opinion, would confound study results, and the patient's anatomy remains amenable to placement of the test device.
Exclusion criteria	General exclusion criteria a. Known history of immune deficiency such as IgG or IgA subclass deficiency, or human immunodeficiency virus (HIV). b. Oral steroid dependent conditions such as chronic obstructive pulmonary disease (COPD), asthma, or other diseases. c. Known history of allergy or hypersensitivity to corticosteroids or MF. d. Clinical symptoms of acute bacterial sinusitis (e.g. acute increase in purulent discharge, pyrexia, and facial pain). e. Clinical symptoms or suspicion of invasive fungal sinusitis (e.g. bone erosion on CT scan and necrotic sinus tissue) f. Clinical symptoms of active viral illness (e.g., tuberculosis, ocular herpes simplex, chickenpox, and measles). g. Concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g., cancer and HIV). h. Clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day follow-up period i. Current participation in another clinical study j. History of insulin dependent diabetes mellitus k. Previously undergone ESS and experienced a CSF leakage (cerebrospinal fluid leakage) or has compromised vision. Surgical exclusion criteria l. Significant complication during the on-study ESS including frontal sinus surgery (e.g., excessive blood loss, cerebrospinal fluid leakage, and punctured lamina papyracea) m. The on-study ESS is aborted for any reason. n. Sinusitis on at least one side is not amenable for placement of the test device.
Number of subjects (number of sites)	80 subjects (informed consent, 89) (11 study sites)
Follow-up period	90 days after surgery

Item	Outline
Concomitant therapy	• No restriction was imposed on oral or intranasal steroids during the preoperative period. • For example, oral steroid inhalation for asthma management was permitted during the study. Use of intranasal steroids in both sinuses was permitted from Day 14 as judged by the investigator. Spraying or irrigating the sinuses with physiological saline as necessary was recommended during the follow-up period. Antibiotic therapy was required for 10 days from the day of surgery (±1 day). Postoperative intervention with oral steroids - Frontal sinus: Oral steroid intervention was permitted to resolve a clinically significant increase in inflammation, edema, and/or nasal polyps in the FSO as judged necessary by the investigator. Frontal sinuses with a need for the intervention were recorded on the Endoscopic Examination page of the CRF. Intervention with other drugs - Other than frontal sinus: Use of oral steroids to treat conditions other than FSO inflammation was permitted after Day 30 provided that those steroids do not influence FSO inflammation. For the treatment of suspected infection at any time point during the study, antibiotic therapy was allowed.
Primary endpoints	Efficacy Reduction in need for postoperative interventions at Day 30 in the test sinus in comparison with the control sinus, as determined based on endoscopic videos reviewed by blinded independent sinus surgeons * Need for postoperative interventions is a composite endpoint included in the following: • Surgical intervention required to remove obstructive adhesions or scarring in the FSO • Postoperative oral steroid intervention required to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.
Secondary endpoints	Efficacy Endoscopic endpoints assessed by blinded independent sinus surgeons: • Incidence and severity of adhesion/scarring in the FSO at Day 30 • Severity of inflammation in the frontal recess/FSO at Day 30 • Incidence and grade of polypoid edema in the frontal recess/FSO at Day 30 Endoscopic endpoints assessed by the investigator: • Need for postoperative interventions at each visit • Severity of inflammation in the frontal recess/FSO at each visit • Incidence and severity of adhesion/scarring in the FSO at each visit • Incidence and grade of polypoid edema in the frontal recess/FSO at each visit • FSO patency rate at Day 90 • Delivery success rate of the test device CT endpoints at Day 90 as assessed by blinded independent sinus surgeons: • Maximum FSO diameter (FSO patency) • LM score • Severity of frontal disease as determined by using radiological image grading scale CT endpoints at Day 90 as assessed by the investigator: • Maximum FSO diameter (FSO patency), • LM score, and • Severity of frontal disease as determined by using radiological image grading scale.
Safety endpoints	• Adverse events through Day 90 • Serious adverse events through Day 90

The PROGRESS Mini study enrolled 89 subjects and randomized 81 subjects after ESS including frontal sinus surgery to the test group (Propel Mini) or the control group (surgery alone).The remaining 8 subjects were excluded because of discontinuation from the study for not meeting the eligibility criteria or other reasons. One of the 81 subjects had hemorrhage from the anterior ethmoidal sinus artery during the surgery before placement of the test device, which made it difficult to place the test device. A total of 80 subjects received the test device. Of these, 79 subjects completed the final follow-up visit at Day 90, and 1 subject failed to return to the site, which was handled as missing data (Figure 4). A total of 80 subjects (ITT population) were included in efficacy and safety analyses. Table 21 presents the patient characteristics of the ITT population.

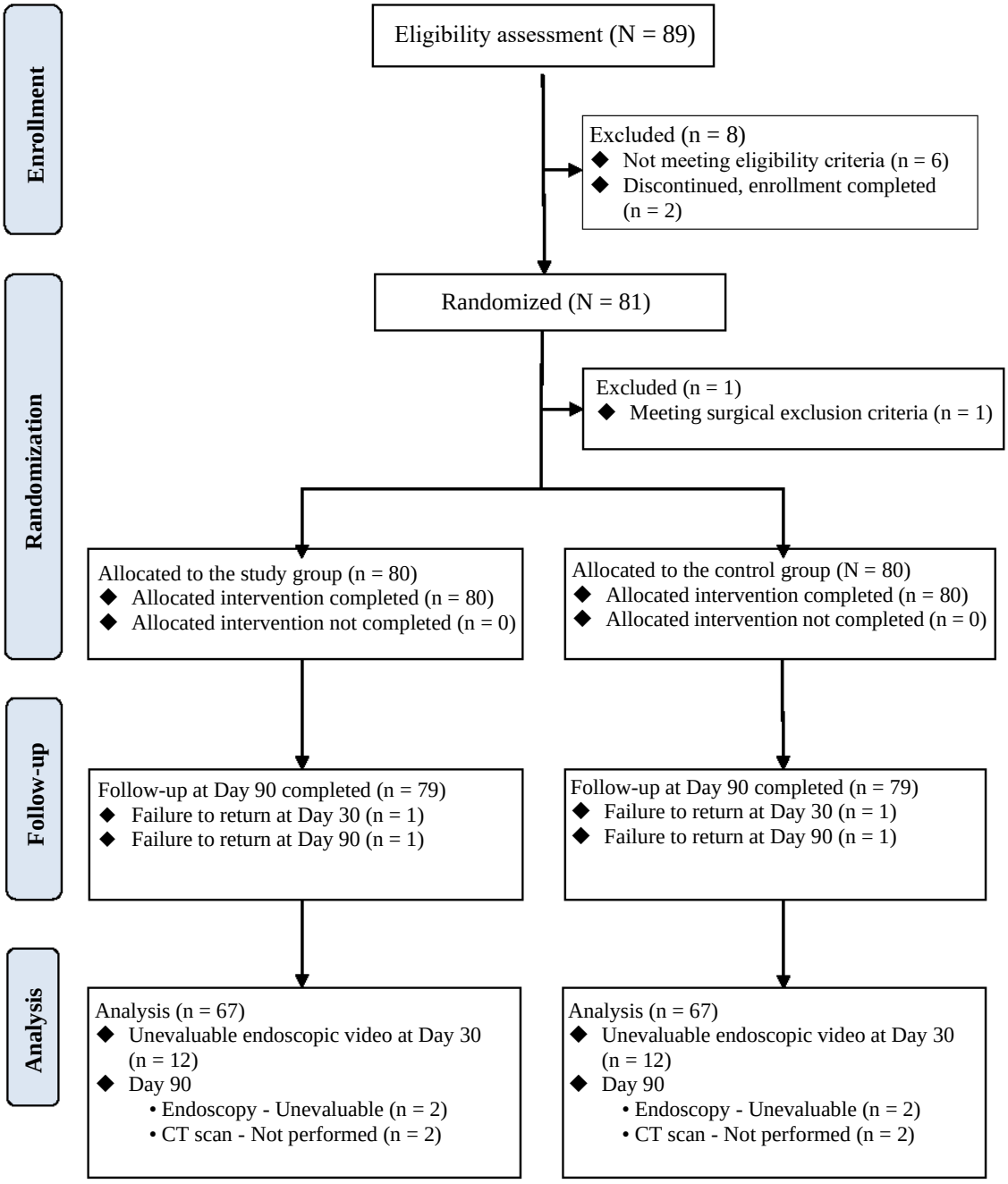


Figure 4. Disposition of subjects by follow-up visit

Table 21. Patient characteristics

	All subjects (N = 80)
Age (years) (mean [SD])	49.9 (13.91)
Sex[1]	
Man	46 (57.5%)
Woman	34 (42.5%)
Ethnicity[1]	
Non-Hispanic or non-Latino	80 (100%)
Race[1]	
White	62 (77.5%)
Black or African American	12 (15.0%)
Asian	6 (7.5%)
Number of previous ESSs	
0	39 (48.8%)
1	20 (25.0%)
2	11 (13.8%)
3	5 (6.3%)
≥4	5 (6.3%)
History of aspirin intolerance or allergy[1]	6 (7.5%)
History of asthma as diagnosed by physician	30 (37.5%)
History of 3 signs of aspirin-exacerbated respiratory disease	6 (7.5%)
History of smoking	28
Current smoker	9 (11.3%)
Previous smoker	19 (23.8%)
Polypoid edema in the frontal recess/FSO, Grade 2[2]	61 (76.3%)
LM score, total (left + right) (mean [SD])	15.8 (4.82)

[1] The percentages were calculated in relation to the ITT population.
[2] Subjects with Grade 2 polypoid edema in the right or left sinus

In the PROGRESS Mini study, 98.8% (79 of 80) of subjects underwent frontal sinusotomy and 36.3% (29 of 80) of subjects underwent frontal natural opening balloon dilation. Table 22 presents concurrent surgical procedures. Because the protocol specified that the FSO diameter should be ≥5 mm after frontal sinus surgery, the following surgical procedures were performed: Bilateral Draf II A dissection in 78.8% (63 of 80) of subjects, bilateral Draf II B dissection in 20.0% (16 of 80) of subjects, and bilateral balloon dilation without surgical dissection in 1.3% (1 of 80) of subjects. The use of hemostatic agents or packing materials was not permitted in the frontal sinuses but permitted in the ethmoid sinuses, a non-target site. Thus, hemostatic agents or packing materials were used in the ethmoid sinuses in 35 subjects. There was no restriction on the use and dose of oral or local intranasal steroids before the conduct of ESS. A total of 27 subjects received oral steroids before Day 90 for FSO obstruction. All subjects received physiological saline sprays or nasal irrigation during the postoperative follow-up period. The delivery success rate of the Propel Mini was 100%.

Table 22. Surgical information

	Test (T) (N = 80)	Control (C) (N = 80)	All subjects (N = 80)
Time required for stent placement, min (mean [SD])			7.4 (33.49)
Endoscopic surgeries			
Anterior ethmoidal sinus surgery	78 (97.5%)	78 (97.5%)	78 (97.5%)
Frontal sinus balloon dilation	29 (36.3%)	29 (36.3%)	29 (36.3%)
Posterior ethmoidal sinus surgery	76 (95.0%)	77 (96.3%)	77 (96.3%)
Frontal sinusotomy	79 (98.8%)	79 (98.8%)	79 (98.8%)
Sphenoidal sinusotomy	63 (78.8%)	64 (80.0%)	67 (83.8%)
Inferior turbinectomy	31 (38.8%)	31 (38.8%)	31 (38.8%)
Middle turbinectomy	11 (13.8%)	7 (8.8%)	12 (15.0%)
Polypectomy	38 (47.5%)	39 (48.8%)	40 (50.0%)
Septoplasty			35 (43.8%)
Instruments			
Balloon dilation	1 (1.3%)	1 (1.3%)	
Rigid surgical tool	51 (63.8%)	51 (63.8%)	
Both	28 (35.0%)	28 (35.0%)	
Dissection			
DRAF IIA	63 (78.8%)	63 (78.8%)	
DRAF IIB	16 (20.0%)	16 (20.0%)	
No surgical dissection, balloon alone	1 (1.3%)	1 (1.3%)	
Postoperative interventions in ethmoid sinus			
Propel	20 (25.0%)	21 (26.3%)	21 (26.3%)
Propel Mini	9 (11.3%)	8 (10.0%)	9 (11.3%)
Steroid-free hemostatic material, spacer, or packing material	30 (37.5%)	30 (37.5%)	30 (37.5%)
Steroid-added hemostatic material, spacer, or packing material	5 (6.3%)	5 (6.3%)	5 (6.3%)
Others	23 (28.8%)	23 (28.8%)	23 (28.8%)

The percentages were calculated in relation to the ITT population.

6.A.(1).4).(a) Efficacy evaluation

The primary efficacy endpoint was a need for postoperative interventions at Day 30. The secondary efficacy endpoints were endoscopic scores, inflammation score of the frontal recess/FSO, and CT images, which were assessed by independent physicians and the investigator.

Primary endpoint

The primary endpoint "need for postoperative interventions" was, as in the Advance II study, a composite endpoint that included (1) surgical intervention in the FSO and (2) oral steroid intervention in the frontal recess/FSO. This endpoint was determined based on endoscopic videos reviewed by third party blinded sinus surgeons independent of the investigator (hereinafter referred to as "independent physicians"). To assess the need for (1) surgical intervention, an element constituting the primary endpoint, the severity of tissue adhesion/scarring was graded using the 4-point scale presented in Table 23. Grade ≥2 represents "need for surgical intervention." Need for (2) oral steroid intervention was assessed based on endoscopic findings and need for medical intervention was determined. To assess the need for surgical intervention to resolve polypoid edema, the severity of the condition was graded using the 3-point scale presented in Table 24. Grade ≥2 represents "need for surgical intervention." One of the 80 subjects failed to return to the site at Day 30. Endoscopic videos of 12 of 80 subjects were not

evaluable because of inadequate imaging of the relevant site or sub-optimal video quality. These cases were handled as missing data. A total of 67 subjects were included in analyses.

