**Randomized Double-Blinded Controlled Trial of Oral Antifungal for the Treatment of Fungal Sensitive Chronic Rhinosinusitis with Nasal Polyps**

**NCT02285283**

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| **Protocol Title:** | Randomized Double-Blinded Controlled Trial of Oral Antifungal for the Treatment of Fungal Sensitive Chronic Rhinosinusitis with Nasal Polyps |
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| **Study Coordinator:** | Faramarz Ashoori, MD, PhD<br>Vivek John, MD |
| **Population:** | Chronic rhinosinusitis patients with nasal polyps (CRSwNP) scheduled for medically indicated sinus surgery between 18 and 75 years of age |
| **Number of Sites:** | Multi-site (UT Houston, UT Southwestern and UT San Antonio) |
| **Study Duration:** | 3 years |
| **Subject Duration:** | 48 weeks |

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**Background and rationale**

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease affecting the paranasal sinuses which results in symptoms of facial pain and pressure, nasal drainage and obstruction, headaches, fatigue and often disturbances in smell and taste plaguing over 40 million Americans annually. These symptoms can negatively influence productivity and is a significant driver of the over $5.8 billion annual direct healthcare cost, making it one of the most costly chronic diseases to manage.

CRS is a syndrome that is grossly classified by the absence (CRSsNP) or presence (CRSwNP) of nasal polyps. This clinical classification is supported by immunologic differences of the diseased sinus mucosa: CRSsNP is characterized by a T helper cell type 1 (Th1) immune profile (predominant presence of neutrophils and increased IFN-$\gamma$ cytokine) while CRSwNP is characterized by a Th2 immune profile (elevated eosinophil presence and increased interleukin (IL-4, IL-5 and IL-13)). Despite sharing a similar immunologic profile, CRSwNP is a common inflammatory presentation for a number of apparently different etiologies including cystic fibrosis, aspirin exacerbated respiratory disease, allergic fungal rhinosinusitis (AFRS), and others not yet classified. There currently remains no objective means of categorizing these various CRSwNP subtypes. Consequently, all CRSwNP patients typically undergo similar non-curative treatment consisting of multiple courses of extended antibiotics and systemic corticosteroids and recurrent sinus surgeries.

Several common fungi (i.e. Aspergillus, Cladosporium, Alternaria and Penicillium species) have been associated with allergic airway diseases including asthma and CRSwNP. However, controversies continue regarding the relevance of fungal culture results from respiratory tract specimens involving a ubiquitous pathogen such as fungi. Randomized controlled trials with oral antifungals are scarce for CRS. In the asthma literature, 3 randomized prospective clinical trials have assessed the efficacy of oral itraconazole, voriconazole, posiconazole and fluconazole in patients with severe asthma with proven

fungal sensitization [1-3]. Significant improvements in both objective measures of lung function and subjective symptoms were recorded in patients receiving oral antifungals relative to patients receiving placebo [1, 3]. In contrast, a systematic review of studies evaluating antifungal therapy in nonspecific CRS patients concluded an overall lack of efficacy with either topical or oral antifungals. Based on our preliminary data, this is not surprising as only 19% of CRSsNP showed positive fungal growth vs 76% of CRSwNP (N=21 and 63, respectively). Despite the fungal presence in the sinuses of some CRSsNP patients, we found no CRSsNP patients with Th2 fungal memory (see Preliminary data). Thus, despite the ubiquitous nature of fungi, we have found that CRSwNP predicts a much higher yield of fungi from surgically acquired sinus cultures and greater presence of fungal Th2 cell memory. But even in the CRSwNP population, there is heterogeneity of evidence for immune memory to fungi. These observations suggest that airway fungi contribute to the pathophysiology of many CRSwNP, but not in CRSsNP. **This proposal aims to test the hypothesis that the addition of oral antifungal may decrease the risk of nasal polyp recurrence after sinus surgery, and provide a novel therapeutic option for fungal-sensitive CRSwNP patients.**

**Objectives**

Chronic rhinosinusitis (CRS) with nasal polyps is a common clinical presentation linking a number of different etiologies and pathophysiologies. Fungus seems to play a role in a portion of patients with CRSwNP, and in these patients, antifungals may be a significant advancement to the current standard treatment. The first challenge is identifying these patients.

