# JHM IRB - eForm A – Protocol

**Title:** Benralizumab Effect on Severe Chronic Rhinosinusitis with Eosinophilic Polyposis: A Phase II Randomized Placebo Controlled Trial

## 1. Abstract

Chronic rhinosinusitis (CRS) has a prevalence of more than 10% in the United States and Europe and is associated with several co-morbidities including asthma, acute infection, and obstructive sleep apnea.[1, 2] There are principally two forms of CRS namely with and without nasal polyps. CRS with nasal polyps (CRSwNP) in particular can be a severe and debilitating disease resulting in significant morbidity, complete anosmia, headaches, missed work, and hospitalizations. Not uncommonly, patients require chronic oral corticosteroids, multiple courses of antibiotics, and repeated surgical polypectomies to control their disease. Total health care expenditure for CRS (which includes both with and without polyps) is more than $60 billion annually in the United States accounting for as much as 5% of the total US health care budget.[3, 4] Annual direct and indirect costs to treat CRS in Europe is estimated to be similar to this amount but data is limited.[5]

For CRSwNP patients suffering with severe and recurrent nasal polyps there are few treatment options. High dose topical nasal steroids and repeated surgical procedures do not halt progression in many patients. Allergen immunotherapy is often non-curative in this population. Similarly, due to the fact that CRSwNP is not exclusively an IgE driven process, omalizumab was shown to have mixed benefit in this population.[6, 7] Likewise, omalizumab resulted in no reduction in polyp size among patients with Aspirin Exacerbated Respiratory Disease (AERD).[8]

More typically chronic nasal polyp disease is an eosinophil mediated process. Patients with demonstrated elevations in serum and mucosal esosinophils tend to have more severe disease and higher nasal polyp recurrence rates.[9] Clinical researchers have begun to recognize this connection. A recent Phase II study in Europe showed a reduction in polyp burden using mepolizumab anti-IL5 monoclonal antibody.[10] Benralizumab which targets IL-5 receptor signaling has been shown to have powerful apoptotic effects on eosinophils and may likely prove to be even more efficacious.[11] Because of its unique mechanism of action, benralizumab may have a profound impact on reducing mucosal eosinophils resulting in great benefit to patients suffering with severe nasal polyps refractory to standard treatment.

## 2. Objectives

- To determine the effect of benralizumab on severe nasal polyp tissue in patients requiring high dose oral corticosteroids.
- To determine the effect of benralizumab on symptoms of severe nasal polyps, computed tomography (CT) scan score, eosinophils, and safety.
- Exploratory objective to determine the need for repeat surgical polypectomy.

# 3. Background

Benralizumab has been shown to be efficacious treating severe asthmatics with eosinophilia.[12] The unique mechanism of action of benralizumab targets the IL-5 receptor leading to degradation of signaling and apoptosis.[11] This direct effect on eosinophils leads to reduction of proinflammatory processes in the asthmatic airways among those with elevated eosinophil counts. While many subjects with allergic asthma do indeed have concomitant local and systemic elevations in eosinophils, the primary driver of inflammation in allergic asthmatics is IgE and IL-4. Allergen immunotherapy and anti-IgE therapy (omalizumab) has long been known to be effective in these atopic individuals.[13] However, a significant portion of non-asthmatics respond poorly to these IgE targeted therapies.

In a similar manner, chronic rhinosinusitis with nasal polyps (CRSwNP) is a disease often associated with atopy and propagated by IgE/IL-4 mediated inflammation. However, more than 50% of patients with CRSwNP have no evidence of allergen sensitivity.[14] Nasal and sinus inflammation in these non-atopic individuals is often characterized by IL-5 upregulation, eosinophilia, leukotrienes, and more severe polyps. These individuals tend to have more aggressive disease requiring frequent surgeries, high dose intranasal budesonide irrigation, and oral steroids yet the polyps more often than not are persistent and may return post surgery.[9] In a subset of patients, concomitant aspirin sensitivity can be managed with aspirin desensitization, however this approach is not always effective and can also be cumbersome. A more universal and potentially more efficient approach to treating severe polyps is to target eosinophils directly using a monoclonal antibody. Previous reports have shown some benefit targeting IL-5 ligand itself with mepolizumab[10] but the potential benefit of directly eliminating eosinophils by shutting down cellular signaling with benralizumab would be expected to have a more dramatic effect and needs to be investigated.

