

Phase I/II Clinical Trial Evaluating Rituximab in Ocular Cicatricial  
Pemphigoid

Study Protocol & Statistical Analysis Plan

NCT00584935

IRB-F060213003

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**STATEMENT OF COMPLIANCE**

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

**1 PROTOCOL SUMMARY****1.1 SYNOPSIS**

<b>Title:</b>	Phase I/II Clinical Trial Evaluating Rituximab in Ocular Cicatricial Pemphigoid
<b>Study Description:</b>	Cicatricial pemphigoid is an autoimmune blistering disease which affects the skin, mucous membranes, and, in a small subset of patients, the eye. Progressive ocular disease can lead to irreversible damage and blindness. Conventional treatments include systemic steroids, dapsone, and immunosuppressive agents. These treatments, however, are not successful with all patients. Rituximab has been very effective in the treatment of other autoimmune disorders, and has recently been shown to be effective for autoimmune blistering pemphigus. We propose that it will also be effective in the treatment of cicatricial pemphigoid.
<b>Objectives:</b>	This is a research study of an investigational product called Rituximab. Rituximab also called Rituxan® is a monoclonal antibody produced by Genentech, Inc. and IDEC Pharmaceuticals using recombinant DNA technology. Antibodies are proteins that protect the body from foreign attackers, such as bacteria and viruses, by binding to substances called antigens. The purpose of this study is to determine if Rituximab is effective in the treatment of Ocular Cicatricial Pemphigoid. Rituximab also called Rituxan® is a monoclonal antibody (Antibodies are proteins that protect the body from foreign attackers, such as bacteria and viruses, by binding to substances called antigens.) produced by Genentech, Inc. and Biogen IDEC Pharmaceuticals using recombinant DNA technology.
<b>Endpoints:</b>	Primary Efficacy Endpoint(s): 1. Number of Participants With no Evidence of Further Scarring

	<p>2. The Proportion of Patients That Experience a Grade 3, Grade 4, or Grade 5 Toxicity Based Reaction on the NCI-CTC System at the Time of Their Infusions and During Follow-up Visits.</p> <p>Secondary Efficacy Endpoint(s):</p> <ol style="list-style-type: none"> <li>1. Stability of Visual Acuity (Snellen's Test) at 16 Weeks</li> <li>2. Stability of Visual Acuity (Snellen's Test) at 24 Weeks</li> </ol>
<b>Study Population:</b>	5 participants, ages 19 and older, recruited from the dermatology clinics
<b>Phase:</b>	I/II
<b>Description of Study Intervention:</b>	The Rituximab dose is 1000mg (1gm) given as an IV infusion every two weeks for 2 doses (days 1 and 15).
<b>Study Duration:</b>	1 year
<b>Subject Duration:</b>	Up to 1 year

## 1.2 SCHEDULE OF ACTIVITIES (SOA)

1.3 PROCEDURE	1.4 FREQUENCY	Time
Informed Consent	Once	1 hour
Demographic Data	Four times	30 minutes
Physical Exam & Medical History	Six times	30 minutes
Pregnancy Testing (If Applicable)	Two times	30 minutes
Vital Signs	Four times	10 minutes
Standard Bloods	Five times	10 minutes
Specialized Bloods	Eleven times	10 minutes
Serology Testing: HBV, HCV, HIV	Once	10 minutes
Rituxan Infusion (Pre-tx Benadryl/Tylenol)	Seven times	10 minutes
Rituxan Serum Levels	Eight times	15 minutes

HACA	Twelve times	5 minutes
CD19 & CD20 B-cells	Multiple	20 minutes
Safety Assessment	Multiple	20 minutes
Chest X-ray	Once	20 minutes
Immunoglobulin	Multiple	10 minutes
Eye Examinations	Seven times	60 minutes

## 2 INTRODUCTION

### 2.1 BACKGROUND

Cicatricial pemphigoid is an autoimmune blistering disease which can affect the skin and mucous membranes. In a subset of patients, there is only ocular involvement. Progressive disease in the eye can lead to irreversible damage and blindness. Conventional treatments which have been effective have included high dose systemic steroids, dapsone, and immunosuppressive agents such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil. However, there are a subgroup of patients who fail to respond to these treatments, develop intolerable side effects, or have contraindications to their use. Alternative treatment modalities which have provided temporary relief have included plasmapheresis and intravenous immunoglobulin therapy. In such patients, these modalities have been used as “rescue” agents and conventional treatments have to be used concomitantly with the alternative treatment modalities to prevent recurrence. Patients also can develop resistance to these treatment modalities. Hence, alternative treatment modalities are needed. Rituximab has been very effective in the treatment of other autoimmune disorders. Ocular cicatricial pemphigoid is also an autoantibody mediated disease. Most recently, Rituximab has been shown to be effective in the treatment of another autoimmune blistering disorder called pemphigus. We propose that Rituximab will also be effective in the treatment of cicatricial pemphigoid. This could help many patients from becoming blind. Indirect immunofluorescence studies can detect low titers of anti-basement membrane zone antibodies. However, these can be negative, and these do not correlate with disease activity.