Table 23. Adhesion/scarring scale

Grade	Assessment criteria
0	No visible granulation/scarring in the FSO
1	Minimum and non-obstructive granulation, scarring, or shrinkage in the FSO (not justifying intervention)
2	Moderate granulation, scarring, or shrinkage in the FSO (justifying intervention)
3	Significant and obstructive scarring, or shrinkage in the FSO with a need for intervention (most likely affecting patency if removed)

Table 24. Polypoid edema scale

Grade	Assessment criteria
0	Normal mucosa of the frontal recess or FSO without visible polyps
1	Minimum mucosal edema in the frontal recess/FSO
2	Swollen polypoid edema in the frontal recess/FSO

The percentage of sinuses with a need for postoperative interventions was 38.8% (26 of 67 sinuses) in the test group and 62.7% (42 of 67 sinuses) in the control group, showing a statistically significant difference between the 2 groups (McNemar's test, $P = 0.0070$). The percentage of sinuses with (1) need for surgical intervention, an element constituting the primary endpoint, was 27.1% (16 of 59 sinuses) in the test group and 44.1% (26 of 59 sinuses) in the control group, showing a reduction in the test group compared with the control group. However, the difference was not statistically significant (McNemar's test, $P = 0.0639$). The percentage of sinuses with (2) need for oral steroid interventions was 31.3% (21 of 67 sinuses) in the test group and 49.3% (33 of 67 sinuses) in the control group, showing a statistically significant difference between the 2 groups (McNemar's test, $P = 0.0227$). Table 25 presents the results regarding the need for postoperative interventions and its constituting elements.

Table 25. Need for postoperative interventions at Day 30 (assessed by independent physicians)

	Test (T) (N = 80)	Control (C) (N = 80)
Subjects with bilateral sinuses evaluable for need for postoperative intervention[1]	67	67
Sinus with a need for postoperative intervention as judged by independent reviewers		
N (%)	26 (38.8%)	42 (62.7%)
95% CI[2]	0.271, 0.515	0.500, 0.742
P-value[3]	0.0070	
Percentage of relative difference[4]	-38.1	
Subjects with bilateral sinuses evaluable for need for surgical intervention by independent reviewers	59	59
Sinus with a need for surgical intervention as judged by independent reviewers		
N (%)	16 (27.1%)	26 (44.1%)
95% CI[2]	0.164, 0.403	0.312, 0.576
P-value[3]	0.0639	
Percentage of relative difference[4]	-38.5	
Subjects with bilateral sinuses evaluable for need for oral steroid intervention by independent reviewers	67	67
Sinus with a need for oral steroid intervention as judged by independent reviewers		
N (%)	21 (31.3%)	33 (49.3%)
95% CI[2]	0.206, 0.438	0.368, 0.618
P-value[3]	0.0227	
Percentage of relative difference[4]	-36.4	

[1] Need for postoperative interventions is a composite endpoint that includes surgical intervention required to resolve obstructive adhesions or scarring (Grade 2 or 3 of the adhesion/scarring scale) and/or oral steroid intervention required to resolve recurrent inflammation and/or recurrent polypoid edema in the frontal recess/FSO.
[2] The 95% CI for each test sinus was calculated using Clopper-Pearson's method.
[3] The 2-sided *P*-values were calculated using McNemar's exact test.
[4] Percentage of relative difference = (Percentage of subjects with a need for intervention [Test sinus − Control sinus])/(Percentage of subjects with a need for intervention [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

Missing data resulting from no availability of evaluable endoscopic videos were imputed using the 4-step approach shown in Table 26. The sensitivity of the results to the different imputation methods was assessed. All of the methods, except for the most conservative one ([redacted]), led to the conclusion that the test device statistically significantly reduced the frequency of postoperative interventions compared to the control device. The most conservative imputation [redacted] did not result in a statistically significant difference between the groups (McNemar's test, $P = 0.4408$). However, the results did not deny the efficacy of the Propel Mini. The results were consistent across all of the imputation approaches, indicating no effect of missing data on the interpretation of the study results.

Table 26. Methods and results of data imputation

Imputation method	Test	Control	*P*-value (McNemar's test)
[redacted]	36.7% (29/79 sinuses)	53.2% (42/79 sinuses)	0.0410
	45.6% (36/79 sinuses)	67.1% (53/79 sinuses)	0.0060
	36.7% (29/79 sinuses)	67.1% (53/79 sinuses)	0.0002
	45.6% (36/79 sinuses)	53.2% (42/79 sinuses)	0.4408

Secondary endpoints

- Endoscopic assessment

Endoscopic results (incidences of adhesion/scarring in the FSO and polypoid edema in the frontal recess/FSO, and inflammation of the frontal recess/FSO) at Day 30 were assessed by independent physicians. Tables 27 and 28 present the results.

Table 27. Incidence of adhesion/scarring in the FSO and polypoid edema in the frontal recess/FSO at Day 30 (assessed by independent physicians)

	Test (T) (N = 80)	Control (C) (N = 80)
Adhesion/scarring in the FSO		
Any adhesion/scarring (Grade 1, 2, or 3)		
N	59	59
N (%)	37 (62.7%)	45 (76.3%)
95% CI[1]	0.491, 0.750	0.634, 0.864
P-value[2]	0.0963	
Percentage of relative difference[3]	-17.8	
Clinically significant adhesion/scarring (Grade 2 or 3)		
N	59	59
N (%)	16 (27.1%)	26 (44.1%)
95% CI[1]	0.164, 0.403	0.312, 0.576
P-value[2]	0.0639	
Percentage of relative difference[3]	-38.5	
Polypoid edema in the frontal recess/FSO		
Any polypoid edema (Grade 1 or 2)		
N	67	67
N (%)	59 (88.1%)	63 (94.0%)
95% CI[1]	0.778, 0.947	0.854, 0.983
P-value[2]	0.2891	
Percentage of relative difference[3]	-6.3	
Swollen polypoid edema (Grade 2)		
N	67	67
N (%)	17 (25.4%)	28 (41.8%)
95% CI[1]	0.155, 0.375	0.298, 0.545
P-value[2]	0.0192	
Percentage of relative difference[3]	-39.3	

[1] The 95% CI for each test sinus was calculated using Clopper-Pearson's method.
[2] The 2-sided *P*-values were calculated using McNemar's exact test.
[3] Percentage of relative difference = (Percentage of subjects with the grade or outcome [Test sinus − Control sinus])/(Percentage of subjects with the grade or outcome [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

Table 28. Inflammation assessment in the frontal recess/FSO at Day 30 (assessed by independent physicians)

	Test (T) (N = 80)	Control (C) (N = 80)	Difference (T−C) (N = 80)
Inflammation - Measurement (mm)			
N	72	68	67
Mean (SD)	36.9 (23.63)	43.4 (23.89)	-7.2 (24.40)
95% CI[1]	31.3, 42.4	37.6, 49.2	-13.1, -1.2
P-value[2]			0.0008
Percentage of relative difference[3]			-16.4

Note: Inflammation assessment using the 100-mm VAS
[1] The 95% CI of mean was calculated assuming a normal distribution.
[2] The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.
[3] Percentage of relative difference = (Mean [Test sinus − Control sinus])/(Mean [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

- Endoscopic assessment by the investigator

Endoscopic results (need for postoperative interventions, incidence and severity of adhesion/scarring in the FSO, incidence and grade of polypoid edema in the frontal recess/FSO, FSO patency, and delivery success rate of the test device) at each time point were assessed by the investigator. FSO patency was assessed using the 3-point scale presented in Table 29. Tables 30, 31, and 32 present the results.

Table 29. Endoscopic patency scale

Grade	Assessment criteria
0	Patent
1	Restenosis/partial obstruction
2	Obstruction

Table 30. Need for postoperative interventions at each time point (assessed by investigator)

	Test	Control	*P*-value (McNemar's test)
Need for postoperative interventions	6.9% (Day 7) 13.2% (Day 21) 16.5% (Day 30) 27.3% (Day 90)	17.2% (Day 7) 39.5% (Day 21) 41.8% (Day 30) 40.3% (Day 90)	0.0703 (Day 7) <0.0001 (Day 21) <0.0001 (Day 30) 0.0129 (Day 90)
Need for surgical intervention	5.2% (Day 7) 5.3% (Day 21) 4.0% (Day 30) 3.9% (Day 90)	15.5% (Day 7) 20.0% (Day 21) 16.0% (Day 30) 10.5% (Day 90)	0.0703 (Day 7) 0.0010 (Day 21) 0.0225 (Day 30) 0.1250 (Day 90)
Need for oral steroid intervention	1.3% (Day 7) 11.4% (Day 21) 15.2% (Day 30) 25.3% (Day 90)	3.8% (Day 7) 31.6% (Day 21) 34.2% (Day 30) 34.2% (Day 90)	0.5000 (Day 7) 0.0001 (Day 21) 0.0015 (Day 30) 0.0654 (Day 90)

Table 31. Incidence of adhesion/scarring in the FSO and polypoid edema in the frontal recess/FSO, and FSO patency at each time point (assessed by investigator)

Endpoint		Test	Control	*P*-value (McNemar's test)
Adhesion/scarring in the FSO	Any adhesion/scarring (Grade 1, 2, or 3)	19.0% (Day 7) 29.3% (Day 21) 28.0% (Day 30) 21.1% (Day 90)	36.2% (Day 7) 52.0% (Day 21) 41.3% (Day 30) 31.6% (Day 90)	0.0020 (Day 7) 0.0002 (Day 21) 0.0414 (Day 30) 0.0768 (Day 90)
	Clinically significant adhesion/scarring (Grade 2 or 3)	5.2% (Day 7) 5.3% (Day 21) 4.0% (Day 30) 3.9% (Day 90)	15.5% (Day 7) 20.0% (Day 21) 16.0% (Day 30) 10.5% (Day 90)	0.0703 (Day 7) 0.0010 (Day 21) 0.0225 (Day 30) 0.1250 (Day 90)
Polypoid edema in the frontal recess/FSO	Any polypoid edema (Grade 1 or 2)	67.2% (Day 7) 55.7% (Day 21) 53.8% (Day 30) 50.0% (Day 90)	76.6% (Day 7) 84.8% (Day 21) 76.9% (Day 30) 59.2% (Day 90)	0.1094 (Day 7) <0.0001 (Day 21) 0.0009 (Day 30) 0.1892 (Day 90)
	Clinically significant polypoid edema (Grade 2)	9.4% (Day 7) 5.1% (Day 21) 12.8% (Day 30) 23.7% (Day 90)	25.0% (Day 7) 39.2% (Day 21) 32.1% (Day 30) 30.3% (Day 90)	0.0020 (Day 7) <0.0001 (Day 21) 0.0026 (Day 30) 0.3593 (Day 90)
FSO patency	Restenosis/obstruction (Grade 1 or 2)	22.6% (Day 7) 18.2% (Day 21) 21.1% (Day 30) 35.5% (Day 90)	35.5% (Day 7) 41.6% (Day 21) 46.1% (Day 30) 46.1% (Day 90)	0.0574 (Day 7) <0.0001 (Day 21) 0.0002 (Day 30) 0.0768 (Day 90)
	Obstruction (Grade 2)	8.1% (Day 7) 2.6% (Day 21) 7.9% (Day 30) 18.4% (Day 90)	9.7% (Day 7) 14.3% (Day 21) 9.2% (Day 30) 18.4% (Day 90)	1.0000 (Day 7) 0.0117 (Day 21) 1.0000 (Day 30) 1.0000 (Day 90)

Table 32. Inflammation in the frontal recess/FSO and FSO diameter at each time point (assessed by investigator)

	Test	Control	*P*-value (t test)
FSO inflammation score Mean ± SD (mm)	31.4 ± 24.19 (Day 7)	40.9 ± 25.95 (Day 7)	<0.0001 (Day 7)
	24.8 ± 22.42 (Day 21)	47.8 ± 28.72 (Day 21)	<0.0001 (Day 21)
	24.7 ± 27.02 (Day 30)	41.3 ± 29.34 (Day 30)	<0.0001 (Day 30)
	32.4 ± 33.27 (Day 90)	39.0 ± 33.67 (Day 90)	0.0057 (Day 90)
Estimated FSO diameter (maximum) Mean ± SD (mm)	7.0 ± 2.48 (Day 21)	4.7 ± 2.48 (Day 21)	<0.0001 (Day 21)
	5.9 ± 2.84 (Day 30)	4.4 ± 2.38 (Day 30)	<0.0001 (Day 30)
	4.8 ± 3.24 (Day 90)	3.9 ± 2.84 (Day 90)	<0.0001 (Day 90)

Note: Inflammation assessment using the 100-mm VAS

The percentage of sinuses with a need for postoperative interventions at Day 30 as assessed by the investigator was 16.5% in the test group and 41.8% in the control group, showing a statistically significant difference as with the assessment by independent physicians.

- CT image assessment by independent physicians

CT image endpoints (maximum FSO diameter, LM score, and severity of frontal sinus disease) at Day 90 were assessed by independent physicians. Severity (range) of frontal sinus disease was assessed using the 3-point scale presented in Table 33. Table 34 presents the results.