For patients currently suffering with chronic severe rhinosinusitis with nasal polyps (CRSwNP) there are limited treatment options. Multiple surgical polypectomies are often supplemented with repeated courses of high dose oral corticosteroids. This leads to a tremendous amount of morbidity, hospitalizations, acute sinus infections and adverse sequelae from chronic steroid use. Many patients with CRSwNP report anosmia so severe that they may not have fully tasted or smelled food in over a decade. Eosinophilia is often so pronounced that subjects are evaluated for clonal hypereosinophilic process, parasitic infections and automimmune disorders. Despite chronic corticosteroid use and dependency, eosinophils may remain elevated. Indeed, high blood and tissue eosinophil counts are associated with disease severity and recurrence rates post surgery.[9,15] In addition, a number of proinflammatory genes that upregulate eosinophil recruitment and survival have been shown to be activated in nasal polyp tissue.[16] Together, these findings highlight the need to target eosinophils directly via the IL-5 receptor.

# 4. Study Procedures

***Procedures***

Fiberoptic rhinoscopy, CT sinus without contrast, skin prick testing and laboratory testing will be performed in the usual manner consistent with standards of care. However, volunteers may not have received the same frequency of investigations if not otherwise enrolled in our study. Subsequently, the results of all investigations may not provide clinically useful information for the subject directly. In addition, subjects will be asked to discontinue regular uses of oral corticosteroids one month prior to and for twenty weeks during treatment. Rescue medication including nasal and oral steroids will be

reintroduced if symptoms become unbearable in a stepwise fashion indicated in the appendix. Clinical surveys will be performed the day of the injection procedure.

Fiberoptic rhinoscopy will be performed using an Olympus flexible video endoscope as per usual standard of care by a blinded physician. Images will be captured using a D-scope digital archival system. Polyps will be scored using the Meltzer polyp grading scale from 0-4. The total combined bilateral score must be at least 5 (of 8 maximum) in order to be enrolled in the study.

Allergen skin prick testing will be performed as per usual standard of care using 30 common aeroallergens, histamine and saline control. Wheal and flare will be measured manually using a ruler and the reaction will also be documented using an automated digital camera for standardization, storage and archival purposes.

Participants and investigators will be blinded as to the active versus placebo treatment. All procedures will be performed in the Johns Hopkins allergy clinic research space. A physician will be present on site at all times.

***Blinding and Randomization***

Randomization will occur by assigning a unique sequential study code to a balanced number of randomly assorted treatment vials. The study codes will be logged to match to each drug vial and kept in a secured locked location. Investigators and participants will be blinded as to which therapy matches to which subject. Only in the event of a serious adverse reaction requiring cessation of treatment will the subject be unblinded.

***Experimental Design and Methods***

Once study subjects are identified and informed consent obtained they will be instructed abstain from taking oral corticosteroids and antihistamines for a period of one month and then return for the first study visit. During the screening visit subjects will receive a CT scan, rhinoscopy, initial bloodwork, physical exam, skin prick testing, smell test, and clinical surveys. Laboratory test will include CBC with differential, basic chemistry, electrolytes, LFTs and total serum IgE as well as other leukocyte inflammatory markers and cellular protein expression. Female subjects will also receive a urine and blood pregnancy screening test at week five before treatment begins. Urine pregnancy test will also be performed at each study visit for woman of child bearing potential. If subjects meet criteria for entry they will be randomized and given their first of four injections (benralizumab or placebo). Each month for two more months, the subject will return to complete clinical surveys, vital signs, review safety/adverse events, and receive another injection. A final injection (number four) will be given 8 weeks later. After five months of therapy a final clinical survey, smell test, CT scan, rhinoscopy and blood test will be repeated. Corticosteroid use will be monitored throughout the study. Subjects with incomplete control of symptoms will be offered a restart of oral corticosteroids at the final visit. 30 days later the subject will be contacted to review safety and adverse events.

When all patients complete the study and the final safety survey is completed, the subjects will be unblinded. The data will be compiled with the assistance of a faculty member from the Johns Hopkins School of Public Health Department of Biostatistics. Figure 1 and Table I illustrates overall study design and the sequence of study events respectively.

