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Losartan Effects on Emphysema Progression (LEEP)

Protocol

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Abstract

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States. Despite advances in pharmacotherapy targeting relief of airflow obstruction, no therapy except for smoking cessation has been shown to slow disease progression. Evaluation of treatments that modify the progression of emphysema have been limited by the requirement for large numbers of participants and extended follow-up to establish efficacy by effects on lung function or mortality. This trial is testing a treatment that may modify the progression of COPD by using losartan, an angiotensin receptor blocker. Preliminary evidence in humans and animals suggests that this drug is effective in blocking key pathways thought to be important in the genesis of COPD.

Losartan is used as an antihypertensive agent, but is also widely used to alter cardiac remodeling after myocardial infarction and renovascular remodeling in diabetes mellitus. Losartan inhibits the effect of TGF-beta on the lung, inhibits apoptosis, and has anti-oxidant properties; all of these modes of action may be effective in altering the pathogenic mechanisms that promote progression of COPD. Currently, losartan is being tested as a disease-modifying agent in Marfan's syndrome, a genetic disorder associated with an increased risk of emphysema; we postulate that it may also be effective in typical smoking-induced emphysema as well. In particular, we want to evaluate whether losartan treatment modifies the structural progression of COPD, particularly emphysema, and whether this is reflected in improved clinical outcomes.

This is a placebo-controlled, randomized clinical trial with a 48-week follow-up. Two hundred and twenty people with COPD and Computed Tomography evidence of emphysema will be assigned to losartan 100 mg daily or placebo. The primary outcomes will be an intermediate end-point reflecting anatomic lung remodeling, i.e. quantitative measures of emphysema by High Resolution Computed Tomography (HRCT). Secondary outcomes that are clinically relevant will include measures of lung function, respiratory symptoms and quality of life.

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1. Introduction

1.1. Title

Losartan Effects on Emphysema Progression (LEEP)

1.2. Sponsor and support

Funded and sponsored by the National Heart, Lung, and Blood Institute (NHLBI) under the Pulmonary Trials Cooperative (PTC).

Organization of the Pulmonary Trials Cooperative (PTC).
The organizational structure of the PTC is outlined in the RFA-HL-15-015 and RFA-HL-15-016 which outlines the responsibilities of each of the components. In brief, an Operations Committee (OC) oversees the organization of the cooperative which consists of a Network Management Organization (NEMO) and multiple Protocol Leadership Groups (PLG). The PLGs (one of which is the LEEP trial) will provide clinical and data coordination for each of the trials while the NEMO is charged with organization, communications, monitoring, quality control, and distribution of capitation payments and study drug.

1.3. Investigators and study centers

Network Chair

David Center	Boston University

PLG – Principal Investigators

Robert Wise	Johns Hopkins University
Janet Holbrook	Johns Hopkins University

Computed Tomography Analysis Core

Robert Brown	Johns Hopkins University

Participating Centers
To be determined by the NEMO of the PTC

1.4. Background and significance

COPD is a heterogeneous disease that is associated with increasing morbidity and mortality in the United States[1]. Current treatments for COPD consist mainly of bronchodilators and anti-inflammatory agents, which are used for treatment of symptoms and prevention of exacerbations. Although smoking cessation slows the progression of the disease[2] [3], there are no pharmacologic agents that clearly modify disease progression. Angiotensin receptor blockers (ARBs) are potential agents to modify the progression of COPD. In a retrospective database study, Mancini found that ARB-treated COPD patients had reduced mortality and COPD

hospitalization regardless of cardiovascular risk factors[4 5]. Andreas and colleagues tested whether 4 months of irbesartan treatment would increase skeletal muscle strength in 30 patients with COPD. Although there was no effect on peripheral or respiratory muscle strength, the FEV_1/FVC ratio increased ($p = 0.07$), and the TLC ($p < 0.001$) and RV ($p<0.08$) decreased in the irbesartan group compared to placebo[6]. There is evidence that these observations reflect direct biological effects of ARBs on the lung beyond the anti-hypertensive effect for which they are clinically indicated. Angiotensin 1 (AT1) receptors are expressed in lung tissue and are involved in apoptosis of alveolar epithelial cells[7 8] which is theorized to be an essential component of emphysema progression[9]. There is evidence that the lung remodeling effects of AT1 receptor activation is mediated by Transforming Growth Factor Beta (TGFb) signaling. Fibrillin-deficient mice exhibit emphysema which is caused by excessive signaling by TGFb, and can be prevented or reversed by the ARB losartan[10 11]. Podowski and Neptune also found that cigarette-smoke exposed mice develop TGFb mediated emphysema that can be inhibited or reversed by losartan[12]. We conducted a placebo-controlled proof of concept study in COPD patients that showed that losartan was well-tolerated and was associated with lack of progression of emphysema in the subgroup of patients who had High Resolution Computed Tomography (HRCT) evidence of emphysema at baseline ($p = 0.06$). Therefore, there is a need to conduct a definitive clinical trial of losartan to determine whether re-purposing this well-tolerated and widely available drug can modify disease progression in COPD patients with emphysema.

Emphysema as a COPD subtype and outcome measure for clinical trials

The widespread adoption of quantitative HRCT scans in clinical research has established emphysema as an important sub-type of COPD that correlates with severity of airflow limitation, symptoms, and longitudinal decline in lung function[13 14 15 16 17 18 19]. It is reasonable, therefore, to target such patients for treatments that modify disease progression, and to use emphysema progression as a primary outcome measure in clinical trials.

Traditionally, the accepted metric for progression of COPD has been FEV_1 decline. However clinical trials that evaluate this measure require 4,000 – 5,000 patients over 4-5 years[20 21 22]. Because of its greater precision, quantitative HRCT measures of lung density have been proposed as a primary outcome for progression of emphysema and has been estimated to be 2.5 times more sensitive for change than pulmonary function[23]. In support of this, investigators were able to demonstrate significant benefit for alpha-1 anti-protease replacement with a pooled study of only 119 patients, and were able to rule out the benefit of retinoic acid therapy in a trial of 260 patients over 1 year[24 25 26].

Although quantitative HRCT has been considered an expensive and technologically complex measure for clinical trials, recent advances in technology have made this a highly tractable research tool. The use of multi-detector scanners with reduced scanning times, increased computer storage capacity and processing speed, use of preset scanning parameters, and commercially available computer-assisted analysis programs have reduced the cost and complexity of HRCT. Therefore, quantitative HRCT is now a mature, cost-effective, and clinically relevant outcome measure for community-based multicenter clinical trials.