In preliminary work on the role of fungi in certain CRSwNP subtypes, we developed a peripheral blood based assay that detects CRSwNP patients who have developed immune memory to fungi suggesting that fungi within their sinuses may be active in the pathophysiology of their sinus inflammation. Oral antifungals have had mixed results in the treatment of non-selected CRS patients, and are more favorable in selected CRSwNP subgroups[4]. However, recent studies only classify CRS subtypes clinically, since an objective assay was not available. **This proposal utilizes our developed ELISpot assay which has a positive predictive value of 100% and a 67% negative predictive value to identify fungal-sensitive CRSwNP subgroup that are most likely to respond to oral antifungal therapy**. **The goal of this proposal is to determine the efficacy of an oral antifungal, itraconazole, on the recurrence of nasal polyps in CRS patients with fungal sensitivity and to identify predictive biomarkers of a positive clinical response**. Towards these goals, the following specific aims are proposed:

**Aim 1.** Determine if adding a 24-week course of oral itraconazole after sinus surgery can prevent recurrence of nasal polyps and improve scores on health assessment questionnaires in CRSwNP patients characterized by fungal IL-4 reactivity and evidence of fungi within diseased sinuses.

Despite sinus surgery, many CRSwNP patients experience recurrence of nasal polyps. There remains no clear consensus of the appropriate post-operative treatment to minimize this recurrence. Approximately 40-70% of CRSwNP patients experience recurrent nasal polyps within 1 year after surgery even with the current post-operative medical management including an extended course of oral steroids, antibiotics and saline irrigations. Using a peripheral blood based ELISpot assay evaluating Th2 cell memory for fungal antigens, we are able to identify CRSwNP patients with fungal sensitivity. **We hypothesize that this CRSwNP subtype will demonstrate positive clinical effects with post-operative itraconazole on nasal polyp recurrence rates and health status assessment**.

**Aim 2**. Determine the effect of post-operative oral itraconazole on gene expression linked to CRS inflammation and to identify genes whose expression may serve as predictive biomarker for positive clinical response to itraconazole by microarray analysis. In preliminary studies, ST2 and other genes were significantly elevated in inflamed sinonasal mucosa from CRSwNP patients as compared to healthy

controls. **We hypothesize that the expression of a number of genes will be affected by treatment of oral itraconazole after sinus surgery and expression of some genes may correlate with a positive clinical response to itraconazole**.

**Study Design**

**AIM 1. Determine if adding a 24-week course of oral itraconazole after sinus surgery can prevent recurrence of nasal polyps and improve scores on health assessment questionnaires in CRSwNP patients characterized by fungal IL-4 reactivity and evidence of fungi within diseased sinuses.**

CRSwNP patients undergoing a medically-indicated sinus surgery are eligible for enrollment (Figure 1). Recruited patients will undergo a blood draw for an *in vitro* ELISpot assay to identify fungal-sensitive CRSwNP patients as determined by positive fungal-induced IL-4 production. Identified fungal sensitive patients will undergo their needed sinus surgery and then randomized into either a placebo or oral itraconazole group. These medications will be added to the usual post-operative saline irrigations and 9 day course of prednisone [5]. Patients will be followed for a total of 48 weeks (24 weeks while on medication and 24 weeks after treatment) with a primary outcome of recurrence of nasal polyps requiring medical intervention. Patients who develop recurrent nasal polyps will be rescued with a prednisone taper.

This study is a **randomized control trial**, in which patients and treating physicians will be blinded, designed to test whether itraconazole after surgery in fungal sensitive, fungal culture positive CRSwNP patients will have decreased rates of nasal polyp recurrence as compared to placebo treated patients (**Figure 1**). The **study population will come from the rhinology practice of the Department of Otorhinolaryngology where 3 rhinologists practice** (Drs. Amber Luong, Martin Citardi, and William Yao) as well as the rhinology practices at UTSW and UTSA. Among the 3 rhinologists of UT Houston, approximately 150 sinus surgeries are scheduled annually involving CRSwNP. Definitions of CRSwNP are based on the criteria outlined by The Rhinosinusitis Initiative[6]. Inclusion and exclusion criteria are listed in Table 1. Up to 500 CRSwNP patients undergoing a medically-indicated sinus surgery over 3-4 years will be screened and recruited to undergo peripheral blood draw that will be used in an in vitro ELISpot assay to identify those that are fungal sensitive. Blood from UTSA and UTSW will be shipped to UT Houston for processing. We anticipate that 80% of those screened patients will meet inclusion criteria allowing us to enroll about 400 CRSwNP patients undergoing sinus surgery. After surgery, patients will be randomized into 1 of 2 groups (1:1 ratio, stratified by presence of asthma): 1) oral itraconazole (200 mg q12 hrs) or 2) placebo for 24 weeks. Patients will be evaluated in the clinic on post-treatment weeks 2 ($\pm$ 1 week), 6 ($\pm$2 weeks), 12 ($\pm$2 weeks), and 24 ($\pm$3 weeks) as per the typical post-operative management protocol (**Figure 2**). Patients will be clinically followed for an additional 24 weeks post-treatment for recurrent nasal polyps. Therefore, patients will be followed for a total of 48 weeks after sinus surgery or until recurrent nasal polyps requiring treatment are noted.