**Figure 1**

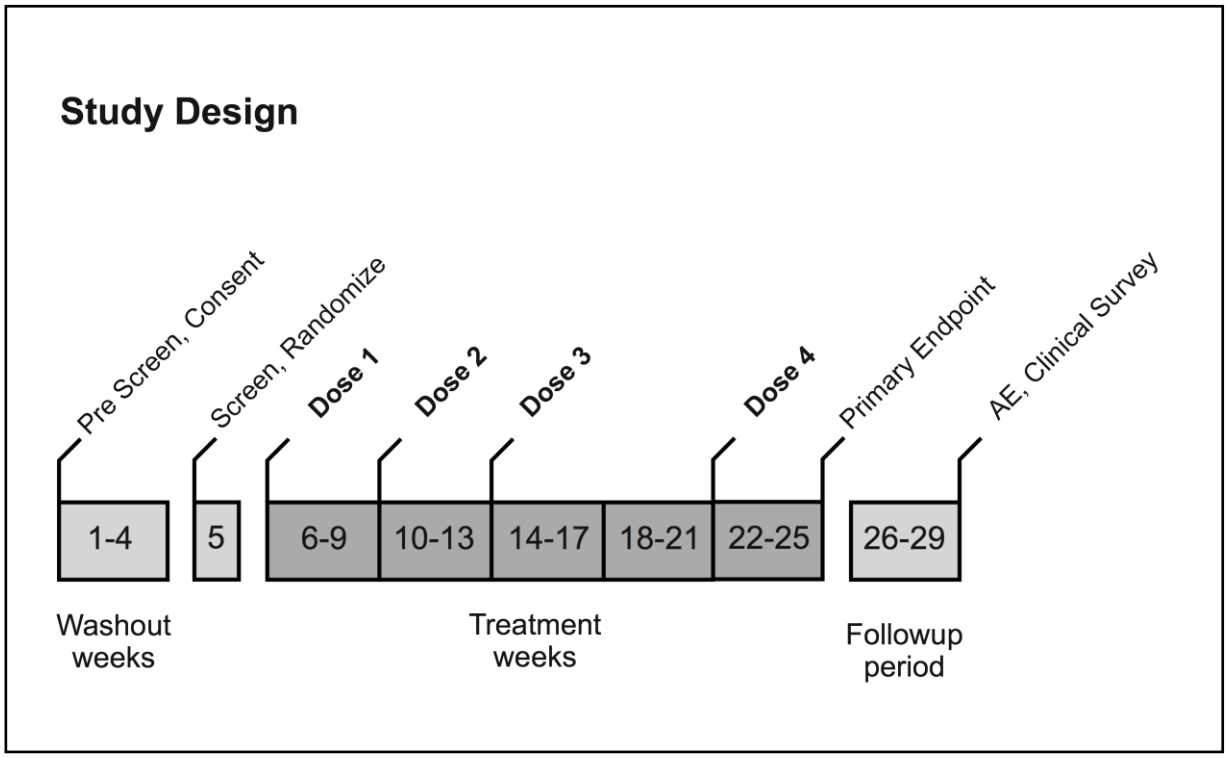


**Table I.** Study Design

| **Study Week:** | **Prescreen** | **Washout (Week 1-4)** | **Screen (Week 5)** | **Treatment (Weeks 622)** | **Final Visit (Week 25)** | **Follow-up (Week 29)** |
|---|---|---|---|---|---|---|
| **Visit Number:** | **1** | **N/A** | **2** | **3-6** | **7** | **N/A** |
| Discussion and Recruitment | X | | | | | |
| Informed consent | X | | | | | |
| Inclusion/exclusion criteria | X | | X | | | |
| Demographics and medical history | X | | X | | | |
| Medication history | X | | X | | | |
| Physical examination | | | X | X | X | |
| Vital signs | | | X | X | X | |
| Weight and height | | | X | X | X | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Concomitant medications | X | | X | X | X | X |
| Concurrent medical conditions | X | | X | X | X | |
| Blood Draw and lab testing | | | X | | X | |
| Serum pregnancy test | | | X | | | |
| Urine Pregnancy test | | | X | X | | |
| Randomization | | | X | | | |
| Administer Drug or Placebo | | | | X | | |
| Clinical Survey, SNOT-22 | | | X | X | X | X |
| UPSIT smell test | | | X | | X | |
| Allergen skin prick test and imaging | | | X | | | |
| Rhinoscopy | | | X | | X | |
| CT Sinus | | | X | | X | |
| Site return compliance | | | X | X | X | |
| Corticosteroid use evaluation | X | X | X | X | X | X |
| PTE (Pre-treatment event) | | X | X | | | |
| AE assessment | X | X | X | X | X | X |

### *Clinical Tools and Polyp Scoring*

Several well-validated clinical tools will be utilized to evaluate the primary and secondary outcomes of the study. Clinical outcomes will be measured primarily by the Sino-Nasal Outcome Test (SNOT-22) and the rescue medication score both attached in the Appendix. Sensation of smell will be evaluated using the University of Pennsylvania Smell Identification Test (UPSIT) which includes 40 common smells imbedded on individual scratch and sniff testing cards. Rhinoscopy will be scored using the grading system proposed by Meltzer et al attached to the appendix.[17] A minimum bilateral total score of 5 is required for entry into the study. For example, a score of 2 on the right side and a score of 3 on the left would qualify. The score will be determined after the four week steroid washout period. CT scan of the sinus performed at screening and at the end of the treatment will be graded using the LundMackay Score (LMS).[18]

### *Demographics, Medical History, and Medication History Procedure*

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the diagnose of nasal polyps, chronic sinusitis, SAR/PAR (i.e., diseases under study) that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions.

