American Lung Association
Airways Clinical Research Centers

Trial of Roflumilast in Asthma Management (TRIM)

Protocol

Version 1.8

NCT #03532490

Supported by NIH grants: R34 HL135361

10 July 2020

Contents

1. Introduction

1.1. Background

Obesity is a risk factor for the development of asthma (approximately 250,000 cases per year of asthma in the U.S. are related to obesity).[1] These patients have poorly controlled asthma (with a nearly 5-fold risk of hospitalization) and do not respond as well to conventional controller therapy as lean asthmatics.[2-6] Obesity particularly affects minority populations:[7] non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). This is thought to account in part for the disparities of asthma in minority populations; there is a pressing public health need to develop interventions specifically for obese asthmatics.

One medication that might be particularly useful for the treatment of asthma in obesity is roflumilast, a medication currently used in the treatment of chronic obstructive pulmonary disease. Data in clinical trials support efficacy of this medication in the treatment of asthma,[8] though it has never been approved for treating asthma in the general population, likely because of concern about side-effects; but these "side-effects" may actually contribute to efficacy in the treatment of asthma in obesity.

Roflumilast has efficacy in mouse-models of asthma and obesity: roflumilast reduced airway remodeling and reactivity in a non-allergic mouse model of obese asthma, and also airway reactivity, inflammation and remodeling in an allergic mouse model of obese asthma.[9] These effects are likely related both to direct effects on inflammatory cells and cells resident in the airway, and also to the beneficial metabolic effects of roflumilast. Roflumilast has significant beneficial incretin-like metabolic effects in patients with the metabolic syndrome,[10] and so might be helpful to mitigate the metabolic dysfunction associated with asthma in obese patients.[11] In addition, roflumilast promotes weight loss, especially in the obese,[12-15] and significant weight loss may improve asthma control in obesity. These direct effects of roflumilast in the airway, and "side-effects" on metabolism and weight loss, make this medication a particularly exciting candidate to treat asthma in obese patients.

1.2. Primary objective

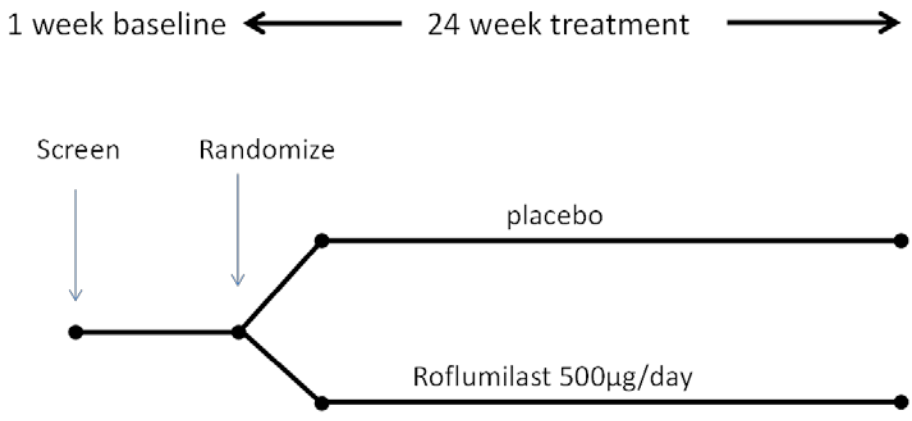
The primary objective of this proposal is to perform a pilot placebo controlled trial of roflumilast for the treatment of poorly controlled obese asthmatics in select centers of the ALA-ACRC to determine the effectiveness and tolerability of our intervention in obese asthma.

The current proposal comprises a pilot randomized, placebo-controlled trial of roflumilast in obese patients with poorly controlled asthma in five centers of the American Lung Association-Airways Clinical Research Centers (ALA-ACRC).

The results of this trial will lay the groundwork for a definitive multicenter clinical trial of roflumilast for the treatment of poorly controlled asthma in obese patients. If ultimately successful roflumilast would represent a new treatment for obese patients with asthma, a patient population refractory to current therapies that represents the majority of poorly controlled asthmatics in the United States.

1.3. Study design

A 24 week, randomized, double-masked, placebo controlled trial in 38 participants.



V1	V2	V3	V4	V5	V6	V7
wk-1	wk0	wk2	wk6	wk12	wk18	wk24

2. Methods

2.1. Eligibility criteria

2.1.1. Inclusion criteria

- Physician diagnosis of asthma and on regular prescribed controller therapy for at least 3 months
- Previous (within five years) evidence of at least a 12% increase in FEV_1 after inhaling 2-4 puffs of albuterol or a positive methacholine challenge or patient reported history of improvement of asthma exacerbation after a course of systemic or inhaled corticosteroids.
- Age: ≥18 years of age
- Obese: BMI > 30 kg/m^2
- Poorly controlled asthma: Asthma Control Test Score < 20, or use of rescue inhaler, on an average of> 2 uses/week for preceding month, or nocturnal asthma awakening, on an average of 1 or more times / week in preceding month, or ED/hospital visit or prednisone course for asthma in past six months.
- Ability and willingness to provide informed consent