It is current standard practice for all CRS patients to complete validated health assessment questionnaires for CRS (SNOT-22) and undergo recorded nasal endoscopic exams at each clinic visit. All medications and any treatment side effects will be recorded at each clinic visit.

Blood will be drawn on the day of surgery for the ELIspot assay and for a baseline hepatic function. Medication compliance will be assessed by counting remaining pills at each follow-up visit. A small amount of diseased ethmoid tissue at time of surgery and post-treatment (either at time of recurrent nasal polyps or completion of 24 week treatment) will be obtained and analyzed by microarray for subjects enrolled at the UT Houston site. Sinus secretions will be sampled from the ethmoid sinus cavity at time of surgery and at clinic visit when study medication is stopped for subjects enrolled at the UT Houston site.

Study endpoints: The primary efficacy endpoint is recurrence of nasal polyps requiring medical intervention over 48 weeks post-surgery. Nasal endoscopy will evaluate for recurrent nasal polyps and will be scored using a nasal endoscopy scoring system. Intervention for recurrent nasal polyps with prednisone will be determined clinically by the blinded treating physician. The secondary endpoints will be validated health assessment scores (SNOT-22) for CRS, nasal endoscopy scores, and qualitative and quantitative fungal cultures.

The safety endpoints will include possible adverse events associated with itraconazole (e.g., EKG changes shortness of breath, and anaphylactic reactions to itraconazole or intolerable side effects requiring the patient to stop study medication).

Treatment blinding and randomization protocol: Itraconazole tablets (200 mg) will be purchased from the manufacturer. Itraconazole 200 mg tablets will be crushed and compounded into a de-identified capsule; matching placebo capsules containing cellulose which will be prepared with good manufacturing practice (GMP) standard (Avicel; FMC BioPolymer, Philadelphia, PA) by Hope Compounding Pharmacy. Each volunteer will take 1 capsules, corresponding to 200 mg of itraconazole or placebo, twice daily. Patients will be stratified by presence of asthma as determined by history and positive pulmonary function test or methacholine challenge test. A randomization schedule using permuted blocks and stratified by presence/absence of asthma will be prepared using a computer-generated random number sequence. Allocation concealment will be achieved using opaque, sealed, sequentially numbered envelopes which will be held by the research coordinator in a locked filing cabinet. A calculated number of 24 weeks of itraconazole or placebo will be dispensed in prepackaged 30-day supply boxes by the Hope Compounding Pharmacy and distributed by the Research Coordinator.

Itraconazole or placebo will be taken with either orange juice, 8 ounces of cola beverage or full meal to maximize oral absorption. Since prescribed proton pump inhibitors or H2-antagonist can interfere with itraconazole absorption, these medications will be taken midday if needed.