### *Physical Examination Procedure*

A baseline physical examination (defined as the assessment prior to first dose of investigational immunotherapy) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first immunotherapy examination.

### *Weight, Height*

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

### *Vital Sign Procedure*

Vital signs will include body temperature, respiratory rate, blood pressure (resting more than 5 minutes), pulse (bpm), and peaked flow (PFR).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

### *Documentation of Concomitant Medications*

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-thecounter medications, and oral herbal preparations, must be recorded in the study Case Report Form (CRF).

### *Documentation of Concurrent Medical Conditions*

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. The investigators will decide upon the significance or nonsignificance of an ongoing clinical condition or laboratory abnormality.

### *Procedures for Clinical Laboratory Samples*

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 10.0 mL, and the approximate total volume of blood for the study is less that 20 mL. Blood will be collected at the screening vist and the final visit. Serum will also be stored for later analysis. Laboratory tests will include CBC with differential, basic chemistry, electrolytes, LFTs and total serum IgE as well as other leukocyte inflammatory markers and cellular protein expression Woman of child bearing years will also obtain blood pregnancy test.

The Johns Hopkins Bayview Medical Center laboratory will perform laboratory tests as indicated above. The investigator or designee is responsible for transcribing or attaching laboratory results to the CRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

***Pregnancy***

Female subjects will receive a urine and blood pregnancy screening test at week five before study treatment begins. Urine pregnancy test will also be performed at each study visit for woman of child bearing potential. If any subject is found to be pregnant during the study she should be withdrawn and study medication should be immediately discontinued. If the pregnancy occurs during administration of active study drug the pregnancy should be reported immediately to the study investigators.

Should the pregnancy occur during or after administration of the study drug the investigator must inform the subject of their right to receive treatment information. Subjects randomized to placebo do not need follow-up.

***Documentation of Screen Failure***

Investigators must account for all subjects who sign an informed consent. If screening factors dictate that the subject is not eligible to continue in the investigation, the investigator should complete the CRF. The primary reason for screen failure is recorded in the CRF.

Subject numbers assigned to subjects who fail screening should not be reused.

***Documentation of Study Randomization***

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the benralizumab versus placebo treatment phase.

***Criteria for Discontinuation or Withdrawal of a Subject***

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the CRF using the following categories. For screen failure subjects, refer to Section on Pretreatment event (PTE) or adverse event (AE).

- The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
- Significant protocol deviation.
- The discovery postrandomization or after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
- Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF. All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.
- Study termination. The IRB or regulatory agency terminates the study.

- Pregnancy. The subject is found to be pregnant.
- The investigator has determined that continued participation would pose an unacceptable risk to the subject.

***Follow-up***

Follow-up will begin the first day after the Final Visit and will continue until for 30 days at which time a telephone follow-up interview (optional in-clinic visit) will be conducted for a safety assessment.

# 5. Inclusion/Exclusion Criteria

***Study Population***

We will recruit both allergic and non-allergic adult individuals aged 18-75 with documented history of severe bilateral nasal polyps defined as an average bilateral endoscopic nasal polyp total score of at least 5, eosinophil count of greater than 300/ul, and requiring at least one prior oral steroid course over the previous twelve months to control symptoms of rhinosinusitis. Potential subjects will also be required to have had at least one prior nasal surgical polypectomy procedure.

**Inclusion Criteria**

- Adults aged 18-75
- Severe bilateral nasal polyps with average endoscopic score of at least 5
- Blood eosinophil count of at least 300/ul at screening
- At least one prior oral steroid course over the previous 12 months to control symptoms
- At least one prior nasal surgical polypectomy
- Informed Consent: Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. Subjects must be able to read, comprehend, and write at a level sufficient to complete study related materials.
- Female subjects: Women of childbearing potential (WOCBP) must use an effective form of birth control (confirmed by the Investigator). Effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective IUD intrauterine device/IUS levonogestrel Intrauterine system, DepoProvera(tm) injections, oral contraceptive, and Evra Patch(tm) or Nuvaring(tm). WOCBP must agree to use effective method of birth control, as defined above, from enrolment, throughout the study duration and within 16 weeks after last dose of IP, and have negative serum pregnancy test result on Visit 0.
- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of visit -1 without an alternative medical cause. The following age-specific requirements apply:
- Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

- Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.
- All male subjects who are sexually active must agree to use an acceptable method of contraception (condom with or without spermicide, vasectomy) from Visit 0 until 16 weeks after their last dose.