2.1.2. Exclusion criteria

- Participation in an investigational study within the past 4 weeks
- Physician diagnosis of chronic obstructive pulmonary disease
- Any condition that puts the participant at risk from weight loss as judged by the site physician
- Liver cirrhosis
- Major psychiatric disorders such as generalized anxiety disorder, major depressive disorder, history of suicidal ideation/ attempt, panic disorder, post-traumatic stress disorder, schizophrenia, schizoaffective, substance abuse or other disorders that in the opinion of the study physician that would affect study participation
- > 0 time use of illicit drugs in the past 12 months
- > 0 time use of cannabis in the past 12 months
- Uncontrolled depression as defined by a score of 15 or greater on the depression questions of the PHQ-9
- Suicidal ideation (a score of greater than 0 on Question 9 on the PHQ-9)
- Uncontrolled anxiety as defined by a score of 10 or greater on the anxiety questions of the GAD-7
- Pregnancy/lactation
- Females of childbearing age who do not agree to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for the duration of the study.
- Greater than 20 pack year smoking history, or smoking within the last 6 months.
- History of bariatric surgery
- Drugs metabolized by cytochrome P450 (rifampicin, phenobarbital, carbamazepine, phenytoin, erythromycin, ketoconazole, cimetidine, fluvoxamine, enoxacin, oral contraceptives containing ethinyl estradiol with gestodene).
- Currently on roflumilast or theophylline (patient may wash out of these medications for 4 weeks prior to visit 1).
- Intention to move out of area within the next 6 months

2.2. Rationale for study duration

We base the duration of the study on the likely time needed to induce weight loss, as well as to improve metabolic control.[8,10,16] We anticipate that this will be the duration of the definitive clinical trial, and so it will be important to ascertain the feasibility of a trial of this duration in our patient population of interest.

2.3. Rationale for dose of active drug

We base the dose of active drug on the dose that is FDA approved for use in COPD in this country, and has also shown efficacy in the treatment of asthma[8] and metabolic disorders:[10] this will be 500 µg, once per day. For the first two weeks we will treat with 500 µg every other day to increase tolerability of the medication.

2.4. Rationale for the seven centers

Collaborating sites: Northwestern University Feinberg School of Medicine, Mount Sinai Icahn School of Medicine, Duke University, University of Arizona, University of Alabama Lung Health Center, University of Illinois – Chicago, and the University of Vermont. Johns Hopkins University will be the Data Coordinating Center (DCC) for the trial.

We will perform this study in seven centers that have a strong record of recruitment and working together as part of the ALA-ACRC, and that represent diverse populations within the network. We will need to recruit 5-6 patients per site within an approximate 12 month period to complete all procedures and study analysis within the time-frame of this proposal, and this is a reasonable recruitment target for these centers. These centers represent diverse patient population, and so if successful, this will likely predict success in the multi-center trial. Many of these centers have established research programs on obesity in asthma.

2.5. Background asthma care

Participants will be treated in accordance with asthma guidelines and best practices using materials that have been already developed by the ALA-ACRC. This includes a written asthma action plan based on peak flow, and instruction on inhaler technique and avoidance of asthma triggers. All participants will be prescribed controller medication that includes medium dose inhaled corticosteroids and additional add-on treatments as needed. Participants who have a regular asthma care provider will continue to receive care from that source. If not, they will be referred to an asthma care provider associated with the study site. All participants will be provided with an asthma action plan, but we will not provide routine asthma care.

2.6. Randomization and drug distribution

Participants will be randomly assigned with an equal allocation to receive either active treatment or matching placebo for 6 months. The treatment assignment will be double-masked, neither the participant nor the clinical center investigators will be informed of the treatment group. Randomization will be accomplished with an auditable, documented generation scheme that produces a reproducible order of assignment, this schema will be generated by the DCC. Randomization will be stratified by center and age and each clinical center randomization schedule will be based on randomly permuted blocks of varying size to ensure appropriate balance between the treatment groups within a center.

Drug bottles will be shipped to the centers from Temple University. These bottles will be identified by a number to maintain masking of the study site. Upon randomization, the site will be advised of the bottle number to issue a particular participant.

2.7. Source of study medication

We will purchase drug, and arrange for matching active drug and placebo through Temple University Research Pharmacy. Drug will be distributed from Temple University to the individual sites. DCC will instruct Temple University on the set of bottle numbers to dispense.

2.8. Randomization and blinding

Treatment assignments will be stratified by clinic and the allocation ratio will be (1:1). Randomization will be accomplished by keying eligibility data into the data system; after verification of eligibility, a treatment assignment number corresponding to unique study kit will be assigned. Study kits will be labeled with two-part tear-off labels with unique identifiers. The tear-off label is affixed to a study form when the kit is assigned to a participant and the information is keyed into data system to verify that assigned treatment was given to the participant.

2.9. Procedures

Sites conducting remote follow up visits must use a secure (password protected) zoom link or other secure online communication method. Participants who are followed up remotely, will complete some questionnaires over the phone and mail back the rest of the questionnaires to the site.