Table 33. Radiological image grading scale

Grade	Assessment criteria
1	Mucosal hypertrophy of <5 mm
2	Partial opacification, air-fluid level, or mucosal hypertrophy of ≥5 mm
3	Total opacification

Table 34. CT image assessment (assessed by independent physicians)

	Test (T) (N = 80)	Control(C) (N = 80)	Difference (T-C) (N = 80)
Estimated maximum FSO diameter (mm)			
N	76	76	76
Mean (SD)	3.1 (2.93)	2.6 (3.04)	0.5 (2.63)
95% CI[1]	2.5, 3.8	1.9, 3.3	-0.1, 1.1
P-value[2]			0.0216
Percentage of relative difference[3]			18.7
Total LM score			
N	77	77	77
Mean (SD)	5.7 (2.03)	5.6 (2.09)	0.1 (1.45)
95% CI[1]	5.2, 6.1	5.1, 6.1	-0.2, 0.4
P-value[2]			0.3728
Percentage of relative difference[3]			1.9
LM score of frontal sinus			
N	77	77	77
Mean (SD)	1.0 (0.59)	1.0 (0.59)	-0.1 (0.66)
95% CI[1]	0.8, 1.1	0.9, 1.2	-0.2, 0.1
P-value[2]			0.1462
Percentage of relative difference[3]			-7.5

[1] The 95% CI of mean was calculated assuming a normal distribution.
[2] The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.
[3] Percentage of relative difference = (Mean [Test sinus − Control sinus])/(Mean [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

● CT image assessment by the investigator

CT image endpoints (maximum FSO diameter, LM score, and severity of frontal sinus disease) at Day 90 were assessed by the investigator. Table 35 presents the results.

Table 35. CT image assessment (assessed by investigator)

	Test (T) (N = 80)	Control (C) (N = 80)	Difference (T-C) (N = 80)
Estimated maximum FSO diameter (mm)			
N	77	77	77
Mean (SD)	4.9 (3.34)	4.3 (3.35)	0.5 (2.45)
95% CI[1]	4.1, 5.6	3.6, 5.1	-0.0, 1.1
P-value[2]			0.0062
Percentage of relative difference[3]			12.6
Total LM score			
N	77	77	77
Mean (SD)	4.2 (2.64)	4.2 (2.67)	0.0 (1.75)
95% CI[1]	3.6, 4.8	3.6, 4.8	-0.4, 0.4
P-value[2]			1.0000
Percentage of relative difference[3]			0.0
LM score of frontal sinus			
N	77	77	77
Mean (SD)	0.9 (0.71)	0.9 (0.73)	-0.0 (0.79)
95% CI[1]	0.7, 1.0	0.7, 1.1	-0.2, 0.2
P-value[2]			0.6845
Percentage of relative difference[3]			-2.9

[1] The 95% CI of mean was calculated assuming a normal distribution.
[2] The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.
[3] Percentage of relative difference = (Mean [Test sinus − Control sinus])/(Mean [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

6.A.(1).4).(b) Safety evaluation

The safety analysis included adverse events that occurred through Day 90.

No test device-related serious adverse event was reported. For 5 adverse events (1 event of headache, 1 event of left upper eyelid swelling, 1 event of epistaxis, 1 event of recurrent chronic sinusitis, and 1 event of feeling of increased pressure due to sinusitis), a causal relationship to the test device could not be ruled out and the relationship was unknown. Recurrent chronic sinusitis did not resolve but was not serious. The remaining 4 events were resolving or resolved.

6.A.(1).5) PROGRESS Nova study (study period, [redacted], 20[redacted] to [redacted], 20[redacted])

The PROGRESS Nova study was conducted at 12 study sites in the US to evaluate the safety and efficacy of the steroid-eluting Propel Contour stent (FSO implant) (test device) in patients with CRS in comparison with ESS alone (control). This was a randomized, single-blind, self-controlled study in which the test device was placed in one sinus and none in the other sinus after ESS for the treatment of the bilateral frontal sinuses. Table 36 presents an outline of the PROGRESS Nova study.

Table 36. Outline of the PROGRESS Nova study

Item	Outline
Study objective	To evaluate the safety and efficacy of the Propel Contour steroid-eluting stent placed in the FSO after frontal sinus surgery in patients with CRS
Type of study	Prospective, multicenter, randomized, blind, self-controlled study
Study population	Patients who met all of the inclusion criteria and none of the exclusion criteria
Inclusion criteria	General inclusion criteria a. Written informed consent obtained using a written information sheet approved by an IRB b. ≥18 years of age c. Willing and able to comply with protocol requirements d. CRS diagnosis confirmed by CT scan with symptoms lasting ≥12 consecutive weeks, accompanied by inflammation of the mucosa of the nose and paranasal sinuses. e. Has a clinical indication and has consented for ESS including bilateral frontal sinus surgery f. Ability to tolerate general anesthesia g. Treatment with the ESS procedure and placement of the Propel in the FSO is technically feasible and clinically indicated in the investigator's opinion h. Women of childbearing potential must not be pregnant and must agree to not become pregnant during the course of the study. i. Women of child-bearing potential must agree to use consistent and acceptable method(s) of birth control during the course of the study. CT imaging inclusion criteria: j. Documented CRS diagnosis confirmed by CT scan within 6 months before the ESS procedure k. Bilateral disease in both frontal sinuses confirmed by LM score of ≥1 on each side Surgical inclusion criteria l. Planned ESS includes bilateral ethmoidectomy (if judged necessary) and frontal sinus surgery using Draf II (A or B) dissection and/or balloon dilation, with minimum of 5-mm diameter opening created. m. Technique used for frontal sinus surgery was the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or surgical dissection and balloon dilation bilaterally). n. Septoplasty for access to the ostiomeatal complex is permitted. o. ESS including bilateral frontal sinus surgery has been successfully completed without significant complication that, in the investigator's opinion, would confound study results, and the patient's anatomy remains amenable to placement of the test device.
Exclusion criteria	General exclusion criteria a. Known history of immune deficiency such as IgG or IgA subclass deficiency, or human immunodeficiency virus (HIV). b. Oral steroid dependent conditions such as chronic obstructive pulmonary disease (COPD), asthma, or other diseases. c. Known history of allergy or hypersensitivity to corticosteroids or MF. d. Clinical symptoms of acute bacterial sinusitis (e.g. acute increase in purulent discharge, pyrexia, and facial pain). e. Clinical symptoms or suspicion of invasive fungal sinusitis (e.g. bone erosion on CT scan and necrotic sinus tissue) f. Clinical symptoms of active viral illness (e.g., tuberculosis, ocular herpes simplex, chickenpox, and measles). g. Concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g., cancer and HIV). h. Clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day follow-up period i. Current participation in another clinical study j. History of insulin dependent diabetes mellitus k. Previously undergone ESS and experienced a CSF leakage (cerebrospinal fluid leakage) or has compromised vision. Surgical exclusion criteria l. Significant complication during the on-study ESS including frontal sinus surgery (e.g., excessive blood loss, cerebrospinal fluid leakage, and punctured lamina papyracea) m. The on-study ESS is aborted for any reason. n. Sinusitis on at least one side is not amenable for placement of the test device.
Number of subjects (number of sites)	80 subjects (informed consent, 89) (12 study sites)
Follow-up period	90 days after surgery

Item	Outline
Concomitant therapy	Use of concomitant drugs was specified as follows: • No restriction was imposed on oral or intranasal steroids during the preoperative period. • For example, oral steroid inhalation for asthma management was permitted during the study. Use of intranasal steroids in both sinuses was permitted from Day 14 as judged by the investigator. Spraying or irrigating the sinuses with physiological saline as necessary was recommended during the follow-up period. Antibiotic therapy was required for 10 days from the day of surgery (±1 day). Postoperative intervention with oral steroids - Frontal sinus Oral steroid intervention was permitted to resolve a clinically significant increase in inflammation, edema, and/or nasal polyps in the FSO as judged necessary by the investigator. Frontal sinuses with a need for the intervention were recorded on the Endoscopic Examination page of the CRF. Intervention with other drugs - Other than frontal sinus: Use of oral steroids to treat conditions other than FSO inflammation was permitted after Day 30 provided that those steroids do not influence FSO inflammation. For the treatment of suspected infection at any time point during the study, antibiotic therapy was allowed.
Primary endpoints	<u>Efficacy</u> Reduction in need for postoperative interventions at Day 30 in the test sinus in comparison with the control sinus, as determined based on endoscopic videos reviewed by blinded independent sinus surgeons * Need for postoperative interventions is a composite endpoint included in the following: • Surgical intervention required to remove obstructive adhesions or scarring in the FSO and/or postoperative oral steroid intervention required to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.
Secondary endpoints	<u>Efficacy</u> Endoscopic endpoints assessed by blinded independent sinus surgeons: • Incidence and severity of adhesion/scarring in the FSO at Day 30 • Severity of inflammation in the frontal recess/FSO at Day 30 • Incidence and grade of polypoid edema in the frontal recess/FSO at Day 30 Endoscopic endpoints as assessed by the investigator: • Need for postoperative interventions at each visit • Severity of inflammation in the frontal recess/FSO at each visit • Incidence and severity of adhesion/scarring in the FSO at each visit • Incidence and grade of polypoid edema in the frontal recess/FSO at each visit • FSO patency rate at Day 90 • Delivery success rate of the test device CT endpoints at Day 90 as assessed by blinded independent sinus surgeons: • Maximum FSO diameter (FSO patency) • LM score • Severity of frontal disease as determined by using radiological image grading scale CT endpoints at Day 90 as assessed by the investigator: • Maximum FSO diameter (FSO patency) • LM score • Severity of frontal disease as determined by using radiological image grading scale
Safety endpoints	• Adverse events through Day 90 • Serious adverse events through Day 90

The PROGRESS Nova study enrolled 89 subjects and randomized 80 subjects after ESS including frontal sinus surgery to the test group (Propel Contour) or the control group (surgery alone). The remaining 9 subjects were excluded because of discontinuation from the study for not meeting the eligibility criteria or other reasons. A total of 79 subjects completed the final follow-up visit at Day 90. One subject was lost to follow-up (Figure 5). A total of 80 subjects (ITT population) were included in analyses. Table 37 presents the patient characteristics of the ITT population.

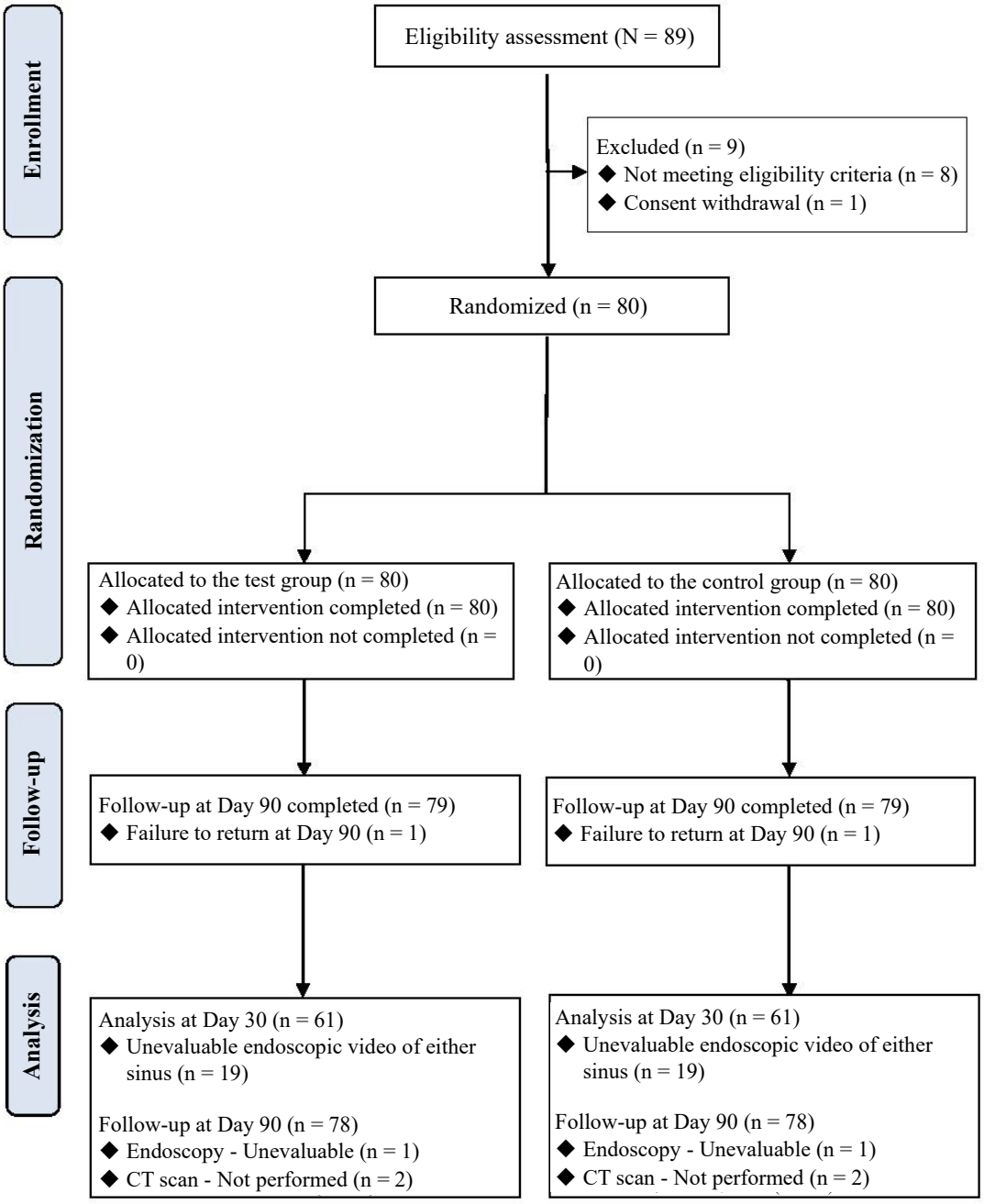


Figure 5. Disposition of subjects by follow-up visit

Table 37. Patient characteristics

	All subjects (N = 80)
Age (years) (mean [SD])	49.5 (13.36)
Sex[1]	
Man	53 (66.3%)
Woman	27 (33.8%)
Number of previous ESSs[1]	
0	39 (48.8%)
1	24 (30.0%)
2	11 (13.8%)
3	1 (1.3%)
>=4	5 (6.3%)
History of aspirin intolerance or allergy[1]	7 (8.8%)
History of asthma as diagnosed by physician[1]	36 (45.0%)
History of 3 signs of aspirin-exacerbated respiratory disease[1]	5 (6.3%)
History of smoking[1]	25
Current smoker	3 (3.8%)
Previous smoker	22 (27.5%)
Polypoid edema in the frontal recess/FSO, Grade 2[1][2]	44 (55.0%)
LM score, total (left + right) (mean [SD])	14.8 (4.87)