A power calculation is displayed below in the section entitled statistical analysis.

***Exclusion criteria***

- Immunosuppression other than oral steroids in the past 3 months
- Allergen immunotherapy build up phase in the past 3 months
- Symptomatic or untreated life threatening cardiopulmonary disorders
- Subjects who are febrile (≥38°C; ≥100.4°F);
- History of cancer: Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable was obtained. Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent, and assent when applicable, was obtained.
- A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to standard of care therapy.
- Pregnant or nursing
- If female and of child-bearing potential, positive pregnancy test or failure to adhere to acceptable method of contraception (with <1% failure rate) during the study and for four months after the study.
- Receipt of any investigational non biologic within 30 days or 5 half-lives prior to visit 0, whichever is longer.
- A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.
- Any other medical illness that precludes study involvement
- Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to be enrolled.
- Patients who are currently receiving or have previously received benralizumab or any other type of anti-interleukin therapy (i.e. mepolizumab, reslizumab, lebrikizumab etc.) within the last 4 months or 5 half-lives whichever is longer.
- History of anaphylaxis to any biologic therapy or vaccine.
- Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained.
- Receipt of live attenuated vaccines within 30 days of starting the study drug.

***Recruitment and Consent***

Subjects will be alerted to our study by noticing a flyer posted in the clinic and/or incidentally by word of mouth from other study participants. Discussion, details and questions about the study will be answered as we are approached. Informed consent will take place in the clinic setting or other similar private room or office.

We will not obtain private health information from subjects prior to joining our study. Subjects will seek our study because they have seen our study flyer posted in the clinic, were alerted to the flyer by physicians, or by word of mouth from other study participants. Patients will be informed about the study by pointing out a posted flyer and/or by attending physician alerting interested parties who to contact regarding details about the study. Patient charts will not be screened before the visit to determine if they fit the study. If patient indicates that he or she would like to be contacted by phone to hear more about the study then a telephone script will be used to communicate with them. Formal consent will be conducted in person with ample time for the study participant to ask any questions, reflect and obtain a copy of the consent form to read at home before hand if desired. All conversations will be conducted in privacy. Study participants will be assigned a random unique numerical identifier that will be stored separately from demographic and/or clinical data.

***Excluded Medications***

- Omalizumab, benralizumab or any other type of anti-interleukin therapy (i.e. mepolizumab, reslizumab, lebrikizumab etc.) within the last 4 months or 5 half-lives whichever is longer
- Receipt of any investigational non biologic within 30 days or 5 half-lives prior to visit 0, whichever is longer.
- Immunosuppressive medications such as methotrexate, azathioprine, cyclosporine, tacrolimus
- Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained.
- High dose aspirin greater than 81mg daily
- Allergen Immunotherapy during build phase during the last three months
- Other medications that could interfere with the action of benralizumab or suppress eosinophils

***Medications to be withdrawn during 30-day washout period***

- Nasal topical steroids such as fluticasone (Flonase), budesonide (Rhinocort), mometasone (Nasonex), triamcinolone (Nasacort) and others
- Topical steroid sinus rinse such as budesonide (Pulmicort Respules)
- Oral corticosteroids such as prednisone methylprednisolone, aldosterone, betamethasone, cortisone, deflazacort, desoxycortone, dexamethasone, fludrocortisone, fluocortolone, trilostane, hydrocortisone, meprednisone, rimexolone paramethasone, prednisolone, triamcinolone
- Oral decongestants such as pseudoephedrine (Sudafed)

***Medications to be withdrawn 14 days prior to screening***

- Oral antihistamines such as cetirizine (Zyrtec), levocetirizine (Xyzal), fexofenadine (Allegra), loratadine (Claritin), diphenhydramine (Benadryl)

Note: If symptoms are not adequately controlled the rescue medications will be added in a stepwise fashion as outlined in the Appendix section entitled Rescue Medication Action Plan.

# 6. Drugs/ Substances/ Devices

Benralizumab and placebo will be supplied in prefilled single dose syringes. 30mg benralizumab or placebo will be administered subcutaneously every 4 weeks for three months and the last dose 8 weeks later at month five as per manufacturer recommendations and protocol. An Investigational New Drug (IND) approval will be needed by the FDA prior to initiating therapy. The IND will be held by the principle investigator. The University of Pennsylvania Smell Identification Test (UPSIT) comprises 40 individual scratch and sniff cards to be used at the first and last treatment visit per manufacturer recommendations. The skin prick test devices and reagents chosen for testing include 32 commonly used aeroallergen extracts available in the US. A skin prick device from a popular manufacturer was selected. Skin test devices and reagents have been FDA approved and will be used with standard manufacturer recommended practices. The individual device, reagents and the associated manufacturers are listed in Table III.