Outline of Study Visits							
Week	-1	0	2	6	12	18	24
Visit number	V1	V2	V3	V4	V5	V6	V7
Consent	•						
Baseline/interim history	•	•	•	•	•	•	•
Randomization		•					
Pill distribution†		•		•	•		
Pill distribution‡		•			•		
Review of paper/electronic diary cards		•	•	•	•	•	•
Pill Counts			•	•	•	•	•
Asthma Control	•	•	•	•	•	•	•
Anxiety/depression questionnaires	•	•	•	•	•	•	•
GSRS	•	•	•	•	•	•	•
QOL	•	•	•	•	•	•	•
Anthropometrics	•	•	•	•	•	•	•
Fasting Blood draw¥		•					•
Pregnancy test*	•	•	•	•	•	•	•
End of study questionnaire							•

† if dose frequency is every day since V3
‡ if dose frequency is every other day since V3
¥ conduct blood draw only if site permits it
*for women of child-bearing potential and participating in remote follow up participants will be mailed testing kit, and asked to send photo of result to coordinator

- Participants will be trained on how to perform peak expiratory flow at the study visit and sent home with asthma action plan.
- Asthma paper/electronic diary cards will be completed by participants throughout the study to record daily morning peak expiratory flow (PEF), daily asthma symptom scores, beta-agonist use, nocturnal asthma awakenings, and health care use.[17,18] Diary data are used to identify episodes of poor asthma control and days with no asthma symptoms (asthma-free days).
- The Asthma Control Test (ACT) is a 4-week recall questionnaire that measures asthma control.[19]
- The Marks Asthma Quality of Life Questionnaire (Marks AQLQ) assesses asthma specific quality of life.[20]
- The Asthma Symptom Utility Index (ASUI) is a 2-week utility-weighted asthma symptom questionnaire.[21]
- GI side effects will be assessed with the Gastrointestinal Symptom Rating Scale. This is a 15-item instrument with five subscales (reflux, diarrhea, constipation, abdominal pain and indigestion) that was originally developed to assess the symptoms associated with the most common GI disorders, and has previously been used to assess tolerability of medications. The five subscales of the questionnaire produce a mean score ranging from 1 (no discomfort) to 7 (very severe discomfort).[22]
- Medical Outcomes Study (SF36) is a measure of general health related quality of life which correlates with asthma outcomes.[23,24]

- The Patient Health Questionnaire for Depression and Anxiety (PHQ9 and GAD7) will be used. The Patient Health Questionnaire is a diagnostic tool for mental health disorders used by health care professionals that is quick and easy for patients to complete. We have used this questionnaire in prior ALA-ACRC studies, and so the centers are familiar with its use. We will use sections specific to mood (PHQ-9) and anxiety (GAD-7). The PHQ-9, a tool specific to depression, scores each of the 9 DSM-IV criteria based on the mood module from the original PRIME-MD. The GAD-7 was subsequently developed as a brief scale for anxiety and scores seven common anxiety symptoms.[25,26]
- Anthropometrics will include blood pressure, height and weight, and waist and hip circumference per NHANES III.[27] Digital scales will be given to participants at visit 2 to take home to measure weight. Participants will be asked to send a photo of the weight shown on the scale along with their feet to the coordinator.
- Adverse effects will be assessed by open-ended questions at each visit and rated in severity.
- Interval health history will be recorded at each clinic visit. Records of all hospitalizations and, if necessary, deaths are obtained for verification of diagnoses and assessment of safety issues.
- Baseline questionnaires and exam will be administered to ascertain demographics including self-reported ethnicity and race, general health, co-morbid conditions, asthma symptoms, and medication use.
- Assessment of Adherence: adherence will be assessed from pill counts when participant returns pills at each study visit after randomization. If only remote visits are permitted, then pill count will be completed when participant mails back drug bottles at the end of the study.
- Exit questionnaires will be administered at the last visit to determine global assessments of treatment, adequacy of informed consent procedures, satisfaction with study procedures and personnel, and opinions about the intervention.
- Blood specimens will be collected for fasting blood glucose and analysis of metabolic and oxidative markers related to asthma if a site permits this. Excess blood specimens will be used for future asthma research with the patient's consent. Fasting blood draw may take place within 7 days of rest of the procedures scheduled for visit 2 or visit 7.

2.10. Rationale for outcome measurements

Our outcome measures are all well validated clinical outcomes for use in studies of asthma, and validated questionnaires for assessing likely side effects. We are including a number of feasibility outcomes that will inform the decision to proceed with a definitive multi-center clinical trial: these include assessment of recruitment and retention, adherence and non-compliance (from pill counts, diary cards, missed visits) and side-effects (from GSRS, PHQ-9 and GAD-7). Participants with scores on the PHQ-9 or GAD-7 that reach the thresholds for exclusion outlined in the eligibility criteria will be discontinued from study drug, the site specific plan for caring for these participants will be instituted, and they will be followed for the rest of the study off of study drug.

Baseline medical and asthma control questionnaires will take 20-30 minutes to complete, will be completed at the Medical Office Building, in a private office. Questionnaires are in paper format, and will be completed by the participant.

