Mepolizumab for the Treatment of Chronic Spontaneous Urticaria: An Open-label, Single-arm, Exploratory Study

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MEPOLIZUMAB FOR THE TREATMENT OF CHRONIC SPONTANEOUS URTICARIA: AN OPEN-LABEL, SINGLE-ARM, EXPLORATORY STUDY

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Study Product:	Mepolizumab (Nucala)
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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSU	Chronic Spontaneous Urticaria
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UAS	Urticaria Activity Score
UCT	Urticaria Control Test

Study Summary

Title	***Mepolizumab for the Treatment of Chronic Spontaneous Urticaria: An Open-Label, Single-Arm, Exploratory Study***
Running Title	Mepolizumab (Nucala) for the Treatment of Chronic Spontaneous Urticaria
Protocol Number	17-009322
Phase	Investigational Exploratory Trial
Methodology	Single arm, Open-label, Exploratory Trial
Overall Study Duration	13 months (10 month accrual period)
Subject Participation Duration	12 weeks
Single or Multi-Site	Mayo Clinic Florida
Objectives	To investigate the potential efficacy of mepolizumab (Nucala) in the treatment of biopsy proven chronic spontaneous urticaria
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Main inclusion criteria: 18 years old or older at time of consent with history and physical exam consistent with CSU, lasting greater than 6 weeks and unresponsive to oral antihistamines
Study Product, Dose, Route, Regimen	Mepolizumab (Nucala) 200 mg SQ every 2 weeks x 10 weeks
Duration of Administration	10 weeks
Reference therapy	None

	This is an exploratory study designed to generate preliminary data in evaluating the efficacy of mepolizumab (Nucala) in the treatment of CSU. The primary outcome measure is derived from the UAS7 used to quantify number of hives and daily pruritus.
Statistical Methodology	A paired t-test will be used to evaluate mean differences before and after treatment at a p=0.05 significance level. The primary endpoint of the study is the UAS7. A 10 point change in the UAS7 has been reported to be the minimal clinically significant difference in therapeutic trials for urticaria. The study is powered at 99% to detect a 10 point change in the UAS7 at a 5% significant level with the proposed accrual target of 20 patients.

1. Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the protocol, Good Clinical Practice standards, and applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Chronic spontaneous urticaria (CSU) is a common skin disorder affecting 0.1 to 1% of the general population and is characterized by recurrent, transitory, pruritic erythematous plaques present for a minimum of 6 weeks. In 30 to 50% of CU cases, there is an autoimmune etiology with autoantibodies against IgE, FcεRI or FcεRII (CD23). These autoantibodies are postulated to bind to the surface of mast cells and basophils initiating a signal transduction cascade resulting in the secretion of histamine and other inflammatory mediators which produce the observed clinical features of edema, erythema, and localized pruritus. The impact of CSU on quality of life is quite significant with most cases lasting an average of 3 to 5 years.

1.2 Investigational Agent

Mepolizumab (Nucala) is a human interleukin-5 antagonist indicated for add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype. For this study, it will be supplied as a 100 mg lyophilized powder for reconstitution to be administered subcutaneously by trained study personnel.

1.3 Preclinical Data

Interleukin-5 has been previously established to stimulate proliferation and maturation of eosinophils. Eosinophils release major basic protein (MBP) which induces mast cell and basophil degranulation [1,3]

1.4 Clinical Data to Date

Since more than half of the patients with CSU do not show evidence of auto-Abs either against the high-affinity IgE receptor or against IgE Ab, additional therapeutic approaches are needed. An alternative pathway for allergen-independent histamine release by basophils and mast cells is through major basic protein (MBP) released by eosinophils. Incubation of human basophils and mast cells with MBP results in a non-cytotoxic, dose-dependent histamine release from target cells within 30 min. Additionally, IgE binding to the low-affinity IgE receptor (FceRII/CD23) on eosinophils also results in eosinophilic activation and MBP release.