**Figure 1**.

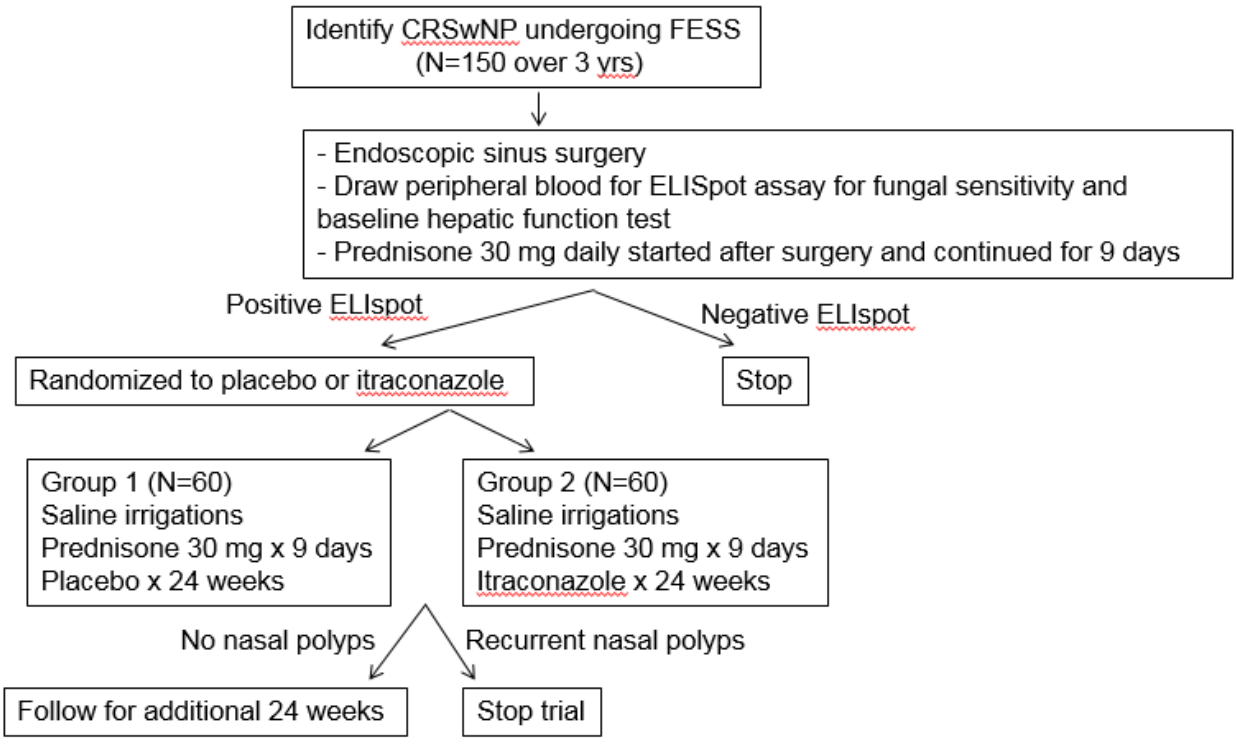
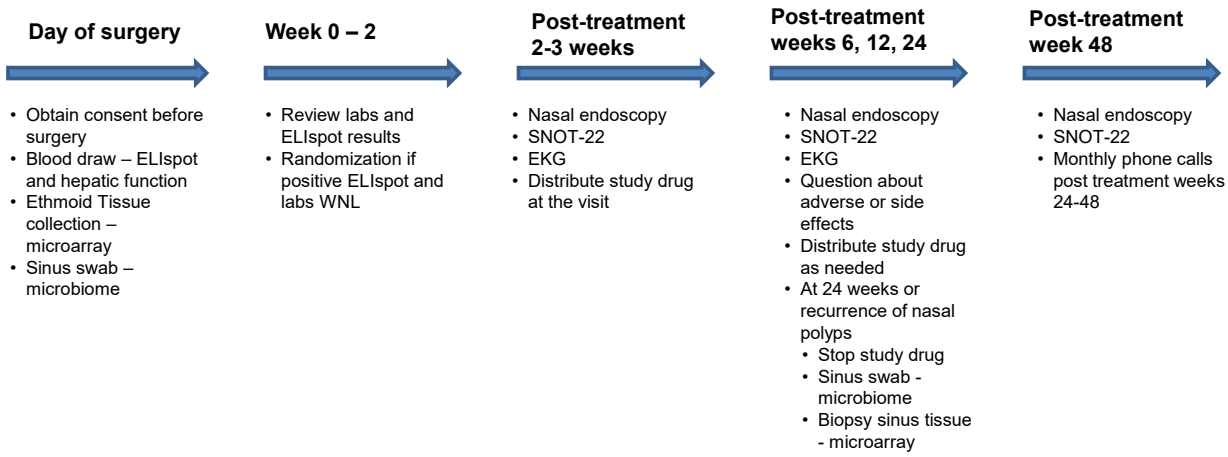


**Figure 2.**




| **TABLE 1** | |
|---|---|
| Inclusion | • 18-75 years old, Sinus symptoms for ≥12 weeks and nasal polyps noted on nasal endoscopy or CT, undergoing medically-indicated sinus surgery for CRS<br>• Nasal polyps noted at time of surgery<br>• Positive ELISpot assay and evidence of fungi within diseased sinus cavities |
| Exclusion | Pregnant, Autoimmune disease, cystic fibrosis, Aspirin exacerbated respiratory disease, chronic disease such as uncontrolled diabetes, cancer or HIV, history of liver or kidney disease that have effects on immune system |

**AIM 2**

**To determine the effect of post-operative oral itraconazole on gene expression linked to CRS inflammation and to identify genes whose expression may serve as predictive biomarker for positive clinical response by microarray.** This analysis will only be performed for subjects enrolled at the UT Houston site.