2. Study design

This is a pragmatic, randomized, blinded placebo-controlled multi-site clinical trial that will enroll 220 patients with emphysema to receive either losartan or placebo for 48 weeks.

2.1. Hypotheses

Administration of losartan at 100 mg/day for 48 weeks will decrease the rate of progression of emphysema as measured by quantitative HRCT compared to placebo.

2.2. Study aims

- To measure the effect of losartan on HRCT-measured emphysema progression at 48 weeks
- To measure the effect of losartan on lung function (spirometry and HRCT-measured lung volumes)
- To explore sub-groups of interest for heterogeneity of treatment effects
- To determine the safety and tolerability of losartan in emphysema patients

2.3. Trial design /Schema

The trial is a parallel, randomized, placebo-controlled trial with two treatment groups, losartan at 100 mg/day and placebo. Participants will be randomly assigned in equal allocation to one of two treatments. The treatment period is 48 weeks with follow-up visits at 12-week intervals. Participants assigned to losartan will start with a dose of 50 mg/day; participants assigned to placebo will start with one capsule per day. A titration visit will be done at 2 weeks; if the systolic BP is >90 mm Hg and the diastolic BP is >60 mm Hg, the drug dose will be increased to 100 mg per day or matching placebo will be increased to two capsules per day. Symptoms, lung function, and specimens are collected at baseline and select follow-up visits. HRCT will be done at baseline and 48 weeks.

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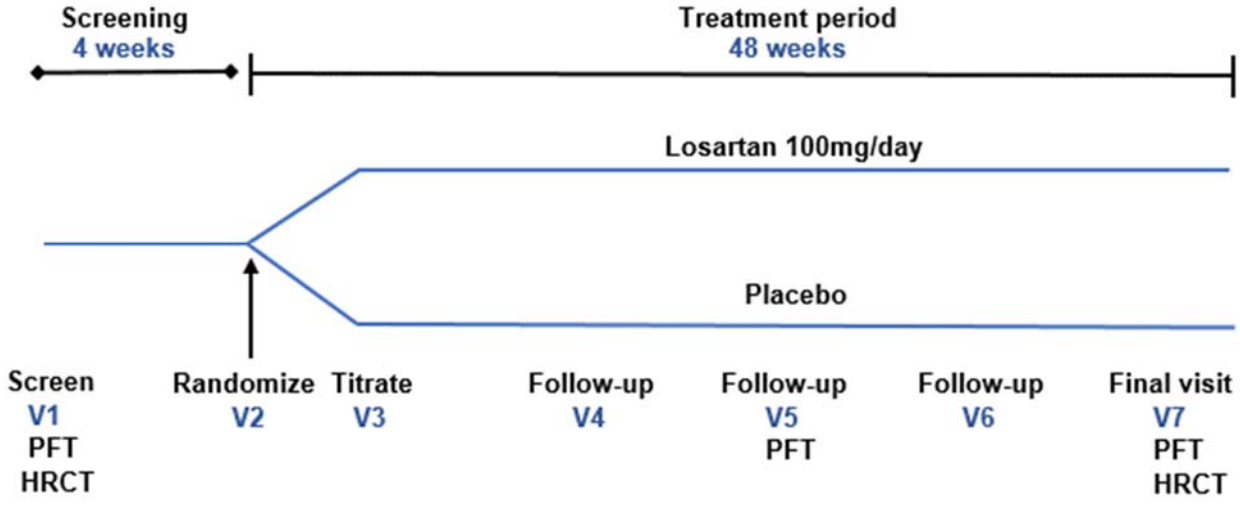

Figure 1: LEEP Trial design - schema

PFT: Pulmonary Function Test; HRCT: High Resolution Computed Tomography

3. Eligibility criteria

Participants with mild to severe COPD will be screened using the criteria below. Participants will be asked to sign informed consent before any screening procedures are performed.

3.1. Inclusion criteria:

- Age of 40 years or older at V1, either gender
- Mild to severe COPD (post-BD FEV_1/FVC ratio ≤ 0.70 and FEV_1 20-80% predicted) at V1
- Current or former smoker (≥ 10 pack-year history at V1)
- HRCT Scan with 5-35% of voxels with density < -950 Hounsfield Units (HU) at V1
- Ability to understand and willingness to sign consent documents

3.2. Exclusion criteria:

- Current therapy with angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- Known intolerance to ACE inhibitor or ARB
- History of angioedema
- Conventional indication for ACE inhibitor or ARB (including history of myocardial infarction, known cardiomyopathy
- Renal insufficiency (GFR <30 mL/min by Cockcroft-Gault calculation)
- Current regular use of NSAIDs defined as daily use 5 or more days of the week for more than one month
- Current treatment with a potassium sparing diuretic
- Potassium supplementation or serum potassium level of ≥ 5.0 mEq/L at V1
- COPD exacerbation requiring treatment within 6 weeks at V1
- Chronic systemic corticosteroid use > 10mg/day of prednisone
- Resting SpO2 <89% on 2L nasal cannula continuous flow; unless at altitude > 4,000 feet, then resting SpO2 <89% on 4L NC continuous flow
- Untreated arterial hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg)
- Blood pressure less than 90 mm Hg systolic or 60 mm Hg diastolic while standing or sitting
- Known unilateral or bilateral renal artery stenosis >70%
- Previous lung resection surgery
- Evidence of interstitial, occupational or chronic infectious lung disease
- Changes to chest that preclude adequate HRCT imaging (e.g. Metallic objects in the chest such as shrapnel or pacemaker leads)
- For women of child bearing potential, positive pregnancy test or unwillingness to use two methods of birth control or abstinence for the duration of the study
- Major chronic illnesses which in the judgment of the study physician would interfere with participation in the study e.g. including but not limited to: cardiac, renal, hepatic

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(LFTs>2.5x normal upper limit), neurological, psychiatric, endocrine or neoplastic diseases, uncontrolled diabetes, uncontrolled HIV infection or other immune system disorder, hyperthyroidism, seizure disorders, non–skin cancer, rheumatic diseases

- Failure to keep screening appointments or other indicators of non-adherence
- Inability to be contacted by telephone
- Intention to leave area within 12 months

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4. Summary of study visits

V1: Screening visit (Week – 4)

The initial visit is to determine eligibility, obtain informed consent, and acquire baseline data. It will include:

- Obtaining informed consent
- Baseline medical history
- Vital signs including pulse oximetry
- Anthropometrics (height and weight)
- Physical examination
- Orthostatic blood pressure check
- Spirometry pre- and post-bronchodilator (2 inhalations of albuterol MDI)
- Blood draw, venous blood will be obtained to assess hepatic, renal, electrolyte, hematological measures
- Pregnancy test for all female participants of childbearing potential
- Administration of questionnaires (ATS-DLD, SGRQ-C, mMRC, CAT, PROMIS -20a)
- HRCT scan (may be scheduled on a different day)

V2: Randomization visit (Week 0)

The purpose of this visit is to confirm eligibility and acquire baseline data and randomly assign and distribute a treatment. It will include:

- Interval medical history, adverse events
- Vital signs including pulse oximetry
- Anthropometrics (height and weight)
- Collection of blood and urine for biorepository
- Pregnancy test for all female participants of childbearing potential
- Administration of questionnaires (SGRQ-C, mMRC, CAT, PROMIS -20a)
- Treatment assignment
- Drug administration (50mg losartan or placebo)
- Orthostatic blood pressure check. A two-hour observation of participants in clinic with blood pressure check for hypotension (systolic blood pressure <90 mm Hg or diastolic blood pressure < 60 or symptoms of lightheadedness or dizziness)
- Drug distribution

V3: Treatment titration (Week 2)

The purpose of this visit is to titrate drug and ensure the participant can tolerate it. It will include:

- Interval medical history, adverse events
- Vital signs including pulse oximetry
- Anthropometrics (height, weight)
- Orthostatic blood pressure check. If the systolic BP is >90 mm Hg and the diastolic BP is >60 mm Hg, the drug dose will be increased to 100 mg per day or the matching placebo will be increased to 2 capsules per day

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- Pregnancy test for all female participants of childbearing potential

V4: Follow-up (Week 12)

This visit is to obtain follow-up data and screen for adverse events. It will include:

- Interval medical history, adverse events
- Vital signs including pulse oximetry
- Anthropometrics (height and weight)
- Orthostatic blood pressure check
- Blood draw, venous blood will be obtained to assess hepatic, renal, electrolyte, hematological measures
- Pregnancy test for all female participants of childbearing potential
- Administration of questionnaires (SGRQ-C, mMRC, CAT, PROMIS -20a)
- Drug distribution and return/capsule count

V5: Follow-up (Week 24)

This visit is to obtain follow-up data and screen for adverse events. It will include:

- Interval medical history, adverse events
- Vital signs including pulse oximetry
- Anthropometrics (height and weight)
- Physical examination
- Orthostatic blood pressure check
- Spirometry pre- and post-bronchodilator (2 inhalations of albuterol MDI)
- Collection of blood and urine specimens for biorepository
- Pregnancy test for all female participants of childbearing potential
- Administration of questionnaires (SGRQ-C, mMRC, CAT, PROMIS -20a)
- Drug distribution and return/capsule count

V6: Follow-up (Week 36)

This visit is to obtain follow-up data and screen for adverse events. It will include:

- Interval medical history, adverse events
- Vital signs including pulse oximetry
- Anthropometrics (height and weight)
- Orthostatic blood pressure check
- Pregnancy test for all female participants of childbearing potential
- Administration of questionnaires (SGRQ-C, mMRC, CAT, PROMIS -20a)
- Drug distribution and return/capsule count

V7: Final visit (Week 48)

This is the final study visit to obtain follow-up data and complete exit tasks. It will include:

- Interval medical history, adverse events
- Vital signs including pulse oximetry
- Anthropometrics (height and weight)
- Physical examination
- Orthostatic blood pressure check
- Spirometry pre- and post-bronchodilator (2 inhalations of albuterol MDI)

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- Blood draw, venous blood will be obtained to assess hepatic, renal, electrolyte, hematological measures
- Collection of blood and urine specimens for biorepository
- Pregnancy test for all female participants of childbearing potential
- Administration of questionnaires (SGRQ-C, mMRC, CAT, PROMIS -20a)
- HRCT scan (may be scheduled on a different day)
- Drug return/capsule count
- Exit interview

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4.1. Study data collection schedule

Visit	V1	V2	V3	V4	V5	V6	V7
Target (weeks)	-4	0	2	12	24	36	48
Visit window (weeks)	-4 to 0	0	2-4	10-14	22-26	34-38	46-50
Informed consent, eligibility evaluation	●						
Baseline medical history	●						
Adverse events/Interval health history		●	●	●	●	●	●
Pregnancy testing as indicated	●	●	●	●	●	●	●
Spirometry (pre and post BD)	●				●		●
Anthropometrics (height & weight)	●	●	●	●	●	●	●
ATS-DLD	●						
SGRQ-C mMRC	●*	●		●	●	●	●
CAT	●	●		●	●	●	●
PROMIS-20a	●	●		●	●	●	●
Vital signs, Orthostatic blood pressure check, SpO2	●	●	●	●	●	●	●
Physical examination	●				●		●
CBC, CMP	●			●			●
Collect blood & urine for biorespository		●			●		●
HRCT	●						●
Treatment assignment		●					
Drug distribution		●		●	●	●	
Drug titration			●				
Drug return/capsule count				●	●	●	●
Exit interview							●

* mMRC included in ATS-DLD at V1

(V#) Visit Number
(ATS-DLD) modified American Thoracic Society Division of Lung Disease Questionnaire
(BD) Bronchodilator
(CAT) COPD Assessment Test
(CBC) Complete blood count
(CMP) Comprehensive metabolic panel
(HRCT) High resolution computed tomography
(mMRC) modified Medical Research Council Dyspnea score
(PROMIS-20a) Patient Reported Outcomes Measurement Information System: Physical Function – Short Form 20a
(SGRQ-C) St. George's Respiratory Questionnaire for COPD Patients
(SpO2) peripheral capillary oxygen saturation

5. Outcomes

5.1. Primary outcome measures

The primary outcome measure is quantitative HRCT measurement of emphysema as indicated by the percent of lung voxels with a density less than – 950 Hounsfield Units (HU), measured using commercially available software (Slicer, NIH developed, open source).