Therefore, we hypothesize the IL-5 neutralizing properties of mepolizumab (Nucala) on eosinophil maturation and function may have therapeutic utility in the management of CSU. Support for the

relevance of these mechanisms in the pathogenesis in CSU is reflected by the accumulation of interstitial and perivascular dermal eosinophils in lesional skin biopsies. Elevated levels of IL-5 mRNA expression have also been demonstrated from both eosinophilic and lymphocytic components of the inflammatory infiltrate.

1.5 Dose Rationale

The dosing of mepolizumab (Nucala) in this study will be 200 mg SQ administered at weeks 0,2,4,6 and 8. We are aware of prior investigations establishing that monthly doses of Nucala are effective in reducing peripheral eosinophilia and that higher and more frequent dosing are not associated with a longer or more sustained clinical response in reducing asthma exacerbations. We are also aware of prior studies where a 300 mg monthly SQ dose has been safe and effective in treating Eosinophilic Granulomatous Polyangiitis and Hypereosinophilic Syndrome. The concern in this study is with respect to what is the minimum effective dose that reduces peripheral eosinophilia and is also sufficiently inhibitory to prevent pathologic eosinophilic accumulation in lesional skin in response to an acute inflammatory signal. We reviewed early published reports of IV Nucala at 750 mg in atopic dermatitis that failed to demonstrate efficacy and the authors raised the possibility that more frequent administration may have been helpful. Although the mechanism of eosinophilic recruitment into the skin in atopic dermatitis and chronic urticaria differs, existing data does suggest more frequent dosing can be beneficial for skin disorders especially given the nature of the inflammatory cascade in chronic urticaria. As this is a proof of concept study and the safety profile of Nucala has been established to be extremely robust, we felt to error on the side of more frequent administration to avoid missing a potential therapeutic effect. We are open to considering a monthly 300 mg SQ dose, if there are significant safety concerns with the proposed dosing interval of 200 mg SQ q2 weeks.

1.6 Risks and Benefits

The postulated benefits of Nucala include sustained immunomodulatory effects resulting in improvement of pruritus and clearance of lesional skin without the direct end organ toxicities seen

The following risks of Nucala are felt to be low and manageable with the study protocol and do not outweigh the aforementioned benefits:

1. Hypersensitivity Reactions

Anaphylaxis has occurred following administration of Nucala. This risk is idiosyncratic and will be minimized by administrating Nucala in a supervised medical setting and requiring study participants to carry epinephrine autoinjectors at all times.

2. Acute Asthma Symptoms or Deteriorating Disease

Nucala is not indicated for the treatment of acute asthma symptoms or acute exacerbations. This risk will be minimized by screening all study participants with asthma via the asthma control test (ACT) questionnaire and peak flow measures at each visit. Those with ACT scores less than 20 and/or peak flow measures greater than 10% below their personal best will not receive the study drug on the day of their visit. Subjects with severe asthma (requiring high-dose inhaled or systemic corticosteroids) will be excluded from the study.

3. Opportunistic Infections: Herpes Zoster

In controlled clinical trials, two serious adverse reactions of herpes zoster occurred in subjects treated with Nucala compared with none in placebo. The mechanism by which this adverse reaction occurs is unclear. Subjects will be monitored for signs and symptoms of shingles and treated should shingles develop.

4. Reduction of Corticosteroid Dosage

Reductions in corticosteroid dose, if appropriate, will be gradual and performed under the direct supervision of a physician.

5. Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if Nucala will influence a patient's response against parasitic infections This risk will be minimized by excluding enrollment of study participants with known tapeworm or roundworm infections.

2 Study Objectives

The primary objective of this study is to investigate the potential efficacy of mepolizumab in the treatment of biopsy proven chronic spontaneous urticaria. The primary measurement of efficacy will be the mean reduction in the seven day urticaria activity score (UAS7) before and after 10 weeks of treatment with mepolizumab. Secondary measure of efficacy will be the mean reduction of the urticaria control test (UCT) score and the weekly itch severity score (ISS) before and after treatment.