2.11. Modifications due to COVID-19 pandemic

Due to the COVID-19 public health emergency, TRIM, will permit remote follow up of enrolled participants as of April, 6, 2020. Participants enrolled after re-opening of the study should be seen at in-person visit for V2 (randomization visit) and V7 (24 weeks), other visits can be conducted in-part or fully remotely. It is possible that research activities will face restrictions in the future or that a participant will prefer to do the V4-V6 remotely, so we will provide participants with a scale and tape measure to collect data for remote visits. All questionnaires can be conducted remotely prior to in-person visits for all visits. Participants who are followed up remotely, will complete some questionnaires over the phone and mail back the rest of the questionnaires to the site. Methacholine challenge tests and spirometry should not be conducted. Women of child-bearing potential and participating in remote follow up will be mailed testing kit, and asked to send photo of result to coordinator

3. Data analysis

The appropriateness of the human, technological and systems components of the data acquisition and management procedures will be analyzed including practicality of data acquisition, estimation of likely participant characteristic and outcome distributions, suitability and functionality of paper and electronic forms, and resources required for participants contact and follow up, and to anticipate rates for missing data.

3.1. Primary analysis

The primary statistical analysis will be an unadjusted comparison of 24-wk change in ACT between treatment groups. A linear mixed effects model will be used to model the change in ACT over time. A saturated means model, including indicators for each time point, treatment and treatment by time interaction, will be specified and a random effect for individual will be used to account for the repeated measurements over time. The 24-week treatment by time interaction term represents the difference in change in ACT between the treatment groups, i.e. the primary outcome. If the data are non-normal, then transformations and non-parametric alternatives (e.g. Wilcoxon Rank-Sum test comparing the raw differences from baseline to 24-weeks between treatment groups) will be explored. If imbalances in influential baseline variables are present, then secondary analyses using appropriate stratification or adjustments will be done. Sensitivity analyses using alternate mean and covariance structures will also be performed. Analyses will be done based upon principles of intention to treat, i.e. all data from all randomized participants will be included in the analysis.

Secondary analyses will focus on the effects of additional covariates including age, gender, site, BMI >40, baseline ACT score, and adherence with treatment. These models will build on primary analysis described above. Potentials risk factors will be added as a main effect to reduce variability and interaction effect to identify potential subgroup effects. Analyses using adherence measures will be performed to explore dose-response relationships.

3.2. Secondary outcomes

Secondary outcomes include ASUI, mAQLQ, and GSRS scores, lung function, weight loss and adverse events. Continuous outcomes, scores and lung function, will be analyzed similarly to the primary outcome. Event outcomes will be analyzed in two ways: negative binomial regression to estimate rates and Kaplan-Meier curves and Cox proportional hazard models for time-to-first event.

3.3. Sample size

The sample size for this pilot is based on the confidence interval approach recommended by Cocks and Torgerson for pilot clinical trials.[29] For the definitive trial, the planned sample size is 190 (95 participants on active drug, 95 on placebo), to provide 90% power to detect a difference of 2.8 in the changes in ACT score from baseline to 24 weeks for the roflumilast versus placebo, with a type 1 error rate of 5%, and a standard deviation (SD) of 5. The SD is based on prior data from studies by our research network, and previous publications.[30,31] A pilot study of 28 to 34 participants provides 90% one-sided confidence limit to exclude a clinical important effect in a definitive trial if we see no effect in the pilot study, and so could inform the decision as to whether to proceed to the full definitive trial. We will inflate this to 38 participants to allow for possible loss to follow up.

Table: Recommended pilot sample size for continuous outcome measures*

Standardized effect size for main trial	Pilot Sample size (90% level)	Upper 90% one-sided confidence limit
0.5	28	0.4844
0.45	34	0.4397
0.4	42	0.3955
0.35	54	0.3488
0.3	74	0.298

* Adapted from Cocks & Torgerson (2013)[29]

3.4. Data confidentiality

Data which includes identifiable personal health information (PHI) are collected at each of the clinical sites. PHI is stored at each of the clinical sites in accordance with HIPAA regulations and local university and hospital policies. This includes the storage of PHI in locked cabinets or rooms, limited access to secure data areas by certified participating study personnel, password protection for electronic medical records, and explanation of HIPAA regulations on the study consent form. Data such as lung function or laboratory tests that are collected as part of this study may be transmitted to the participants treating physicians with the consent of the participant. Participants are informed in the consent that PHI may also be disclosed for auditing purposes by the FDA or other regulatory bodies and is subject to subpoena.

Information transmitted to the coordinating center is identified by an anonymous study ID, and other identifying information such as birthdate, visit dates, and study site is removed from limited use datasets. Source records that are transmitted to the coordinating center for data quality audits have identifying information redacted.