5.2. Secondary outcome measures

- Spirometry. FEV_1 and FVC are measured before and after 2 inhalations of albuterol in accordance with ATS/ERS standards and using NHANES reference values[27 28].
- Other HRCT measures. Emphysema (pct950) will be measured in each of the lobes of the lung separately. Other measures include TLC[29], mean lung density, 15th percentile density, and airway lumen and wall thickness will be measured for small, medium, and large airways[30].
- Respiratory questionnaires. The St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) is a widely used measure of disease impact as an indicator of disease-specific quality of life. The mMRC dyspnea scale (mMRC) will serve as our primary measure of dyspnea and be used for risk stratification[31] The COPD Assessment Test (CAT) is designed to quantify the impact of COPD symptoms on the health status of participants[32].
- Patient reported outcomes. The Patient Reported Outcomes Measurement Information System Questionnaire: Physical Function – Short Form 20a (PROMIS-20a) is used to indicate patients' state of wellbeing or suffering as well as their ability or lack of ability to function[33].
- Laboratory testing. Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP) of blood chemistries will be obtained at local labs to detect hematologic, electrolyte, renal, or hepatic abnormalities that indicate exclusion from treatment or adverse events. Pregnancy tests will be done on women of child-bearing potential at each visit and prior to performing a HRCT scan
- Adverse effects to assess safety and tolerability are assessed by open-ended questions at each visit and rated in severity. Targeted symptoms, e.g. orthostasis, cough, and angioedema will be asked directly.
- Interval health history is recorded at each clinic visit. With participant permission, records of hospitalizations and deaths are obtained for verification of diagnoses and assessment of safety.
- Adherence is recorded at each visit by self-report and by capsule counts from returned containers.

5.3. Other data

- General health history: Questionnaires to collect demographic and general information (including race, gender, COPD history) as well as information about COPD symptoms,

medication use, other diseases and illnesses that affect eligibility for the trial. These data along with clinical measures such as height and weight will be used to characterize the population and allow for analysis of subgroups.

- Respiratory questionnaires: The ATS-DLD questionnaire is a general respiratory symptom questionnaire. We will use the LHS-III modified version that includes information regarding occupational exposures and asthma.
- An exit interview is administered at the last visit to determine global assessments of treatment, adequacy of informed consent procedures, satisfaction with study procedures and personnel, and effectiveness of the blinding procedures.
- Biospecimens: Blood and urine will be drawn for future studies and will stored in the American Lung Association Airways Clinical Research Center (ALA ACRC) biorepository at Nemours Children's Health System, Jacksonville, FL. Although it is beyond the scope of this study, ancillary studies may be done to measure elastin fragments, inflammatory biomarkers, or measures of oxidative stress.

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6. Study treatments

6.1. Description of study treatments

- V2 – V3
  - Losartan 50 mg per day (one capsule) OR placebo (one capsule)
- V3 – V7
  - If well tolerated and systolic BP is >90 mm Hg and the diastolic BP is >60 mm Hg blood pressure is above at V3: Losartan 100mg once per day (two capsules of 50 mg each) OR placebo (two capsules per day)
  - If not tolerated at V3: Losartan 50 mg per day (one capsule) OR placebo (one capsule)

Drug titration

Participants will receive their first dose of drug in the clinic under observation for at least two hours to ensure that there are no immediate adverse effects. Participants will take 50 mg/day (one capsule) or one capsule of placebo for the first two weeks. If well tolerated and systolic BP is >90 mm Hg and the diastolic BP is >60 mm Hg will be increased to 100 mg/day (two capsules) or two capsules of placebo, which will be taken in clinic under observation for at least one hour.

6.2. Side effects of drug

Losartan is an FDA-approved angiotensin receptor blocker that is widely prescribed for treatment of hypertension, heart failure, and for renal protective effects in diabetics. The dose proposed in this study is well tolerated by non-hypertensive patients without significant effect on blood pressure. The most common side effects are fatigue and dizziness. Serious adverse events that are rare include angioedema, hypotension, renal dysfunction, blood dyscrasias, hepatitis or rhabdomyolysis. According to the FDA-approved prescribing information, the adverse event profile is as follows:

“Cozaar has been evaluated for safety in more than 3300 adult patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over six months and more than 800 for over one year. In general, treatment with Cozaar was well tolerated. The overall incidence of adverse experiences reported with Cozaar was similar to placebo. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with Cozaar and 3.7 percent of patients given placebo.”[34]

“In the RENAAL study involving 1513 [Type II Diabetic Patients with Nephropathy] patients treated with Cozaar or placebo, the overall incidences of reported adverse experiences were similar for the two groups. Cozaar was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo (19% for Cozaar, 24% for

placebo). The adverse experiences, regardless of drug relationship, reported with an incidence of ≥ 4% of patients treated with Cozaar and occurring more commonly than placebo, on a background of conventional antihypertensive therapy are shown in the table below.” [35]

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	Losartan and Conventional Antihypertensive Therapy Incidence % (n=751)	Placebo and Conventional Antihypertensive Therapy Incidence % (n=762)
Body as a Whole		
Asthenia/Fatigue	14	10
Chest Pain	12	8
Fever	4	3
Infection	5	4
Influenza-like disease	10	9
Trauma	4	3
Cardiovascular		
Hypotension	7	3
Orthostatic hypotension	4	1
Digestive		
Diarrhea	15	10
Dyspepsia	4	3
Gastritis	5	4
Endocrine		
Diabetic neuropathy	4	3
Diabetic vascular disease	10	9
Eyes, Ears, Nose and Throat	7	5
Cataract	6	5
Sinusitis		
Hemic		
Anemia	14	11
Metabolic and Nutrition		
Hyperkalemia	7	3
Hypoglycemia	14	10
Weight gain	4	3
Musculoskeletal		
Back pain	12	10
Leg pain	5	4
Knee pain	5	4
Muscular weakness	7	4
Nervous System		
Hypesthesia	5	4
Respiratory		
Bronchitis	10	9
Cough	11	10
Skin		
Cellulitis	7	6
Urogenital		
Urinary tract infection	16	13

Figure 2: Adverse events in the RENAAL study

6.3. Handling of drug

Study drugs will be supplied by a central drug distribution center and shipped to the investigators from a central drug repository. The study drug will be kept in a secure, limited access, storage area within a controlled, appropriate temperature range (room temperature). Each container of study medication will be identified by protocol name and labeled as required by federal law. Study drug receipt, distribution, and destruction will be documented in the drug accountability log. Adherence will be monitored by capsule count at follow-up visits. Unused study drug distributed to participants enrolled in the study should be returned to the clinic site. Unused drug will be destroyed at the clinical sites in accordance with the local policy and procedures.

6.4. COPD treatment

All participants enrolled in this study will continue to have their usual care for COPD as determined by their primary care provider or their usual COPD caregiver. No treatments will be discontinued. Study physicians will render emergency care for participants, refer to appropriate treating sources, and confer with treating sources, but will not provide comprehensive medical care to participants. With permission of the participant, treating physicians will be notified of the participant's enrollment in the study and results of study evaluations, e.g., spirometry, as appropriate.