Diseased ethmoid sinus tissue before and after treatment or at time of recurrent nasal polyps will be analyzed by microarray analysis. Basically, a small amount of diseased ethmoid tissue will be taken at the time of surgery and again at the end of 24 weeks or at time of nasal polyp recurrence. Only a small amount of tissue, approximately 3 mm squared area of tissue is needed to extract the 100 ng of total RNA needed for microarray analysis. The collected tissue will be quick frozen in liquid nitrogen and stored at -80C. Then, RNA will be isolated from the tissue and assessed for quality.

One hundred nanograms of total RNA will be amplified on an ArrayPlex (Beckman Coulter, Inc., Brea,CA) using the Ovation® RNA Amplification System V2 and WB reagent (Nugen, Inc., San Carlos, CA). Of the amplified cDNA, 4.4 µg will be labeled using the FL Ovation™ cDNA Biotin Module V2 (Nugen, Inc.) according to the manufacturer's recommendations. The labeled cDNA will be hybridized onto

Affymetrix human genome HT HG-U133+ PM arrays (Affymetrix, Santa Clara, CA) and processed according to Affymetrix technical protocols.

The data will be expressed as normalized gene expression levels and pictorially can be expressed on a heat map to show up or down regulated genes between patient groups (i.e. patients treated with itraconazole that do not develop recurrence of nasal polyps as compared to placebo treated patients that develop recurrent nasal polyps, etc).

**Study Population**

Recruitment of human subjects

For these studies, CRSwNP patients aged between 18 to 75 years of age scheduled for medically indicated sinus surgery will be recruited from the Otorhinolaryngology clinics associated with UT Houston Medical School, UT Southwestern Medical School and UT San Antonio Medical School. CRSwNP patients meeting inclusion and exclusion criteria who are undergoing clinical evaluation by the investigators will be approached for enrollment into the study (see Table 1).

*Inclusion*: Definitions of CRSwNP are based on the criteria outlined by The Rhinosinusitis Initiative[5]. All CRSwNP patients will have had 2 or more sinonasal symptoms for longer than 12 weeks and nasal endoscopic exam and/or CT imaging results consistent with paranasal sinus inflammation and nasal polyposis.

*Exclusion*: Patients with cystic fibrosis or aspirin exacerbated respiratory disease will be excluded. Pregnant women, patients who have smoked in the last month, subjects with a co-morbid disease that can alter their immune system such as uncontrolled diabetes , cancer, or an immunodeficiency, or subjects with known pulmonary disease other than asthma will be excluded as these conditions may affect the immune system and/or pulmonary physiology. In addition, patients with pre-existing liver, congestive heart failure, known EKG abnormalities, or any disease or allergy preventing patient from taking itraconazole will be excluded.

To screen for ventricular dysfunction, study candidates will be asked about history of orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion with routine activities and changes in exercise tolerance over the previous year.

A baseline EKG and hepatic function panel will be required.

**Study Procedures**

*EKG*

Enrolled patients who respond negative to all screening questions about ventricular dysfunction will undergo a baseline EKG. Only those patients with normal EKGs, no evidence of ST changes or prolonged Q-T interval, will be able to participate in the study. The EKG will be performed before any study medication is dispensed.

A baseline EKG will be required. A follow-up EKG will be performed at each follow up visit.

*Peripheral Blood Draw*

No more than fifty milliliters (about 3 tablespoons) of venous blood will be drawn on any one day. This is a relatively small amount and is not associated with hypovolemia or anemia. For comparison, approximately 500 ml of blood is drawn for blood drives.

The blood on the initial blood draw will be used to isolate peripheral blood mononuclear cells. These cells will be analyzed by an *in vitro* ELISpot assay to determine if patients have memory to a panel of fungal antigens commonly found in diseased sinuses. Those with positive ELISpot assays, meaning evidence of immune memory to common fungal antigens, will be eligible for randomization into either itraconazole or placebo group. Blood collected on the day of surgery will also be used to measure baseline liver enzyme levels. At week 24, an extra vial of no more than 8.5 mL will be drawn to assess inflammatory markers after treatment course.

