PROTOCOL TITLE: S-I: A randomized, 52-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week after endoscopic sinus surgery in patients with allergic fungal rhinosinusitis (AFRS) on a background therapy with intranasal corticosteroid spray
Short: Add-on Dupilumab for AFRS as Postoperative Therapy (ADAPT)

EMORY PRINCIPAL INVESTIGATOR:
[redacted], MD
Assistant Professor, Rhinology and Skull Base Surgery Division
Department of Otolaryngology – Head & Neck Surgery
Emory University School of Medicine
[redacted]

EXTERNAL (NON-EMORY) COLLABORATORS
[redacted], Associate Professor of Otolaryngology McGovern Medical School at the University of Texas Health Science Center at Houston, Department of Otolaryngology-Head & Neck Surgery
The University of Texas IRB will review the engagement in human participants research activities.

SPONSOR INVESTIGATOR:
[redacted]
Office of the Clinical Director
[redacted]

VERSION: 3.7.3

FUNDING SOURCE: Sanofi

REVISION HISTORY

Revision #	Version Date	Summary of Changes
2.1	07 Dec 2019	**Protocol formatting** Format of entire protocol updated to reflect current standards of practice **Table 1. Schedule of Activities – CT sinus scan** Timing of post-treatment CT scan adjusted from EOS to EOT **Table 1. Schedule of Activities - Pregnancy Test** Frequency of urine pregnancy testing increased to facilitate testing during each study visit prior to IMP administration (5 per subject). **Section 13. Safety Definitions, Reporting, And Monitoring** Required subject safety activities included.
2.2	15 Oct 2020	**Statistical methods** Stratification strategy updated with removal of asthma Blinded central reader introduced **10.1 Study Database** Introduction of Microsoft OneDrive as a central data repository **12.1 Objective measures of disease** Introduction of blinded central reader to determine mLK scores **13.1 Missing data handling** Introduction of multiple imputation approach **13.6 Primary Analysis** Strategy for handling of intercurrent events is further described **13.7 Secondary and Exploratory Analysis** Revision surgery during follow-up will be considered a treatment failure **14.3 Recording and Reporting Adverse Events** Reporting expectations are clarified, to include 24-hour notification
2.3	02 Mar 2021	**6.1 Overall Design** Background medication changed from Budesonide irrigations to standard of care intranasal corticosteroid sprays (INCS), as chosen by the treating physician **8.1.2 Non-Investigational Products** Background medication changed from Budesonide irrigations to standard of care intranasal corticosteroid sprays (INCS), as chosen by the treating physician **8.3.5 Rescue Therapy** Topical corticosteroid irrigations allowed as rescue per treating physician
2.4	12 Nov 2021	**Table 1: Schedule of Activities** Defined frequency of pregnancy testing and assessment of subject compliance **4.6.3 Accountability** Westat included as external study monitor with defined monitoring plan

		4.8 Pharmacy Belmar Pharma Solutions included as dispensing pharmacy **8. Study Timelines** Updated timeline for study milestones **16.2 Database Set-up and Management** Inclusion of FDA Part 11 compliance **17.1 Obligations of Sponsor-Investigator** Inclusion of 21 CFR 312 **17.4.3 Evaluation of Causality** Defined IND Safety Reporting
3.0	28 Dec 2021	**Protocol Formatting** Clarification provided to define protocol mandated study activities versus those completed per standard of care (sinus surgery, nasal saline irrigations, topical corticosteroid sprays) **1.0 Study Summary** Addition of reminder text messages the day of scheduled IMP injections. **Table 4: Investigational study treatments** Clarification of Placebo **4.6 Preparation/handling/administration/accountability** Description of central pharmacy and delivery of study drug, as well as internal monitoring for drug receipt and subsequent use / disposal **Appendix C: Data and Safety Monitoring Board Charter** DSMB Charter included **Appendix E: List of Study Vendors** Reference list of study vendors included
3.1	31 Jan 2022	**15.4.1 Evaluation of Severity** Addition of Common Terminology Criteria for Adverse Events (CTCAE) to evaluate AE event severity
3.2	17 Feb 2022	**Title:** Added S-I **1. Study Summary** Addition of SNOT-22 and ACT in the table **6. Data Specimen Banking** Changed “mandatory” to “optional” **7.1 Inclusion Criteria** Added the language that non-English speakers will be included **7.1.5 Reproduction** Added men criteria

3.3	31 May 2022 28 Jun 2022	**3. Study Objectives and Endpoints** Addition of co-primary endpoint **15.3 Recording and Reporting Adverse Events** Added details for clarification Copied a section about FDA reporting (that was initially under 15.4 Evaluation of Severity and Causality) **14.6 Primary Analysis** Added specific details about • the statistical model • analysis for subject with unilateral disease • plan for Type I error control
3.4	14 Jul 2022	**14.11 Safety evaluation plan** Added **1. Study Summary** Removed Randomization from visit 3 and added it to surgery period. Clarified Surgery period length: 7 days ± 4 weeks **Study design is summarized in Figure 1** Updated the Figure with correct running timeframe **4.1 Overall Design** Clarified that randomization is before visit 3 (week0) **15.7 Monitoring Table 2** Added to this version
3.5	9 Aug 2022	**2. Background** Added more details on dupilumab mechanism of action and rationale. **4.6.2 Administration** Clarified that participants who prefer to get injection at the clinic can do so. **13. Compensation** Clarified how compensation will be done at study visit
3.6	7 Mar 2023	**Appendix D: List of Study Personnel** Addition of [redacted] Removal of [redacted] **5.2.1 Objective measures of disease** *Incentive Spirometry:* Removed "Incentive" to reflect the correct procedure **6. Data Specimen Banking** Renamed this section "Data Specimen collection and Banking" to clarify that the specimen is not only for banking. Rearranged the section to explain the required collection first and then the optional. **Appendix E: List of Study Vendors** Changed Westat contact person to Michele Snyder
3.7	21 Mar 2023	**Investigators** Added [redacted] as PI of Emory site.

		Changed [redacted] (S-I) address to the NIH site **Across the protocol** Added the fourth site: NIH and changed the number of sites from three to four, and the number of participants per site from 44 to 33. Removed RSDI to be consistent with the SoA
3.7.1	1 Sep 2023	**Across the protocol** Removed Vanderbilt as a site and changed the number of sites from four to three, and the number of participants from 33 to 44. Clarified that study visits and dosing of IMP can be within 7 days of planned date in line with prescribing package information for dupilumab for CRSwNP. Formatting adjustments. Subjects updated to participants Standardized treatment for nasal polyps to daily include saline irrigations and INCS spray. Standardized that pregnancy test will be done until visit 8 **Table 1.** Clarified that CT scan is per SoC and can be up to 6 months before surgery. Clarified that randomization occurs post-operatively **4.5.3 Postoperative care / 7.1.4 Sinus Surgery** Post operative pain regimen at discretion of treating physician. Oral steroid regimen specified to be prednisone. Removed from section 7.1.4 (duplicated information) **4.7 Randomization and blinding** Randomization, blinding, and emergency unblinding provided by study data team **6. Data Specimen Collection and Banking** Clarified that routine laboratory monitoring is not planned but can be obtained for SoC if needed **7.2.1. Exclusion Criteria** Removed mucocele as exclusion criteria as this frequently seen in AFRS.
3.7.2	9 Oct 2023	**Schema** Updated the schema to reflect the changes made to the protocol
3.7.3	2 Apr 2024	**Across the protocol** Asthma Control Test (ACT) was replaced by Asthma Control Questionnaire (ACQ) throughout the protocol. **4.1 Overall Design** Protocol clarified to allow enrollment of participants within 2 weeks of surgery if they have been on background therapy for a minimum of 2 weeks and meet all other eligibility criteria.

Table of Contents

1. Study Summary

Table 1: Schedule of Activities

	Run-in	Surgery	Randomized Treatment period								EOT	EOS
Visit[a]	1	2	3		4		5		6		7	8
Week Day ± 7	W-6 D-42	W-1 D-7[g]	W0 D0	2,4,6,8,10[b]	12 D84	14,16,18,20,22[b]	24 D168	26,28,30,32, 34[b]	36 D252	38,40,42,44,46,48, 50[b]	52 D364	64 D448
Informed consent	X											
Inclusion and exclusion criteria	X		X									
Patient Demography	X											
Medical / surgery history	X											
Physical exam	X		X		X		X		X		X	X
Urine Pregnancy Test[c]	X		X		X		X		X		X	X
Transfer diagnostic nasal endoscopy to online repository	X		X		X		X		X		X	X

Determination of mLK endoscopic score[d]	X		X		X		X		X		X	X
Spirometry[e]	X		X		X		X		X		X	X
SNOT-22	X		X		X		X		X		X	X
ACQ	X		X		X		X		X		X	X
CT sinus scan	X[i]										X	
Randomization[f]		X										
Collect peripheral blood[h]	X		X		X		X				X	X
Sinus mucus sample[h]	X		X		X		X				X	X
Ethmoid sinus tissue		X										
Treatment:												
IMP: Dupilumab/ placebo injection[b]			X	X	X	X	X	X	X	X		
Record concomitant medications	X	X	X		X		X		X		X	X
Text reminder for IMP self-administration[b]				X, X, X, X, X		X, X, X, X, X		X, X, X, X, X		X, X, X, X, X, X, X		
Assessment of IMP compliance (phone call)[b]				X, X		X, X		X, X		X, X, X		

Assessment of IMP compliance (device collection)[b]					X		X		X		X	
Record planned surgery for NP, OCS use and other rescue medications	|----------X----------|											

[a] Patients who discontinue treatment early will be assessed as soon as possible using the procedures normally planned for the EOT Visit.
[b] Patients will self-administer investigational drugs between study visits (v3-8). Compliance will be ensured by reminder text messages the day of each home injection, monthly phone calls and collection of injection materials at following study visits.
[c] Urine pregnancy test completed by all WOCBP, (i.e., post-pubescent, premenopausal females).
[d] Determination of mLK endoscopic scores will be completed by a blinded, central reader for all study sites.
[e] Lower airway assessments completed for participants with medical history of comorbid asthma (~25% of study cohort).
[f] Patients will be randomized once pathology report is available post-operatively to confirm presence of fungus.
[g] Surgery period can be extended to 4 weeks to accommodate operating room availability, unforeseen personal events, or other occurrences that delay randomization.
[h] Optional, only in participants that consent to collection and banking of these materials.
[i] If not previously obtained within prior 6 months.