### 2.2 RISK/BENEFIT ASSESSMENT

#### 2.2.1 KNOWN POTENTIAL RISKS

**General Infusion-Related Reactions.** If an infusion related reaction develops, the infusion should be temporarily slowed or interrupted. The infusion may be continued at one half the previous rate upon improvement of the patient’s symptoms.

**Life Threatening Reaction.** In the event of a life threatening reaction, the infusion should be discontinued and the patient should receive medical treatment. Patients who experience a life-threatening reaction will be discontinued from study treatment.

**Severe Infusion Reaction.** The infusion should be interrupted for severe reactions, and supportive care measures should be instituted as medically indicated (e.g., IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). The infusion should not be restarted until all the symptoms have disappeared. On the restarting of the infusion, the rate should be half of that which precipitated the reaction. Further specifications are detailed in Appendix C.

**Note:** these recommendations do not address life-threatening events, including anaphylaxis, for which all appropriate standard measures, including full resuscitation medications and equipment, must be available and should be used as clinically indicated.

**Hypersensitivity Reactions.** Hypersensitivity reactions (non-IgE-mediated reactions) may respond to adjustments in the infusion rate and in medical management. The infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen (or their equivalents) is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-

threatening hypersensitivity reactions have been able to complete the full course of therapy. Medications for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and corticosteroids) should be available for immediate use in the event of a reaction during administration. Cardiovascular. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions. Patients with preexisting cardiac conditions, including arrhythmias and angina, have had recurrences of these events during therapy and should be monitored throughout the infusion and the immediate post infusion period.

**Severe Mucocutaneous Reactions.** Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and should seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of re-administration of study drug to patients with mucocutaneous reactions has not been determined.

#### Overdosage

There has been no experience with overdosage in human clinical trials. Single doses higher than 500 mg/m<sup>2</sup> have not been tested in controlled studies.

The following serious side effects may occur during infusion:

- Chest pain
- Abnormal heart beat
- Severe shortness of breath
- Severe skin rash
- Lung inflammation
- Heart failure
- Kidney failure from rapid killing of tumor cells (approximately 1 in 10,000; seen only in cancer patients)

Other side effects, not necessarily occurring during the Rituximab infusion, may include the following:

- Anemia
- Low platelet count (uncommon)
- Joint pain
- Infection
- Flu-like symptoms
- Decreased appetite (uncommon)
- Fatigue
- Sleep problems (uncommon)
- High blood pressure (uncommon)

### 2.2.2 KNOWN POTENTIAL BENEFITS

Subjects will have the opportunity to participate in a research study that may benefit their Ocular Cicatricial Pemphigoid, however it is also possible that they may not benefit from the treatment in this study. The possible benefit would definitely outweigh the risk for many participants.

## 3 STUDY DESIGN

## 4 STUDY POPULATION

#### 4.1 INCLUSION CRITERIA

Participants meeting the following inclusion criteria may participate in this study:

- A clinical diagnosis of ocular cicatricial pemphigoid (symptoms of conjunctivitis, irritation, burning, increased lacrimation, photophobia, and dryness of the eyes along with conjunctival inflammation, trichiasis, and scarring).
- Failed response to the use of one or more conventional treatments (systemic steroids, azathioprine, cyclophosphamide, mycophenolate, dapsone) for a minimum of 10 weeks.
  - Minimal conventional medication doses, including but not restricted to:
    - Systemic corticosteroids-5mg/day
    - Azathioprine-50mg/day
    - Cyclophosphamide-50mg/day
    - Mycophenolate mofetil-1/gm/day
    - Dapsone-50mg/day
- Significant adverse effects of conventional therapy which are potentially fatal or cause significant morbidity and failure to carry on daily routine activities, or
- A contraindication to the use of the conventional treatments (including but not restricted to systemic corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil, dapsone), ~~or~~
- Progressive disease despite the use of the conventional agent.
- Adults 19 years and older.
- Adequate renal function as indicated by serum creatinine levels less than 1.5.

#### 4.2 EXCLUSION CRITERIA

*Participants meeting the following exclusion criteria are not eligible to participate in this study.*

- *Patients with known hypersensitivity to rituximab or any of its components.*

Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were to be initiated.