*Medically-Indicated Endoscopic Sinus Surgery with collection of diseased sinus tissue and sinus swab (for subjects enrolled at the UT Houston site)*

Recruited patients will be CRSwNP patients that are scheduled for medically-indicated sinus surgery. Diseased sinus tissue and nasal polyps are removed as a part of the surgery. A portion of diseased ethmoid tissue will be collected and stored at -80C for later processing.

After initial polypectomy to expose some of the sinus cavity, a swab of the sinus cavity will be collected. This sample will be collected and processed for PCR analysis to quantitate and speciate fungal microbiome. No additional risk to the patient is incurred with either tissue or sinus swab collection.

Randomized into itraconazole versus placebo group

Patients with positive ELISpot assay (indicating fungal immune sensitivity) will be stratified based on asthma and randomized as described above. The Hope Compounding Pharmacy will distribute the appropriate drug to patients in 30-day supply boxed in de-identified pills. The patient randomization list will be kept stored and secured within the Otorhinolaryngology research offices.

Itraconazole is an oral antifungal that can cause adverse reactions. Itraconazole is clinically used routinely for treatment of nail fungus and other fungal diseases. All enrolled patients will be asked about history of congestive heart failure, liver disease, alcohol consumption history, shortness of breath, skin reactions, hearing loss, nerve pain, nausea, vomiting, diarrhea, headaches, chest pain, current medications and any psychological symptoms. In addition, liver function will be measured at baseline before subjects begin their treatment course. With itraconazole, the FDA only recommends routine liver function monitoring in patients with preexisting hepatic function abnormalities. Patients with hepatic disease or elevated liver enzymes at baseline will be excluded from the study.

Monitored post-operative by nasal endoscopy, subjective symptoms, adverse reactions, and collection of ethmoid tissue

As noted in Figure 2, patients will be seen for routine post-operative clinic visits as per typical post-operative standardized care. During these clinic visits, patients routinely undergo review of sinus symptoms, health, medication, and nasal endoscopy and complete health assessment questionnaires. In addition, patients will be asked about any specific adverse events commonly associated with itraconazole as noted above.

For those noted to have recurrent nasal polyps requiring medical intervention, a small biopsy of ethmoid diseased sinonasal polyp mucosa was will be obtained and stored at -80C for microarray analysis.

For those without recurrent nasal polyps, a small biopsy of ethmoid sinonasal mucosa will be obtained and stored at -80C for microarray analysis at post-treatment week 24.

Biopsy of ethmoid sinus tissue (for subjects enrolled at the UT Houston site)
As a part of medically indicated sinus surgery, diseased ethmoid sinonasal tissue is removed and a small amount of this tissue will be collected for microarray analysis. The remainder of the tissue will be sent to pathology per routine.

At the time of nasal polyp recurrence or at post-treatment week 24, a small biopsy of ethmoid sinus tissue will be collected. First the site will be topically anesthesized by spraying the nasal and sinus cavity with 1% lidocaine. This is typically done prior to nasal endoscopy which all CRS patients undergo during routine clinic visit. Then, a lidocaine soaked cotton ball will be applied to the biopsy site which will be the posterior medial wall of maxillary antrostomy, for about 5 minutes. After that elapsed time period, endoscopic thru-cutting instrument will be used to obtain a biopsy of ethmoid sinus tissue, approximately 3 mm squared area. Topical afrin will be applied to biopsy site for hemostasis. The collected tissue will be stored at -80C and processed to extract RNA for microarray analysis.

In addition, a swab of the sinuses will be collected and processed for PCR analysis to quantitate and speciate fungal microbiome after treatment.

**Possible Risks to Subjects**
Specific to this study, there are potential risk associated with peripheral blood draws, itraconazole use and biopsy of ethmoid tissue at end of treatment.

Risk associated with the blood draw
The main risk associated with the phlebotomy includes discomfort by the needle stick. The amount of blood requested, no more than 50 cc at any one draw, is small and is not associated with anemia or hypovolemia.