ACQ: Asthma Control Questionnaire, AE: Adverse Event, CT: Computed Tomography, IMP: Investigational Medical Product, mLK: Modified Lund Kennedy Endoscopic Score, NP: Nasal Polyp, OCS: Oral Corticosteroid, SAE: Serious Adverse Event, SNOT-22: 22-item SinoNasal Outcomes Test, WOCBP: women of childbearing potential

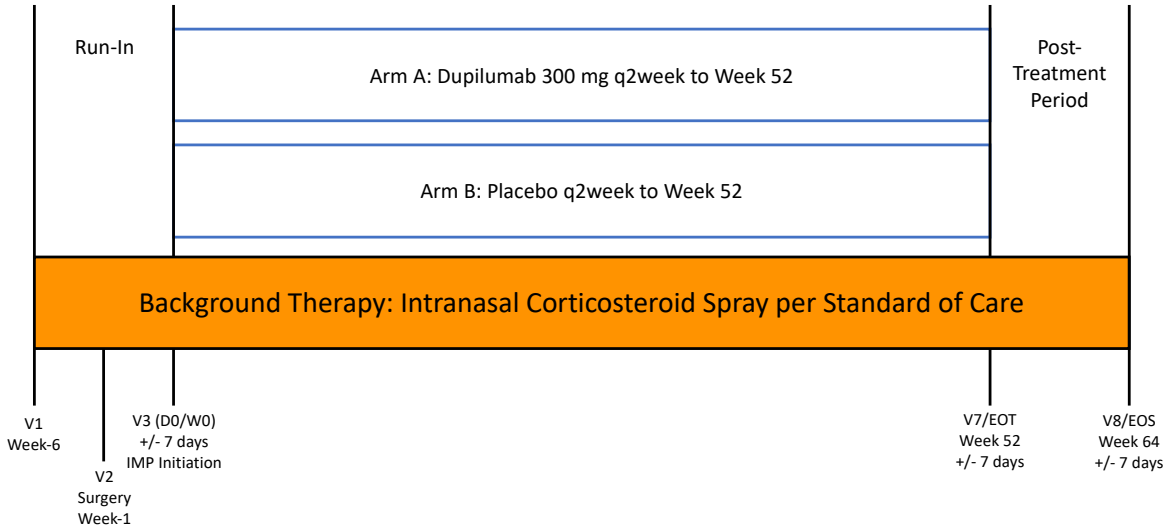
Project Title	S-I A randomized, 52-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week after endoscopic sinus surgery in participants with allergic fungal rhinosinusitis (AFRS) on a background therapy with intranasal corticosteroid spray **Short:** Add-on Dupilumab for AFRS as Postoperative Therapy (ADAPT)
Project Design	Multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy of dupilumab to placebo in allergic fungal rhinosinusitis (AFRS) participants after sinus surgery on a background treatment with intranasal corticosteroid spray **Study periods:** The clinical trial consists of 4 periods: **1. Run-in period (2 weeks + 4 weeks):** All participants will enter a run-in period of 2-6 weeks receiving saline irrigations and INCS spray daily. All oral steroids and antibiotics as well as corticosteroid rinses will be stopped. **2. Surgery period (7 days + 4 weeks):** Patients will undergo surgery as scheduled. Sinonasal mucus, peripheral blood and ethmoid tissue will be collected from all participants at the time of surgery. **3. Randomized treatment (52 weeks ± 7 days):** Patients will be randomized to one of the following treatments: • Arm A: dupilumab 300 mg subcutaneous (SC) q2w until Week 52 • Arm B: placebo given SC q2w until Week 52 **4. Posttreatment period (12 weeks ± 3 days):** After completing 52 weeks of treatment with IMP (or following early discontinuation of IMP or discontinuation from the study), participants will be instructed to • Return to the study site for the last scheduled visits for physical examination, nasal endoscopy, NPS, PROs (SNOT-22 and ACQ), FEV1 measurement in those with asthma and safety. • Continue on stable dose of INCS spray during the posttreatment period. • Report any adverse event (AE).
Co-Primary Objectives	a) Determine the efficacy of dupilumab in controlling sinonasal inflammation and preventing nasal polyp recurrence after complete sinus surgery for AFRS, as measured by change in the mLK score b) Evaluate the effect of dupilumab on oral corticosteroid utilization following complete sinus surgery for AFRS
Secondary Objectives	To evaluate the effect of dupilumab on: • Prevention of revision surgery for AFRS • Secondary objective measures of sinonasal inflammation following sinus surgery using the NPS and LMS • Lower airway dysfunction following sinus surgery in the subgroup of participants with asthma (~25%) • Upper and lower airway, disease-specific, health-related quality of life, as measured by ACQ and SNOT-22 • Reducing utilization of rescue medications for acute exacerbations of CRS following sinus surgery

<table>
<tr><td>Research Interventions / Interactions</td><td>Dupilumab 300 mg will be administered SC every 2 weeks with an EOT at week 52. Matching placebo will be administered SC at the same time points. Patients will receive a total of 26 doses of IMP. Patients will receive IMP directly from the central pharmacy, with compliance assessments via reminder text messages the day of each scheduled home administration, as well as monthly phone calls and injection device collection at recurring 3-month study visits (W0, 12, 24, 36). Self-administration of IMP will be completed at home to maintain a 2-week treatment schedule (W2, 4, 6, 8, 10, 14, 16, 18, 20, 22, 26, 28, 30, 32, 34, 38, 40, 42, 44, 46, 48, 50). Pregnancy testing in WOCBP will be completed during each study visit (W0, 12, 24, 36, 52, 64).
All participants will undergo standardized background therapy with intranasal corticosteroid sprays (INCS) per standard of care (SoC). This will be continued throughout the entire study. The systemic bioavailability of INCS varies from <1% to up to 40-50%, which is why we will standardize the dose of INCS. Participants will either receive fluticasone propionate or mometasone furoate at the following dosages below.
<table>
<tr><th>INCS</th><th>Frequency</th><th>Total Daily Dosage</th></tr>
<tr><td>Fluticasone propionate</td><td>2 sprays (50mcg) in each nostril once daily</td><td>200mcg</td></tr>
<tr><td>Mometasone furoate</td><td>2 sprays (50mcg) in each nostril twice daily</td><td>400mcg</td></tr>
</table>
</td></tr>
<tr><td>Study Population</td><td>Allergic Fungal Rhinosinusitis</td></tr>
<tr><td>Sample Size</td><td>This study will be completed at 3 North American sites. A total of 132 participants will be randomized.</td></tr>
<tr><td>Study Duration for individual participants</td><td>The total duration of the study (per subject) is expected to be approximately 71 weeks:
• Run-in period (2-6 weeks*)
• Surgery period (7 days + 4 weeks)
• Randomized treatment period (52 weeks ± 7 days)
• Posttreatment period (12 weeks ± 3 days)

*Participants may be consented & enrolled at any time during run-in or presurgical period, provided the failure of appropriate medical therapy has been documented as outlined in the inclusion criteria</td></tr>
<tr><td>Study Specific Abbreviations / Definitions</td><td>
<table>
<tr><th>Abbreviation or Term</th><th><u>Definition</u></th></tr>
<tr><td>ACQ</td><td>Asthma Control Questionnaire</td></tr>
<tr><td>AE</td><td>Adverse event</td></tr>
<tr><td>AERD</td><td>Aspirin exacerbated respiratory disease</td></tr>
<tr><td>AM</td><td>Morning</td></tr>
<tr><td>AFRS</td><td>Allergic Fungal Rhinosinusitis</td></tr>
</table>
</td></tr>
</table>

	BID	Twice a day
	CFR	Code of Federal Regulations
	CRSwNP	Chronic Rhinosinusitis with nasal polyps
	CT	Computed tomography
	EDC	Electronic Data Capture
	FU	Follow-up
	GCP	Good clinical practice
	ICF	Informed consent form
	IMP	Investigational medicinal product
	INCS	Intranasal corticosteroids
	IP	Investigational product
	IPD	IP discontinuation
	IRB	Institutional Review Board
	LMS	Lund-Mackay score
	mLK	Modified Lund Kennedy Endoscopic Score
	SNOT-22	SinoNasal Outcome Test, 22 item
	SoC	Standard of Care
	WOCBP	Women of childbearing potential
Funding Source	Sanofi	

Schema


Run-In
Arm A: Dupilumab 300 mg q2week to Week 52
Post-Treatment Period
Arm B: Placebo q2week to Week 52
Background Therapy: Intranasal Corticosteroid Spray per Standard of Care
V1 Week-6
V2 Surgery Week-1
V3 (D0/W0) +/- 7 days IMP Initiation
V7/EOT Week 52 +/- 7 days
V8/EOS Week 64 +/- 7 days

2. Background

Allergic fungal rhinosinusitis (AFRS) is a severe form of eosinophilic nasal polyposis with critically inadequate treatment options for the 10% of chronic rhinosinusitis participants affected by the disease. Occlusive eosinophilic mucus and severe nasal polyposis presents in early adulthood, with an unrelenting course marked by sinus expansion and pressure-induced dehiscence of the surrounding orbit and skull base. Despite appropriate therapies with oral/topical corticosteroids, saline irrigations and comprehensive sinus surgery, nasal polyps aggressively recur, frequently within months of surgery. Medical options beyond topical and systemic steroids are limited. Neither antifungal nor allergen immunotherapy are beneficial. *Due to persistent sinonasal inflammation, patients with AFRS receive an average of three corticosteroid bursts per year and revision sinus surgery every 42 months.*

Rationale

In addition to the activation of type 2 inflammatory mediators found in other CRSwNP phenotypes, AFRS is uniquely characterized by an exaggerated activation of the adaptive immune response with serum IgE levels often above 1000 kU/L and defined by an upregulation of fungal specific IgE levels [1]. Marked eosinophilic inflammation is found throughout the upper airway, and the degree of mucosal eosinophil infiltration has been repeatedly reported as a potent predictor of poor surgical outcomes. *We therefore hypothesize that dupilumab, a human monoclonal antibody that targets the type-2 inflammatory cascade, is a safe and effective treatment for nasal polyps as add-on therapy following endoscopic sinus surgery.*

AFRS represents an extreme form of type 2 inflammation. In a study of immune profiling in 130 participants with different CRS subtypes [2], inflamed sinus mucosa from AFRS participants demonstrated increased local IgE levels when compared to other subtypes, including CRSwNP. While all subtypes demonstrated increased levels of canonical type 2 inflammatory markers, only AFRS demonstrated markedly increased IL-4 levels. Other studies have also reproduced increased mucosal levels of allergen-specific IgE when compared to other CRS subtypes that was not limited to fungal antigens.

The same authors more recently sought to describe the gene expression variations in AFRS that distinguish it from CRSwNP [3]. In a cohort of 86 patients (37 AFRS, 34 CRSwNP, 15 healthy controls), AFRS tissue demonstrated nearly 3,000 unique gene expression variations, while CRSwNP only demonstrated 30. These unique gene expression variations in AFRS were strongly linked with T helper 2 inflammation, co-stimulatory signaling, and T-cell receptor signaling.

Recent Phase III trials with dupilumab have excluded AFRS given the above uniqueness of AFRS from other CRSwNP phenotypes and its regional geographic distribution, despite the exaggerated levels of type-2 inflammatory mediators such as IL-4 and IL-13. In addition, all trials to date have included patients who were at least 6 months removed from a prior sinus surgery. However, the efficacy of the combination of sinus surgery followed by dupilumab has yet to be evaluated in AFRS and exemplifies an attractive treatment regimen for this highly recalcitrant disease.

IMP Mechanism of Action
Dupilumab is a humanized monoclonal antibody that binds to the alpha-subunit of IL4 and IL13 receptors, two key mediators of type-2 inflammation. This represents the first and only dual inhibitor of IL-4 and IL-13. Receptor binding reduces expression of these proinflammatory markers, ultimately leading to decreased total and specific IgE, eosinophil activation, and trafficking.