[1] The percentages were calculated in relation to the ITT population.
[2] Subjects with Grade 2 polypoid edema in the right or left sinus

In the PROGRESS Nova study, 81.3% (65 of 80) of subjects underwent frontal sinusotomy and 47.5% (38 of 80) of subjects underwent frontal natural opening balloon dilation. Table 38 presents concurrent surgical procedures. Because the protocol specified that the FSO diameter should be ≥5 mm after frontal sinus surgery, the following surgical procedures were performed: Bilateral Draf II A dissection in 68.8% (55 of 80) of subjects, bilateral Draf II B dissection in 12.5% (10 of 80) of subjects, and bilateral balloon dilation without surgical dissection in 18.8% (15 of 80) of subjects. The use of hemostatic agents or packing materials was not permitted in the frontal sinuses but permitted in the ethmoid sinuses, a non-target site. Thus, hemostatic agents or packing materials were used in 48 subjects. There was no restriction on the use and dose of oral or local intranasal steroids before the conduct of ESS. A total of 31 subjects received oral steroids up to Day 90 for FSO obstruction, and a total of 12 subjects received antibiotics for frontal sinus symptoms. All subjects received physiological saline sprays or nasal irrigation during the postoperative follow-up period. The delivery success rate of the Propel Contour was 100%.

Table 38. Surgical information

	Test (N = 80)	Control (N = 80)	All subjects (N = 80)
Time required for stent placement, min (mean [SD])			1.6 (2.45)
Endoscopic procedures			
Anterior ethmoidal sinus surgery	75 (93.8%)	75 (93.8%)	76 (95.0%)
Frontal sinus balloon dilation	38 (47.5%)	38 (47.5%)	38 (47.5%)
Posterior ethmoidal sinus surgery	71 (88.8%)	72 (90.0%)	73 (91.3%)
Frontal sinusotomy	65 (81.3%)	65 (81.3%)	65 (81.3%)
Open surgery of maxillary sinus	67 (83.8%)	67 (83.8%)	69 (86.3%)
Maxillary sinus balloon dilation	7 (8.8%)	6 (7.5%)	7 (8.8%)
Sphenoidal sinusotomy	58 (72.5%)	57 (71.3%)	61 (76.3%)
Inferior turbinectomy	41 (51.3%)	42 (52.5%)	42 (52.5%)
Middle turbinectomy	6 (7.5%)	9 (11.3%)	10 (12.5%)
Polypectomy	40 (50.0%)	39 (48.8%)	41 (51.3%)
Septoplasty			42 (52.5%)
Instruments			
Balloon dilation	15 (18.8%)	15 (18.8%)	
Rigid surgical tool	42 (52.5%)	42 (52.5%)	
Both	23 (28.8%)	23 (28.8%)	
Dissection range			
DRAF IIA	55 (68.8%)	55 (68.8%)	
DRAF IIB	10 (12.5%)	10 (12.5%)	
No surgical dissection, balloon alone	15 (18.8%)	15 (18.8%)	
Postoperative interventions in ethmoid sinus			
Propel	11 (13.8%)	11 (13.8%)	11 (13.8%)
Propel Mini	15 (18.8%)	15 (18.8%)	15 (18.8%)
Steroid-free hemostatic material, spacer, or packing product	37 (46.3%)	36 (45.0%)	37 (46.3%)
Steroid-added hemostatic material, spacer, or packing product	11 (13.8%)	11 (13.8%)	11 (13.8%)

The percentages were calculated in relation to the ITT population.

6.A.(1).5).(a) Efficacy evaluation

The primary efficacy endpoint was a need for postoperative interventions at Day 30. The secondary efficacy endpoints were endoscopic scores and CT images, which were assessed by independent physicians or the investigator.

Primary endpoint

The primary endpoint "need for postoperative interventions" was, as in the PROGRESS Mini study, a composite endpoint that included (1) surgical intervention in the FSO and (2) oral steroid intervention in the frontal r3ecess/FSO. This endpoint was determined based on endoscopic videos reviewed by blinded independent physicians. The constituting elements of the primary endpoint were also assessed as in the PROGRESS Mini study. Endoscopic videos of 19 of 80 subjects were not evaluable because of inadequate imaging of the relevant site or sub-optimal video quality and were handled as missing data. A total of 61 subjects were included in analyses.

The percentage of sinuses with a need for postoperative interventions was 11.5% (7 of 61 sinuses) in the test group and 32.8% (20 of 61 sinuses) in the control group, showing a statistically significant difference between the 2 groups (McNemar's test, $P = 0.0023$). The percentage of sinuses with a need for (1) surgical intervention, an element constituting the primary endpoint, was 6.9% (4 of 58 sinuses) in the test group and 25.9% (15 of 58 sinuses) in the control group, showing a statistically significant difference between the 2 groups (McNemar's test, $P = 0.0074$). The percentage of sinuses with a need for (2) oral

steroid intervention was 9.8% (6 of 61 sinuses) in the test group and 16.4% (10 of 61 sinuses) in the control group, showing a reduction in the test group compared with the control group. However, the difference was not statistically significant (McNemar's test, $P = 0.2891$). Table 39 presents the results regarding the need for postoperative interventions and its constituting elements.

Table 39. Need for postoperative interventions at Day 30 (independent physicians)

	Test (T) (N = 80)	Control (C) (N = 80)
Number of subjects with bilateral sinuses evaluable for need for postoperative intervention[1]	61	61
Sinus with a need for postoperative intervention as judged by independent reviewers		
N (%)	7 (11.5%)	20 (32.8%)
95% CI[2]	0.047, 0.222	0.213, 0.460
P-value[3]	0.0023	
Percentage of relative difference[4]	-65.0	
Number of subjects with bilateral sinuses evaluable for need for surgical intervention by independent reviewers	58	58
Sinus with a need for surgical intervention as judged by independent reviewers		
N (%)	4 (6.9%)	15 (25.9%)
95% CI[2]	0.019, 0.167	0.153, 0.390
P-value[3]	0.0074	
Percentage of relative difference[4]	-73.3	
Number of subjects with bilateral sinuses evaluable for need for oral steroid intervention by independent reviewers	61	61
Sinus with a need for oral steroid intervention as judged by independent reviewers		
N (%)	6 (9.8%)	10 (16.4%)
95% CI[2]	0.037, 0.202	0.082, 0.281
P-value[3]	0.2891	
Percentage of relative difference[4]	-40.0	

[1] Need for postoperative interventions is a composite endpoint that includes surgical intervention required to resolve obstructive adhesions or scarring (Grade 2 or 3 of the adhesion/scarring scale) and/or oral steroid intervention required to resolve recurrent inflammation and/or recurrent polypoid edema in the frontal recess/FSO.

[2] The 95% CI for each test sinus was calculated using Clopper-Pearson's method.

[3] The 2-sided *P*-values were calculated using McNemar's exact test.

[4] Percentage of relative difference = (Percentage of subjects with a need for intervention [Test sinus − Control sinus])/(Percentage of subjects with a need for intervention [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

Missing data resulting from no availability of evaluable endoscopic videos were imputed using the 4-step approach shown in Table 40 as in the PROGRESS Mini study. The sensitivity of the results to the different imputation methods was analyzed (Table 40). All of the methods, except for the imputation that treated missing data as "no need for postoperative interventions" ([redacted]) and the most conservative imputation ([redacted]), led to the conclusion that the test device statistically significantly reduced the frequency of postoperative interventions compared to the control device. The imputation that treated missing data as "no need for postoperative interventions" ([redacted]) and the most conservative imputation ([redacted]) did not result in a statistically significant difference between the groups (McNemar's test, $P = 0.0931$ and 1.0000, respectively). However, for no need for postoperative interventions ([redacted]), the results after the imputation did not deny the efficacy of the Propel. The most conservative imputation ([redacted]) resulted in a slightly higher point estimate in the test group than the control group, which was explained by the assumption that the missing data for non-treatment related reasons in the test group were excessively unfavorably treated. The imputation results do not deny the efficacy of the Propel

Contour, regardless of the imputation approaches, indicating no effect of missing data on the interpretation of the study results.

Table 40. Methods and results of data imputation

Imputation method	Test	Control	*P*-value (McNemar's test)
[redacted]	15.0% (12/80 sinuses)	26.3% (21/80 sinuses)	0.0931
	27.5% (22/80 sinuses)	45.0% (36/80 sinuses)	0.0066
	15.0% (12/80 sinuses)	45.0% (36/80 sinuses)	<0.0001
	27.5% (22/80 sinuses)	26.3% (21/80 sinuses)	1.0000

Secondary endpoints

- Endoscopic assessment by independent physicians

Endoscopic results (incidence of adhesion/scarring in the FSO and polypoid edema in the frontal recess/FSO, and inflammation score of the frontal recess/FSO) at Day 30 were assessed by independent physicians. Tables 41 and 42 present the results.

Table 41. Incidence of adhesion/scarring in the FSO and polypoid edema in the frontal recess/FSO at Day 30 (assessed by independent physicians)

	Test (T) (N = 80)	Control (C) (N = 80)
Adhesion/scarring in the FSO		
Any adhesion/scarring (Grade 1, 2, or 3)		
N	58	58
N (%)	32 (55.2%)	37 (63.8%)
95% CI[1]	0.415, 0.683	0.501, 0.760
P-value[2]	0.3323	
Percentage of relative difference[3]	-13.5	
Clinically significant adhesion/scarring (grade 2 or 3)		
N	58	58
N (%)	4 (6.9%)	15 (25.9%)
95% CI[1]	0.019, 0.167	0.153, 0.390
P-value[2]	0.0074	
Percentage of relative difference[3]	-73.3	
Polypoid edema in the frontal recess/FSO		
Any adhesion/scarring (Grade 1 or 2)		
N	61	61
N (%)	48 (78.7%)	50 (82.0%)
95% CI[1]	0.663, 0.881	0.700, 0.906
P-value[2]	0.7266	
Percentage of relative difference[3]	-4.0	
Swollen polypoid edema (Grade 2)		
N	61	61
N (%)	6 (9.8%)	10 (16.4%)
95% CI[1]	0.037, 0.202	0.082, 0.281
P-value[2]	0.2891	
Percentage of relative difference[3]	-40.0	

[1] The 95% CI for each test sinus was calculated using Clopper-Pearson's method.
[2] The 2-sided *P*-values were calculated using McNemar's exact test.
[3] Percentage of relative difference = (Percentage of subjects with the grade or outcome [Test sinus − Control sinus])/(Percentage of subjects with the grade or outcome [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

Table 42. Inflammation assessment in the frontal recess/FSO at Day 30 (assessed by independent physicians)

	Test (T) (N = 80)	Control (C) (N = 80)	Difference (T-C) (N = 80)
Inflammation - Measurement (mm)			
N	70	65	61
Mean (SD)	28.5 (18.20)	30.0 (18.99)	-2.9 (17.40)
95% CI[1]	24.2, 32.9	25.2, 34.7	-7.3, 1.6
P-value[2]			0.2055
Percentage of relative difference[3]			-9.5

Note: Inflammation assessment using the 100-mm VAS
[1] The 95% CI of mean was calculated assuming a normal distribution.
[2] The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.
[3] Percentage of relative difference = (Mean [Test sinus − Control sinus])/(Mean [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

- Endoscopic assessment by the investigator

Endoscopic results (need for postoperative interventions, inflammation score of the frontal recess/FSO, incidence and severity of adhesion/scarring in the FSO, incidence and grade of polypoid edema in the frontal recess/FSO, and FSO patency at Day 90) at each time point were assessed by the investigator. FSO patency was assessed as in the PROGRESS Mini study. Tables 43, 44, and 45 present the results.