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7. Specific procedures

7.1. HRCT scans

HRCT scans of the lung will be acquired from individuals with COPD at V1 to confirm emphysema, and if eligible and randomized, at V7 (total of two scans). These data will be obtained specifically for research purposes using standardized protocols for different model scanners. Variation between scanners is minimized by designating the same scanner to be used for all scans on an individual before and after study treatment. The participant should have taken 2 puffs of albuterol within 6 hours of the HRCT scan.

For the HRCT scans:

- A pregnancy test will be administered at each visit before imaging for women of child bearing potential
- The lungs and trachea will be included
- The scanning protocol will begin below the lung bases and end above the lung apexes at the mandible
- Scans will be performed with the subjects in the supine position
- Each participant will have one standard scout (AP/PA) scan over the chest at Total Lung Capacity (TLC). Then a complete chest HRCT will be done at Total Lung Capacity (TLC)

Since the scans will be done at TLC, it is important for the coordinators and radiology technologists to ensure that the participant is appropriately coached prior to performing the actual scanning procedures. Study coordinators will be provided with a script to coach participants in the appropriate breathing technique to take and hold a TLC breath during spirometry prior to the HRCT exam. They will also provide the script for the radiology technologist to coach participants in the breathing technique. The scan will take about one hour including preparation and coaching. In order to minimize errors in scan acquisition, we will ask coordinators to accompany the participants to the HRCT scanner and provide the radiology technologist with the LEEP HRCT protocol including the proper acquisition parameters to program into the HRCT scanner. The model and serial identification number of the scanner will be recorded so that the same scanner is used for the second scan.

7.2. Pulmonary Function Testing

Spirometry before and after 2 inhalations of albuterol will be performed in accordance with ATS/ERS recommendations and PTC procedures. Spirometry is a common clinical test used to diagnose asthma, COPD, and certain other conditions that affect breathing. It measures how much and how fast air is inhaled and exhaled. It should be administered at the same time of the day. Spirometry reference values will be those of Hankinson et al from NHANES[36].

7.3. Randomization

Treatment assignment will be randomly allocated in a 1:1 ratio with stratification by clinic using a permuted block randomization scheme. Randomization will occur at V2 after the participant meets all eligibility criteria. The clinic staff will complete a randomization form for each eligible participant and enter it into a web-based randomization system. Eligibility criteria are verified via computer program, which then provides a unique study treatment assignment number according to an encrypted table on the server; the assignment number will correspond to a specific drug bottle.

The initial drug supply will be dispensed and a tear-off label will be affixed to a study form to provide an audit trail for drug distribution.

7.4. Phlebotomy and biospecimens

Whole blood and serum will be collected for measurement of complete blood counts and serum chemistry panels. The purpose of this testing is to monitor for potential adverse events that might lead to discontinuation of study treatment.

For participants willing to provide specimens for future analyses, (e.g. possible biomarker analysis), additional blood and urine specimens will be collected and stored at the ALA ACRC biospecimen repository. Specimens will be stored at -70 or -80C at the local site and shipped periodically in batches on dry ice for storage at the biospecimen repository.

Approximately 10 mL of blood is collected by venipuncture at V1, V4 and V7. Two 5 mL tubes are transmitted to the local hospital laboratory without processing for measurement of CBC and chemistries. Also, approximately 20 mL of blood is collected at V2, V5, and V7. This will be divided into eight, 1mL aliquots of serum and plasma for freezing and bulk storage pending shipping. DNA will be collected at V2. Instructions for processing the blood are provided in the manual of operations. Note that the total blood drawn at V7 is approximately 30mL for lab testing and for storage.

Approximately 20 mL of urine is collected by clean catch and is divided into 1.8 mL aliquots for freezing and storage pending shipping to the biorepository.

7.5. Unmasking

Unmasking of treatment assignment before the end of participant's treatment period is rarely necessary. If adverse events occur that may be related to the study treatment, then the study treatment is stopped and the participant continues scheduled follow-up.

Routine unmasking will occur at the end of the participant's V7 visit. The treatment assignment will only be provided to the participant and not the staff at the clinical center. Sealed envelopes with treatment assignment are provided to the clinic to provide the participants. In addition,

clinics can contact the DCC if necessary for unmasking information. All participants are provided with a wallet card that provides information that they are participating in a clinical trial and gives the contact numbers of personnel at the clinic.

7.6. Treatment termination

Participants may be withdrawn from the treatment if they have a serious adverse event or are intolerant of the treatment. All participants will be asked to return for study visits in order to maintain the intent to treat paradigm for the primary analysis. Participants will be treated by their usual COPD care provider according to best medical judgment regardless of whether they continue to use study treatment. Any female participant with a positive pregnancy test at any time during the study will be taken off study drug and followed to the outcome of pregnancy.

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8. Analysis plan

8.1. Primary analysis

The primary goal of analysis is to precisely estimate the difference in response between the losartan and placebo groups by comparing between-group means of changes from baseline pct950 over the time course of treatment. The secondary goals require estimation of analogous differences in response trajectories separately for each secondary response variable. For analytic methods, we propose a series of generalized linear mixed models (GLMMs) for responses (Y) with possibly g-transformed) expected primary or secondary responses, $g(E(Y_{ij}|b_{0i},\beta_i X_{ij})$, where 1.) $(\beta_0 + b_{0i})$ for the ith patient response is a random intercept (to account for serial correlations in the within-patient responses) with fixed mean β_0 and random normal distributed offsets b_{0i}, with mean zero and standard deviation $\sigma_{b_{0i}}$ and 2.) X_{ij} are fixed values of jth covariate for the ith patient and β_i is the fixed unknown regression coefficient to be estimated for covariate X_j. Covariates will include site (14 binary spline indicator variables for the 15 category site stratification), baseline values of the Y response, an indicator variable for treatment group (*trt = 1 losartan, 0 placebo*), and either spline indicators for time or a continuous function for the fixed time trend in mean response, and, if needed, interaction terms between the time covariates and the (*trt*) treatment group indicator. The primary outcome is change in pct950 from baseline after 48 weeks of treatment ($Y=pct950-pct950_{bl}$) and g(.) is the identity function, so the above model simplifies to $Y_i+\varepsilon_i = E(Y_i|b_{0i},X_i)) = \beta_0 + b_{0i} + \beta_1 trt + \beta_2 pct950_{i\,bl} + \{\beta_j X_{ij}\ j\}+ \varepsilon_{ij}$, where β_0 is the intercept for the fixed effects, b_{0i} is the normal $(0, \sigma_{b_{0i}})$ random intercept offset for each participant, β_1 is the primary losartan vs placebo treatment effect = mean difference in 48 week change in pct950 from baseline, losartan vs. placebo, $\{\beta_j\}$ is the set of regression coefficients to account for stratification by site, and ε_i is a normal $(0, \sigma^2)$ random error for the ith change from baseline in pct950. The primary analysis will focus on β_1,= mean losartan vs. placebo mean change over 48 weeks in pct950. We will estimate a 95% confidence interval for the losartan vs placebo mean difference, β_1, using the regression estimate and the t-distribution; we will reject the null that losartan is equivalent to placebo if the 95% interval excludes 0.0. A robust variance estimate[37] will be used to guard against incorrect inferences due to misspecification of the assumed serial correlation structure among repeated observations on each subject.