3 Study Design

3.1 General Description

This is an open-label, single arm exploratory study of mepolizumab in the treatment of CSU. The primary endpoint will be the mean reduction in the seven day urticaria activity score (UAS7) before and after 10 weeks of treatment with mepolizumab. Secondary endpoints will be the mean

reduction of the urticaria control test (UCT) score and the weekly itch severity score (ISS) before and after treatment. Enrollment examination will include a standardized history and examination, baseline UCT score, CBC with differential, serum IgE level, chronic urticaria index, IgE Fc receptor antibody functional assay, and a 4 mm punch biopsy of lesional skin. Patients will discontinue all anti-histamines and start cetirizine 10 mg PO BID which will be continued throughout the study duration. Patients will be provided with a log book to track daily urticaria signs and symptoms in a standardized manner for UAS scoring. At week 0 (enrollment visit +7 days), baseline UAS7 and ISS score will be assessed and skin biopsy results reviewed. Patients with a confirmatory skin biopsy will receive 200 mg SC of mepolizumab at week 0,2,4,6,and 8. UAS-7 and weekly ISS score will be calculated at week 0, 4, 8, and 10. UCT scoring will be calculated at week 0 and at week 10. Repeat CBC with differential, serum IgE level, and measures of basophil serum activation (chronic urticaria index, IgE FC Receptor antibody functional assay) will be assessed at week 10. Attached to this document is a protocol summary.

4 Number of Subjects

Twenty

4.1 Duration of Participation

Twelve weeks

4.2 Primary Study Endpoints

The primary endpoint of the study will be the mean UAS7 reduction before and after 10 weeks of treatment with mepolizumab. The urticaria activity score (UAS) is a widely used CSU measure for daily pruritus and number of hives, which summed over a week, gives a UAS7 score. Study participants will document their CSU symptoms using a diary during the 10 week study period using the following daily scoring for a) the number of wheals [none (=0 points), <10 (=1 point), 10–50 (=2 points), or >50 per day (=3 points)], and b) the intensity of pruritus [none (=0 points), mild (=1 point), moderate (=2 points), severe (=3 points)]. The daily UAS score is summed over a week to calculate the UAS7 score (range: 0–42).

4.3 Secondary Study Endpoints

The secondary endpoints of the study are the mean reduction in the weekly itch severity score (ISS) and mean average change in the urticaria control test (UCT) score before and after 10 weeks of treatment with mepolizumab. The weekly itch severity score is calculated using the pruritus score of the daily UAS score summed over a week (range: 0-21). The urticaria control test (UCT) is a more recently developed and validated outcome instrument to retrospectively assess urticaria

control. Each UCT item has 5 answer options scored 0-4 with low points indicating high disease activity and low disease control. The minimum and maximum UCT scores are 0-16 with 16 points indicating complete disease control.

4.4 Primary Safety Endpoints

This is an exploratory efficacy study with no specific primary safety endpoint. Adverse events will be tracked and reported using Good Clinical Practice standards.

4.5 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- UCT score
- ISS score
- UAS7 score
- Screening and documentation of adverse events
- Confirmation of patient counseling and education

The following source data will not be directly recorded in the CRF, but will be captured in supportive documentation to include study source documents and the EMR:

- Laboratory results and clinical interpretation of the values
- Histopathologic interpretations of skin biopsy tissue. This will include the use of immunohistochemistry to identify IL-5 receptor expression in lesional skin taken prior to treatment.

5 Subject Selection Enrollment and Withdrawal

5.1 Inclusion Criteria

Informed subject consent will be obtained from those patients meeting the following inclusion criteria:

- Male and female patients 18 years or older.
- Clinical and/or histopathological diagnosis of conventional CSU
- Unresponsive to oral antihistamine therapy
- Good general health as confirmed by medical history
- Patients who are willing and capable of cooperating to the extent and degree required by the protocol; and
- Patients who read and sign an approved informed consent for this study

5.2 Exclusion Criteria

Patients are to be excluded based on the following criteria:

- Vulnerable study population
- If you are female and pregnant
- Biopsy proven neutrophilic rich urticarial which is unlikely to respond to mepolizumab given the postulated therapeutic mechanism
- Known history of adverse reaction to mepolizumab (Nucala)

5.3 Subject Recruitment, Enrollment and Screening

Subjects will be enrolled from the Departments of Allergy and Dermatology at the Mayo Clinic in Florida. The study has an accrual target of 20 patients. In the year 2014, 188 unique patients with CSU were evaluated in the Dermatology and Allergy outpatient clinics at Mayo Clinic in Florida and thus no difficulties in accrual based on historical volumes are anticipated. Co-departmental participation aids in reaching accrual targets and minimizing referral bias. The accrual period will last 10 months. Patients will be provided with a Research Participant Consent and Privacy Authorization Form describing the study drug, protocol, inclusion and exclusion criteria, as well as risks and benefits of participation.