Risk associated with itraconazole, an oral anti-fungal
Itraconazole is an oral anti-fungal introduced in 1984 that has been utilized in a number of different reported retrospective studies and clinical trials. The FDA has a boxed warning for cardiac effects and drug interactions. From these studies, no serious adverse events were reported with approximately 10% reporting side effects with an incidence no higher than 11% (nausea). Patients experiencing any intolerable side effects may choose to withdraw from the study. Itraconazole is metabolized in the liver and as such patients will be screened for a history of impaired hepatic function.

Patients will be excluded for concomitant use of drugs considered to be contraindicated with the use of Itraconazole. These drugs are:

a. quinidine (such as Cardioquin® , Quinaglute® , Quinidex® ) ·
b. dofetilide (such as Tikosyn™) ·
c. cisapride (such as Propulsid® ) ·
d. pimozide (such as Orap® ) ·
e. methadone (such as Dolophine® ) ·
f. disopyramide (such as Norpace® ) ·
g. dronedarone (such as Multaq® ) ·
h. ranolazine (such as Ranexa® ) ·
i. lovastatin (such as Mevacor® , Advicor® , Altocor™)
j. simvastatin (such as Zocor® )
k. triazolam (such as Halcion® )

l. midazolam (such as Versed® ) ·
m. lurasidone (such as Latuda® ) ·
n. nisoldipine (such as Sular® ) ·
o. felodipine (such as Plendil® ) ·
p. ergot alkaloids (such as Migranal® , Ergonovine, Cafergot® , Methergine® ) ·
q. eplerenone (such as Inspra® ) ·
r. irinotecan (such as Camptosar® ) ·
s. colchicine (such as Colcrys™) [if you also have pre-existing kidney or liver impairment]

Patients will be screened at each study visit for impaired liver function by asking about symptoms of nausea, vomiting, abdominal pain, swelling of the feet or yellowing of the eyes and skin. Baseline hepatic function will be determined via bloodwork and those with elevated levels will be excluded from the study. Cardiac changes will be monitored at each study clinic visit by asking questions specifically about history of orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion with routine activities and changes in exercise tolerance over the treatment course. EKG changes from baseline as defined below will be stopped on study medication.

1) Use a QTc interval of 470 ms (males) and 480 ms (females) as the upper limit of normal.
2) Discontinue the medication if the QTc > 500 or if it increases by more than 60 ms from baseline.
3) Federicia formula to calculate the Qtc (QTc = QT/(RR)1/3) will be used
4) Patients that have a QTc > 470 (male) or > 480 (female) but still < 500, ECG recheck after 4 half-lives (10 days). If the QTc meets any of the exclusion criteria then they are excluded from the study. If the Qtc remains acceptable then recheck at 1 month.

Risk associated with biopsy of ethmoid tissue at end of treatment course

The main risk associated with biopsy of ethmoid tissue performed in clinic is discomfort and bleeding at biopsy site. These risks will be minimized by application of topical anesthetics prior to the biopsy and vasoconstrictor (afrin) after the biopsy is performed.

Risk associated with confidentiality

The research data may need to be reviewed by the IRB and/or sponsor. This may be necessary for internal audits or for review of the raw data prior to publication. In order to maintain confidentiality, patients will be assigned a study ID number which will be used to associate the blood samples and tissue biopsies to the patient. A data sheet correlating the patient's names and date of birth with their study number will be made and stored electronically on Dr. Luong's institutionally-proved computer in a password protected encrypted file. In addition, electronic data sheets will be stored on Dr. Luong's institutionally-proved computer in a password protected encrypted file to minimize this risk of breach of confidentiality.

**Patient Withdrawal from Study**

Patients are free to withdraw from the study at any point in the study. In additions, patients can be withdrawn from the study by investigators if patients do not fulfill inclusion criteria, meet exclusion criteria, develop any complications from administered medications, and/or develop recurrent nasal polyps requiring medical or surgical intervention.

**Data and Safety Monitoring**

A Data Safety Monitoring Board will be established and chaired by Dr. Dat Tran (Pediatric Allergist). In addition, other members of the Board will consist of Dr. Davide Cattano (anesthesiologist and member of IRB) and Dr. Luis Ostrosky-Zeichner (Director of the Laboratory of Mycology Research). This committee will meet at the beginning of the study and regularly throughout the duration of the clinical trial to oversee the progress of the trial including any adverse events and to ensure patient safety. Any adverse events occurring during the duration of the study will be recorded on the patient's data sheets. If the adverse event such as bleeding is controlled, the subject will be offered the opportunity to continue or discontinue involvement in the study. They will be promptly reported to the CPHS according to the established protocol. Again, subjects may opt to discontinue involvement of the study at any time. The CPHS will be updated to the progress of the study per established protocol**.**

If at any time >5% of the study population experiences a serious adverse reaction, the study will be stopped until the Data Safety Monitoring Board has time to convene and discuss the event and safety of the trial.