Table 43. Need for postoperative interventions at each time point (assessed by investigator)

	Test	Control	*P*-value (McNemar's test)
Need for postoperative interventions	5.9% (Day 7) 9.2% (Day 21) 16.0% (Day 30) 29.9% (Day 90)	11.8% (Day 7) 35.4% (Day 21) 33.3% (Day 30) 41.6% (Day 90)	0.3750 (Day 7) 0.0002 (Day 21) 0.0010 (Day 30) 0.0117 (Day 90)
Need for surgical intervention	3.9% (Day 7) 4.6% (Day 21) 4.0% (Day 30) 7.8% (Day 90)	7.8% (Day 7) 13.8% (Day 21) 14.7% (Day 30) 16.9% (Day 90)	0.6250 (Day 7) 0.1094 (Day 21) 0.0078 (Day 30) 0.0156 (Day 90)
Need for oral steroid intervention	2.0% (Day 7) 9.2% (Day 21) 14.7% (Day 30) 27.3% (Day 90)	9.8% (Day 7) 29.2% (Day 21) 22.7% (Day 30) 33.8% (Day 90)	0.1250 (Day 7) 0.0023 (Day 21) 0.1094 (Day 30) 0.1250 (Day 90)

Table 44. Incidence of adhesion/scarring in the FSO and polypoid edema in the frontal recess/FSO, and FSO patency at each time point (assessed by investigator)

Endpoint		Test	Control	*P*-value (McNemar's test)
Adhesion/scarring in the FSO	Any adhesion/scarring (Grade 1, 2, or 3)	29.4% (Day 7) 21.9% (Day 21) 16.0% (Day 30) 15.5% (Day 90)	35.3% (Day 7) 45.3% (Day 21) 40.0% (Day 30) 26.8% (Day 90)	0.4531 (Day 7) 0.0015 (Day 21) 0.0001 (Day 30) 0.0386 (Day 90)
	Clinically significant adhesion/scarring (Grade 2 or 3)	3.9% (Day 7) 6.3% (Day 21) 4.0% (Day 30) 8.5% (Day 90)	7.8% (Day 7) 12.5% (Day 21) 14.7% (Day 30) 18.3% (Day 90)	0.6250 (Day 7) 0.3437 (Day 21) 0.0078 (Day 30) 0.0156 (Day 90)
Polypoid edema in the frontal recess/FSO	Any polypoid edema (Grade 1 or 2)	67.8% (Day 7) 56.0% (Day 21) 46.8% (Day 30) 45.3% (Day 90)	81.4% (Day 7) 82.7% (Day 21) 63.6% (Day 30) 57.3% (Day 90)	0.0386 (Day 7) <0.0001 (Day 21) 0.0146 (Day 30) 0.0784 (Day 90)
	Clinically significant polypoid edema (Grade 2)	8.5% (Day 7) 10.7% (Day 21) 10.4% (Day 30) 22.7% (Day 90)	23.7% (Day 7) 36.0% (Day 21) 22.1% (Day 30) 28.0% (Day 90)	0.0117 (Day 7) <0.0001 (Day 21) 0.0039 (Day 30) 0.3877 (Day 90)
FSO patency	Restenosis/obstruction (Grade 1 or 2)	11.4% (Day 7) 8.3% (Day 21) 13.3% (Day 30) 23.2% (Day 90)	20.5% (Day 7) 31.9% (Day 21) 36.0% (Day 30) 40.6% (Day 90)	0.3437 (Day 7) 0.0002 (Day 21) <0.0001 (Day 30) 0.0018 (Day 90)
	Obstruction (Grade 2)	0% (Day 7) 2.8% (Day 21) 2.7% (Day 30) 13.0% (Day 90)	2.3% (Day 7) 12.5% (Day 21) 13.3% (Day 30) 18.8% (Day 90)	∸ (Day 7) 0.0391 (Day 21) 0.0078 (Day 30) 0.2891 (Day 90)

Table 45. Inflammation score in the frontal recess/FSO and FSO diameter at each time point (assessed by investigator)

	Test	Control	*P*-value (t test)
FSO inflammation score Mean ± SD (mm)	35.5 ± 22.66 (Day 7) 28.8 ± 23.11 (Day 21) 23.1 ± 24.23 (Day 30) 26.0 ± 31.17 (Day 90)	42.0 ± 23.92 (Day 7) 43.3 ± 30.91 (Day 21) 35.6 ± 31.12 (Day 30) 31.9 ± 32.08 (Day 90)	0.0463 (Day 7) <0.0001 (Day 21) <0.0001 (Day 30) 0.0633 (Day 90)
Estimated FSO diameter (maximum) Mean ± SD (mm)	6.4 ± 2.05 (Day 7) 6.5 ± 2.61 (Day 21) 6.3 ± 2.68 (Day 30) 5.7 ± 3.22 (Day 90)	5.8 ± 2.86 (Day 7) 4.7 ± 3.14 (Day 21) 4.5 ± 3.16 (Day 30) 4.7 ± 3.44 (Day 90)	0.0164 (Day 7) <0.0001 (Day 21) <0.0001 (Day 30) 0.0095 (Day 90)

Note: Inflammation assessment using the 100-mm VAS

● CT image assessment by independent physicians

CT image endpoints (maximum FSO diameter, LM score, and severity of frontal sinus disease) at Day 90 were assessed by independent physicians. The severity (range) of frontal sinus disease was assessed as in the PROGRESS Mini study. Table 46 presents the results.

Table 46. CT image assessment (assessed by independent physicians)

	Test (N = 80)	**Control (N = 80)**	**Difference (Tx−C) (N = 80)**
Estimated maximum FSO diameter (mm)			
N	78	78	78
Mean (SD)	2.9 (2.93)	2.2 (2.60)	0.7 (2.42)
95% CI[1]	2.3,3.6	1.6,2.8	0.2,1.3
P-value[2]			0.0103
Percentage of relative difference[3]			32.9
Total LM score			
N	78	78	78
Mean (SD)	5.2 (2.11)	5.6 (2.17)	-0.5 (1.70)
95% CI[1]	4.7, 5.7	5.2, 6.1	-0.8, -0.1
P-value[2]			0.0191
Percentage of relative difference[3]			-8.2
LM score of frontal sinus			
N	78	78	78
Mean (SD)	0.9 (0.52)	1.0 (0.56)	-0.1 (0.47)
95% CI[1]	0.8, 1.0	0.8, 1.1	-0.2, 0.0
P-value[2]			0.0589
Percentage of relative difference[3]			-10.5

[1] The 95% CI of mean was calculated assuming a normal distribution.
[2] The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.
[3] Percentage of relative difference = (Mean [Test sinus − Control sinus])/(Mean [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

● CT image assessment by the investigator

CT image endpoints (maximum FSO diameter, LM score, and severity of frontal sinus disease) at Day 90 were assessed by the investigator. Table 47 presents the results.

Table 47. CT image assessment (investigator)

	Test (N = 80)	Control (N = 80)	Difference (Tx−C) (N = 80)
Estimated maximum FSO diameter (mm)			
N	78	78	78
Mean (SD)	5.6 (3.33)	4.7 (4.05)	1.0 (2.95)
95% CI[1]	4.9, 6.4	3.8, 5.6	0.3, 1.6
P-value[2]			0.0054
Percentage of relative difference[3]			20.5
Total LM score			
N	78	78	78
Mean (SD)	3.7 (2.95)	4.0 (2.87)	-0.3 (1.52)
95% CI[1]	3.1, 4.4	3.4, 4.7	-0.6, 0.1
P-value[2]			0.1213
Percentage of relative difference[3]			-6.7
LM score of frontal sinus			
N	78	78	78
Mean (SD)	0.7 (0.64)	0.9 (0.69)	-0.2 (0.60)
95% CI[1]	0.6, 0.9	0.7, 1.1	-0.3, -0.0
P-value[2]			0.0097
Percentage of relative difference[3]			-20.0

[1] The 95% CI of mean was calculated assuming a normal distribution.
[2] The *P*-values of score differences between the test and control sinuses were calculated using a paired t-test.
[3] Percentage of relative difference = (Mean [Test sinus − Control sinus])/(Mean [control sinus]) × 100. In this calculation, the number of subjects with evaluable bilateral sinuses was used.

6.A.(1).5).(b) Safety evaluation

The safety analysis included adverse events that occurred through Day 90.

No test device-related serious adverse event was reported. For 3 adverse events (1 event of headache, 1 event of epistaxis, and 1 event of acute sinusitis), a causal relationship to the test device could not be ruled out and the relationship was unknown. All of the events resolved without sequelae.

6.A.(1).6) Summary of the results of the US clinical studies

The following efficacy endpoints were selected for evaluation of the Propel based on the factors contributing a poor outcome of ESS; (1) need for post-ESS interventions, (2) lateralization of the middle turbinate, (c) restenosis/obstruction of the FSO, (d) significant adhesion/scarring, and (3) definite nasal polyps. These endpoints were evaluated at 30 days after ESS, around which tissue adhesions are more likely to occur and need for postoperative interventions is assessed in the standard medical practice. Table 48 summarizes the results of each endpoint in the US clinical studies.

Table 48. Efficacy evaluation at Day 30 in the US clinical studies

Study title/ treatment site	Cohort	Need for postoperative interventions	Need for surgical intervention	Need for steroid intervention	Lateralization of the middle turbinate	Restenosis/ obstruction of the FSO	Significant adhesion/ scarring	Definite nasal polyps (Grade ≥2)
Consensus II (pilot)/ ethmoid sinus	PROPEL= 25	NA	NA	NA	4.0% (1/25)	NA	8.0% (2/25)	-
	Control = 25	NA	NA	NA	24.0% (6/25)	NA	24.0% (6/25)	-
Advance/ ethmoid sinus	PROPEL= 90	NA	NA	NA	7.8% (7/90)	NA	6.7% (6/90)	2.2% (2/90)
Advance II (pivotal)/ ethmoid sinus	PROPEL= 105	33.3% (32/96)*	14.0% (14/100)*	23.3% (20/86)	4.8% (5/105)	NA	7.7% (8/104)	18.8% (16/85)*
	Control = 105	46.9% (45/96)	29.0% (29/100)	32.6% (28/86)	9.5% (10/105)	NA	15.4% (16/104)	34.1% (29/85)
PROGRESS Mini/frontal sinus	PROPEL Mini = 80	38.8% (26/67)*	27.1% (16/59)	31.3% (21/67)*	NA	21.1% (16/76)*	27.1% (16/59)	25.4% (17/67)*
	Control = 80	62.7% (42/67)	44.1% (26/59)	49.3% (33/67)	NA	46.1% (35/76)	44.1% (26/59)	41.8% (28/67)
PROGRESS Nova/frontal sinus	PROPEL Contour = 80	11.5% (7/61)*	6.9% (4/58)*	9.8% (6/61)	NA	13.3% (10/75)*	6.9% (4/58)*	9.8% (6/61)
	Control = 80	32.8% (20/61)	25.9% (15/58)	16.4% (10/61)	NA	36.0% (27/75)	25.9% (15/58)	16.4% (10/61)

NA: Not evaluated in the clinical study
− The assessment results of polyp-like tissue change (Grade ≥1) were available, but no definite nasal polyps (Grade ≥2) were observed.
* The between-group difference was statistically significant ($P < 0.05$).

- Need for postoperative interventions

The percentage of subjects with "need for postoperative interventions" was 11.5% to 38.8% in the test group and 32.8% to 62.7% in the control group. It was statistically significantly lower in the test group than the control group in all of the Advance II, the PROGRESS Mini, and the PROGRESS Nova studies. The "need for surgical intervention" was statistically significantly lower in the test group than the control group in the Advance II and the PROGRESS Nova studies. "The need for oral steroid intervention" was statistically significantly lower in the test group than the control group in the PROGRESS Mini study. These results confirmed the efficacy of the Propel in reducing the need for postoperative interventions.

- Lateralization of the middle turbinate

The incidence of "lateralization of the middle turbinate" was 4.0% to 7.8% in the test groups. None of the Consensus II, the Advance, and the Advance II studies, where this endpoint was evaluated, showed a statistically significant difference between the groups. However, lateralization of the middle turbinate occurred less frequently in the test group than the control group.

- Restenosis/obstruction of the FSO

The incidence was 13.3% to 21.1% in the test groups and 36.0% to 46.1% in the control groups. Both the PROGRESS Mini and the PROGRESS Nova studies, where this endpoint was evaluated, showed a statistically significantly lower incidence in the test group than the control group, suggesting the effect of the Propel in reducing restenosis/obstruction of the FSO.

- Significant adhesion/scarring

The incidence was 6.7% to 27.1% in the test groups and 15.4% to 44.1% in the control groups. Only the PROGRESS Nova study among the studies that evaluated this endpoint showed a statistically significantly lower incidence in the test group than the control group, suggesting the effect of the Propel in reducing significant adhesion/scarring.

- Other endpoint (definite nasal polyps)

The incidence was 2.2% to 25.4% in the test groups and 16.4% to 41.8% in the control groups. Only the PROGRESS Mini study among the studies that evaluated this endpoint showed a statistically significantly lower incidence in the test group than the control group, suggesting the effect of the Propel in reducing definite nasal polyps.

The above results of the efficacy endpoints show a reduction in need for postoperative interventions in the test group compared with the control group, suggesting the efficacy of the Propel.

There were no deaths or serious adverse events for which a causal relationship to the device could not be ruled out. The following adverse events for which a causal relationship to the device could not be ruled out (related or unknown) were reported: 3 device-related adverse events and 18 adverse events for which a causal relationship to the device was unknown. Recurrent chronic sinusitis for which a relationship to the device was unknown did not resolve but was not serious. The other events were resolving or resolved (Table 49). Since the Propel sustainably releases a steroid in the sinus mucosa and is placed close to the eye, the Advance and the Advance II studies included ophthalmological safety evaluation in order to assess the potential risks of increased intraocular pressure and lenticular opacities. Neither study showed a clinically significant increase in intraocular pressure nor suggested any effect on lenticular opacities (Table 49).