5.4 Early Withdrawal of Subjects

5.4.1 When and How to Withdraw Subjects

Patients are free to withdraw at any time and for whatever reason. No data will be collected for withdrawn subjects. Withdrawn subjects may be replaced within the 6-month accrual period. There will be no follow-up for withdrawn subjects. Pre-specified reasons for discontinuing include, but are not limited to, the following:

- Patient Request: Patient decided that he/she did not want to continue (for any reason)
- Adverse Event: Patient experienced a related or unrelated event that would interfere with the study objectives/evaluation
- Lost to Follow-up: Patient did not come in for a visit and could not be reached by phone
- Treatment Failure: If in the Principal Investigator and/or Investigators' judgment, the patient's condition required another form of treatment
- Inclusion/Exclusion Discrepancy/Violation: Patient should not have been enrolled
- Noncompliance: Patient is not complying with the protocol requirements (i.e. visit schedule, dosing, regimen, etc.); a patient is to be withdrawn if he/she misses two consecutive visits
- Other: Any other reason

5.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a Participant withdraws from the study, no additional attempts will be made to contact the Participant.

6 Study Drug

6.1 Description

Nucala (mepolizumab) is a humanized IL-5 antagonist monoclonal antibody. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

Nucala is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for subcutaneous injection after reconstitution. Upon reconstitution with 1.2 mL of Sterile Water for Injection, the resulting concentration is 100 mg/mL and delivers 1 mL.

6.2 Treatment Regimen

All study participants will receive Nucala 200 mg SQ at week 0, 2,4,6, and 8 for a total of 5 injections.

6.3 Method for Assigning Subjects to Treatment Groups

This is an open-label pilot investigation and all study participants are assigned to active treatment. There is no placebo arm in this study.

6.4 Preparation and Administration of Study Drug

The study drug will be stored and dispensed at each study visit from the Mayo Clinic Research Pharmacy in Florida.

6.5 Subject Compliance Monitoring

Study participants will receive Nucala subcutaneous injection at each follow-up visit.

6.6 Prior and Concomitant Therapy

Study participants will stop other first-generation antihistamines and start cetirizine (Zyrtec) 10 mg 1 tablet bid two weeks prior to the first dose of Nucala, and continue throughout the duration of the study.

Epinephrine auto-injectors will be dispensed to the participants on baseline visit and must be carried at all times.

6.7 Packaging

Each single-dose vial delivers mepolizumab 100 mg, polysorbate 80 (0.67 mg), sodium phosphate dibasic heptahydrate (7.14 mg), and sucrose (160 mg), with a pH of 7.0.

A quantity of 200 Nucala (100 mg) vials will be shipped to the Mayo Clinic research pharmacy in Florida and then labeled upon receipt with statement "Caution: New Drug Limited by Federal law for investigational use."

6.8 Masking/Blinding of Study

This is an open-label pilot investigation. Masking and blinding procedures are not applicable. Qualitative and quantitative evaluations of response to treatment will be recorded.

6.9 Receiving, Storage, Dispensing and Return

6.9.1 Receipt of Drug Supplies

The drug will be shipped by GlaxoSmithKline to the Mayo Clinic research pharmacy in Florida. The pharmacy site will receive 200 100-mg vials of Nucala (mepolizumab). Upon receipt, an inventory will be performed and a drug receipt log filled out by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

6.9.2 Storage

Prior to dispensing, Nucala will be stored in a refrigerator, below 25°C (77°F) in the original carton and protected from light. Prior to SQ administration, Nucala will be reconstituted with 1.2 mL Sterile Water for Injection, USP.

6.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation

form, and signed and dated by the study team. Drug dispensation will occur at scheduled follow-up visits.