Given minimal adverse events with study drug and additional documentation from other larger clinical trials using oral itraconazole, the protocol was changed and approved such that hepatic function only needed to be checked at the beginning of the trial and monitored via symptoms and cardiac function was monitored with EKG and symptoms. As such, the DSMB with outside expertise on possible itraconazole adverse events seemed unnecessary. In its place, Drs. Yao, Citardi and Luong meet monthly to review all active trials and research projects associated with the rhinology group. At this meeting, any adverse events or irregularities with the trial will be reviewed and documented.

**Statistics**

Power analysis

This is a pilot study focused on estimating a range of plausible treatment effects. We anticipate enrolling **500 patients over a 3-4 year period** with an anticipated 15% dropout rate. A total of 340 subjects should be available for final analyses. However, we also performed a power analysis should the number of possible patients be as low as 120 patients over the 3 years with similar 15% drop rate for possible N=102. Although the goal of this study is to estimate an unbiased treatment effect, we calculated power (Table 2) to detect a range of effect sizes (as reported in the literature) assuming a two-sided test with alpha of 0.05 and N=320 and 102. The study would have adequate power to detect a large effect size. The planned complementary Bayesian analyses will provide probabilities of clinically important treatment benefits to guide the conduct of future trials.

**Table 2**

| Recurrence Rates | | Power | Power |
|---|---|---|---|
| Placebo | Treatment | N=320 | N=102 |
| 50% | 20% | 1.00 | 0.86 |
| 50% | 25% | 0.99 | 0.68 |
| 50% | 30% | 0.93 | 0.46 |
| 50% | 35% | 0.61 | 0.26 |

**Ethics**

IRB approval is being sought from CPHS.

Potential subjects will be recruited from the Otorhinolaryngology clinics associated with UT Houston Medical School, UT Southwestern Medical School and UT San Antonio Medical School. CRSwNP patients meeting inclusion and exclusion criteria who are undergoing clinical evaluation by investigators will be approached for enrollment into the study.

One of the above co-investigators will review the study and consent form with identified potential subject. The subject will have an opportunity to ask questions and review the forms in private. If he/she consents to the study, the consent form will be signed. The patient will be given the option to review the paperwork at home and enroll in the study at a later time.

**Data handling and record keeping**

In order to maintain confidentiality, patients will be assigned a study ID number which will be used to associate collected tissue samples to the patient. Therefore, samples can be processed with any linked identifiers. A data sheet correlating the patient's names and date of birth with their study number will be made and stored electronically on Dr. Luong's institutionally-proved computer in a password protected encrypted file.

Datasheets containing collected various data points for the study will be stored in individual binders for each patient in a locked cabinet drawer in the Department of Otorhinolaryngology. Electronic data sheets which will allow for data analysis will be stored on Dr. Luong's institutionally-proved computer in a password protected encrypted file to minimize this risk of breach of confidentiality. Access to these data sheets in which patient identifiers are linked to study ID number will be limited to Drs. Luong, Citardi and Yao who also serve as treating physicians. However, other collaborators on this study will only have access to de-identified data.

**Quality control and assurance**

This study is supported by KL2 funding. The mentoring committee consisting of Drs. Citardi, Wetsel, Corry and Kao will meet regularly throughout the duration of this study to review the progress of the study and review the collected data. In addition, data analysis will be assisted by Drs. Pedroza, Assassi, and Russell. So, quality control and assurance will be maintained by having the study and its data scrutinized by various people.

All datasheets will be kept by Dr. Amber Luong and reviewed by at least one of the other 2 co-investigators to ensure accuracy in the recording of clinical data.

**Publication Plan**

This study has been funded by the Center for Clinical and Translational Sciences KL2 Grant. Results from this study will be submitted for oral presentation to national meetings such as the American Academy of Allergy, Asthma and Immonology or American Rhinologic Society. It is anticipated several publications will emerge from this study, one focused on the outcomes of the clinical trial and others on the microarray analyses.

Patients will have access to the results of their clinical work up, but will not be given data on specific in vitro studies. All enrolled subjects will be notified of any publication resulting from this study, but these publications will present data on only the aggregate group.

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