The primary analysis will be intention-to-treat so that the indicator trt is the group to which the person is randomized without regard to whether they complied with the treatment assignment or not. We anticipate some degree of loss-to-follow-up (less than 10%) that will not affect our analyses. However, the regression model above will be estimated using the method of maximum likelihood so that missing data will effectively be imputed by their expected values given the other measurements. If the loss-to-follow is 10% or greater, then multiple imputation will be used to construct the 95% confidence limits for β_1 estimated across 50 imputations of the dataset.

8.2. Secondary analyses

As indicated above, the same basic model specified above can be used for the secondary outcomes, most of which are continuous. For a binary secondary outcome, we will use the logistic regression analog in which g() above is the logistic function, g(u)=log{u/(1-u)}. Since the strict interpretation of odds ratios from mixed models with the logistic link is dependent on the value of the random effect variable (participant), we will also use maximum likelihood estimation and robust variance estimation described for the primary analysis above. The same assumptions and methods for missing data for the primary outcome will also be used in the secondary analyses.

In particular, we seek to estimate the treatment effect for each of 5 lobes of the lung. A simple approach is to use the basic change-from-baseline model described above separately for data from each lobe and then use a gate-keeper Chi-square test and Bonferroni correction to account for the multiplicity of tests. This method, while valid, does not provide evidence about the correlation among the estimates from the 5 lobes that is itself of scientific interest. Therefore, we will use a multivariate version of the GLMM from Section 8.1 that simultaneously estimates the treatment effect for the 5 lobes and produces both the 5 estimates of treatment effect as well as their covariance matrix[38]. We will use these results to conduct gate-keeper Chi-square test of the null hypothesis that the 5 treatment effects are all the same across lobes and if this null is rejected, provide lobe-specific treatment effect estimates with 99% Bonferonni-corrected confidence limits to ensure that the joint coverage probability is 95%. In addition, we will also show estimates and 95% confidences limits for the between lobes correlations.

8.3. Exploratory analyses

Preliminary to the main analyses, the data will be checked for obvious errors that cause outliers and for systematic errors due to improper coding at one or a few centers. For each *time* x *trt* cell, the distribution of outcome values will be summarized by its mean, standard deviation, and five number summary. Boxplots of the cell-specific distributions will be made to see the basic patterns of change over time and to detect outlying values. The autocorrelation matrix of repeated measures on the individual will be estimated separately for each treatment group.

After the main analyses, numerous exploratory analyses will be conduct using variants of the model above to generate hypotheses for future research.

8.4. Subgroups of interest

We will quantify the evidence in the study data in support of the possibility that the treatment effect differs between persons with (Z=1) versus those without (Z=0) pre-specified characteristics. Subgroups of interest include: Current vs. Former smokers; severe emphysema (pct950 >15) vs mild emphysema (pct950 <15); severity of airflow limitation (FEV_1 < 50% predicted vs FEV_1 > 50% predicted); and men vs women. In addition, other baseline characteristics may be explored. The model above will be extended to include the variables Z

*and Z*trt*. The coefficient for the 2-way interaction is the difference in the treatment group effects (losartan vs placebo) between the Z=1 and Z=0 subgroups. We will reject the null of no difference in treatment effects between the subgroups if the 95% confidence interval for this 3-way interaction coefficient excludes 0.

Other subgroups may be identified post hoc. The same model can be used to quantify the evidence for a difference in treatment effect for these subgroups. However, we view such analyses as hypothesis generating, not hypothesis testing.

8.5. Sample size

To estimate the sample size for a given power, we note that the variance of the change in mean for one of the two groups is given by $V=SD^2/n$ where SD is the standard deviation of the changes across people within a group and n is the number of subjects in each group. Then, the main hypothesis that the two treatment groups change an equal amount is just a two sample comparison for which the sample size is given $V*\{Z(1-\beta) + Z(1-\alpha/2)\}^2 / \delta 2$ where $Z(1-\beta)$, $(1-\alpha/2)$, are the $1-\beta$ and $1-\alpha/2$ quantiles for the standard normal distribution, and δ is the anticipated difference in change from baseline between the two groups[39]. Figure 3 shows the requisite sample size per group to attain 80% and 90% power respectively for varying values of the difference in change denoted δ on the horizontal axis. For the estimated minimally important difference (MID) of pct950, (delta = 2%/year), SD = 4%/year, alpha = 0.05 two-sided, and power = 90%, the required sample size is 88 participants per group which is inflated 20% (110 per group) to account for poor adherence, missing data, or to have adequate power to detect smaller treatment effects.