6.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Remaining drug will be destroyed on site will be documented in the study files.

7 Study Procedures

7.1 Visit 1 (Week -2/Screening & Enrollment)

a) Informed Consent
b) History & Physical
c) 4 mm punch skin biopsy (4 mm punch skin biopsy within 6 months prior to visit 1 is acceptable)
d) UCT score assessment
e) Review and distribute UAS log book
f) Blood work: CBC with differential, serum IgE level, chronic urticaria index, IgE Fc receptor antibody functional assay (Blood work within 6 months prior to visit 1 is acceptable)
g) Urine Pregnancy Test (if applicable)
h) Photograph Biopsy site (Photograph Biopsy site within 6 months prior to visit 1 is acceptable)
i) Dispense cetirizine (Zyrtec) 10 mg PO BID (#140 tablets)

7.2 Visit 2 (Week 0± 5 days Baseline)

a) UAS7 score assessment
b) ISS score assessment
c) Nucala 200mg injection
d) Dispense epinephrine auto-injector

7.3 Visit 3 (Week 2± 5 days)

a) UAS7 score assessment
b) ISS score assessment
c) Nucala 200mg injection
d) Screen for adverse events

7.4 Visit 4 (Week 4 ± 5 days)

a) UAS7 score assessment
b) ISS score assessment
c) Nucala 200mg injection
d) Screen for adverse events

Visit 5 (Week 6 ± 5 days)

a) UAS7 score assessment
b) ISS score assessment
c) Nucala 200mg injection
d) Screen for adverse events

7.5 Visit 6 (week 8± 5 days)

a) UAS7 score assessment
b) ISS score assessment
c) Nucala 200mg injection
d) Screen for adverse events

7.6 Visit 7 (week 10± 5 days)

a) UAS7 score assessment
b) ISS score assessment
c) UCT score assessment
d) 4mm punch skin biopsy if residual disease
e) Collect UAS log book
f) Blood work: CBC with differential, serum IgE level, chronic urticaria index, IgE Fc receptor antibody functional assay
g) Screen for adverse events
h) Photograph biopsy site

Week	Wk -2 screen	Wk 0 baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Consent/Enroll	X						
Distribute log book	X						
Collect log book							X
Cbc with Diff	X						X
Serum IgE	X						X
CIU index	X						X
IgE Fc Recpt Ab	X						X
Urine HCG	X						
UCT		X					X
UAS		X	X	X	X	X	X
ISS		X	X	X	X	X	X
Skin Biopsy	X						X***
Nucala Inj*		X	X	X	X	X	
Cetirizine (Zyrtec) Dispense	X						
Epinephrine auto-injector Dispense		X					
AE Screening**		X	X	X	X	X	X

** Nucala Inj = denotes Nucala SQ injection during a visit*
*** AE Screening = protocol directed screening for adverse events*
****At end of study if subjects have residual disease, will biopsy, as necessary, to check for lesional eosinophil tissue density*

8 Statistical Plan

8.1 Sample Size Determination

The statistical methods proposed in the study were reviewed with a Mayo staff statistician who also assisted in a formal power analysis. Demographic and laboratory characteristics will be analyzed using descriptive statistics. A paired t-test will be used to evaluate mean differences before and after treatment at a p=0.05 significance level. The primary endpoint of the study is the UAS7. A 10 point change in the UAS7 has been reported to be the minimal clinically significant difference in therapeutic trials for urticaria. The study is powered at 99% to detect a 10 point change in the UAS7 at a 5% significant level with the proposed accrual target of 20 patients.

8.2 Statistical Methods

Descriptive Statistics

Continuous variables will be summarized using the sample mean, median, standard deviation, interquartile range, and range. Categorical variables will be summarized using number and percentage of patients

Handling of Missing Data

This is a prospective study and therefore we do not anticipate any missing data. In the event of any unexpected missing data, no attempt to impute this missing data will be made; missing data will simply be treated as missing in the statistical analysis.

Multiplicity

Since this is an exploratory pilot study, no adjustment for multiple testing is needed.

Interim Analysis

There will not be any interim analysis given the low risk profile of the study formulation.