4. Human subjects

4.1. Risks of Individual Procedures

4.1.1. Roflumilast

Roflumilast will be provided to 19 subjects for 24 weeks at the 7 centers. While roflumilast has been approved for use in patients with COPD, the label includes warnings about psychiatric events (including suicidality), weight loss, and drug interactions. The psychiatric adverse reactions included insomnia, anxiety and depression (rate of psychiatric adverse reactions was 2.6% higher in roflumilast group than placebo). Instances of suicidal ideation and behavior, including completed suicides, were observed in clinical trials and in the post-marketing surveillance of the drug, in individuals with and without any prior history of depression. Of note, the safety data for roflumilast were based on 4438 patients between the ages of 40-91 years, 73% of whom were male and 92.9% were Caucasian. Given these limitations (in comparison to the planned trial in patients with asthma), the safety risks are taken from a pooled analysis of asthma patients receiving the 500 mcg dose of roflumilast to be used in the current trial (n=1567; Chervinsky, P et al Pulmonary Pharmacology and Therapeutics 2015 (35):S28-34). (This asthma population was 42.2% male, 80.2% white, and had a mean BMI of 27.47 as well as including 96.7 % of subjects between the ages of 12-65 years. Treatment duration varied between 4-24 weeks.) In these studies of patients with asthma, the risks that occurred with more than 5 events per 100 patient years follow up in excess of the control group included:

Excess incidence rate of adverse events for roflumilast compared to placebo by System Organ Class (SOC)*:

- Gastrointestinal disorders (61.7 cases per 100 patient years)
    - Diarrhea (21.0 cases per 100 patient years)
    - Nausea (24.0 cases per 100 patient years)
- Psychiatric disorders (7.1 cases per 100 patient years)
    - Insomnia (6.0 cases per 100 patient year)
- Nervous system disorders (33.7 cases per 100 patient years)
    - Headache (20.8 cases per 100 patient year)
    - Dizziness (6.2 cases per 100 patient years)
- Musculoskeletal and connective tissue (19.8 cases per 100 patient years)
- Infections and infestations (19.2 cases per 100 patient years)

*Includes SOCs and the associated preferred terms for events with an excess of >5.0 cases per 100 patient years for the difference between roflumilast and placebo where 95% confidence interval does not include 0.

Anticipated % patients experiencing an event compared to placebo if treated for 24 weeks with roflumilast 500 mcg per day (based on data above):

- diarrhea (9.7%)
- nausea (11.1%)
- insomnia (2.8%)
- headache (9.6%)
- dizziness (2.9%)

The psychiatric risks of roflumilast treatment are mitigated through the monitoring and management of symptoms as described below.

Weight loss is considered to be an advantageous outcome in the population being studied*. If a participant loses ≥ 10% of baseline weight during the course of the trial, this will be discussed with the study physician (preferably the study PI) as soon as possible*.

The GSRS will be used primarily to monitor GI side-effects, if a participant scores ≥ 6 on any item (indicative of severe or very severe discomfort), this will be discussed with the study doctor immediately, and the study PI as soon as possible.

The potential for drug interactions with roflumilast is mitigated through excluding participants on medications known to interact with roflumilast. We will exclude participants with uncontrolled anxiety and depression, and suicidal ideation, and screen for these at every visit, we will discontinue the patient from drug treatment if they develop these symptoms (threshold as defined in eligibility criteria). Plans for dealing with elevated symptoms of depression, anxiety and self-harm are outlined below.

4.1.2. Venipuncture

The main risk of this is bruising and minor discomfort. We may find elevated fasting blood glucose, which requires clinical follow up. Our plan is as follows:
< 100: no action
100-125: notify participant and PCP within 3 months
126-199: notify participant and PCP within 5 working days
200-299: notify participant and PCP within 24 hours
≥ 300: contact participant immediately, and advise to go to PCP/ ED/ urgent care

4.2. Handling elevated symptoms: Depression, anxiety, and self-harm

This proposed plan will be subject to DSMB review.

We will ask all patients if they have a mental health care provider at the beginning of the study.

The questionnaires used in this study include questions regarding the participant's health - both physical and mental. If a participant is experiencing a mental health crisis, we will provide them with additional support and referrals as needed. Information provided will include the following:-

- The National Strategy for Suicide Prevention, 1-800-273-TALK (8255) 24 hour hotline
- Howard Center 300 Flynn Ave. Burlington, VT 802-488-6400 local Crisis 24 hour hotline
- Seneca Center 1 South Prospect, St Burlington VT 802-847-3333
- Northeastern Family Institute 30 Airport Rd. South Burlington VT 802-657-8890
- UVMMC Psychiatry: 111 Colchester Ave. Burlington VT 802-847-4727

In addition, each site will identify a psychiatrist or licensed psychologist to be available to discuss any issues related to depression/anxiety with the PI.

4.2.1. Protocol for participant with elevated depression and anxiety symptoms

The PHQ-9/ GAD-7 captures the presence and severity of depression and anxiety symptoms. Scores above the specified thresholds suggest a clinically significant level of psychological distress. It does not necessarily mean that the participant has a clinical diagnosis of depression or anxiety but may indicate the need for appropriate care**. Study personnel will be instructed to tabulate and review the scores for these instruments before the participant is released from the study visit.**

Participants with scores on the PHQ-9 or GAD-7 (including those being screened for the eligibility who do not qualify for the study) that reach or exceed the thresholds for exclusion outlined in the study eligibility criteria will be discontinued from study drug under the supervision of the site PI (if on study drug), and the site PI will ensure that the site specific plan for managing these participants is instituted. Participants already randomized into the study will continue to be followed for the rest of the study off of study drug (unless they decide to withdraw). Subsequent scores exceeding the threshold score, or the minimally clinically important difference for the questionnaires when compared to Visit 2 (≥ 5) will be considered an adverse event, and, as such, followed until resolution or a plan for care under the supervision of another medical provider is established. This will be considered an adverse event, and, as such, followed until resolution or a plan for care under the supervision of another medical provider is established. Participants will be informed that the elevated score could be related to the study drug, though investigators and subjects will not be unblinded to treatment assignment.