3. Study Objectives and Endpoints

3.1 Primary Objectives

Co-Primary objectives	Endpoint/variable(s) Change from baseline at 52 weeks both within and between treatment and placebo arms
• Determine the efficacy of dupilumab in controlling sinonasal inflammation and preventing nasal polyp recurrence after complete sinus surgery for AFRS	• Endoscopic modified Lund-Kennedy (mLK) score
• Evaluate the effect of dupilumab on oral corticosteroid utilization following complete sinus surgery for AFRS	• Incidence of oral corticosteroid utilization per participant

3.2 Secondary Objectives

Secondary objectives	Endpoint/variable(s) Change from baseline at 52 weeks both within and between treatment and placebo arms
To evaluate the effect of dupilumab on:	
• Prevention of revision surgery for AFRS	• Prevalence of revision sinus surgery for recurrent nasal polyps, and comparison of survival curves
• Secondary objective measures of sinonasal inflammation following sinus surgery	• Endoscopic nasal polyp score (NPS) • CT generated Lund-MacKay score
• Lower airway dysfunction following sinus surgery in the subgroup of participants with asthma (~25%)	• Spirometry
• Upper and lower airway, disease-specific, health-related quality of life	• 22-item sinonasal outcomes test (SNOT-22) • Asthma Control Questionnaire (ACQ)
• Reducing utilization of rescue medications for acute exacerbations of CRS following sinus surgery	• Prevalence of oral / topical corticosteroid utilization per treatment cohort • Incidence of oral / topical antibiotic utilization per subject • Prevalence of oral / topical antibiotic utilization per treatment cohort

Other secondary objectives	Endpoint/variable(s) Change from end of treatment (EOT) to end of

	study (EOS)
To evaluate the effect of dupilumab on:	
• Objective measures of sinonasal inflammation following sinus surgery	• Endoscopic modified Lund-Kennedy (mLK) score • Endoscopic nasal polyp score (NPS)
• Upper and lower airway, disease-specific, health-related quality of life	• 22-item sinonasal outcomes test (SNOT-22) • Asthma Control Questionnaire (ACQ)

3.3 Safety Objectives

Safety objective	Endpoint/variable(s)
• Assess the safety of dupilumab after sinus surgery	• Continual reporting of events of special interest (ESIs) and serious adverse events (SAEs) • Physical examination

3.4 Exploratory Objectives

Exploratory objectives	Endpoint/variable(s)
• Generation of novel AFRS biobank to support future study of predictive biomarkers associated with positive clinical outcomes following IMP	• Exploratory biomarker parameters: - Serum and plasma - Whole blood - Nasal secretions - Nasal polyp biopsies

4. Study Intervention/Investigational Agent

4.1 Overall Design

This is a multi-center, randomized, double-blinded, placebo-controlled, parallel group study to evaluate the efficacy of dupilumab 300mg administered subcutaneously (SC) every 2 weeks versus placebo in participants with AFRS following planned sinus surgery.

132 participants will be randomized to receive dupilumab 300mg SC or matching placebo while on a background of intranasal corticosteroid sprays twice daily. Patients will be stratified by study site and by baseline comorbid asthma status (yes vs no). ~25% of the randomized participants will have comorbid asthma.

Eligible participants will enter a screening/run-in period on twice daily nasal saline irrigations followed by INCS spray for 2-6 weeks prior to planned sinus surgery. Participants may be consented and enrolled at any time during this 2-6 week run-in period, provided the failure of appropriate medical therapy has been documented as outlined in the inclusion criteria. Eligible participants already on study background therapy for at least two weeks may be consented and enrolled during the pre-surgery period.

Both saline irrigations/INCS and sinus surgery will be completed per standard of care (SoC) and not according to the study protocol. Patients who continue to meet eligibility criteria following surgery will be randomized 1:1 before Visit 3 (Day 0) when they receive placebo or dupilumab 300mg SC every 2 weeks. Patients will receive a total of 26 doses of IMP, via either study

personnel (Visit 3-6 at W0, 12, 24 and 36) or home-administration (W2, 4, 6, 8, 10, 14, 16, 18, 20, 22, 26, 28, 30, 32, 34, 38, 40, 42, 44, 46, 48, 50) to maintain a 2-week treatment schedule. Patient compliance will be recorded via text messages the day of scheduled home administration, as well as monthly phone calls and collection of used syringes during scheduled study visits (Visit 4-7 at W12, 24, 36 and 52). An EOT visit will be conducted at Week 52 (Visit 7). Patients will then be monitored on daily saline irrigation and INCS spray for 12-weeks to evaluate potential disease recurrence after discontinuation of IMP. An EOS visit will be conducted at Week 64 (Visit 8).

Participants will return to their respective study site for dosing visits (Visit 3-6), EOT and EOS for evaluation of efficacy and safety. Collection of optional blood and nasal secretions for exploratory biomarker analysis will be completed at study visits 1, 3, 4, 5, 7 and 8. Nasal polyp tissues will be collected at time of surgery (Visit 2).

Sinus surgery will be completed per SoC. Study protocol will determine cohort assignment (use of IMP versus placebo) with all other SoC interventions allowed throughout the entire study. Physician prescribed SoC medications for the treatment of nasal polyps include INCS sprays and nasal saline irrigations. Rescue medications are allowed per the treating physician's discretion.

Rescue medications (topical/oral corticosteroids, topical/oral antibiotics, or revision sinus surgery) will be allowed as deemed clinically necessary for the treatment of an acute exacerbation of CRS (AECRS) by the treating physician. See Table 3 for standardized criteria to diagnose AECRS [1]. If at any point a subject meets discontinuation criteria, an early discontinuation visit will be performed (see Section 8.1- Discontinuation of study treatment).

Table 3: Diagnostic Criteria for AECRS

AECRS may be diagnosed if all of the following are present:
- Duration of symptoms $\geq$7 days
- Total SNOT-22 score increased $\geq$9 from baseline
- Objective evidence of sinonasal inflammation by nasal endoscopy or CT scan

AECRS; Acute exacerbation of chronic rhinosinusitis

4.2 Scientific Rationale for Study Design

This study is designed to evaluate the safety and efficacy of fixed dose dupilumab (300mg) administered SC every 2 weeks, on top of intranasal corticosteroid spray in participants undergoing sinus surgery for medically recalcitrant nasal polyps in AFRS. The population is composed of participants with ongoing chronic symptoms despite appropriate medical management who elect to undergo sinus surgery per SoC. The randomized, placebo- controlled design allows for determination of IMP efficacy in preventing recurrence of severe sinonasal disease.

The sample size (n=132) and 52-week treatment duration are appropriate to capture maintenance effects while providing 1-year treatment safety data in the intended study population. Following completion of the treatment phase, all participants will enter an additional 12-week observation period to demonstrate durability of response and provide off-treatment safety data.

4.3 Justification for Dose

The dupilumab dose and regimen will be consistent with the product insert for the treatment of nasal polyps, i.e., 300mg by SC injection every two weeks. No dose adjustment for the AFRS nasal polyp endotype is warranted.

4.4 End of Study Definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study. A subject is considered to have completed the study when he/she has completed their last scheduled visit.

4.5 Treatments administered

4.5.1 Investigational products

Table 4: Investigational study treatments

	Treatment 1	Treatment 2
Treatment name:	Dupilumab	Placebo^
Dosage formulation:	150 mg/mL in pre-filled syringe to deliver 300 mg in 2 mL	Pre-filled syringe to deliver 2 mL
Route of administration:	Subcutaneous	Subcutaneous
Dosage regimen:	Every 2 weeks during treatment period	Every 2 weeks during treatment period
Provider:	Sanofi	Sanofi

^ Placebo contains vehicle and other non-pharmacoactive components contained in Dupilumab IMP

4.5.2 Non-investigational products

All enrolled participants will receive a background of INCS spray and nasal saline irrigations as prescribed by their treating physician per SoC.

4.5.3 Postoperative care

All participants will undergo the following standardized post-operative care:

- Intraoperative packing: hemostatic packing only with either Chitogel, Merogel, Nasopore or PosiSepX dressings. No steroid eluting packing will be used.
- Saline irrigations 2-3 times per day and once or twice daily INCS spray
- Pain medication: at discretion of treating physician
- Oral steroids, prednisone 30 mg x 4 days, 20 mg x 4 days, then 10 mg x 4 days and then stop

Alterations from the above are allowed at the discretion of the treating physician and will be recorded in the study database.

4.6 Preparation/handling/administration/accountability

4.6.1 Preparation and handling

Study drug/placebo will be mailed directly to participants from the study's central pharmacy

(Belmar Pharma Solutions, Lakewood, CO). Batch deliveries will occur at three-month intervals and be sent on ice via overnight delivery with temperature monitoring. Injection site and IMP preparation will be completed per product insert and SoC. Site investigators or designees must confirm appropriate storage conditions for all study treatments. Any discrepancies will be reported and resolved prior to treatment administration. Only enrolled participants may receive study treatment.

4.6.2 Administration

The IMP will be administered by licensed study staff at randomization (V3, W0) and study visits V4-6 (W12, 24, 36).

Training of subject/caregiver to complete home administration of IMP will be completed after randomization (V3, W0). Home administration of IMP will be completed during weeks (2, 4, 6, 8, 10, 14, 16, 18, 20, 26, 28, 30, 32, 34, 38, 40, 42, 44, 46, 48, 50) to maintain a 2-week treatment schedule. Patients will receive a total of 26 doses of IMP. Reminder text messages, as well as confirmatory phone calls and used syringe collection will be completed to verify home-administration. Participants who cannot administer at home can come to the clinic for injections.

4.6.3 Accountability

The Sponsor-Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

A study coordinator at each site will verify patient receipt of all study treatments from the central pharmacy. Delivery confirmations will be automatically stored in the central study database. Additional text reminders, monthly phone calls and collection of IMP will be completed. Coordinators will account for all study treatments, and for appropriate destruction or return of unused treatments. Certificates of delivery, destruction, and/or return should be signed.

External study monitoring will be managed by Westat (Rockville, MD).
Specific monitoring activities include the following:
- On-Site Initiation Visit (2-day visit per site)
- On-Site Interim Monitoring Visits (3- day visit, twice a year; five visits per site)
- Ad hoc Remote Interim Monitoring Visits
- On-Site Closeout Visit (2-day visit)

4.7 Randomization and blinding

Randomized participants will be stratified by enrollment site. Randomization will be assigned on a 1:1 basis to treatment group (dupilumab 300 mg every 2 weeks) or placebo. The study data team will prepare a randomization list based on computer-generated random numbers retrieved using a randomization procedure available in statistical packages such as SAS. Block randomization with varying block sizes will be employed to ensure that equal numbers of treatment and placebo participants occur within strata (site) and are balanced with respect to observed and unmeasured baseline factors.

This is a double-blind investigation. Patients, treating physicians and local study personnel will not be aware of cohort allocation.

4.7.1 Unblinding

The study data team will maintain individual treatment codes for each randomized subject. Randomization assignment will only be broken in the setting of a medical emergency, per the discretion of the treating physician, where the appropriate management of the subject requires knowledge of the treatment cohort. This event will be centrally recorded and monitored.

4.7.2 Treatment compliance

The study treatment provided for this study will be used only as directed in this Protocol. The IMP will either be administered at the study site during treatment visits (V3-6) or at home during weeks (2, 4, 6, 8, 10, 14, 16, 18, 20, 26, 28, 30, 32, 34, 38, 40, 42, 44, 46, 48, 50) to maintain a 2-week treatment schedule. Reminder text messages will be sent to all participants the day of a home-administration. Home-administration will be confirmed by recording of both confirmatory phone calls and used syringe collection.

If a home-administered IMP dose is missed and can be given within 7 days from the planned dose date, the IMP should be given. The patient's original schedule should be resumed. If the missed dose is not administered within 7 days, the IMP should not be given. This dose should be designated as a missed dose. IMP will then be given at the next date on the original schedule.

If a treatment visit needs to be rescheduled, the visit must be performed, and the IMP must be administered within 7 days of the original visit window. Investigators should make every effort to assure that no treatment visits are missed during the course of the study. A subject will be discontinued from the study if they miss either two consecutive study visits or IMP doses, or a total of three IMP doses throughout the study period. Any change from the dosing schedule will be recorded.

Investigators should also assure that participants are compliant and on a stable dose of the background INCS spray throughout study period. Any changes to background INCS spray will be recorded for subsequent analysis.

4.7.3 Concomitant therapy

All medications, including over the counter and herbal preparations, will be recorded from study enrollment until completion. Associated information will be recorded, including: reason for use, dosage (amount and frequency) and beginning/ending dates.

4.7.4 Background medication

Patients will be allowed to continue INCS spray prior to surgery. Following surgery all participants will undergo standardized postoperative treatment with continued INCS spray. This will be completed throughout the EOS visit.

Intranasal corticosteroid compliance will be recorded during study visits and compliance phone calls. If a subject cannot tolerate sinonasal irrigations, they should be screen failed prior to randomization.