**TABLE III.** Devices and reagents used for the study.

| Item | Manufacturer | Type |
|---|---|---|
| Benralizumab | AstraZeneca | Biologic |
| Multi-Test PC device | Lincoln Diagnostics | Multiple SPT device |
| Histamine | Hollister-Steir | Control Reagent |
| Diluent | Hollister-Steir | Control Reagent |
| Allergens | Hollister-Steir, Greer, ALK | Allergens |
| UPSIT smell test | Sensonics, Inc | Smell test survey |

## Storage of drugs and reagents

Investigational drug and placebo solutions will be refrigerated at 4 degrees celcius and stored in an appropriate, limited-access, secure location until it is used for the investigation or designated for destruction. Storage will comply with the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

# 7. Study Statistics

*Outcome Measures*

**Primary Endpoint**

1. Reduction in endoscopic nasal polyp score after 20 weeks of treatment

**Secondary Endpoints**

2. SNOT-22 nasal symptoms score
3. Lund-Mackay CT scan score
4. Rescue medication use
5. Total Combined SNOT-22 and Rescue Medication Score (TCS)

6. UPSIT smell identification test score
7. Blood eosinophil count
8. Time to nasal polyp surgery
9. Drop out rate
10. Significant Adverse Reactions

*Statistical Analysis*

Based on a prior study using anti-IL5 monoclonal antibody therapy there was an average of 32% reduction in nasal polyp score after 20 weeks of active treatment for an effect size of 0.535 and standard deviation of 1.5. Benralizumab would be expected to have the same or even greater effect on polyp burden. Thus to achieve 80% power (alpha 0.05) using the same effect size, a total sample size of 22 is required (11 per arm). To accommodate for dropout we will randomize 24 total subjects. We expect a total of 32 subjects will sign the consent form (about 6-8 expected screen failures).

The primary outcome measure is a comparison of the average rhinoscopy nasal polyp score among the two groups at the final visit. A two tailed t-test with 0.05 significance will be used to compare mean change in rhinoscopy nasal polyp score, Lund-Mackay CT score, SNOT-22, UPSIT, eosinophil count, and rescue medication use. A Kaplan-Meier or similar product limit estimator function will also be used to calculate the effect of treatment over time. The SNOT-22 and rescue medication score will be combined to yield the Total Combined Score (TCS) as outlined in the Appendix. Consistent with previous studies, subjects who require oral steroid rescue medication may be dropped from the primary outcome measure calculation.[6] All patients who initiate treatment will be included in the TCS calculation.
As an exploratory outcome, the need for repeat polypectomy will be determined at the final study visit. Statistical consultation and support will be provided during and after study completion by the Johns Hopkins University Biostatistics Department.

*Alternatives/Pitfalls*

It is possible that the study drug may not be effective in reducing polyps after 20 weeks of therapy. As this is an initial proof of concept study there are no prior studies for comparison. Nonetheless, previous studies performed with anti-IL5 monoclonal antibody were indeed effective. Since the mechanism of action of benralizumab is more targeted, our expectation is that the study will reach statistical significance.

It is possible that subjects may have difficulty weaning off all nasal and oral steroids for one month and for the duration of treatment. Should this occur, we will wean the patient to the lowest dose tolerated. At each visit medication use will be assessed with rescue medication added if symptoms are not tolerated. The disadvantage of allowing some steroid use during the study is that the eosinophil count will be suppressed somewhat which may attenuate the effect of this secondary outcome. Nonetheless, steroid requirements are an important outcome and will be expected to differ in the treatment group versus placebo. Furthermore, rescue mediation use and symptom scores will be combined to yield the TCS. This outcome measure accounts for the effect of medications that may be added.

Some degree of patient drop off can be expected. There are several ways we plan to deal with this issue. First, we recruit an additional 6 subjects to account for screen failure and 4 (15%) additional subjects to account for drop off. Second, since the treatment is only 20 weeks in duration (four study

visits) we expect most patients to comply. Lastly, reimbursement will be split between the start and completion of the study so that subjects are incentivized to return.