- *Age less than 19 years of age.*

Those patients with a known anaphylaxis or IgE hypersensitivity to murine proteins or any component of rituximab). (Please refer to package insert)

- *Significant extraocular disease (blisters on the skin, including mucus membranes) requiring systemic therapy (including but not restricted to systemic corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil, dapsone),*

## 5 STUDY INTERVENTION

### 5.1 STUDY INTERVENTION(S) ADMINISTRATION

#### 5.1.1 STUDY INTERVENTION DESCRIPTION

Name of Drug: Rituximab IND Number: 12,890

*This is a research study of an investigational product called Rituximab. Rituximab also called Rituxan® is a monoclonal antibody produced by Genentech, Inc. and IDEC Pharmaceuticals using recombinant DNA technology. Antibodies are proteins that protect the body from foreign attackers, such as bacteria and viruses, by binding to substances called antigens. The purpose of this study is to determine if Rituximab is effective in the treatment of Ocular Cicatricial Pemphigoid. Rituximab also called Rituxan® is a monoclonal antibody (Antibodies are proteins that protect the body from foreign attackers, such as bacteria and viruses, by binding to substances called antigens.) produced by Genentech, Inc. and Biogen IDEC Pharmaceuticals using recombinant DNA technology.*

#### 5.1.2 DOSING AND ADMINISTRATION

The Rituximab dose is 1000mg (1gm) given as an IV infusion every two weeks for 2 doses (days 1 and 15).

## 6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

### 6.1 DISCONTINUATION OF STUDY INTERVENTION

The investigator will assess efficacy, safety, and compliance at each follow-up visit. Safety will be evaluated based on participant-reported adverse events and premature study discontinuations due to study drug-related adverse events.

It is the right and duty of the Investigator to interrupt treatment if the participant's health or well being is threatened by continuation in the study. Such participants should be withdrawn from the study, not continued under a modified study drug regimen. The reason for early discontinuation should be noted on the final case report form with comments as necessary.

At any time the investigator feels that it would be in the best interest of one or more participants at our site to discontinue the study, he will inform them of the new information, and they would be given the opportunity to discontinue or be withdrawn from the study, whichever is appropriate.

### 6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a subject from the study for the following reasons:



- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

### 6.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to be available for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 7 STUDY ASSESSMENTS AND PROCEDURES

### 7.1 STUDY ASSESSMENTS

The investigator and study staff will review all data during the study.

A complete evaluation will be done at the end of the trial. This is an investigator initiated trial. There will be no monitoring done by Genentech/Biogen Idec.

All serious adverse events occurring at UAB, related to this clinical trial, will be reported within one week of notification. Any research related injuries, at the UAB site, in which a death has occurred, will be reported to the IRB within 24-48 hours of notification.

### 7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

#### 7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

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### 7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (of note, the term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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### 7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

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#### 7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious.”

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#### 7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

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#### 7.2.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

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#### 7.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Study Coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

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#### 7.2.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

## 7.3 UNANTICIPATED PROBLEMS

### 7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

## 8 STATISTICAL CONSIDERATIONS

### 8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

3. Number of Participants With no Evidence of Further Scarring
  4. The Proportion of Patients That Experience a Grade 3, Grade 4, or Grade 5 Toxicity Based Reaction on the NCI-CTC System at the Time of Their Infusions and During Follow-up Visits.
- Secondary Efficacy Endpoint(s):
    3. Stability of Visual Acuity (Snellen's Test) at 16 Weeks
    4. Stability of Visual Acuity (Snellen's Test) at 24 Weeks

## 8.2 SAMPLE SIZE DETERMINATION

Recruit 5 participants.

## 9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

### 9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

#### 9.1.1 INFORMED CONSENT PROCESS

The participant will not be in a stressful, painful, or drugged condition during the consent process. The time period between informing the subject and soliciting a decision will be at least 24 hours. Participants will be recruited from the Dermatology Clinics and surrounding clinics of UAB. Participants will be given a copy of the informed consent to review. After they have read the consent form, study staff will review the entire consent form (page by page) with the participant. A witness is present during this procedure.

##### 9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting study screening procedures. A separate screening consent form will not be used.

##### 9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about

it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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### 9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

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### 9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB Department of Otolaryngology research office. This will not include the subject's

contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

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#### 9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

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#### 9.1.5 DATA HANDLING AND RECORD KEEPING

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##### 9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of source document worksheets will be used for recording data for each subject enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

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##### 9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

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#### 9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

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#### 9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.



## 9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

## 10 REFERENCES