4.7.5 Rescue therapy

During study treatment and off treatment follow-up, based on clinical evaluation, in case of worsening signs and/or symptoms consistent with an AECRS, the Investigator may consider rescue treatment. This typically involves corticosteroids or antibiotics delivered orally or topically to the sinonasal mucosa. Rescue therapies are not prescribed in this Protocol but will be recorded in the study database.

Patients receiving rescue treatment other than surgery during the study should continue on study drug unless the Investigator decides to withdraw the study treatment.

4.7.6 Treatment following study conclusion

Following the EOS visit, participants should resume standardized therapies [4] at the discretion of their healthcare team and local practice.

4.8 Pharmacy

Belmar Pharma Solutions (Lakewood, CO) will maintain and dispense study drug. Samantha Lebsock, PharmD will be the lead pharmacist for this study. Once participants are randomized the pharmacy will be notified via REDCap. Study drug will be mailed directly to the subject in three-month intervals (Visits 3-6) during the course of the study and be sent on ice via overnight delivery with continuous temperature monitoring. The patient will bring their first dose with them to the clinic during Visit 3.

5. Procedures Involved

5.1 Nasal endoscopy

All study participants will undergo diagnostic nasal endoscopies at each study visit, per SoC, to monitor treatment outcomes[1]. Unique to this Protocol, a digital recording of the nasal endoscopy will be collected and stored centrally on a study approved repository. This will be completed in accordance with appropriate care for the management of CRSwNP.

5.2 Study Measures

The study design and endpoints will answer important clinical questions about the efficacy of dupilumab on mucosal inflammation and symptoms and effect on the number of rescue medications per subject after sinus surgery. Examining the effect of dupilumab after comprehensive sinus surgery for AFRS with clinically relevant endpoints addresses a clinical treatment pathway that has yet to be formally explored.

5.2.1 Objective measures of disease

Modified Lund-Kennedy Endoscopic Score:

Modified Lund-Kennedy score (mLK) is a validated measure of sinonasal inflammation, as evaluated by means of nasal endoscopy. The composite score ranges from 0 to 12, with increasing score representing worsening inflammation among three separate findings (Nasal polyps, Discharge, Edema). Each finding is rated from 0 (absent) to 2 (severe). A $\geq$ 2-point increase from baseline total postoperative score represents clinically significant worsening of sinonasal inflammation[5]. The treating physician will complete the nasal endoscopy per SoC,

with automated recording on local storage drives . Following completion of the patient encounter, study personnel will transfer this recording to the study database for central review and scoring. A blinded reader will review all nasal endoscopies to determine the mLK score.

Lund-MacKay Radiologic Score:

The change in radiographic opacification between baseline and EOT will be analyzed by the Lund- MacKay radiologic score (LM) [6]. The LM Radiologic scoring system assigns a value of 0, 1, or 2 to each of the following sinuses: maxillary, anterior ethmoid, posterior ethmoid, frontal, and sphenoid. Score assignments are 0 if the sinus is totally patent, 1 if the sinus is partially opacified, and 2 if the sinus is completely opacified. The osteomeatal complex is scored either 0 if not occluded or 2 if occluded. The maximum score for each side is thus 12, with a total score determined out of 24. Baseline LM scores will be assessed from baseline preoperative CT scan. Preoperative and EOT CT scans will be transferred to the study database by trained personnel, where the blinded reader may determine the associated LM score.

Endoscopic Nasal Polyp Score:

Endoscopic nasal polyp score is determined by the treating Investigator. Unlike prior study of dupilumab in nasal polyps, [7] we will separately record the Nasal Polyp Score for each side, with a maximum unilateral score of 4. This is appropriate for monitoring efficacy in AFRS, as a subgroup of participants may present with unilateral disease. This will be considered in statistical analysis and reporting of results (see Section 14.6- Primary Analysis).

Table 5: Endoscopic Nasal Polyp Score

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or large polyps of score 2 with additional large polyps medial to the middle turbinate
4	Large polyps causing complete or near-complete obstruction of the inferior nasal cavity i.e. touching the floor of the nose

Spirometry:

Pulmonary function testing is performed according to the standardized methods of the lung function tests of the American Thoracic Society and European Respiratory Society. (Miller et al. 2005). The following parameters are measured or calculated: percent predicted vital capacity (%VC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), percent predicted FEV1 (%FEV1) and FEV1/FVC ratio.

5.3 Patient Reported Outcome Measures

22-item Sino-nasal Outcome Test (SNOT-22):

The SNOT-22 score is a validated disease-specific questionnaire quantifying quality-of-life among participants with chronic rhinosinusitis. The individual question scores range from 0 (no problem) to 4 (as bad as can be) among 22 individual questions. The threshold value for minimal clinically significant change is ≥ 8.90 [8].

Asthma Control Questionnaire (ACQ) (only for participants with asthma):
The Asthma Control Questionnaire (ACQ) is a validated, self-administered survey used to assess a participants' perception of disease control over the preceding week using Likert scale responses (range: 0 - 6) [9]. The ACQ consists of 7 items surveying the frequency of asthma related symptoms, the need for rescue medications, and perceived control of disease. The items are equally weighted and the ACQ score is the mean of the 7 items and therefore between 0 (well controlled) and 6 (extremely poorly controlled)[9]. Score change of 0.5 on the 7-point scale has previously been defined as the Minimal Important Difference (MID).

6. Data Specimen Collection and Banking

There is no routine laboratory monitoring planned. If laboratory monitoring is needed to provide standard of care for participants, this will be performed and monitored. Whole blood will be collected for research purposes for metabolomic profiling and for preparation of serum and plasma samples for analysis of proteins and inflammatory markers. Nasal secretions will be collected for analysis of inflammatory markers at specified study visits. Blood samples and nasal secretions will be collected prior to IMP dosage (V1,3-5,7-8). Additionally, nasal polyps will be collected from all participants, concurrent with their sinus surgery and per SoC. Samples will be processed, frozen, and shipped to the central study repository (Mike Koval Laboratory; Emory University, 615 Michael St., Suite 235, Atlanta GA 30322).
The subject's consent to the collection and storage of biologic samples is optional. Samples will be collected for future, exploratory analysis to query the effect of dupilumab on biomarkers of upper and lower airway inflammation, NP recurrence and predictors of therapeutic response.

7. Inclusion and Exclusion Criteria

Each subject must meet all inclusion and none of the exclusion criteria for the study in order to be consented into the study; ie. enrolled. Further, each subject must continue to meet all inclusion and none of the exclusion criteria for the study post SoC surgery in order to be randomized to a study intervention. Participants who do not meet I/E requirements prior to randomization are screen failures (see section 9.3- Screen failures)

In this protocol, "enrolled" participants are defined as those signing informed consent. "Randomized" participants are defined as those undergoing randomization and receiving IMP.

7.1 Inclusion Criteria

Patients are eligible for study participation if all inclusion and no exclusion criteria are met. Non-English-speaking people will be included if they fulfill the criteria.

7.1.1 Informed consent

1. Patients must be capable of giving signed informed consent as listed in the informed consent form (ICF) and this protocol.
2. ICF must be signed and dated prior to study specific procedures. Informed consent process is described in Appendix A3.

7.1.2 Age

3. Patients must be aged >18 years at the time of signing the ICF.

7.1.3 Types of subject and disease characteristics

4. Patients with nasal polyps in the setting of suspected AFRS and electing to undergo comprehensive sinus surgery per established criteria. [1, 4]
   - Diagnosis of nasal polyps by consensus criteria.
   - Failure of appropriate medical therapy, including topical intranasal corticosteroid (spray or irrigation) > 8 weeks duration, systemic corticosteroid trial of 1-3 weeks duration and nasal saline irrigation of > 4 weeks duration.
   - A minimum SNOT-22 score of 20 at time of enrollment.
   - A minimum CT Lund-MacKay score of > 1 at time of enrollment.

5. Suspected AFRS based on Bent and Kuhn criteria [10]
   - Patients must meet 3/5 criteria at time of enrollment
     - Environmental atopy by skin or serum testing
     - Nasal polyposis
     - Characteristic CT findings
     - Eosinophilic mucous
     - Fungal identification on histopathology
   - Patients must meet 5/5 criteria at time of randomization

Enrolled participants are expected to undergo SoC allergy testing and sinus surgery prior to randomization. This will complete evaluation for suspected AFRS, thus enabling further study participation.

7.1.4 Sinus Surgery

6. All study participants will have met criteria for sinus surgery and undergo a comprehensive surgery prior to randomization. The surgery will not be assigned and will be completed per SoC for the management of nasal polyps in suspected AFRS. [4]

7.1.5 Reproduction

7. Negative urine pregnancy test will be required at enrollment and study visits 3-8 throughout treatment period for female participants of childbearing potential (i.e., post-pubescent, premenopausal females).

8. Women of childbearing potential must use an effective form of birth control (confirmed by the Investigator) e.g., total sexual abstinence, vasectomized sexual partner, tubal occlusion, intrauterine device or levonorgestrel Intrauterine system, Depo-Provera injections, oral contraceptive, Evra Patch, or Nuvaring. Women of childbearing potential must agree to use a highly effective method of birth control, as defined above, from enrollment, throughout the study duration and for 12 weeks after the last dose of IMP.

9. To protect against possible side effects, men should not get a sexual partner pregnant while taking the study drug and for 13 weeks after the last dose. Men should agree on a method of birth control to use throughout the study.

7.2 Exclusion criteria

7.2.1 Medical conditions

1. Patients who have undergone nasal or sinus surgery within 3 months prior to enrollment.
2. Patients with conditions or comorbid disease findings that exclude nasal endoscopy for evaluation of primary outcome, such as:
   - Current rhinitis medicamentosa
   - Nasal cavity tumors
   - Occlusive septal deviation following surgery
3. Clinically important comorbidities that may confound interpretation of clinical efficacy, including:
   - Aspirin-exacerbated respiratory disease
   - Cystic fibrosis
   - Primary ciliary dyskinesia
   - Hereditary Hemorrhagic Telangiectasia
   - Antrochoanal polyposis
   - Non-asthma eosinophilic disease, such as bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome
   - Granulomatosis with polyangiitis
   - Any corticosteroid dependent condition
4. A comorbid health disorder that is not medically controlled in the opinion of the Investigator, and has the potential to:
   - Affect the safety of the subject throughout the study
   - Impede the subject's ability to complete the duration of the study
   - Influence the primary or secondary outcomes of the study
5. Patient experiencing a symptomatic asthma exacerbation requiring systemic corticosteroids or hospitalization (>24 hours) within 4 weeks of randomization.
6. Infection requiring systemic antibiotics within 4 weeks of randomization.
   - Parenteral and/or oral antibiotics associated with surgery are allowed (see Section 4.5.3-Postoperative care)
7. Medical contraindication to receiving dupilumab:
   - Know hypersensitivity to dupilumab or any of its excipients
   - Live vaccine administration within 30 days of randomization or during study period
   - Known helminth infection
8. Unable to tolerate sinonasal irrigations.
9. Pregnancy, current lactation, or lack of effective contraception plan, as determined by the site investigator.

7.2.2 Prior/concomitant therapy

10. Initiation of allergen immunotherapy within 3 months prior to randomization or a plan to begin therapy or change its dose during the study period.
11. Immunosuppressive medication within 3 months prior to randomization and during the study period from randomization through EOS.
12. Receipt of any marketed or investigational biologic products (monoclonal or

polyclonal antibody) within 6 months or 5 half-lives, whichever is longer, prior to randomization during the study period.
13. Previous use of dupilumab.
14. Receipt of immunoglobulin or blood products within 30 days prior to randomization.
15. Receipt of any investigational drug within 30 days or 5 half-lives, whichever is longer prior to randomization.
16. Scheduled systemic corticosteroid treatment during the study period:
    - Standardized corticosteroid taper associated with planned surgery is allowed (see Section 4.5.3-Postoperative care.)
17. Receipt of leukotriene antagonists or modifiers for participants who were not on a stable dose for > 30 days prior to randomization.