4.2.1.1. Elevated depression scores

Elevated depression scores are defined as:

- Total score of 15 or greater on the depression questions of the PHQ-9 or an increase of 5 points or more from score at Visit 2.

If depression score is elevated, we will tell the participant the following:

- "*It seems that you are "down" or somewhat distressed. I would like to give you a few names and numbers of people in the community you can contact for assistance.*" OR "*Your score is a bit high. Are you feeling "down" or upset? Would you like to have some names and numbers to contact for help?*"
- Offer patient the mental health resource information
- We will follow up with participants who have elevated depression by phone within 7 days to check on follow up with mental health care resources, or mail them a letter with resources if we are unable to reach them by phone.

4.2.1.2. Elevated anxiety scores

Elevated anxiety scores are defined as:

- Total score of 10 or greater on the anxiety questions of the GAD-7 or an increase of 5 points or more from score at Visit 2.

If anxiety score is elevated, we will tell the participant the following:

- "*It seems that your anxiety may be causing you a lot of stress. I would like to give you a few names and numbers of people in the community you can contact for assistance.*" OR "*Your score is a bit high. Are you feeling anxious or 'on edge' a lot? Would you like to have some names and numbers to contact for help?*"
- Offer patient the mental health resource information
- We will follow up with participants who have elevated anxiety scores by phone within 7 days to check on follow up with mental health care resources, or mail them a letter with resources if we are unable to reach them by phone.

4.2.2. Protocol for participants exhibiting potential for self-harm

If a participant discloses that they may do harm to themselves, we will follow up with the participant and report to PI. This will be indicated with a score of greater than 0 on Question 9 on the PHQ-9. We will then administer the Suicidality Severity Screener (SSW form), adapted from the Columbia-Suicide Severity Rating Scale (C-SSRS), by Posner, K., et al, and used in prior ALA-ACRC studies.

We will proceed as follows

Suicidal Severity Screener

You mentioned on some of the questions that you have thought about killing yourself. Tell me about those thoughts.

1. Have you been thinking about how you might kill yourself?
   YES /NO
2. Have you had these thoughts and had some intention of acting on them?
   YES /NO
3. Have you started to work out or worked out the details of how to kill yourself?
   YES/ NO
4. Do you intend to carry out any plans you have?
   YES/ NO
5. Do you have a current mental health provider?
   If yes- when is your next appointment?

Risk will be determined as outlined below:

Mild Risk

If participant answers NO to questions 1, 2, 3, AND 4 of the SSW:

- Notify PI
- Provide resource guide, including suicide hotline number, with statement: "*It sounds like currently you have some thoughts about suicide but do not plan to go through with it. If you notice the thoughts become more frequent, or you want to talk with someone, please call this number.*"
- If they have a provider, make sure there is an upcoming appointment scheduled to talk about their concerns. If they do not have a provider, indicate possible providers on resource sheet.
- Complete an adverse Event Report (UE) form documenting the outcome of this questionnaire and subsequent action taken.
- Contact the participant by phone 7 days after visit to confirm they are receiving follow up care. Update AE form with results of phone call.
- A letter will be mailed with resources if we are unable to reach them by phone, and this will be discussed with the study physician

Moderate Risk

If participant answers YES to questions 1 or 2 but not to questions 3 or 4 of the SSW:

- Notify study physician immediately
- Provide resource guide, including suicide hotline number, with statement: "*It sounds like currently you have some thoughts about suicide but do not plan to go through with it. If you notice the thoughts become more frequent, or you want to talk with someone, please call this number.*"
- If they have a provider, make sure there is an upcoming appointment scheduled to talk about their concerns. If they do not have a provider, staff should strongly encourage them to contact the suicide hotline and/or one of the local providers listed to schedule a follow up call or appointment.
- Staff should encourage participants to contact the hotline or schedule an appointment before concluding the study visit.
- Complete an Adverse Event Report (AE) form documenting the outcome of the questionnaire and subsequent action taken.
- Contact the participant by phone 7 days after visit to confirm they are receiving follow up care. Update AE form with results of phone call.
- A letter will be mailed with resources if we are unable to reach them by phone, and this will be discussed with the study physician

Immediate Risk

If participant answers YES to questions 3 or 4 of the SSW:

- Notify study physician immediately
- Instruct participant to call PCP, 911, or appropriate crisis number and give participant resource guide highlighting 24-hr help lines.
    - If participant does not call for assistance, let them know you are obligated to report this to emergency services; walk participant to ER or call 911
- If concerned there is an immediate risk, walk the participant to the ER or call 911
- Complete a Serious Adverse Event Report (SR) form documenting the outcome of this questionnaire and subsequent action taken.
- Contact the participant by phone 7 days after visit to confirm they are receiving follow up care. Update SR form with results of phone call.

If unsure about the patient's risk, contact a study physician (preferably the PI) to notify them immediately and discuss action to take.