# 8. Risks

***Safety and Confidentiality***

Currently, there is no adequate evidence of an association of benralizumab with any safety risks that could have a significant impact on individual patient or public health. Important potential risks that need to be closely monitored among patients on benralizumab include serious infections, helminth infections, hypersensitivity including anaphylaxis/anaphylactic reactions, and malignancy. Adverse events will be monitored during the screening period, throughout the duration of treatment and for the 30 days afterwards. The most common adverse event associated with SPT is mild discomfort when the device is first placed on the skin, and moderate itch as the reaction develops. The itch usually resolves spontaneously. Testing will be performed at the Johns Hopkins Asthma and Allergy Center. An attending physician will be present at the time of testing and during treatment and 2 hour observation period. Emergency medications such as albuterol, oxygen, diphenhydramine, and at least two epi-pens will be readily available in the treament area.

All adverse events (AEs) will be reported to the PI immediately and will be recorded electronically. Any serious issues, unanticipated problems, or unanticipated reactions will be reported to the IRB. Data will be stored in a secure, private, locked and password protected computer. Subjects will be assigned a unique random numerical study code. Demographic or clinical information will be stored separately from the study data. Only the PI will have access to the password protected information. Data will be analyzed continuously. If any information arises that impacts the safety of the subject or impacts clinical decision-making, the IRB/compliance office and risk management team will be contacted and the subjects will subsequently be notified.

There is no financial risk to the subject associated with the treatment or investigations.

# 9. Benefits

There is no direct benefit to subjects for being in this study. Taking part in this study, may help others in the future.

***Justification for Research***

While there are no direct benefits to the subject, the knowledge gained from the proposed study will help fulfill serious unmet scientific and clinical need. For patients suffering with severe recurrent nasal polyps, currently the only significant treatment options are repeated surgical interventions and/or high dose corticosteroids. The side effects and morbidity associated with these interventions further highlight the need for additional treatment options. Based on our current understanding and the good safety profile of benralizumab, the benefits to the community at large far outweigh the risks to justify the proposed study.

Other biologics such as mepolizumab, and to a lesser extent omalizumab have shown some benefit in this severe nasal polyp population, but the mechanism of action of benralizumab is unique. By targeting the IL-5 receptor directly there may be better efficacy and more convenient dosing options. This needs to be proven.

## 10. Adverse Events and Reporting

### *PTEs Definition*

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

### *AEs Definition*

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

### *Additional Points to Consider for PTEs and AEs* An

untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless

related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, gout, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with the immunotherapy without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the CRF.

***SAEs***

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

- Results in DEATH.
- Is LIFE THREATENING. The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
- Results in persistent or significant DISABILITY/INCAPACITY.
- Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
- Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    a. May require intervention to prevent items 1 through 5 above.
    b. May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    c. Includes any event or synonym described in the Takeda Medically Significant AE List (Table II).

## Table II Medically Significant AE List

| Term | |
|---|---|
| Acute respiratory failure/acute respiratory distress syndrome | Hepatic necrosis |
| Torsade de pointes / ventricular fibrillation / ventricular tachycardia | Acute liver failure |
| Malignant hypertension | Anaphylactic shock |
| Convulsive seizure | Acute renal failure |
| Agranulocytosis | Pulmonary hypertension |
| Aplastic anemia | Pulmonary fibrosis |
| Toxic epidermal necrolysis/Stevens-Johnson syndrome | Confirmed or suspected endotoxin shock |
| | Confirmed or suspected transmission of infectious agent by a medicinal product |
| | Neuroleptic malignant syndrome / malignant hyperthermia |
| | Spontaneous abortion / stillbirth and fetal death |

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner.

### *Severity of PTEs and AEs*

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

### *PTE and AE Collection Period*

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug. Routine collection of AEs will continue for 60 days after the final dose is given.

### *PTE and AE Reporting*

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study immunotherapy or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the CRF, whether or not the investigator concludes that the event is related to the study drug The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study drug (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to the study drug, including the details of the suspected drug administration.

6. Action concerning study drug (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

### *Collection and Reporting of SAEs*

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported to the institutional safety board and the drug manufacturer (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The principal investigator should submit the completed SAE form within 10 days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug.
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the institutional safety board and the drug manufacturer (Astrazeneca) if considered related to study participation. Reporting of Serious PTEs will follow the procedure described for SAEs.

### *Follow-up of SAEs*

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

### *Safety Reporting to the Johns Hopkins IRB and Regulatory Authorities*

The study site investigators, in conjunction with the manufacturer (Astrazeneca), will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to the Hopkins IRB. Relative to the first awareness of the event by/or further provision to Astrazeneca or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 3 business days for fatal and life-threatening events and 10 business days for other serious events, unless otherwise required by Hopkins IRB regulations.