7.2.3 Prior/concurrent clinical study experience
18. Concurrent enrollment in another investigational drug trial during the study period.

7.2.4 Other exclusions
19. Patient involvement in the planning or conduct of the study.
20. Investigator assessment that the subject is unlikely to comply with study procedures.
21. Prior randomization in the present study.
22. Unable to undergo sinus surgery due to comorbid medical condition.

7.3 Screen Failures
Defined as participants appearing to qualify for study participation, sign the ICF, but ultimately do not meet randomization criteria. Reporting of screen failure information is required to ensure transparent reporting. Minimal information includes subject demographics, screen failure details and eligibility criteria.

Re-screening is allowed once for each subject.

Re-screening is allowed prior to surgery for transient reasons (including operating room availability or unforeseen personal events) that result in delayed randomization.

For participants who require oral corticosteroids and/or antibiotics for an asthma exacerbation or an acute exacerbation of CRS during the run-in period (prior to surgery), the run-in period may be extended for up to 6 weeks beyond the initially planned 6 weeks, provided the treatment duration with corticosteroids and/or antibiotics is ≤ 14 days. If the duration of treatment is >14 days, participants should be screen failed but can be considered for re- screening.

Re-screened participants should re-sign ICF. All procedures from the screening period should be repeated. Re-screening should be documented so that its effect on study results may be assessed.

8. Local Number of Participants
The study will be completed at 3 North American sites. A total of 132 participants will be randomized. While we intend to enroll equal numbers of participants from each site (44 participants at each), variability in available participants may require an unequal distribution of participants to support target enrollment within the study period.

9. Recruitment Methods

All three sites taking place in this research study will recruit participants who are undergoing elective endoscopic sinus surgery for the treatment of AFRS. The participants will be identified from the clinics of the site Investigators and their colleagues during the subject's pre-operative consultation.

10. Withdrawal of Participants

10.1 Discontinuation of study treatment

Participants may be discontinued from study treatment under the following circumstances:

- Subject decision. Participants may discontinue treatment at any time
- AE that, in the opinion of the Investigator, contraindicates continuation.
- Pregnancy
- IMP unblinding
- Development of any study specific criteria for discontinuation:
    - Anaphylactic reaction to the IMP requiring epinephrine
    - Helminth parasitic infestations requiring hospitalization
    - If 2 consecutive study visits or 2 doses of IMP are missed during the course of the study

All participants who discontinue treatment should remain enrolled and complete their discontinuation visit within 8 weeks of last IMP. At that visit, although no longer receiving IMP, participants should be encouraged to complete all subsequent study visits and procedures. Data collection should continue according to the study protocol.

10.2 Lost to follow-up

A subject is considered lost to follow-up if they fail to return for scheduled study visits and are unable to be reached by study staff. This includes 3 attempts of either phone calls or emails; having sent 1 certified letter; or 1 unsuccessful effort to check the vital status of the subject using publicly available sources.

10.3 Study Withdrawal

Patients may withdraw study consent at any time without prejudice to further treatment. They may request destruction of collected samples, which will be completed and documented in study records.

11. Risk to Participants

Dupilumab is an add-on maintenance treatment in adult participants with uncontrolled CRSwNP. The most common adverse reactions that took place in 2 randomized, placebo-controlled, multicenter trials were injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.

12. Potential Benefits to Participants

There are no direct benefits for participating in this study.

13. Compensation to Participants

Participants will be reimbursed a subject stipend for participating in the research study to help with the cost of expenses/travel for the research visit and to compensate for their time and effort. Participants will receive a stipend of $50 after completing the following visits: V1, V3, V4, V5, V6, V7, and V8. They will also receive $25 for each visit of dupilumab/placebo injection. If they complete all study visits, they will get a total of $1000. The payment will be processed when participants come in person and will include that clinic visit' payment and injections payments since the last clinic visit. Each site will decide how participant stipends will be given to the subject.

14. Data Management and Confidentiality

The site-Investigator will ensure that all data are recorded appropriately and consistent with good clinical and research practice.

14.1 Sample Size and Power analysis

A sample size of 66 participants per group achieves 90% power to detect a mean difference of 2 points on the modified Lund-Kennedy Endoscopic score at 52 weeks with a standard deviation of 3.5 and significance level of 0.05 using a two-tailed test. The clinically meaningful mean difference of 2 points and the standard deviation are based on previous study of mLK in a heterogeneous population with nasal polyps [5].

14.2 Database Set-up and Management

The REDCap (Research Electronic Data Capture, Nashville, TN) system will be used as a central resource for data processing and management. REDCap is an open-source software program supported through a consortium led by Vanderbilt University. REDCap is a metadata driven electronic data capture system available for investigators to use for form-based data collection. The system is supported by Emory Library and Information Technologies Services (LITS) and hosted on a LITS virtual machine (VM) environment with nightly backup and full redundancy for high application availability and reliability.

REDCap is a web-based system with the Apache/PHP web server located in the DMZ and the MySQL database backend hosted in a HIPAA- and FDA 21 CFR Part 11-compliant secure data zone. Access to the system requires an Emory University or Emory Healthcare user account with external users (e.g. University of Texas Health Science Center at Houston and NIH) supported using Emory University sponsored accounts. REDCap provides an intuitive interface for data entry with data validation, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, including SAS, and procedures for importing data from external sources. A dedicated database developer will create a study-specific application for data collection.

All data management standards will reflect the goal of reproducible research. To reduce data entry errors and omissions, we will take advantage of REDCap’s built-in quality control functions such as branching logic, range and data-type limits, pop-up messages, and prompted data entry. Data integrity is aided by the system’s automated logging of all input and edits. Datasets will be clearly identified according to a pre-specified naming system that includes download date. SAS or other programs will be well-commented and be checked for errors by a second programmer or statistician. For quality control and assurance, we will periodically

complete reports on data stored in REDCap. This entails export to our local secure drive, imports as SAS datasets, and production of multiple types of output for data management and reporting. Reports, overall and site-specific, will be provided for data management (e.g., flagging of questionable or missing data and missing forms, variable description, flagging of overdue visits) and for investigators (e.g., screening and enrollment, follow-up tracking, exits).

Microsoft OneDrive will be used as a central repository to store all nasal endoscopy and CT files collected during the course of the study. This HIPPA compliant database will provide access for our central reader while maintaining a backup of study files should additional review be required. All data will be stored with study identification numbers.

14.3 Clinic site data management

Trained study staff will enter data directly to the REDCap application. We will enable auto-validation (via range and data checks) and use skip logic to facilitate data entry and ensure adequate quality.

Data entry personnel will receive standardized training. The study's statistician will examine the distribution of the data for purposes of maintaining integrity of the data. Quality control metrics such as timeliness and completeness of data entry will be reported.

14.4 Randomization

After eligibility is established and consent is obtained, the participants will be randomized on a 1:1 basis to treatment (dupilumab 300 mg every 2 weeks) or placebo. The study biostatistician will prepare a randomization list based on computer-generated random numbers retrieved using a randomization procedure available in statistical packages such as SAS. Block randomization with varying block sizes will be employed to ensure that equal numbers of treatment and placebo participants occur within strata (site) and are balanced with respect to observed and unmeasured baseline factors.

14.5 Statistical Approach

All data will first be assessed by the data management staff, under direction of the lead biostatistician, for missing data and out-of-range values with basic statistical procedures such as univariate statistics (means, standard deviations, ranges, frequencies, proportions, percentiles) and graphs such as histograms, box and whisker plots, scatter plots and Q-Q plots. In addition, plots may be produced of individual and average trajectories of all repeated measures over time according to assigned treatment. All questions of data quality and integrity will be investigated before any statistical modeling, as complete and accurate data are essential for unbiased estimates and confidence intervals.

Baseline and demographic characteristics will be summarized overall for all participants and when applicable, by treatment group. Univariate summary statistics will be provided for continuous variables and frequencies for categorical variables. Graphical methods mentioned above will be used to examine distributions and identify potential influential points. Data transformations for variables may be considered. The balance of baseline measures across the two treatment groups will be compared using appropriate 2-sample tests, including Wilcoxon rank-sum and t-tests, and Fisher's exact and Pearson Chi-square tests. All analyses will be

conducted using SAS version 9.1 for Windows (SAS Institute, Inc., Cary, NC). All analyses will be two-tailed with significance level of 0.05 and conducted using the intention-to-treat principle.

14.6 Primary Analysis

To examine changes in the co-primary outcomes, the modified Lund-Kennedy score and the incidence of oral corticosteroid utilization per participant, a mixed effects longitudinal model will be fit that includes group (dupilumab, placebo) as a between participants factor and time (randomization through post-treatment period) as a categorical within participants factor plus their interaction term. Time is treated as categorical so that we can use the group-time interactions with the time main effect to estimate and test intent-to-treat (ITT) group differences at each time point, with 52 weeks as our primary ITT test. As randomization is stratified by site, site will also be included in the model. This mixed effects model allows incorporation of a random intercept term for each subject, different numbers of measurements (in case a visit is skipped), and the choice of appropriate variance-covariance structure. The mixed model will also permit identification of any significant changes in the post-treatment period from 52 to 64 weeks. This primary mixed model will incorporate all subject's randomized.

The primary objective will be assessed by testing this null hypothesis: treatment with Dupilumab post-surgery is equivalent to treatment with placebo post-surgery at 52-week end of treatment. The additional time point at 64 weeks is included in the model to ensure efficient evaluation of both co-primary outcomes at the EOT and 12 weeks after EOT. Significant changes between weeks 52 and 64 will be examined by linear contrast. We will test the following null hypotheses against two-sided alternatives:

- H_{01}: there is a lack of difference between the changes in mLK from baseline to 52 weeks and from baseline to 64 weeks for the untreated.
- H_{02}: there is a lack of difference between the changes in mLK from baseline to 52 weeks and from baseline to 64 weeks for the treated.
- H_{03}: the treatment effect dissipates between 52 and 64 weeks.

The primary estimand for the primary endpoint is the composite/treatment policy strategy. The intercurrent events will be handled as follows:

- Undergoing sinus surgery for AFRS: data after surgery will be assigned the worst possible score (composite strategy)
- Taking SCS or other rescue medications: data collected after use will be used in the analysis (treatment policy strategy)
- Discontinuing treatment: all data collected after discontinuation will be used in the analysis (treatment policy strategy)

We will examine the treatment effect in the subgroup of patients with unilateral disease by recording patients' time until next sinus surgery. We will investigate differences in this subgroup by examining the Kaplan-Meier curves and utilizing the log rank test of the difference between treated and non-treated. If there is a difference between survival times, we will use the Cox proportional hazard model to account for other relevant covariates such as disease severity.

The Bonferroni correction will be used to account for multiple testing and ensure Type-I error rate remains nominal.

14.7 Secondary and Exploratory analyses

In a secondary analysis, a similar mixed model as described above will be fit that includes the subset of participants who are receiving treatment (dupilumab or placebo) for both nostrils. This model will incorporate nesting factors to identify repeated measures by subject and by nostril.

In an exploratory analysis, we will also compare the proportion of participants whose modified Lund- Kennedy score improved by greater than or equal to 2 units. For participants who undergo sinus surgery for AFRS prior to Week 52, non-responder imputation will be used. We will utilize a Chi-square or Fisher's exact test to examine if this proportion is significantly different by treatment group (dupilumab or placebo) at 52 weeks.