8.3 Subject Population(s) for Analysis

Each participant who received the study drug will be included in the primary analysis regardless of study withdrawal for any reason. In the event of any study withdrawals, in secondary analysis we will examine the sensitivity of our results to the exclusion of patients who withdrew.

9 Safety and Adverse Events

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of Nucala in a research subject. Initial screening for AE will include non-directed questioning of the patient at each follow-up visit during the study period.

Serious Adverse Event
Adverse events defined as serious will the following:

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity

- birth defect/anomaly

and any problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, will be regarded as **non-serious adverse events** as previously defined above.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is defined as the last scheduled visit.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
Any clinical laboratory abnormality that can reasonably be related to the administration of Nucala should be documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Hospitalization, prolonged hospitalization, or surgery is to be reported as an adverse event if it can reasonably be related to use of Nucala.

9.2 Recording of Adverse Events

At each contact with the subject, the study team will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be

recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results will be recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

9.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The Principal Investigator and/or Investigators will report, as soon as possible, but no later than 5 working days after first learning of the problem/event, to the Mayo Clinic IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo Clinic IRB Policy and Procedures.

Documentation of adverse events will include the following information collected in the adverse event section of the case report form (and entered into the research database):

- Subject's name:
- Medical record number:
- Disease:
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research:
- If the adverse event was expected:
- The severity of the adverse event (defined by a severity scale):
- If any intervention was necessary:
- Resolution (was the incident resolved spontaneously, or after discontinuing treatment):
- Date of Resolution:

The Principal Investigator and/or Investigators will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The Principal Investigator and/or Investigators will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

9.3.2 Sponsor-Investigator reporting: Notifying the FDA

This protocol is not being conducted under an FDA investigational new drug application.

9.4 Unmasking/Unblinding Procedures

This is an open-label pilot investigation. Unmasking and unblinding procedures are not applicable.

9.5 Stopping Rules

This investigation is of low risk to study subjects. Stopping or interruption of the study may be necessary if a significant number of study participants develop unexpected clinical flaring or significant worsening that appears temporally linked with Nucala administration.

9.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the Principal Investigator and Investigators, by regulation, retain the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Case Report Forms

All data requested on the Case Report Form (CRF) will be recorded for each participant. A standardized CRF will be generated by REDCap. All missing data will be explained. If a space on the CRF is left blank because the question was not asked, "N/D" will be recorded. If the item is not applicable to the individual case, "N/A" will be recorded. All entries will be printed legibly in black ink. If any entry error has been made, a single straight line through the incorrect entry will be drawn and the correct data will be written above it. All such changes will be initialed and dated. Errors will not be erased or whited-out. For clarification of illegible or uncertain entries, a clarification will be printed above the item, then initialed and dated. If the reason for the correction is not clear or needs additional explanation, details to justify the correction will be neatly included.

Data Management

Study data to be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data Processing

All study date will be stored and analyzed at Mayo Clinic in Florida using the REDCap electronic data capture tool.

Data Security and Confidentiality

All source documents including clinical findings, observations or other activities will be stored in a REDCap database that will be designed by the Statistician. Access to the REDCap database will be limited to the Principal Investigator, Investigators, and Statistician.

Data Quality Assurance

Once the study is completed the Principal Investigator will randomly select 3 participants and compare the data documented for each on the CRF with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 12 patients to ensure accuracy.

Data Clarification Process

For any data query the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus.

10.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to

all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

12 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent. This study will not include vulnerable study populations.

13 Study Finances

13.1 Funding Source

This investigator initiated study is funded by a research grant from GlaxoSmithKline to Mayo Clinic.

13.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

No financial conflicts of interested are anticipated or have been identified for this study.

13.3 Subject Stipends or Payments

No payment is given to study participants.

14 Publication Plan

The primary responsibility for publication of the study results is with the Primary Investigator. After the complication of study and prior to publication, the study results will be shared with GlaxoSmithKline. The study will be registered at ClinicalTrials.gov prior to subject recruitment along with the posting of the results within 12 months of final data collection for the primary outcome measure.

15 References

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16 Attachments

None