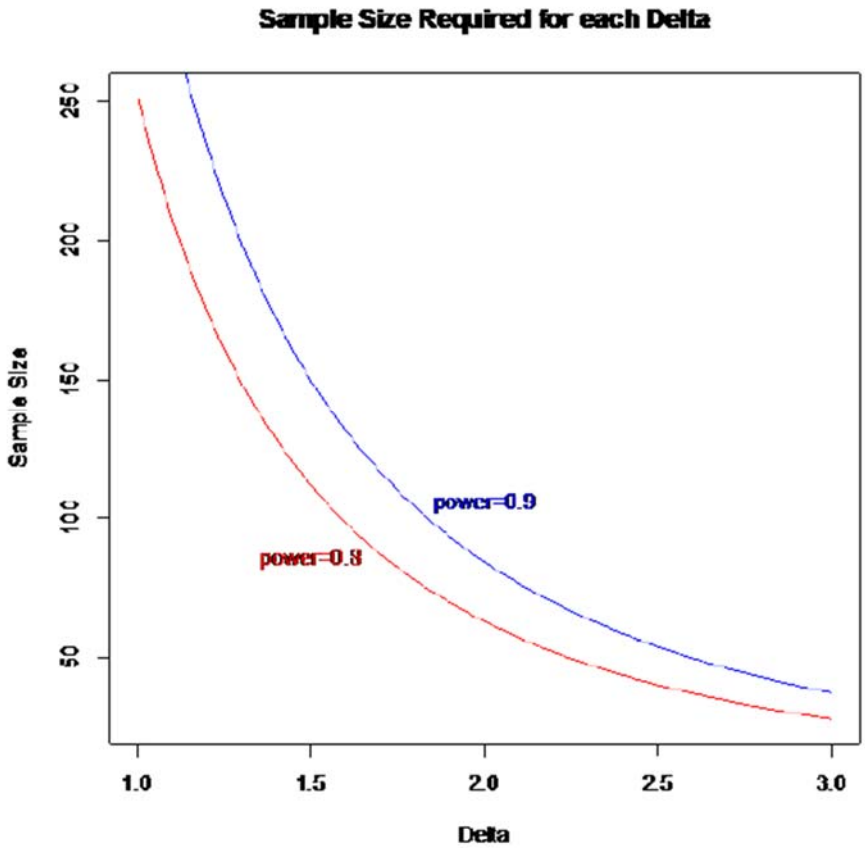

Figure 3: Sample size required for indicated power and difference (Delta) between change for losartan and placebo groups, assuming alpha=0.05, and standard deviation of the change within a group of 4.0

9. Protection of human subjects

9.1. Recruitment and consent procedures

Participants will be recruited by each participating clinic by their own methods. These methods may include social media campaigns, solicitation in physician offices, clinics, workplaces, and public media advertisements, patient and research subject registries and electronic medical records. All public advertisements are subject to approval by the local Institutional Review Board (IRB) and must indicate that it is a research study. The NEMO will help coordinate recruitment among clinics and promote sharing of effective recruitment strategies within the network. The study encourages prescreening of participants for prior HRCT evidence of emphysema, presence of comorbidities, and concurrent medications.

Potential enrollees will be approached either in person, by telephone or by mail to establish general eligibility criteria. A general description will be provided prior to their initial visit. If the potential enrollees are interested in participating, they will meet with the study coordinator and local physician co-investigators to review the study and to ask questions. They will be asked to sign consent, and if appropriate provide assent, and undergo the screening procedures.

The consent form will be subject to approval by the clinical center IRB. A copy of the consent form will be given to each participant, and the signed original will be kept in the participant's research chart.

9.2. Potential risks and procedures to minimize risk to the participants

During this study, participants will continue to receive their usual care for COPD as per their treating physician. If any medical illness requiring treatment is discovered during the collection of data for the course of this study protocol, individuals will be referred to their primary care providers for further evaluation and treatment.

Potential risks associated with this study are outlined below. In order to minimize risk to participants, the following actions will be taken.

- Treatment with losartan: Losartan is an FDA-approved angiotensin receptor blocker that is widely prescribed for treatment of hypertension, heart failure, and for renal protective effects in diabetics. The dose proposed in this study is well-tolerated by non-hypertensive patients without significant effect on blood pressure. The most common side-effects are fatigue and dizziness. Serious adverse events that are rare include angioedema, hypotension, renal dysfunction or failure, blood dyscrasias, hepatitis, or rhabdomyolysis. In order to minimize risk to participants, the following actions will be taken. The first dose of medication will be administered in the clinic (50mg/placebo) and the participant observed for two hours thereafter with a blood pressure check for

hypotension. Participants with hyperkalemia, significant renal dysfunction, or who are taking potassium supplements will not be enrolled into the study. Participants are given written descriptions of potential side-effects and appropriate means of dealing with them. For example, mild postural hypotension can often be minimized by arising slowly and maintaining adequate hydration. Skin rashes, palpitations or other moderate or severe (defined as those that interfere with usual daily activities) adverse events without other clear explanation should warrant immediate cessation of treatment and notification of study personnel. If the study physician warrants that it is unlikely that the event is related to the medication, then it may be restarted after resolution or stabilization of the adverse event.

After the initial two weeks of treatment, subjects will return for titration up to 100mg of losartan or two placebo capsules. They will be observed for one hour thereafter with a blood pressure check for hypotension. Adverse events will be monitored at each of the study visits by specific and open-ended questions. Losartan is a potential human teratogen particularly in the second trimester of pregnancy. Therefore, pregnancy testing will be performed prior to randomization and at each visit for persons of child bearing potential. As well, participants of child-bearing age will be counseled on the risk of pregnancy as delineated in the consent form.

- High Resolution Computed: Tomography: HRCT is a standard medical procedure for imaging of the lung, is widely used in research and clinical care of patients with COPD, and is recommended by the US Preventive Services Task Force for annual lung cancer screening. Risks to the volunteers are minimal. This will involve a small amount of radiation exposure to our subjects. The HRCT Dose is standardized so each manufacturer and model are matched within ± 3% of the Target CTDIvol. For the current proposal, to limit the risk of radiation exposure, we have determined what we consider the best balance between high quality data and minimal radiation exposure. We intend to perform two high-resolution chest HRCT scans of the subjects over 48 weeks. The chest HRCT protocol will be adjusted; based on the weight of the subjects. For average-weight adults of 80 kg, the effective dose estimation for each CT scan, is 4 mSv. The total effective dose for the study protocol will be 8 mSv. This compares to the annual allowed limit on radiation workers is 50 mSv in the US. The risk of radiation overexposure will be mitigated by ensuring that all centers are certified for performance of the tests in an ACR accredited facility that performs the required daily calibration of instrumentation. Moreover, prior to participant enrollment and regularly during the trial, HRCT scanners at each site will be calibrated using a Lung Phantom (e.g. CPT674, The Phantom Lab, Salem, NY) and reviewed by the HRCT reading center. While there are some variations between HRCT scanners, a standardization of the parameters and exposure levels has been developed to allow multiple scanners to output reliable quantitative measures and minimize risk across a given patient population.

  There is risk of discomfort while lying in the scanner, or cough with breath holding, and participants will be continuously supervised by radiology staff during the procedure.