For the continuous secondary outcomes (e.g. SNOT-22 score, NPS, FEV1), a mixed effects longitudinal model will be fit that includes group (dupilumab, placebo), time (randomization through post-treatment period), and their interaction term in a similar fashioned as described for the primary outcome modified Lund-Kennedy score. For the secondary outcomes that compare the number of participants requiring rescue treatment and the number of adverse events (safety) over 52 weeks, similar mixed effects models will be fit but with consideration of a Poisson distribution (as opposed to normal distribution). The mixed effects models for both primary and secondary outcomes will permit the inclusion of any significant potential confounders.

14.8 Missing data handling

Analyses will be conducted using a multiple imputation (MI) procedure. The imputed items are obtained from combining two components, a random component based on a normal distribution using the mean and standard deviation from the non-missing items from the variable being imputed, and a predicted component based on a multivariable regression model consisting of a set of variables with no missing data and the non-missing items from the variable being imputed. Multiple imputation does not attempt to estimate each missing value through simulated values but rather to represent a random sample of the missing values. This process results in valid statistical inferences that properly reflect the uncertainty due to missing values.

14.9 Interim analyses

No interim analysis is planned for this study.

14.10 Expected Results

We expect to detect a significant protective effect of dupilumab on the postoperative control of sinonasal inflammation among participants with AFRS. This will be detected as a significant worsening of postoperative endoscopic mLK score and more frequent occurrences of needed rescue medications among the placebo group. We also anticipate a more conspicuous response to IL-4/13 blockade parallel with decreasing levels of Type 2 cytokines and eosinophil activation markers. While this study is not designed to detect a significant difference in secondary outcome measures, the collected data will nonetheless complement our exploratory studies seeking to define predictive biomarkers and mechanisms of treatment response.

14.11 Safety evaluation plan

Safety outcomes will include the occurrence of any adverse events of special interest (AESI) as described in section 15.3.3. Cumulative incidence of AESIs will be used to evaluate safety. We will compare treatment groups using the risk difference and a 95% confidence interval for that difference at each of the five follow up time points in the study.

15. Provisions to Monitor the Data to Ensure the Safety of Participants

15.1 Obligations of Sponsor-Investigator

A sponsor-investigator assumes all sponsor responsibilities required by the FDA of the sponsor and the investigator, including those related to record keeping and prompt reporting of safety reports to the FDA. The responsibilities include:

- Selection of research staff qualified by training and experience
- Commitment to personally conduct or supervise the investigation according to the research plan
- Selection of study monitor(s) qualified to monitor the progress of the project
- Maintenance of accurate, complete, and current records, including correspondence with the FDA, monitor and IRB, records on shipment and disposition of drug and records of participants' case histories and exposure to the device
- Completion of regulatory filings, including amendments (supplemental applications)
- Timely submission of Final Report within 30 days of completion of investigation

15.2 Definitions

15.2.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug. An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug. Routine laboratory monitoring is not a component of this study. If laboratory abnormalities are noted on laboratory testing obtained for other reasons or for work-up of an AE, these should be reported.

15.2.2 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death – includes all deaths, even those that appear to be completely unrelated to study drug (e.g., a car accident in which a subject is a passenger).
- Is life-threatening – in the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect

- Is an important medical event - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

15.3 Recording and Reporting Adverse Events

See Section 10.1- Discontinuation of study treatment for safety criteria resulting in study discontinuation.

Recording and reporting will be performed from the time the informed consent is signed until the EOS. The Participants or their legally authorized representative will report adverse events to the investigator or trained members of the study team.

The investigator is responsible for detecting, evaluating, recording, and evaluating all events that meet the definition of AEs and SAEs, by following the following steps:

- Review all documentation related to the event, including symptoms, clinic progress notes, laboratory reports, and diagnostic reports,
- Attempt to establish a diagnosis of the event and document as the AE /SAE
- Record the AE/SAE on the CRF
- Report to the sponsor

The investigator will also be reporting and following up with the events related to the study intervention or that caused the participant to discontinue the intervention.
The follow-up consists of further tests and examinations (laboratory, histopathological, consultation with other healthcare professionals) to demonstrate the nature and/or causality of the AE/SAE.

15.3.1 Adverse events

The site-Investigator (or designee) will transcribe the information in the CRF and enter in REDCap. The source documents will be kept with patients' records and be available for further review upon request.

15.3.2 Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the Sponsor-Investigator within 24 hours. The S-I will be notified electronically through REDCap and/or email.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

15.3.3 Other Events that Require Accelerated Reporting

The following events are considered Adverse Event of Special Interest (AESI) and require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in the study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial will be qualified as an SAE only if it fulfills one of the seriousness criteria.
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
  - Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Significant ALT elevation
  - ALT >5 × ULN in participants with baseline ALT ≤2 × ULN;
    OR
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Symptomatic overdose (serious or nonserious) with IMP or other medication (NIMP)
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of less than 7 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on the AE forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified.

Per FDA regulation 312.32, written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of the sponsor determining that the event qualifies for reporting. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days of receipt of such information. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to participants or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

15.4 Evaluation of Severity and Causality

15.4.1 Evaluation of Severity

The severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE). Available:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

For adverse events not included in the standardized toxicity grading scale, the following scale will be used:

- Mild: Awareness of sign or symptom but is tolerated. Does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the subject.
- Moderate: Discomfort that causes interference with normal activities. Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- Severe: Incapacitating, with inability to perform normal activities. Produces significant impairment of functioning and is a definite hazard to the subject's health. Treatment for symptom may be given and/or subject hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

An event is "serious" if it meets one of the definitions described in section 15.2.2 (SAE), NOT when assessed as severe.

15.4.2 Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

- Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity
- Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity
- Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis.

15.4.3 Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs/SAEs to study drug will be assessed by the masked investigator and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE/SAE may have been caused by the study drug? The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by the study drug

- **Related:** There is a reasonable possibility that the event may have been caused by the study drug

A list of factors to consider when assessing the relationship of AEs to study drug is provided in Appendix B. The investigator should consult the Investigational Brochure, which lists the possible adverse events.

The investigator should justify the causality assessment of each SAE.

15.5 Safety Monitoring

The site investigator will monitor the safety of study subject at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). The sponsor-investigator will monitor the safety data from across all study sites. Safety monitoring will be performed on an ongoing basis (e.g., individual review of SAEs) and on a biannual cumulative aggregate basis by the DSMB.

15.6 External Study Monitor

Westat (Rockville, MD) will serve as the independent study monitor. All on-site monitoring visits are expected to require a maximum of 3 days and will be conducted according to Westat's standard operating procedures (SOPs). The site monitor will perform 100 percent informed consent review, 100 percent review of eligibility and SAE documentation, 30 percent overall source data verification, and 100 percent source data verification for queries.

15.7 Monitoring Table 2

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	*There should be a standard operating procedure to review data (whether a sample or 100%) at pre-determined intervals to ensure that there is adequate documentation of critical elements such as eligibility criteria. Monitoring is required at the following timepoints (but may be done more frequently):* • *study initiation* • *at least every six months while participants are receiving intervention and* • *annually while participants are in follow-up*	*At a minimum, a review is required annually when no one has been enrolled or the study is in long term follow up. Additional interim monitoring at least once every 12-24 weeks based on the site activity, and more as needed, to include the possibility of remote monitoring.*	*Delegate a responsible party for each requirement below*. Self-assessment is NOT acceptable. An experienced, knowledgeable person* ***who is independent of the study team*** *should serve as monitor. A Contract Research Organization (CRO) may be used. Consult the IRB Office regarding acceptable qualifications for the independent monitor, if not using an outside expert such as a CRO.*
Real-time review of participant data during initial data collection.	Follow the Quality management Plan and the Manual of Operating Procedures	*Expectation is that this happens every time you obtain information.*	*Everyone on the study team responsible for primary data collection.*
100% review of regulatory files	Based on the site monitoring plan developed by Westat	*Reviewed at a minimum of first and close-out visits*	Westat
100% review of consent forms	Based on the site monitoring plan developed by Westat	Biannually	Westat
Review of credentials, training records, the delegation of responsibility logs (if applicable)	Included in the regulatory startup package from Westat	Biannually	Westat
Comparison of case report forms (CRF) to source documentation for accuracy and completion	Included in the Manual of Operating Procedures	Biannually	Westat
Review of documentation of all adverse events	Monitoring plan and startup package	Biannually	Westat
Monitoring of critical	Monitoring plan	Biannually	Westat

data points (eligibility, study endpoints, etc.)			
Laboratory review of processing and storage of specimens	Monitoring plan	*Reviewed at first and close-out visits and at least biannually*	Westat
Assessment of laboratory specimens stored locally	Monitoring plan and startup package	*Biannually*	Westat
Test article accountability review	Monitoring plan and startup package	*Reviewed at first and close-out visits and at least biannually*	Westat
Accountability logs, dispensing records, and other participant records	Monitoring plan and startup package	*At least biannually*	Westat
For FDA regulated studies, the following requirements apply:	**How this Requirement is Met**	**Timing, frequency, and intensity of monitoring**	**Responsible Party(ies)**
Monitoring methods (may include centralized, on-site, and self-monitoring)	Self-monitoring	Annually	Sponsor-Investigator
*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.			

16. Provisions to Protect the Privacy Interest of Participants

Each subject will be assigned a unique identifier. Any subject records or data sets transferred to the coordinating study center will contain only the identifier. Patient names or any information which would make the subject identifiable will not be transferred. The subject must be informed that his/her personal study-related data will be used by the study team in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by study Investigators, appropriate IRB/IEC members, and by inspectors from RAs.

17. Informed Consent

The Investigator or his/her representative will explain the nature of the study to the subject in a private setting and answer all questions regarding the study. Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent and authorization that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements and the IRB/IEC or study site.

The research record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study as deemed appropriate by the overseeing IRB.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative. Patients who are re-screened are required to sign a new ICF.

The ICF will contain a separate section addressing the use of subject samples for future exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the future exploratory research. If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, the Investigator will not be obliged to destroy the results of this research.

18. Setting

Research procedures will take place in the clinic of the principal investigators. Patients will be identified from the schedules of the investigators and collaborators.

19. Appendix

Appendix A: Regulatory, ethical and study oversight considerations

A1. Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) Guidelines;
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated at that site.
Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
The Investigator will be responsible for the following:

- Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

A2. Financial disclosure

Investigators and Sub-Investigators will provide accurate financial information as requested to allow for complete and accurate financial certification or disclosure statements to the appropriate Regulatory Authorities. Investigators will provide information on financial interests during the course of the study and for 1 year after completion of the study.

A3. Informed Consent

The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent and authorization that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements and the IRB/IEC or study site.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Patients who are re-screened are required to sign a new ICF.
The ICF will contain a separate section addressing the use of subject samples for future exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the future exploratory research. If a subject withdraws consent to the use of donated

biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, the Investigator will not be obliged to destroy the results of this research.

A4. Data Protection

Each subject will be assigned a unique identifier. Any subject records or data sets transferred to the coordinating study center will contain only the identifier. Patient names or any information which would make the subject identifiable will not be transferred. The subject must be informed that his/her personal study-related data will be used by the study team in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by study Investigators, appropriate IRB/IEC members, and by inspectors from FDA.

A5. Dissemination of Study Data

A description of this clinical trial and summary of results (when available) will be available on http://www.clinicaltrials.gov.

A6. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Sponsor-Investigator agrees to submit all manuscripts or abstracts to Sanofi before submission. This allows Sanofi to protect proprietary information and to provide comments. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B: Factors in Assessing the Relationship of Adverse Events to Study Drug

Is there a reasonable possibility that the event may have been caused by the study drug?