Table 49. Adverse events in the US clinical studies

Study title/ treatment site	No. of subjects (N = 365)	Death	Causality could not be ruled out		Ophthalmological safety evaluation
			SAE	AE	
Consensus II (pilot)/ ethmoid sinus	N = 50	0	0	Unknown: Headache 2.0% (1)	NA
Advance/ ethmoid sinus	N = 50	0	0	Related: Headache and nose burning sensation 2.0% (1) Unknown: Acute bilateral sinus 2.0% (1) Headache with a feeling of pressure on the eyes and removal of bilateral stents 2.0% (1) Bilateral sinusitis 2.0% (1) Headache and removal of bilateral stents 2.0% (1) Unilateral intraocular pressure increased 2.0% (1)	No clinically significant change in intraocular pressure or lenticular opacity
Advance II (pivotal)/ ethmoid sinus	N = 105	0	0	Related: Acute sinusitis 1.9% (2) Unknown: Acute sinusitis 1.0% (1) Acute bilateral ethmoid sinusitis 1.0% (1)* Headache 1.0% (1)	No clinically significant change in intraocular pressure or lenticular opacity
PROGRESS Mini/ frontal sinus	N = 80	0	0	Unknown: Headache 1.3% (1) Swelling of left upper eyelid 1.3% (1) Epistaxis 1.3% (1) Recurrent chronic sinusitis 1.3% (1) Feeling of increased pressure on the sinus 1.3% (1)	NA
PROGRESS Nova/ frontal sinus	N = 80	0	0	Unknown: Headache 1.3% (1) Epistaxis 1.3% (1) Acute sinusitis 1.3% (1)	NA

NA: Not evaluated in the clinical study
The incidence of each event was calculated by dividing the number of subjects with the event by the sample size of the clinical study.
* One subject experienced 2 cases of acute bilateral ethmoid sinusitis.

A total of 27 malfunctions were reported in the US clinical studies including the Consensus II, the Advance, and the Advance II studies. Table 50 presents the details of the malfunctions. Malfunctions of the non-drug-eluting stent used as the control device were also reported in these studies. The number of malfunctions presented here is the total of malfunctions of the test and control devices. The following malfunctions were reported: 10 cases of crimping problems (2.3%), 10 cases of improper placement (2.3%), 4 cases of strut crossover due to crimping problems (0.9%), and 1 case each of unresolved strut crossover, unintentional removal, and breakage of the crimping joint (0.2%). These events were found before or immediately after stent placement. The stents with malfunctions that occurred after placement were immediately removed and replaced. The procedure was completed in all cases. None of the malfunctions led to any adverse event. Since the delivery success rate (the study implant placed with not more than 2 attempts) was 100% in all studies, these malfunctions do not raise any safety concern.

Table 50. Malfunctions in the US clinical studies

Test device	Number of units used[*1]	Number of malfunctions[*2]	Malfunctions (number of cases, incidence[*3])
Propel	424	27	Crimping problem (10, 2.4%)
			Improper placement (10, 2.4%)
			Strut crossover due to crimping problem (4, 0.9%)
			Unresolved strut crossover (1, 0.2%)
			Unintentional removal (1, 0.2%)
			Breakage of crimping joint (1, 0.2%)

*1 Number of units used represents the total number of the test and control devices placed or replaced.
*2 Total number of malfunctions of the test and control devices
*3 The denominator of the incidence is the number of units used.

The above results suggest no safety risk of the Propel placement.

6.A.(2) Literature review of efficacy and safety

The applicant conducted literature searches as summarized below. The databases PubMed, Cochrane, NICE, MEDLINE, and EMBASE were searched with the keywords of "nasal" and "sinus" as treatment sites, "stent" and "implant" as therapy names, "steroid," "drug eluting sinus stent," and "steroid-eluting implant" as product characteristics, "Intersect ENT" as the manufacturer, and "PROPEL sinus stent" as the product name (Tables 51 and 52). Because the articles captured by these keywords included those on similar medical devices, the articles regarding the Propel were separately categorized from those regarding other products (Figure 6).

Table 51. Literature search conditions 1

Item		Details
1)	Search period	Up to December 31, 2016
	Database	PubMed
	Search keywords	(nasal OR sinus) AND (stent OR implant) AND steroid, Drug eluting sinus stent, Steroid-eluting implant, Intersect ENT, PROPEL sinus stent
	Number of articles identified	98
2)	Search period	From August 1, 2016 through December 31, 2016
	Database	Cochrane, NICE
	Search keywords	Sinus stent, Nasal stent
	Number of articles identified	236
Inclusion criteria 1		Articles include information regarding the safety, performance, efficacy, and risks of the Propel. Products are used according to the same methods as those for the indication of the Propel. Articles include a statement that the results are from studies conducted in accordance with scientific research principles, including verifiable and proper endpoints, inclusion and exclusion criteria, and proper and effective sample size. Observational, randomized or non-randomized, prospective or retrospective studies, including a follow-up period and clinical outcomes, regardless of their evidence levels
Exclusion criteria 1		Articles include no information on the safety or efficacy of the Propel. Technical studies using animals or cadavers, or non-clinical studies Articles are not about the intended treatment area of the Propel therapy (e.g., the Propel not placed in any sinus). Opinions or conclusions with an unclear basis Articles include no sufficient information for scientific evaluation. Articles are about medical devices that are not considered as a substitute or equivalent to the Propel because they have no similarities to the Propel or use different materials. Case reports include no new information on risks or adverse events. Reports exclusively about medical economic reviews Editorials, memorandums, comments, letters, books, meeting materials, medical practice guidelines, or patents Articles are written in languages other than English.

Table 52. Literature search conditions 2

Item		Details
3)	Search period	From August 1, 2016 through December 31, 2022
	Database	MEDLINE, EMBASE
	Search formula	((“PROPEL” NEAR/3 steroid*) OR (Intersect OR “Intersect ENT” OR Sinexus)) AND (sinus* OR stent* OR bioabsorbable* OR steroid* OR mometasone* OR implant* OR nasal OR drug-eluting OR steroid-eluting OR “drug eluting” OR “steroid eluting”)
		(chronic NEAR/3 (rhinosin* OR rhino NEAR/3 sin*)) AND (stent* OR packing* OR gel* OR (bioabsorbable NEAR/3 implant*))
	Number of articles identified	848
4)	Search period	From August 1, 2016 through December 31, 2022
	Database	MEDLINE, EMBASE
	Search formula	((“PROPEL” OR “PROPEL Mini”) NEAR/3 steroid*) OR (Intersect OR “Intersect ENT” OR Sinexus)) AND (sinus* OR stent* OR bioabsorbable* OR steroid* OR mometasone* OR implant* OR nasal OR drug-eluting OR steroid-eluting OR “drug eluting” OR “steroid eluting”) AND (PD(20160801-20221231))
		(Sinus* near/3 (balloon* OR dil*ation OR sinuplasty)) AND (sinusitis OR rhino* OR nasal)AND (PD(20160801-20210630))
		(chronic NEAR/3 (rhinosin* OR rhino NEAR/3 sin*)) AND (stent* OR packing* OR gel* OR(bioabsorbable NEAR/3 implant*)) AND (PD(20160801-20210630))
		('drug eluting sinus stent'/exp OR (('drug coat*' OR 'drug elut*' OR 'drug releas*') NEAR/5sinus NEAR/5 stent*)) AND (PD(20210701-20221231))
		('drug eluting sinus stent'/exp OR (('drug coat*' OR 'drug elut*' OR 'drug releas*') NEAR/5sinus NEAR/5 stent*) OR 'sinus stent'/exp OR ((sinus* NEAR/2 stent*):ti,ab,kw)) AND(PD(20210701-20221231))
	Number of articles identified	686
5)	Search period	From August 1, 2016 through October 31, 2022
	Database	MEDLINE, EMBASE
	Search formula	((“PROPEL” OR “PROPEL Contour”) NEAR/3 steroid*) OR (Intersect OR “Intersect ENT” OR Sinexus)) AND (sinus* OR stent* OR bioabsorbable* OR steroid* OR mometasone* OR implant* OR nasal OR drug-eluting OR steroid-eluting OR “drug eluting” OR “steroid eluting”)
		(chronic NEAR/3 (rhinosin* OR rhino NEAR/3 sin*)) AND (stent* OR packing* OR gel* OR (bioabsorbable NEAR/3 implant*))
	Number of articles identified	829
Inclusion criteria 2		Articles include information regarding the safety, performance, efficacy, and risks of the Propel. Products are used in a surgery for treatment according to the same methods as those for the indication of the Propel or those described in its instructions for use (IFU). Observational, randomized or non-randomized, prospective or retrospective studies, including a follow-up period and clinical outcomes, regardless of their evidence levels
Exclusion criteria 2		Articles include no information on the safety, performance, efficacy, or risk of the Propel. Technical studies using animals or cadavers, or non-clinical studies Articles are not about the intended treatment area of the Propel therapy (e.g., different anatomical structures and the Propel not placed in any sinus). Opinions or conclusions with an unclear basis Articles include no sufficient information for scientific evaluation. Articles are about medical devices that are not considered as substitute, equivalent, or similar to the Propel because they have no similarities to the Propel or use different materials. Case reports include no new information on risks or adverse events. Reports exclusively about medical economic reviews Editorials, memorandums, comments, letters, books, meeting materials, or patents Articles are written in languages other than English. Outside search period

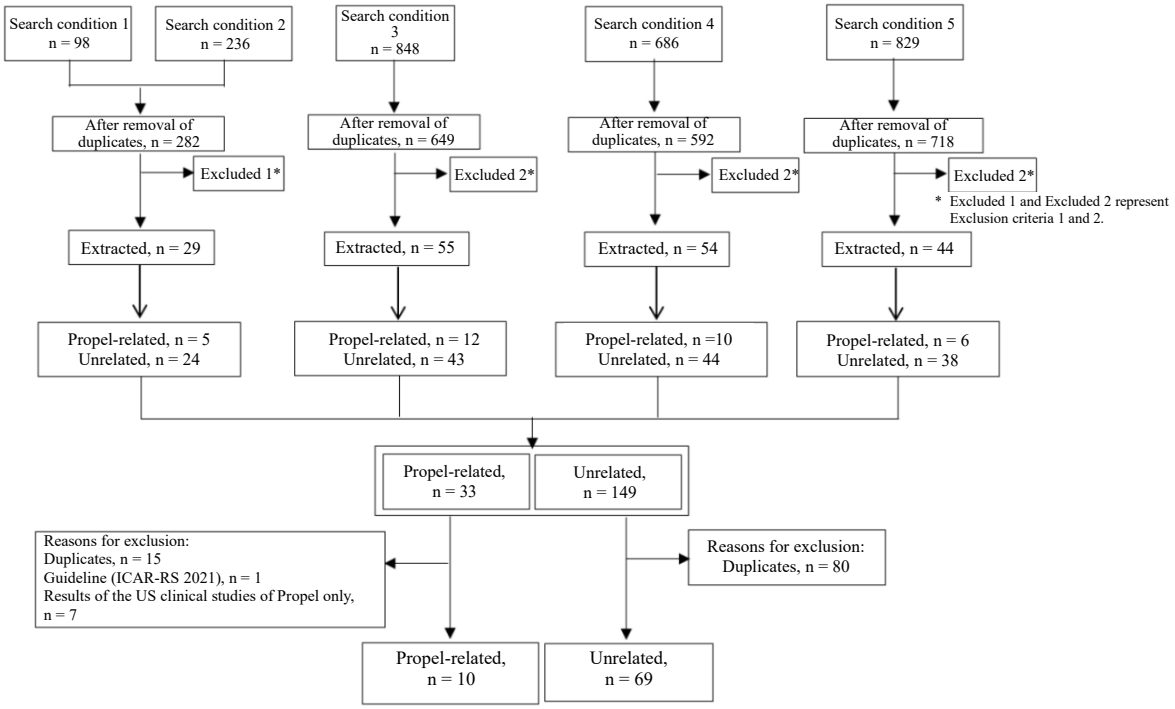


Figure 6. Literature extraction flow

Data to be used in the clinical evaluation were reviewed and classified into evidence levels according to the criteria in Table 53. Table 54 presents a list of published articles used for the evaluation of the Propel.