Although the scans are done only for research purposes, we are requiring that all HRCT scans be interpreted by a certified radiologist on site. The scans will be inspected for adequate inspiration, absence of motion artifact and inclusion of all parts of the chest. It may occur that other findings are found on these images that may represent clinically significant findings (e.g. lung nodules). If any incidental findings are discovered during study, the clinical site study physician will be notified, the information will be given to the participant and, with their permission, the information will also be transmitted to the participant's usual care-giver for appropriate medical care or follow-up.

- Pulmonary Function Testing: Spirometry is a routine clinical procedure that entails little risk. Participants are coached to make repeated forceful breathing efforts that sometimes makes their chest sore for a day or so. In some unusual cases participants may become light-headed during these efforts. The risk to the participant is minimized by having these procedures done with the participant seated during the testing.

- Phlebotomy: This may cause pain during the insertion of the needle or slight bruising afterward. This risk is minimized by the use of disposable single use needles, trained personnel, and application of pressure after the blood draw.

- Questionnaires: Health History acquires information that is routinely collected in the process of medical care of patients with COPD. There are no significant physical risks from these procedures. As with all medical information, there is always the risk of psychological distress if personal health information is not held confidential within the wishes of the participant. In order to minimize this risk, electronic medical records are held in HIPAA compliant password-protected databases, and written information is stored in locked files or file-rooms when not attended by study personnel. Medical information is provided to treating sources consistent with HIPAA guidelines.

- Physical examination: Physical examinations and the collection of vital sign including pulse oximetry are usual medical procedures for patients with COPD. There are no significant physical risks from these procedures.

9.3. Data and safety monitoring plan

A Data and Safety Monitoring Board (DSMB) will be appointed by NHLBI to monitor the entire PTC and will be chartered and managed by the NEMO. The DSMB will serve in a consultative capacity to NHLBI and will make recommendations regarding the initiation and conduct of the study to the institute. 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 information gained from the study. Typically, the DSMB would meet every six months or more frequently to review the progress of the trial. The investigators will present the DSMB with 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; these will be reported by treatment group. After sufficient data are acquired, the DSMB may request to see outcome data, although for this type of translational study, it is unlikely that any finding would be sufficiently clinically directive to use for interim recommendations. Accordingly, we are not proposing formal interim efficacy analyses or stopping guidelines.

Reporting of Serious Adverse Events

A serious adverse event (SAE) is an adverse event that results in one of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. Also, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention (treatment) to prevent any of the outcomes previously listed in this definition. When an investigator or clinical center staff member becomes aware of an SAE, it should be reported to the DCC within 72 hours with follow up reporting until the event is terminated. The DCC will send these reports to the DSMB, the network coordinating center, and NHLBI representatives; these reports will be distributed with a ballot for DSMC members to indicate whether an ad hoc meeting should be convened to discuss the SAE, The DCC will distribute reports of SAEs that are possibly related to the study treatment or study participation all centers for review by their local IRBs and to the DSMB in a timely fashion.

Interim Analysis for Safety

The DSMB will evaluate reported adverse events and treatment-emergent symptoms by treatment group at each meeting. These analyses will review both expected and unexpected events by severity and treatment-emergent symptoms reported by participants at follow-up visits. A standard set of symptoms will be queried at each visits along with an open-ended question about other symptoms. Analysis of treatment effects on adverse events and treatment-emergent symptoms will include cumulative percentages of participants with events by severity. While no formal stopping guidelines for safety are planned, the DSMB will evaluate whether the burden of treatment exceeds the potential benefits of treatment at each meeting and be responsible for making a recommendation to the NHLBI regarding continuation of the trial.

9.4. Data confidentiality

Participant data, which includes identifiable personal health information (PHI), are collected at each of the clinical sites. PHI will be 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 study personnel, password protection for electronic medical records, and explanation of HIPAA regulations on the study consent form. Analytic files will not contain personal identifiers (e.g. name, address). All

reports/manuscripts will be prepared in such a way that individual participants cannot be identifiable.

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 will be informed in the consent that PHI may also be disclosed for auditing purposes by the NIH or other regulatory bodies and is subject to subpoena.

All HRCT scans will be de-identified at the scanning institution and a unique study ID will be assigned by the DCC. De-identified HRCT scans are transmitted electronically to the NEMO, then to the DCC and are logged, quality-controlled, and analyzed in a blinded fashion by a trained technician using a semi-automated Slicer workstation at the HRCT reading center supervised by Dr. Brown. HRCT scans and other data will also be transmitted to the NEMO at University of Pittsburgh for the purposes of ensuring quality control.

Personal identifiers (e.g. name, address, EMR number) are not transmitted to the DCC or central laboratory in that all biospecimens and records are identified by a study ID, and other identifying information such as names are not entered into the central study database. Source records that are transmitted to the DCC for data quality audits have identifying information redacted. No highly confidential information is routinely collected, although the data collection does include PHI, so a breach of confidentiality would constitute a HIPAA violation. If a participant is harmed from this study as a consequence of negligence, then the investigators or University might be liable for damages.

We will advise participants that the U.S. Department of Health and Human Services has the right to inspect medical records relating to this research for the purposes of verifying data. Where data are shared with other research entities, it will comply with the HIPAA definition of a limited dataset, and appropriate IRB approvals and waivers will be obtained.

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10. Acronyms

ACE	Angiotensin converting enzyme
ACR	American College of Radiology
ARB	Angiotensin receptor blocker
AT1	Angiotensin 1
ATS	American Thoracic Society
ATS-DLD	modified American Thoracic Society - Division of Lung Disease questionnaire
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood pressure
CAT	COPD Assessment Test
CBC	Complete blood count
CMP	Comprehensive metabolic panel
COPD	Chronic Obstructive Pulmonary Disease
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
ERS	European Respiratory Society
FDA	US Food and Drug Administration
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRCT	High resolution computed tomography
HU	Hounsfield Units
IRB	Institutional Review Board
LEEP	Losartan Effects on Emphysema Progression
LFT	Liver Function Test
MDI	Metered dose inhaler
mEq/L	Milliequivalent/ iliter
MID	Minimal important difference
mMRC	Modified Medical Research Council
mSv	millisievert
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NSAID	Non-steroidal anti-inflammatory drug
OC	Operations Committee
PFT	Pulmonary Function Test
PHI	Protected health information
PROMIS-20a	Patient Reported Outcomes Measurement Information System: Physical Function – Short Form 20a
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
SAE	Serious adverse event
SD	Standard deviation
SpO2	Peripheral capillary oxygen saturation
TGFb	Transforming Growth Factor Beta
SGRQ-C	St. George's Respiratory Questionnaire for COPD Patients
TLC	Total Lung Capacity

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