No:

- Due to external causes such as environmental factors, ESIs or other treatment(s) being administered
- Due to the subject's disease state or clinical condition
- Do not follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure, study procedure, or background treatment, etc.
- Do not reappear or worsen when dosing with study drug or injection procedure, study procedure, or background treatment, etc. is resumed are not a suspected response to the study drug or injection procedure, study procedure, or background treatment, etc. based upon preclinical data or prior clinical data

Yes:

- Could not be explained by environmental factors or other treatment(s) being administered
- Could not be explained by the subject's disease state or clinical condition follow a reasonable temporal sequence following the time of administration of the dose of study drug, etc.
- resolve or improve after discontinuation of study drug, etc.
- reappear or worsen when dosing with study drug is resumed
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data detailed in the package insert.

NOTE: This list is not exhaustive.

Appendix C: Data and Safety Monitoring Board Charter

Data and Safety Monitoring Board (DSMB) Charter

Protocol:
S-I: A randomized, 52-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week after endoscopic sinus surgery in patients with allergic fungal rhinosinusitis (AFRS) on a background therapy with intranasal corticosteroid spray

Short:
Add-on Dupilumab for AFRS as Postoperative Therapy (ADAPT)

Sponsor-Investigator:
[redacted]
Office of the Clinical Director
[redacted]

Emory Principal investigator:
[redacted]
Assistant Professor, Rhinology and Skull Base Surgery Division
Department of Otolaryngology – Head & Neck Surgery
Emory University School of Medicine
[redacted]

TABLE OF CONTENTS

INTRODUCTION

The Data and Safety Monitoring Board (DSMB) acts in an advisory capacity to the Sponsor-Investigator to review participant safety and study progress for "A randomized, 52-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week after endoscopic sinus surgery in patients with allergic fungal rhinosinusitis (AFRS) on a background therapy with intranasal corticosteroid spray". This study is funded by Sanofi (Paris, FR). The purpose of this document is to outline the charge to the DSMB regarding its responsibilities, composition, and processes for the above-mentioned study. The NIH mandate requires safety oversight and monitoring for all interventional studies to be commensurate with risks, nature, size, and complexity of the study. This Charter is intended to be a living document to be modified at any time.

DSMB RESPONSIBILITIES

Responsibilities of the DSMB are to:

a) Review the research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents, including all proposed revisions.

b) Evaluate the progress of the study on an ongoing basis, as needed, including periodicassessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of study sites, and other factors that can affect the outcome.

c) Consider the impact of factors external to the study when new information, such as scientific or therapeutic developments, becomes available and may affect safety of participants, their willingness to participate in the study or the ethics and conduct thereof.

d) Review unanticipated problems, serious and non-serious adverse event reports and documentation and make recommendations to the Sponsor-Investigator regarding protection of the study participants.

e) Assist the Sponsor-Investigator by commenting on any problems with study conduct or performance.

f) Ensure that the plan for maintaining the confidentiality of the study data and the results by the investigative team is appropriate.

g) Review and evaluate requests for protocol modifications.

h) Review accumulating data at the specified intervals, and as appropriate, and make a recommendation to continue, terminate or modify the study based on observed benefit or harm.

The Sponsor-Investigator may discharge one or all of the DSMB members from their duties when:

a) "A randomized, 52-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week after endoscopic sinus surgery in patients with allergic fungal rhinosinusitis (AFRS) on a background therapy with intranasal corticosteroid spray" is complete;

b) a member is not able to fulfill the DSMB responsibilities as outlined in the Charter;

c) the Sponsor-Investigator no longer has oversight responsibilities of the study and/or;

d) a member is found to have a Conflict of Interest (COI).

Additionally, a DSMB member may resign at any point during the study when:

e) a member is not able to fulfill the responsibilities, as outlined in the Charter;
f) a member believes a Conflict of Interest (COI) exists.

DSMB MEMBERSHIP

The DSMB consists of four members who have been appointed by the Sponsor-Investigator. Three members will constitute a quorum for voting. Membership consists of persons independent of the study who have no financial, scientific, or other conflicts of interest with the Principal Investigator (PI) or any Co-Investigators.

The DSMB includes experts in or representatives from the fields of Otolaryngology, Allergy/Immunology and Biostatistics.

Individuals with additional expertise may be invited to participate as non-voting membersin the DSMB meeting in certain situations. Non-voting members must also be independent of the study and have no financial, scientific, or other conflicts of interest with the PI or any Co-Investigators.

DSMB Chairperson

The DSMB Chairperson is appointed by the Sponsor-Investigator and confirmed by DSMB vote at the first meeting. The DSMB members must provide a full consensus vote when electing the DSMB Chairperson. The Chairperson is responsible for overseeing the meetings, working with the Sponsor-Investigator and/or the Executive Secretary (ES) to develop the agenda, and summarizes all DSMB recommendations. The Chairperson is the primary contact person for the DSMB.

Dr. Mihir Patel has been appointed as the DSMB Chairperson.

DSMB Safety Officer

The DSMB Safety Officer (SO) is appointed by the DSMB Chairperson and confirmed by DSMB vote at the first DSMB Meeting. The DSMB must provide a full consensus vote when electing the DSMB Safety Officer. The Safety Officer is the DSMB contact person for expedited reports (e.g., SAEs, protocol violations, and unanticipated problems). Expedited reports must be reported to the DSMB Safety Officer and Executive Secretary within 48 hours of the study personnel receiving notification of the event. The Safety Officer provides an assessment of the action taken by the investigative team and makes a recommendation as to whether further action should be taken (e.g. collection of follow up information or a full DSMB discussion).

While the FDA requires expedited reporting of Serious Adverse Events (SAEs) through the Executive Secretary, the Safety Officer does not provide real time assessment of SAEs. It is the responsibility of the Sponsor-Investigator to provide real time assessment and take the necessary, immediate action with regard to participant safety.

Dr. Edward McCoul has been appointed as the DSMB Safety Officer.

DSMB Executive Secretary
The Executive Secretary (ES) drafts meeting agendas in consultation with the Sponsor-Investigator, DSMB Chairperson, and program staff. The agenda is sent to the full DSMB and the Sponsor-Investigator for input. The ES coordinates the DSMB meetings and conference calls and provides logistics support and meeting summaries. The ES will transcribe the meeting recommendations and minutes and will distribute them to the Sponsor-Investigator, DSMB Chairperson and members. The ES is the primary contact point for DSMB communication with the Sponsor-Investigator.

Dr. Mark Arnold has been appointed as the DSMB Executive Secretary.

CONFLICT OF INTEREST
Individuals invited to serve on the DSMB as must disclose any potential conflicts of interest, whether real or perceived, to the Sponsor-Investigator. Conflicts of interest can include, but are not limited to, professional, proprietary, and miscellaneous interests. Any real or potential conflicts that develop during a member's tenure on a DSMB must be disclosed for the Sponsor-Investigator consideration at the time the potential conflict is realized. In addition, written documentation attesting to an absence of conflict of interest is required annually.

Confidentiality
Each member of the DSMB must sign a statement of confidentiality annually. All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

BOARD PROCESSES
Prior to commencement of recruitment, the study team drafts or revises study materials (protocol, DSMP and report templates, and any other materials required for the DSMB's review). The study team delivers relevant materials to the ES, who facilitates the review process with the DSMB.

a) Upon completion of the initial review, the DSMB members are to send the ES their comments for consideration. Accepted comments and recommendations are sent to the Sponsor-Investigator for review.
b) ES concurrently schedules an introductory teleconference between the Sponsor-Investigator and DSMB. All discussions are confidential.

The first meeting is held either by teleconference or in-person before initiation of the study to discuss the materials and whether the study is ready to commence, establish guidelines for monitoring and determine the format for future meetings. The Sponsor-Investigator and ES prepare the agenda to 1) review the study materials, 2) appoint the DSMB Chairperson and Safety Officer, 3) discuss the plan and timing for safety monitoring 4) make recommendations to initiate the study and/or modify the study materials and 5) review the charter. During the initial DSMB meeting, a representative provides a training session outlining the board process and DSMB procedures for all meeting participants (DSMB members, study staff and coordinator).

Reports for both the open and closed sessions should be established at the initial DSMB meeting,

although changes throughout the study may be requested by the DSMB. In addition, the DSMB members will vote to recommend commencement of the study.

Routine meetings of the DSMB are held two times a year via video conference call. Attendance at all meetings is highly critical for all DSMB members. Each DSMB member is specifically selected for his/her expertise and thus the member's consistent participation ensures rigorous monitoring throughout the course of the study. The DSMB coordinator also attends all DSMB meetings and meeting sessions to provide logistical support and transcribe meeting summaries. Meetings are to be closed to the public because of participant confidentiality considerations.

All DSMB discussions are confidential. An ad hoc meeting of the DSMB may be called at any time by the Chairperson should ethical or patient safety issues arise. The suggestion to convene an ad-hoc meeting should be transmitted to the ES, who will notify the Sponsor-Investigator and DSMB coordinator. Depending on the situation, this meeting may include the Chairperson alone, a quorum of the DSMB, or the full DSMB.

Meeting Format
DSMB meetings consist of open and closed sessions. Discussion held in all sessions is confidential. All invited meeting participants, including the investigators, institution staff and the ES, may attend **open sessions**. All sessions are normally attended by a minimum of three voting DSMB members. The Sponsor-Investigator and the study statistician must be present. The number of coordinating staff attending DSMB meetings should be minimized and only include experienced and trained staff. Other staff may be invited to attend only when appropriate. Open session discussion focuses on the conduct and progress of the study, including patient accrual, protocol compliance, and problems encountered. **Unmasked data are not presented in the open session.**

The **closed session** is normally attended by the DSMB members, the ES, and the unmasked study statistician or unmasked study team designee. **If necessary, all unmasked safety data and efficacy data by treatment group may be presented during the closed session.** The DSMB determines in advance, in what format it wishes to see the data during the closed session. The discussion during the closed session is completely confidential, and thus attendance is limited to the members listed in this section, based on their safety monitoring and oversight roles and responsibilities**. The DSMB remains unmasked at all times during the closed session.**

If necessary, an **open session** may be called following the closed session to clarify any questions that arise from the DSMB. A second **closed session** may also be held, if needed.

Ad-hoc meetings may be held at any time should ethical or safety issues arise. The suggestion to convene an ad-hoc meeting should be transmitted to the ES, who will notify the Chairperson.

Each meeting, whether routine or ad-hoc, must include a recommendation made by a formal DSMB majority to initiate, continue, place on hold or to terminate the study. The decision is ultimately made by the Sponsor-Investigator and sponsoring institution IRB, taking into consideration the recommendation of the DSMB. The vote may be postponed until further information is acquired. Should the DSMB decide to issue a termination recommendation, the full DSMB must vote. In the event of a mixed vote, majority vote will rule and a minority report will be appended.

Specific recommendations will be transmitted in writing to the Sponsor-Investigator within 7 days of meeting completion.

Meeting Materials
DSMB report templates are prepared by the study staff, typically the statistician and/or the data coordinating center in consultation with the Sponsor-Investigator, to be reviewed by the DSMB members at the first meeting. Additions and modifications to the reports can be requested at any time throughout the study. The reports list and summarize safety data, as relevant, and describe the status of the study. All meeting materials must be sent to the ES at least two weeks prior to the meeting for distribution to the DSMB. The ES distributes study materials via the HIPPA compliant, central study data repository (Microsoft OneDrive, Redmond WA). Access will be limited to DSMB members and trained staff. Hard copies of the materials may be sent via express mail to DSMB members at their request. Materials are divided into two parts if requested: Part 1 contains open session materials, which may be shared with the study staff and meeting participants and referenced during any session of the meeting; and Part 2 contains closed session materials, which may contain sensitive or unmasked data and should be discussed in closed sessions only.

Part 1 – Open session materials include administrative reports by study site that describe patients screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population. Listings and summaries of adverse events and serious adverse events, along with any other information requested by the DSMB may also be in the open session report, but none of the data should be presented in an unmasked manner.