Table 53. Classification of evidence levels

Evidence level	Details
I	Systematic reviews or meta-analysis of randomized controlled studies
II	≥1 randomized controlled study
III	Non-randomized controlled studies
IVa	Analytical epidemiological studies (cohort studies)
IVb	Analytical epidemiological studies (case-control studies and cross-sectional studies)
V	Descriptive studies (case reports or case series)
VI	Opinions of expert committees or expert individuals, not based on patient data

Table 54. List of extracted articles, n = 10

No	Author, title (positioning of study)	Test (Number of subjects with the Propel)	Control	Follow-up period	Evidence level
1	Goshtasbi K et al. *Int Forum Allergy Rhinol*. 2019 Dec;9(12):1443-50. (meta-analysis)	Propel, Propel Mini, Propel Contour, Others (steroid-eluting stents, SinuBand, and fluticasone propionate) (n = 462)	Non-drug-eluting stents, intranasal packing, surgery alone, etc.	Day 30 (mean)	I
2	Li W, et.al. *Laryngoscope*. 2020 Dec; 130(12):2754-59. (meta-analysis)	Propel, Bioabsorbable, steroid-eluting implants (n =143)	Non-drug-eluting stents, non-drug-eluting dressing materials, non-drug-containing spacers, etc.	Day 30	I
3	Smith KA et.al. *Int Forum Allergy Rhinol.* 2020 Jul;10(7)856-70. (meta-analysis)	Propel, Propel Mini, Propel Contour, SINUVA, Others (SinuBand, Relieva Stratus Micro Flow Spacer, etc.) (n = 421)	NA	-	I
4	Rawl JW et.al. *Int Forum Allergy Rhinol.* 2020 Mar;10(3):328-333. (clinical research)	Propel, ethmoid sinus (n = 22)	Merocel filled in a non-latex glove	Day 30	II
5	Matheny KE, et al. *Int Forum Allergy Rhinol.* 2014 Oct;4(10):808-15. (clinical research)	Propel, ethmoid sinus (n = 20)	NA	Week 4	III
6	Shipman P, et al. *Ann Otol Rhinol Laryngol.* 2022 Jun;131(6):678-682. (clinical research)	Propel, ethmoid sinus (n = 1)	NA	NA	V
7	Schneider AL, et al. *Int Forum Allergy Rhinol.* 2022;12:1330-9 (retrospective cohort research)	Propel Mini (n = 8) Propel Contour (n = 25)	NA	NA	IVa
8	Hoffman V, et al. *Research and Opinion.*2022; 38:375-381 (retrospective cohort research)	Propel (n = 1983)	NA	Month 18	IVa
9	Shah SJ, et al. *Ann Otol Rhinol Laryngol.* 2022;131:5-1 (retrospective cohort research)	Propel (n = 245)	NA	NA	IVa
10	Narwani V et.al. *A MAUDE Database Analysis Otolaryngology Head and Neck Surgery.*2021 Apr 13:1945998211006930 (retrospective cohort research)	Propel (n = 23) Propel Mini (n = 3) Propel Contour (n = 2)	NA	NA	IVa

6.A.(2).1) Efficacy evaluation

The meta-analyses in Literature reports 1 to 3 evaluated the efficacy of drug-eluting stents, including the Propel. Literature report 1 by Goshtasbi et al. that includes most cases of the Propel therapy reported that the odds ratio (95% CI) in the test group (drug-eluting stents including the Propel) compared with the control group (non-drug-eluting stents, etc.) was 0.45 (0.33-0.62, $P < 0.001$) for "need for postoperative interventions," 0.30 (0.18-0.52, $P < 0.001$) for "need for surgical intervention," 0.58 (0.40-0.84, $P = 0.004$) for "Need for oral steroid intervention," 2.53 (1.61-3.97, $P < 0.001$) for "FSO patency," 0.42 (0.25-0.74, $P = 0.002$) for "nasal polyps," and 0.28 (0.13-0.59, $P < 0.001$) for "moderate to severe adhesion/scarring." The authors concluded that the results suggested improved post-ESS outcomes with drug-eluting stent placement. As with Literature report 1, Literature reports 2 and 3 also concluded the usefulness of post-ESS placement of drug-eluting stents. These reports included no data denying the efficacy of the Propel. Literature report 5, which is a report from clinical research of the Propel that evaluated the safety, outcome, etc. in patients who underwent ESS and received the Propel in the bilateral ethmoid sinuses after hemostasis was established (5-7 days postoperative), reported the lateralization of the middle turbinate with an incidence of 5% (2 of 40 sinuses), which required neither surgery nor oral steroid in any patient.

The following results were also reported in other published articles. Reduced inflammatory markers and reduced use of healthcare resources suggested the long-term usefulness of the Propel therapy.

- Matheny et al. (Literature report 5) used Sino-Nasal Outcome Test (SNOT)-20, which is a QOL questionnaire that evaluates therapeutic effect on rhinosinusitis, in their research and reported a statistically significant reduction in the score in 4 weeks after the Propel therapy.
- Schneider et al. (Literature report 7) measured IL-5 and IL-3, which are inflammatory markers, and reported a statistically significant reduction in these markers in 6 to 12 months after the Propel therapy.
- Hoffman et al. (Literature report 8) continued follow-up through 18 months after the Propel therapy and reported a statistically significantly lower rate of healthcare resource use, including outpatient visits and visits to otorhinolaryngology for any reasons, in the Propel group than the non-Propel group. Fewer patients in the Propel group required re-surgeries than the non-Propel group although the difference was not clinically significant.

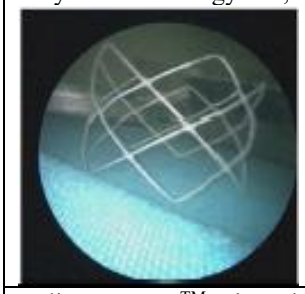
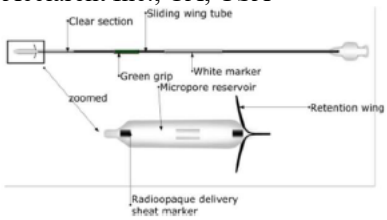
6.A.(2).2) Safety evaluation

Literature report 6 reported 1 event of infection (fungus), which was recorded as a serious adverse event for which a causal relationship to the Propel could not be ruled out. The patient received the Propel in the bilateral frontal sinuses and visited the study site because of pain, etc. on the left side of the face 14 days after ESS. Endoscopy revealed fungal elements and suspected tissue necrosis in the left frontal sinus. Debridement improved the symptoms. The event resolved in 4 months without recurrence. The report concluded that no definite cause for the event was identified, however, the necrosis caused by mechanical pressure from the stent and the local steroid-induced immunodeficiency state might have led to the fungal infection in the sinus. However, fungal infection is a common event after ESS and is not specific to the Propel. The other published articles reported neither deaths nor unexpected adverse events.

6.A.(2).3) Literature review of the efficacy and safety of similar medical devices

From 69 articles that were deemed irrelevant to the Propel therapy during the literature search, those that provide clinical data of the products developed to physically prevent tissue adhesion and maintain sinus patency were identified, and the clinical data of these products were summarized. Xiangtong sinus stent (BISORB), Relieva Stratus™ MicroFlow Spacer, and LYR-210 are placed in the ethmoid or frontal sinuses of patients with CRS after ESS, use a steroid, and have a similar shape or structure to that of the Propel (Table 55).

Table 55. Outline of the similar medical devices

Product name, picture, etc.	Authorization, indications, etc. overseas
Xiangtong sinus stent (BISORB) /Puyi Biotechnology Co., Ltd, China 	China, November 2013 (ZL201210454911.2) BISORB is intended for use in the ethmoid or frontal sinus for physical spacing and anti-inflammatory effect in patients with CRS after ESS. BISORB contains 652 μg of MF and is bio-absorbed in approximately 30 days.
Relieva Stratus™ MicroFlow Spacer /Acclarent Inc., CA, USA 	US 510(k), Frontal sinus type K083574 (Jan 29, 2009), Ethmoid sinus type K093594 (Mar 3, 2010) MicroFlow Spacer are intended for use as a postoperative spacer in the frontal or ethmoid sinus to maintain a sinus opening by its self-retaining mechanism within the first 14 days following surgery. The MicroFlow Spacer also prevents obstruction. In Europe, injection of a steroid solution in the balloon is approved. In the US, injection of physiological saline alone is approved. The sales of the product in the US was discontinued in May 2013.
LYR-21055 /Lra Therapeutics, Inc., MA, USA 	The product is not approved in the US. LYR-210 has a tubular mesh configuration with bioabsorbable MF-containing polymers that are designed to release the drug over 24 weeks to exhibit a local anti-inflammatory effect (2 types having different contents, 2500 and 7500 μg, under development). The uniquely designed elastomer characteristics ensure the contact of the product with the surrounding mucosal membrane to dilate and maintain the middle meatus.

A randomized, controlled study of BISORB, which resembles most closely the Propel, in the treatment of the post-ESS ethmoid sinus[17] demonstrated that BISORB was associated with a reduction in need for postoperative interventions and prevention of polyp formation at Day 30 compared with a hydrolyzable packing material (Nasopore) used as a control, showing a significant improvement in early postoperative outcome. Another clinical study[18] showed statistically significantly lower scores of edema, nasal obstruction, and total nasal symptom score (TNSS) in the BISORB group than the group that received no implant after ESS.

A randomized, controlled study of "Relieva Stratus™ MicroFlow Spacer" in the treatment of the post-ESS ethmoid sinus[19] showed no significant difference between the test device and nasal steroid sprays

used as the control in QOL outcome as assessed using SNOT22. Both the Relieva group and the control group had a decrease in VAS score over time, which was significant in the Relieva group compared with the control group at Month 3. A clinical study that compared the need for re-ESS in an intermediate-term follow-up with a nasal steroid spray[20] showed that approximately half of both groups did not require re-ESS at Month 6.

A clinical study of "LYR-210"[21] compared 2 doses (2500 and 7500 μg) of MF contained in LYR-210. The evaluable sample size of this study was too small to provide sufficient power for statistical analysis. SNOT-22 symptom scores improved similarly at the 2 doses, showing no dose-dependent improvement. The SNOT-22 score decreased at Days 14 and 56 in both groups. Most adverse events occurring after placement of LYS-210 were mild or moderate in severity as determined by treating physicians. No serious adverse event was reported.

The above clinical results suggest that the medical devices similar to the Propel are expected to decrease the need for postoperative interventions, prevent polyp formation, reduce edema and nasal obstruction, and improve nasal symptoms, compared with packing materials or surgery alone. These results are consistent with the results of the US clinical studies and literature reports of the Propel. Therefore, the Propel is also expected to have similar therapeutic effects.

6.B Outline of the review conducted by PMDA

Taking account of comments raised in the Expert Discussion, PMDA focused on the following issues:

(1) Extrapolation of the foreign clinical data
(2) Clinical positioning of the Propel
(3) Efficacy of the Propel
(4) Safety of the Propel
(5) Post-marketing safety measures
(6) Intended use or indication

6.B.(1) Extrapolation of the foreign clinical data

PMDA asked the applicant to explain the extrapolation of the results of the US clinical studies and foreign literature data to Japan.

The applicant's explanation:

- Medical environment

Table 56 presents comparisons of the medical environment between Japan and Europe/US. The diagnostic criteria for CRS are common to Japan and the other countries. The treatment policy, ESS procedures, and postoperative treatments are also similar in and outside Japan.

Table 56. Medical environment in Japan and overseas

	Japan	US	Europe
Guidelines	The "Guidelines for clinical practice of rhinosinusitis" was issued by the Japanese Rhinologic Society in 2024. The guidelines explain the definition, epidemiology, etiology, symptoms, diagnosis (tests and flowchart), treatment, etc. of rhinosinusitis that reflect the current situations in Japan.	The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021 (ICAR-RS 2021) issued by the US Rhinology Society classifies the use of drug-eluting stents (e.g., implants such as the Propel) as Grade A.	The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) issued by the European Rhinology Society recommends the use of steroid-eluting stents with Evidence level 1a.
Diagnostic criteria for CRS	Definition: Nasal symptoms such as nasal congestion, rhinorrhea, postnasal drip, and olfactory dysfunction lasting for ≥3 months Objective findings: The key diagnostic imaging of sinus disease is CT. (Y Kurono. Treatment of chronic sinusitis according to the Guidelines for clinical practice of sinusitis [in Japanese]. *Journal of Otolaryngology of Japan*, 2018;121:1118-20)	Definition: Persistent sinus inflammation lasting for ≥12 weeks Symptoms: At least 2 of the following symptoms: Nasal discharge (rhinorrhea or postnasal drip), nasal obstruction/congestion, facial pain or pressure, and hyposmia Objective findings: At least 1 of the following objective findings: Signs of inflammation, or purulent signs derived from the sinus cavity or ostiomeatal complex as confirmed by nasoendoscopy or CT scans CRS is classified into CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP). (ICAR-RS 2021)	Definition: Persistent sinus inflammation lasting for ≥12 weeks Symptoms: At least 2 of the following symptoms, including nasal obstruction or nasal discharge (rhinorrhoea or postnasal drip): Facial pain or pressure, and hyposmia or anosmia Objective findings: Nasoendoscopic signs (nasal polyps, mucopurulent discharge, edema, and mucosal obstruction) and CT signs of inflammation (change in intranasal mucosa) CRS is classified into CRSwNP or CRSsNP according to evidence of nasal polyps. (EPOS2020)
Therapeutic policy	Surgical therapy is indicated to treat CRS that has not responded to conservative therapies, such as drug therapy and intervention/local therapy, or is accompanied by complications.	ESS is recommended to both CRSwNP and CRSsNP when symptoms do not respond to drug therapy. (ICAR-RS 2021)	ESS is recommended, regardless of nasal polyp status, when symptoms do not respond to drug therapy. (EPOS2020)
Procedure and concept of ESS	The basic procedure of ESS, which dilates the drainage pathway of a narrowed or obstructed sinus, and removes the pathological mucous membrane and pus, is common throughout the world.		
Post-ESS treatment	Irrigation with physiological saline, sinus debridement, local steroids, oral antibiotics, and packing materials (H Moriyama, S Haruna, N Ootori. *Endoscopic sinus surgery. From sinus disease to skull base disease* [in Japanese]. Igaku Shoin 2015)	Irrigation with physiological saline, sinus debridement, local steroids, oral antibiotics, and packing materials (ICAR-RS 2021)	Irrigation with physiological saline, sinus debridement, local steroids, and packing materials (EPOS2020)

- Effects of race

The reported healthy sinus volumes (maxillary sinuses, frontal sinuses, and sphenoid sinuses) of non-Japanese people (Turkish and Spanish) were within the range of healthy Japanese sinus volumes (frontal sinus, 2.4-28.8 cm^3; maxillary sinus, 3.5-45.2 cm^3; sphenoid sinus, 3.2-28.8 cm^3) reported by Ikeda et al.[22,23] The sinus volumes of the subjects enrolled in the US clinical studies were consistent with the data in these articles. No difference in the size of the frontal and sphenoid sinuses indicates that there are no differences in the ethmoid and maxillary sinuses substantial enough to affect the efficacy and safety of the Propel. Although the shape and size of the sinuses vary among individuals, the Propel stent dilates so that it fits the inside of the sinus. The sinus shape and size do not compromise the efficacy and safety of the Propel.