If patient is contacted and it is determined that they are not receiving follow up care/ it is not possible to reach the patient, contact the study physician immediately, who will contact their site's psychiatrist or licensed psychologist to discuss appropriate next steps.

FOR ALL SUICIDALITY RISK ASSESSMENTS:

Speak with a study doctor immediately and the study PI as soon as possible.

Assessment of Insomnia: sleep difficulties will be assessed by response to PHQ9 questions #3, if a participant scores > 2 this will be discussed with the study physician (preferably the study PI) as soon as possible.

4.3. Management of GI side effects

If a participant loses ≥ 10% of baseline weight during the course of the trial, this will be discussed with the study physician (preferably the study PI) as soon as possible.

The GSRS will be used primarily to monitor GI side-effects, if a participant scores ≥ 6 on any item (indicative of severe or very severe discomfort), this will be discussed with the study doctor immediately, and the study PI as soon as possible.

4.4. Potential benefits of the proposed research to human subjects and others

Patients assigned to either treatment group will benefit from asthma education and attention to their asthma care program. Moreover, some participants in research studies report that they enjoy participation because they have the opportunity to assist in the development of new knowledge that may be helpful to others and that the relationship with the research staff is rewarding. If this study shows that participants assigned to roflumilast experience improved asthma control, this might lead to a specific therapy to treat asthma in obese patients.

4.4.1. Importance of the knowledge to be gained

If this study shows that participants assigned to roflumilast experience improved asthma control, this might lead to a specific therapy to treat asthma in obese patients. This patient population currently suffers with poor asthma control, and do not respond as well to standard therapies, so this would be a very important finding.

4.4.2. Financial considerations

At the University of Vermont, participants will receive a stipend of $50 per visit, for a total of $350 for completion of the study.

We will also reimburse for mileage at standard UVM rates if participants pick up/drop off study supplies.

5. Data safety monitoring plan

- Significant changes or amendments to the protocol or consent form will be submitted to the DSMB, and included in the DSMB reports.
- We will follow the ALA ACRC annual reporting requirements for management of conflict of interest.
- There are no plans for interim data analysis for this pilot study.
- The American Lung Association appoints a DSMB to oversee trials conducted by the ACRC. The primary responsibility of the DSMB is to protect participants but may also have recommendations regarding the scientific conduct of the study to optimize the risk-benefit ratio for participants. The DSMB is typically composed of a pulmonary specialist, an ethicist, a statistician, a patient representative, and specific content experts, in this case a psychiatrist. Typically, the DSMB would have an initial meeting to review and approve the protocol, and then meet every six months or more frequently to review the progress of the trial. The investigators present the DSMB study performance data including screening and enrollment data, and measures of data quality and timeliness. Safety data will include reporting of adverse events, protocol deviations, and unexpected or unusual events that may affect the safety or scientific validity of the study.
- Dr. Wise of the DCC at Johns Hopkins serves as the medical monitor for the research group and reviews all serious adverse event or unusual event reports to determine whether any immediate local or study-wide actions are indicated. Interim serious adverse events or adverse events related to study procedures are transmitted to the DSMB by the DCC with concurrent notification of the clinical site IRBs and, if appropriate, NIH.
- At the end of each DSMB meeting, the board will vote whether to continue the study as planned or whether to recommend changes to the study. The DSMB may recommend that the study be stopped early if there is evidence that the risk-benefit ratio does not warrant continuation of the trial.

5.1. Composition of the DSMB

We will use the ALA-ACRC standing DSMB, and in addition a psychiatrist and patient representative.

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5.2. Adverse events and unanticipated problem reporting

The PI will submit a completed serious adverse event report to the DCC and the IRB, and then the DCC will report to the NIH, FDA and Chair of the DSMB within 7 calendar days after initial receipt of information pertaining to any potentially life-threatening (grade 4) unexpected, suspected serious adverse reactions.

The PI will submit a completed serious adverse event report to the DCC and the IRB, and then the DCC will report to the NIH, FDA and Chair of the DSMB within 15 calendar days after initial receipt of information pertaining to any non-fatal, non-life-threatening unexpected, suspected serious adverse.

Unanticipated Problems that are not SAE'S will be reported to the NIH, FDA and DSMB within 14 days of the investigator becoming aware of the problem.

All unanticipated problems will be reported to OHRP and external IRB's within 30 days of the IRB's receipt of the report of the UP from the investigator.

A summary of all adverse events will be reported to the DSMB, NIH, FDA and IRB at least annually.

6. Drug

- Roflumilast (Daliresp®), 500 mcg tablets, will be obtained from a commercial vendor, and supplied to Temple University Research Pharmacy. Temple will also supply matching placebo.
- Temple will provide bottles with a 6 week supply of study drug or placebo. This will be shipped to the study sites.
- Storage and stability
- Capsules will be stored at room temperature (20-25^{o}C), excursions permitted to 15-30^{o}C, per labeling standards for this medication.
- Administration: oral administration

6.1. FDA considerations

This medication is FDA approved for the treatment of recurrent exacerbations of COPD. It has not been approved for the treatment of asthma. This study has been deemed exempt from requiring an IND by the FDA.