Part 2 – Closed session materials may contain safety data in aggregate, by masked treatment group (A/B presentation), by unmasked treatment group, or in other formats as requested by the DSMB. The closed session reports are confidential. Printed copies of the closed reports should be destroyed immediately following the meeting.

It is important that access to outcome data, when necessary, be limited to the study statistician and/or unmasked study team designee and the DSMB to protect the study from bias in patient entry and/or evaluation. Any unmasked study personnel should be pre-designated.

Meeting Recommendations
Meeting recommendations are drafted by the ES and are distributed for review by the DSMB Chairperson within two working days after the meeting. Once the recommendations are accepted by the Chairperson, the ES sends the recommendations to the full DSMB. Comments from DSMB members are obtained within two working days. Once finalized, the recommendations are circulated to the DSMB and the Sponsor-Investigator for their review. The Sponsor-Investigator has 14 calendar days to submit a formal, written response to the recommendations. If the DSMB has any further questions or concerns, the ES will notify the Sponsor-Investigator for further clarification via email. It is the responsibility of the Sponsor-Investigator to distribute this report to all co-investigators and to assure copies are submitted to all the IRBs associated with the study. The response will also be discussed at the following DSMB meeting.

Meeting Minutes
The full meeting minutes are drafted by the ES and distributed for review and approval by the Chairperson within 5 business days after the meeting. Any recommendations are inserted at the end of the minutes. Once approved by the Chairperson, the ES sends the minutes to the full DSMB. Comments from DSMB members are generally obtained within 5 working days after the meeting and meeting minutes finalized no later than 30 calendar days after the meeting. Each report concludes with a recommendation to continue, place on hold or to terminate the study. A formal vote to approve the minutes is held at the next DSMB meeting.

Additional Reporting
Status Reports (during active enrollment)
All clinical trials must provide semi-annual enrollment reports once the first participant is enrolled into the study. These reports will contain an Actual versus Expected graph and a CONSORT diagram and should be submitted to the Sponsor-Investigator through the ES. The reports will be shared with the DSMB for their reference.

Unanticipated Problems
Unanticipated problems are 1) unexpected events that are 2) related or possibly related to participation in the research that 3) place participants or others at greater risk of harm than was previously known or recognized. All three criteria above must be met to qualify the event as an unanticipated problem. The Office for Human Research Protections (OHRP), the Department of Health and Human Services (HHS), provides a complete definition and the following guidance for reporting unanticipated problems to the IRBs: *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events.* (http://www.hhs.gov/ohrp/policy/advevntguid.html). Unanticipated problems must be reported within 48 hours of the PI receiving notification of the event.
The DSMB Chairperson reviews the unanticipated problems to determine if further action is required.

Serious Adverse Events
All Serious Adverse Events (SAEs) (regardless of expectedness, relatedness, or if they meet the definition for unanticipated problems) must be reported to the DSMB Chairperson within 48 hours of the Sponsor-Investigator receiving notification of the event. The report will include a description of the event, as well as the Investigator's assessment of expectedness, relatedness, and other information, as relevant. Any action taken by the investigative team should be provided in the report. The DSMB Chairperson will be provided with this information but will provide an independent assessment on attribution and expectedness, as well as whether further action is recommended (e.g. collection of follow up information).

Discrepancies with Assessments Concerning Unanticipated Problems
On occasion, there may be disagreements between the Sponsor-Investigator and the DSMB regarding the assessment and/ or management of an event that qualifies as an unanticipated problem. The following excerpt gives guidance for cases where there is a difference of opinion among the DSMB (referred to as the "monitoring entity" in the excerpt below) and the investigator
http://www.hhs.gov/ohrp/policy/advevntguid.html.

> *If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the*

monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB (45 CFR 46.103(b)(5)).

Please note: The DSMB and the Sponsor-Investigator may have iterative discussions regarding the assessment and may later come to agreement regarding the assessment and/or management of an AE. In cases where the DSMB and Investigator come to an agreement after discussions and the event is determined not to be an unanticipated problem, the Investigator is not required to report the event as an unanticipated problem to the IRB. Such discussions should take place promptly so as not to delay appropriate reporting to the IRB.

Please also note that additional reporting requirements [e.g., to the Food and Drug Administration (FDA) and the IRB] are the responsibility of the Sponsor-Investigator.

Protocol Deviation/Violations

Protocol deviations/violations that impact participant safety should be reported to the DSMB Chairperson (through the ES) within 48 hours of the Sponsor-Investigator becoming aware of the event. Protocol deviations/violations that occur but do not affect participant safety are submitted with the routine DSMB meeting report. The Investigator must also adhere to the Institution's policy on reporting protocol deviations/violations to the IRB.

Additional reporting may be required if the violation meets the definition of an unanticipated problem as described in the OHRP, HHS guidance (http://www.hhs.gov/ohrp/policy/advevntguid.html).

Protocol Amendments

Requests for protocol amendment approvals must be submitted by the Sponsor-Investigator for review by the DSMB between regularly scheduled meetings. Approvals may be conducted via email correspondence, deferred until the next regularly scheduled meeting, or a call may be scheduled if immediate discussion is warranted. The Sponsor-Investigator is notified by the ES of the approved changes. IRB review of protocol amendments are separate from this process and are the Sponsor-Investigator's / site-investigator's responsibility.

Communication with the DSMB

To maintain the independent nature of the DSMB, the Sponsor-Investigator and study staff should only communicate DSMB-related requests, questions, or concerns through the ES. The DSMB members should only communicate with the Sponsor-Investigator through the ES.

Release of Study Data

Publications and abstracts containing primary study results are the responsibility of the investigator(s), and prior review or approval by the DSMB is not required. However, the perspective of the DSMB can add value to such publications/abstracts, and their comments may be useful to the investigator(s). Therefore, the PI is encouraged to provide the DSMB with a copy of all abstracts or manuscripts reporting primary study results well in advance of submission to a journal or scientific meeting.

APPENDICES

DSMB Membership

Role	Name	Affiliation	Contact
Chairperson	Mihir Patel, MD	Emory University	Mihir.r.patel@emory.edu
Safety Officer	Edward McCoul, MD, MPH	Ochsner Clinic	Edward.mccoul@ochsner.org
Study Statistician	Christina Mehta, PhD, MSPH	Emory University	Christina.Mehta@emory.edu
Executive Secretary	Mark Arnold, MD	SUNY Upstate	arnoldm@upstate.edu

Template for DSMB Recommendations

Protocol: A randomized, 52-week treatment double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week after endoscopic sinus surgery in patients with allergic fungal rhinosinusitis (AFRS) on a background therapy with intranasal corticosteroid spray

The **Data and Safety Monitoring Board (DSMB)** met on: MMDDYYYY for a Data Review Meeting that included: review of current study status and review and discussion of the Safety Report.

Materials provided for review:

- Agenda:
- Charter:
- Contact List:
- Informed Consent:
- Manuscript:
- Presentation:
- Protocol:
- Safety Report:

Recommendations from the DSMB:

- No safety concerns were identified; the study may continue as planned.

Add:

Signatures and Dates of DSMB Chair and any other required approvals

Appendix D: List of Study Personnel

Coordinating Sponsor Investigator:	[redacted] Office of the Clinical Director [redacted]
Emory University School of Medicine	
Co-Investigators:	[redacted] Assistant Professor Department of Otolaryngology – Head & Neck Surgery
	[redacted] Professor of Medicine and Cell Biology Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
Collaborators:	[redacted] Department of Otolaryngology – Head & Neck Surgery
	[redacted] Professor Department of Otolaryngology – Head & Neck Surgery
	[redacted] Department of Otolaryngology – Head & Neck Surgery
Research Coordinators:	[redacted] Department of Otolaryngology – Head & Neck Surgery
	[redacted] Department of Otolaryngology – Head & Neck Surgery [redacted]
McGovern Medical School at the University of Texas Health Science Center at Houston	
Site Principal Investigator:	[redacted] Associate Professor of Otolaryngology Department of Otolaryngology – Head & Neck Surgery [redacted]

	[redacted]
Collaborators:	[redacted] Professor & Chair of Otolaryngology Department of Otolaryngology – Head & Neck Surgery
	[redacted] Assistant Professor of Otolaryngology Department of Otolaryngology – Head & Neck Surgery
Research Coordinators:	[redacted] Department of Otolaryngology – Head & Neck Surgery
	[redacted]

Appendix E: List of Study Vendors

Vendor	Role	Contact	Email	Address
Belmar Pharma Solutions	Investigational Pharmacy	Sam Lebsock	sam@belmarpharmacy.com	231 Violet Street, Ste 140 Golden, CO 80401
Clear Analytics	Database construction and data management	Jesse Chittams	clearanalyticsllc@gmail.com	17121 Aspen Leaf Drive Bowie, MD 20716
Daniel Spielman, MD	Central reader	Daniel Spielman, MD	dbspielman@gmail.com	3800 Reservoir Road NW Gorman Building, 1st Floor Washington, DC 20007
Westat	External study monitoring	Michele Snyder	MicheleSnyder@Westat.com	1600 Research Boulevard Rockville, Maryland 20850-3129

20. Resources Available

AFRS participants are seen in clinic at all three sites participating in this study. We do not anticipate recruitment barriers in identifying and enrolling participants.

21. Multi-Site Research monitoring

There will be a total of 132 participants across the three sites participating. Each site will enroll 44 participants. The sponsor-investigator will communicate regularly among sites to ensure each site has the current version of the protocol, consent documentation, and HIPAA authorization. Site visits to the other participating sites may be done to review progress of the study. In addition, Principal Investigators will meet regularly to discuss any issues that may arise during the study.

22. References

1. Orlandi, R.R., et al., *International consensus statement on allergy and rhinology: rhinosinusitis 2021.* International Forum of Allergy & Rhinology, 2021. **11**(3): p. 213-739.
2. Tyler, M.A., et al., *Large-scale gene expression profiling reveals distinct type 2 inflammatory patterns in chronic rhinosinusitis subtypes.* J Allergy Clin Immunol, 2017. **139**(3): p. 1061-1064 e4.
3. Tyler, M.A., et al., *Distinguishing Molecular Features of Allergic Fungal Rhinosinusitis.* Otolaryngol Head Neck Surg, 2018. **159**(1): p. 185-193.
4. Rudmik, L., et al., *Defining appropriateness criteria for endoscopic sinus surgery during management of uncomplicated adult chronic rhinosinusitis: a RAND/UCLA appropriateness study.* Rhinology, 2016. **54**(2): p. 117-28.
5. Psaltis, A.J., et al., *Modification of the lund-kennedy endoscopic scoring system improves its reliability and correlation with patient-reported outcome measures.* The Laryngoscope, 2014. **124**(10): p. 2216-2223.
6. Lund, V.J. and I.S. Mackay, *Staging in rhinosinusitus.* Rhinology, 1993. **31**: p. 183 184.
7. Bachert, C., et al., *Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials.* Lancet, 2019. **394**(10209): p. 1638-1650.
8. Hopkins, C., et al., *Psychometric validity of the 22-item Sinonasal Outcome Test.* Clin Otolaryngol, 2009. **34**(5): p. 447-54.
9. Juniper, E.F., et al., *Development and validation of a questionnaire to measure asthma control.* Eur Respir J, 1999. **14**(4): p. 902-7.
10. Bent, J.P. and F.A. Kuhn, *Diagnosis of Allergic Fungal Sinusitis.* Otolaryngology–Head and Neck Surgery, 1994. **111**(5): p. 580-588.

A Randomized, 52-week Treatment Double-blind, Placebo-controlled Efficacy and Safety Study of Dupilumab 300 mg Every Other Week After Endoscopic Sinus Surgery in Patients With Allergic Fungal Rhinosinusitis (AFRS) on a Background Therapy With Intranasal Corticosteroid Spray

NCT05545072

Date: April 02, 2024
STUDY00000090