MF, used in the Propel stent, has been shown to have a local anti-inflammatory effect in published articles. The daily dose of Nasonex for the treatment of allergic rhinitis is the same in Japan and the US, and there is no racial difference in CYP3A4 that is involved in the metabolism of MF. Thus, the efficacy and pharmacokinetics of the Propel are unlikely to differ between Japanese and Caucasian subjects. A US clinical study (the Consensus II study) revealed that the plasma concentrations of MF in subjects in the pharmacokinetics (PK) group were below the lower limit of quantification at all time points. The maximum amount of MF released with 4 units (the maximum allowable) of the Propel is estimated to be [redacted] μg/day (worst case). No systemic transfer of MF was observed after repeated nasal spray administration of Nasonex at 800 μg/day to adult Japanese men for 7 days.[14] Taken together, there is no MF-related systemic safety concern after the placement of the Propel.

PMDA asked the applicant to explain the justification of evaluating the efficacy of the Propel in the Japanese medical setting based on the US clinical study data, in view of the prevailing use of packing materials following ESS of the ethmoid sinus in Japan and the fact that the US clinical studies did not directly compare the Propel and packing materials.

The applicant's explanation:

In the US clinical studies of the Propel (the Consensus II and the Advance II studies), the control groups received "non-drug-eluting stents," which is different from the use of packing materials as commonly practiced in Japan. As mentioned in Section 2.(6), however, the performance comparison between non-drug-eluting stents and packing materials proved the patency of non-drug-eluting stents equal to or greater than that of packing materials, showing the validity of the comparison. In addition, in order to compare clinical performance between the Propel and packing materials, data from the US clinical studies and from the randomized, controlled studies reported in published articles[24,25,26] were indirectly compared. The incidence of adhesion with non-drug eluting stents was 24.0% in the Consensus II study and 12.5% in the Advance II study, which were similar to that with packing materials reported in published articles (11.3%-27%).

The US clinical studies with the Propel Mini and the Propel Contour targeted the frontal sinus, and the control group received surgery alone. It is reasonable to use the US clinical study results for comparison with the existing treatment in Japan because packing materials are not used for the frontal sinus in Japan as well.

PMDA's view:
There is no substantial difference between Japan and overseas in extrinsic factors such as the diagnostic criteria for CRS and intervention with ESS, or intrinsic factors such as the anatomical structure of the sinuses and the pharmacokinetics of MF used in the Propel stent. Thus the efficacy and safety of the Propel in the Japanese medical settings can be discussed based on the results of the US clinical studies. Accordingly, efficacy and safety evaluation of the Propel is feasible in Japanese patients based on US clinical study results and findings from overseas literature articles.

6.B.(2) Clinical positioning of the Propel

As described in Section 1.(1), the use of the packing materials in the ESS-treated ethmoid sinus prevents tissue adhesion and bleeding. PMDA asked the applicant to explain the clinical positioning of the Propel as a post-ESS therapy in Japan.

The applicant's explanation:
In Japan, bleeding from the cutting process during ESS can generally be controlled by cauterization with an electric scalpel. If bleeding persists even after the surgery and tissue adhesion in the ESS-treated sinus (ethmoid sinus) is suspected, packing materials are placed in the ethmoid sinus to stop bleeding and prevent tissue adhesion at the surgical site, with drug therapy (e.g., antibiotics, local nasal steroid sprays, and oral steroids) as patient's pathological condition requires (hereinafter referred to as "the conventional treatment"). The Propel physically prevents stent-associated tissue adhesion and is expected to reduce inflammation by sustainably releasing MF, the coating material, at the site. With these mechanisms, the Propel enables a treatment that will replace the conventional post-ESS treatment. The Propel is decomposed over 30 to 45 days. In contrast, hydrolysable packing materials are hydrolyzed and excluded from the body in approximately 3 to 5 days, which precludes continuous support for the middle turbinate. In case of incomplete decomposition, residuals have to be removed, which is a painful procedure. In view of these, the Propel is useful.

The Propel does not have a hemostatic effect. PMDA asked the applicant to explain how to use the Propel in the bleeding sinus after the surgery.

The Propel can be placed in the bleeding sinus immediately after the surgery unless bleeding is so severe that it interferes with the procedure. Otherwise, the Propel should be placed after the temporary use of packing materials to stop bleeding.

In response, the Expert Discussion raised the following opinions with regard to the introduction of the Propel to Japanese clinical practice:

- The use of packing materials is the mainstream method after ESS in Japan, the Propel is most likely be indicated for patients with CRS who will benefit from it as an add-on treatment to packing materials.
- In Japan, packing materials are placed in the sinus for 1 to 2 weeks after ESS primarily for hemostatic purpose, while the Propel was placed on the day of ESS in the US clinical studies. In Japanese clinical practice, the timing of Propel placement may be different from that in the US clinical studies.

- The US clinical studies evaluated postoperative interventions at Day 30. Since the frequency of hospital visits before Day 30 in Japanese clinical practice may differ from that in the US clinical studies, it is meaningful to discuss the appropriate use of the Propel based on the standard frequency of hospital visits in Japan.
- In Japan, refractory eosinophilic rhinosinusitis, which is associated with recurrent nasal polyps, is treated with oral steroids and nasal steroid sprays for a short period after ESS. In the US clinical studies, CRS categories were not taken into consideration in the evaluation of the Propel. Data by CRS category (eosinophilic or non-eosinophilic) and by severity will help the proper use of the Propel in Japan.
- There is no objection to the approval of Propel based on the results of the US clinical studies, etc. However, it is desirable to obtain information on the usefulness of the Propel in Japan taking the above-mentioned points into account.

PMDA's view on the clinical positioning of the Propel:
The results of the US clinical studies, etc. have demonstrated the performance of the Propel in post-ESS treatment that is expected to replace packing materials and alleviate inflammation with the effect of MF. The Propel will be useful in view of the risk of pain and bleeding associated with the removal of packing materials, However, in Japan, as pointed out in the Expert Discussion, the use of packing materials is the established mainstream method to stop bleeding and maintain sinus patency after ESS, and the Propel will not replace this conventional method anytime soon after its introduction to Japan. In response to PMDA's request to address the issue pointed out at the Expert Discussion, the applicant informed that data on the concomitant use of the Propel with packing materials and data by CRS category (eosinophilic or non-eosinophilic) would be collected in cooperation with the Japanese Rhinologic Society to evaluate the clinical usefulness of the Propel [see Section 6.B.(5)]. Including these data, the applicant and the related academic society should appropriately provide healthcare professionals with information in terms of when to use the Propel and whether to use it with packing materials, and make clear the clinical positioning of the Propel and the conventional treatment.

The US clinical studies evaluated postoperative interventions at Day 30. As pointed out during the Expert Discussion, postoperative management should be provided at appropriate timings on a patient-by-patient basis. PMDA instructed the applicant to provide healthcare professionals with proper post-marketing cautions. The applicant responded accordingly [see Section 6.B.(5) described later].

6.B.(3) Efficacy of the Propel

The primary endpoint "need for postoperative interventions" of the US verification clinical studies was appropriate because the Propel was developed to reduce postoperative interventions by maintaining the post-ESS sinus patency and preventing tissue adhesion and inflammation.

All of the Advance II, PROGRESS Mini, and PROGRESS Nova studies demonstrated that the Propel was associated with a statistically significant reduction in the primary endpoint "need for postoperative interventions at Day 30" in comparison with the control, indicating the efficacy of the Propel. None of these 3 verification studies showed a statistically significant reduction in "surgical intervention" or "oral steroid intervention," which comprise the primary endpoint, in the Propel groups in comparison with

the control groups. However, this does not to raise any particular concern about the efficacy of the Propel because all of the studies showed a reduction in the Propel groups as compared with the control groups. The efficacy evaluation based on the literature reviews described earlier indicated a similar tendency to that observed in the US clinical studies, supporting the efficacy of the Propel.

6.B.(4) Safety of the Propel

PMDA's view:

The data revealed no serious adverse event for which a causal relationship to the Propel could not be ruled out in the US clinical studies. One event of infection (fungus) was reported in a published article. It is clinically acceptable because it is not a Propel-specific event but a common one that may occur after general ESS, and the Propel can be removed in the event of infection. For some adverse events in the US clinical studies, a causal relationship to the Propel could not be ruled out, these events appear not to raise any particular safety concern for the following reasons: Recurrent chronic sinusitis for which a causal relationship to the test device was unknown did not resolve but was not serious; the other events were resolving or resolved; and neither deaths nor unknown adverse events occurred in these studies.

The Propel is a biodegradable stent. The drug release rate test in the rabbit maxillary sinus, one of the non-clinical studies described earlier in Section 2.(6), demonstrated that 90% of the stent base material was absorbed by Day 30. The US clinical studies showed no serious adverse event through Day 90 or Month 6. As reported by Narwani et al. (n = 28) (Literature report 10), neither unexpected nor significant new adverse event has been reported in the US post-marketing malfunction report (MAUDE database; search period August 1, 2011-December 1, 2020). The 18-month follow-up research by Hoffman et al. (n = 1,983) (Literature report 8) revealed that the risk of post-ESS infection increased with systemic steroid therapy but not with the Propel therapy. These findings indicate the long-term safety of the Propel.

6.B.(5) Post-marketing safety measures

PMDA's view:

No serious adverse event has been reported over 10 years of clinical experience with the Propel overseas. The US clinical studies and published articles have identified no adverse event of concern. Since the Propel appears to be associated with a low safety risk, no use-results survey of the Propel is required. All of the US clinical studies demonstrated a reduction in need for postoperative interventions, regardless of a particular patient's baseline characteristics. Currently, therefore, it is unnecessary to establish requirements for patients to ensure the efficacy and safety of the Propel. The basic procedure of the Propel therapy is intranasal stent placement, which involves no new procedure and can be implemented by physicians at medical institutions qualified for ESS. There is no need to newly establish requirements for treating physicians or medical institutions, or guidelines for proper use.

The applicant's explanation:

On the basis of the discussion in Section "6.B.(2) Clinical positioning of the Propel," the applicant explained was currently discussing issues regarding the introduction of the Propel into Japan with the Japanese Rhinologic Society. Taking into consideration the advice from them, the applicant is planning to collect data that might facilitate the smooth introduction of the Propel into the Japanese medical environment, as well as the current usage of packing materials and steroids. The applicant's plan on data

collection in cooperation with the related academic society is reasonable. The applicant should provide collected information to healthcare professionals in a timely manner.

The following issues were raised from the Expert Discussion: (1) The Propel has no hemostatic effect unlike the packing materials; (2) there is no clinical experience of using the Propel in combination with the packing materials; (3) and it is necessary to stress that the Propel does not eliminate the need for post-ESS interventions and that post-ESS follow-up should be continued. PMDA instructed the applicant to communicate this information to healthcare professionals. The applicant agreed with this.

6.B.(6) Intended use or indication

On the basis of the above discussions, PMDA concluded that the intended use or indication of the Propel proposed by the applicant should be modified as shown in Table 57. The applicant agreed with this.

Table 57. Change in the proposed intended use or indication

Before change	After change
Propel Sinus Implants is intended for use to maintain nasal patency following sinus surgery in patients [1)]aged ≥18 years with chronic sinusitis. [2)]Propel Sinus Stent provides stabilization of the turbinate, prevents obstruction by tissue adhesions, and reduces inflammation and edema thereby reducing the need for postoperative interventions.	Propel Sinus Implants is intended for use to maintain nasal patency following sinus surgery in [1)]adult patients with chronic rhinosinusitis.

1) The expression was modified.
2) The description that is included in the maintenance of sinus patency was removed.

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

As described in Section 6, PMDA concluded that no post-marketing use-results survey was necessary for the Propel.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

PMDA's review on the Propel focused on (1) its clinical positioning and (2) efficacy and safety. Based on comments raised by the Expert Discussion, PMDA reached the following conclusions:

(1) Clinical positioning of the Propel

In Japan, the use of packing materials has been the mainstream method to stop bleeding and maintain sinus patency post-ESS, and the Propel will not replace this conventional method anytime soon. Nevertheless, the US clinical studies, etc. have demonstrated promising efficacy of the Propel as an

alternative to packing materials and to alleviate inflammation with the effect of MF. It is important that, based on data collected in cooperation with the related academic society, the applicant appropriately offers information to the healthcare professionals in terms of when to use the Propel and whether to use it with packing materials, and make clear the clinical positioning of the Propel and the conventional treatment.

(2) Efficacy and safety of the Propel

The US verification clinical studies (Advance II, PROGRESS Mini, and PROGRESS Nova studies) have demonstrated that the Propel stent and MF alleviate inflammation and lessen the need for post-ESS interventions. Published articles also suggested the effectiveness the placement of drug-eluting stents including the Propel in reducing the post-ESS interventions, and reported no findings contradicting the US clinical studies. The safety was also evaluated based on the results of the US clinical studies and literature reviews. One case of infection (fungus) was reported in an article as serious adverse event for which a causal relationship to the Propel could not be ruled out. It was, however, not Propel-specific but a common event that could occur after ESS. The adverse events for which a relationship to the Propel could not be ruled out were confirmed as resolving or resolved, other than 1 case of non-serious recurrent chronic sinusitis. Neither deaths nor unknown adverse events occurred. Thus, PMDA has concluded that the safety of the Propel is clinically acceptable.

As a result of the above review, PMDA has concluded that the Propel may be approved for the intended use shown below.

Intended Use

Propel Sinus Implants is intended for use to maintain nasal patency following sinus surgery in adult patients with chronic rhinosinusitis.

The product is not classified as a biological product or a specified biological product.

PMDA has concluded that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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