7. Special populations

7.1. Inclusion of women

Both women and men will be enrolled in these studies. Asthma is more prevalent among female adults, and so we anticipate a slight majority of participants will be women.

7.2. Women of childbearing potential

Women of childbearing potential have been included, but women of childbearing age who do not agree to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for the duration of the study will be excluded.

Pregnant women will not be enrolled in the trial, as the safety of roflumilast in pregnancy is not known. Women of child-bearing potential will be required to use adequate contraception, and undergo a pregnancy test at every visit in SA1. Any pregnancy that might occur would be followed to term if patient consents.

7.3. Inclusion of minorities

We anticipate minority enrollment will reflect prior enrollment in ALA-ACRC studies, with approximately 50% Caucasian, 40% African American, and 15% Hispanic in the study overall. We anticipate that minority enrollment at UVM will reflect the demographics of Vermont.

7.4. Inclusion of children

We will not include children as the phenotype of asthma in obese children is likely to be different that in obese adults.

7.5. Vulnerable populations

None

8. References

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9. Appendix

A. Changes log

Protocol section	Version 1.6	Version 1.7	Version 1.8
2.1.1. Inclusion criteria	Physician diagnosis of asthma on regular prescribed controller therapy for at least 3 months Current or previous (within five years) evidence of at least a 12% increase in FEV1 after inhaling 2-4 puffs of albuterol or a positive methacholine challenge test	Same as Version 1.6	Physician diagnosis of asthma and on regular prescribed controller therapy for at least 3 months Previous (within five years) evidence of at least a 12% increase in FEV1 after inhaling 2-4 puffs of albuterol or a positive methacholine challenge or patient reported history of patient reported improvement of asthma exacerbation after a course of systemic or inhaled corticosteroids
2.4.	2.4. Rationale for the five centers Collaborating sites: Northwestern University Feinberg School of Medicine, Mount Sinai Icahn School of Medicine, Duke University, University of Arizona, and the University of Vermont. Johns Hopkins University will be the Data Coordinating Center (DCC) for the trial. We will perform this study in five centers that have a strong record of recruitment and working together as part of the ALA-ACRC, and that represent diverse populations within the network. We will need to recruit 7-8 patients per site within an approximate 12 month period to complete all procedures and study analysis within the time-frame of this proposal, and this is a reasonable recruitment target for these centers.	2.4. Rationale for the seven centers Collaborating sites: Northwestern University Feinberg School of Medicine, Mount Sinai Icahn School of Medicine, Duke University, University of Arizona, University of Alabama Lung Health Center, University of Illinois – Chicago, and the University of Vermont. Johns Hopkins University will be the Data Coordinating Center (DCC) for the trial. We will perform this study in seven centers that have a strong record of recruitment and working together as part of the ALA-ACRC, and that represent diverse populations within the network. We will need to recruit 5-6 patients per site within an approximate 12 month period to complete all procedures and study analysis within the time-frame of this proposal, and this is a reasonable recruitment target for these centers.	Same as Version 1.7

Protocol section	Version 1.6	Version 1.7	Version 1.8
2.9. Procedures	a. All procedures will be performed exclusively for study purposes b. Old randomization/drug distribution with in-person visits c. Only paper diary cards d. Spirometry and methacholine tests for in-person visits e. Pregnancy testing in clinic f. Peak flow given and demonstrated in clinic at V1 g. Only paper completion of asthma diaries h. Blood pressure not listed i. No scales given j. Medicine adherence at each clinic visit after V2 k. Blood draw not optional	Same as Version 1.6	a. Sites conducting remote follow up visits must use a secure (password protected) zoom link or other secure online communication method. Participants who are followed up remotely, will complete some questionnaires over the phone and mail back the rest of the questionnaires to the site. b. Clarified when randomization/drug distribution will occur c. Added review of paper or electronic diary cards to study visit table d. Removed spirometry and methacholine challenge tests from study visit table e. Clarified new procedure for pregnancy testing f. Added when peak expiratory flow will be trained g. Asthma diaries can be completed on paper or electronically h. Added blood pressure to anthropometrics. i. Digital scales will be given to eligible participants at visit 2 to take home to measure weight. Participants will send photo of weight along with feet on scale. j. Modified when medicine adherence will be assessed k. Clarified that blood draw is optional

Protocol section	Version 1.6	Version 1.7	Version 1.8
2.11. Modifications due to COVID-19 pandemic	Section not there	Same as Version 1.6	New section
4.1. Risks of individual procedures	4.1.1. Pulmonary function testing, 4.1.2. Methacholine challenge, 4.1.3. Bronchodilator all present	Same as Version 1.6	Old 4.1.1., 4.1.2., and 4.1.3. removed 4.1.1. Roflumilast 4.1.2. Venipuncture No more section 4.1.3.
4.4.2. Financial considerations	We will also reimburse for mileage at standard UVM rates.	Same as Version 1.6	We will also reimburse for mileage at standard UVM rates if participants pick up/drop off study supplies.
5.1. Composition of DSMB	Vernon Chinchili, Donald Tashkin, Paul Lanken, Frederic Wamboldt, Tricia Williams	Same as Version 1.6	Vernon Chinchili, James Donohue, Paul Lanken, Cristine Oropez, Jess Fiedorowicz