***Safety Reporting to (AstraZeneca)***

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to the AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed or emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page to AstraZeneca by email to AE Mailbox Clinical Trial (TCS) <AEMailboxClinicalTrialTCS@astrazeneca.com> or by fax to 1-302-886-4114 (US Fax number). Email is the preferred method.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events at least on a monthly basis.

# 11. Payment and Remuneration

We will pay subjects up to $400 for the participants time and effort ($50 per visit). Total payment will be prorated based on the number of study visits completed and paid in two lump sums made once the study regimen begins and the rest will be paid at the end of the study. Checks will be mailed to the address provides at the time of the consent. Subjects who sign the consent form but fail screening tests will be paid $100. A parking pass will also be provided for subjects who need this. Payment will be made by mailing a check within one to two weeks.

# 12. Costs

There will be no direct costs to the subject. Nothing will be billed to the subject or the insurer.

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# 13. Appendices

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

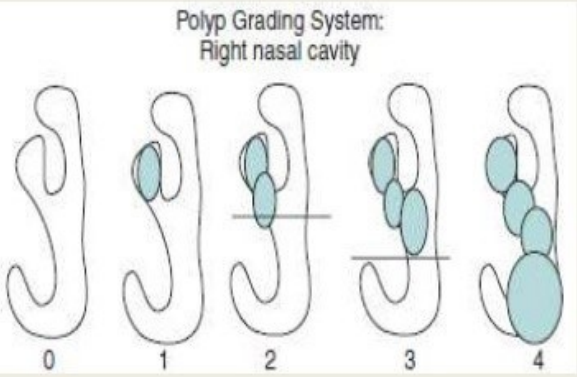
Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

| 1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: → | No Problem | Very Mild Problem | Mild or slight Problem | Moderate Problem | Severe Problem | Problem as bad as it can be | | 5 Most Important Items |
|---|---|---|---|---|---|---|---|---|
| **1. Need to blow nose** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **2. Nasal Blockage** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **3. Sneezing** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **4. Runny nose** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **5. Cough** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **6. Post-nasal discharge** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **7. Thick nasal discharge** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **8. Ear fullness** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **9. Dizziness** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **10. Ear pain** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **11. Facial pain/pressure** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **12. Decreased Sense of Smell/Taste** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **13. Difficulty falling asleep** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **14. Wake up at night** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **15. Lack of a good night's sleep** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **16. Wake up tired** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **17. Fatigue** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **18. Reduced productivity** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **19. Reduced concentration** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **20. Frustrated/restless/irritable** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **21. Sad** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |
| **22. Embarrassed** | **0** | **1** | **2** | **3** | **4** | **5** | | ○ |

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

## Rhinoscopic Grading of Polyps

- Polyp grading system. ( Meltzer et al)




| Endoscopic appearance | Score |
|---|---|
| no visible NP | 0 |
| small amount of polypoid disease confined within the middle meatus | 1 |
| multiple polyps occupying the middle meatus | 2 |
| polyps extending beyond the middle meatus | 3 |
| polyps completely obstructing the nasal cavity | 4 |

## Rescue Medication Action Plan

Ask patient if symptoms are bearable at each visit. The response dictates whether a medication is added or subtracted.

| Symptoms Bearable? | Medication Action |
|---|---|
| no | Add medication |
| yes | Subtract medication |

| Step | Rescue Medication | Score |
|---|---|---|
| A | None | 0 points |
| B | Triamcinolone Two sprays each nostril Daily | 5 points |

| | | |
|---|---|---|
| C | Triamcinolone Two sprays each nostril BID | 10 points |
| D | Triamcinolone Two sprays each nostril BID plus Prednisone 20mg x 5 days | 20 points |

**Note**: To calculate the daily medication score add the total points for all medications noted above. Any other rescue medications inadvertently added will also be counted in a similar manner as follows; other nasal steroids (5 points QD, 10 points BID), other PO steroids (20 points). Symptoms and medication use are recorded at each study visit. The SNOT-22 score and medication score together yield the Total Combined Score (TCS)

**Clinical Visit Summary**

**Subject ID** **Date** **Visit #**
**Initials**

Medications currently taking _____

_____

_____

Today's SNOT-22 Score _____

Baseline SNOT-22 Score _____

Symptoms bearable Y/N

Medication added _____

Medication removed _____

| | | | | | | |
|---|---|---|---|---|---|---|
| Initial Vitals | P | BP | Sats | PFR | Time | Initials |
| Urine Pregnancy Test | | Neg | Pos | N/A | Time | Initials |

Physical Exam _____ Time Initials

_____

_____

_____

Vial ID _____ _____ Time Initials

Exit Vitals P BP Sats PFR Time Initials

Reactions or Other Notes _____

_____

_____