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General Information

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.  
How did you learn about the YODA Project?: Other

Conflict of Interest


Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.  
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01106014 - A Multicenter, Double-blind, Placebo-controlled Phase 3 Study Assessing the Safety and Efficacy of Selexipag on Morbidity and Mortality in Patients With Pulmonary Arterial Hypertension

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Influence of Selexipag on Kidney Function in People with Pulmonary Arterial Hypertension: A Secondary Analysis of the GRIPHON Trial

Narrative Summary:

Kidney dysfunction is common in people with pulmonary arterial hypertension (PAH) and closely tied to clinical outcomes in this population. Despite this bidirectional relationship between kidney disease and PAH, the influence of some of the most common therapies for PAH on kidney function remains unclear. Selexipag is an oral prostacyclin agonist approved to treat PAH. While robust studies of the influence of selexipag on kidney function are lacking, prostacyclin plays a key role in mitigating...
kidney fibrosis and ischemic kidney injury. Therefore, we aim to analyze the effect of selexipag treatment on kidney function in people with PAH using data from the GRIPHON phase 3 randomized trial of selexipag versus placebo.

**Scientific Abstract:**

**Background:**
Kidney dysfunction is common in people with pulmonary arterial hypertension (PAH) and closely tied to clinical outcomes in this population. Despite this bidirectional relationship between kidney disease and PAH, the influence of some of the most common therapies for PAH on kidney function remains unclear. Selexipag is an oral prostacyclin receptor agonist approved to treat PAH which may play an integral role in mitigating select types of kidney injury.

**Objective:**
The objectives of this study are to analyze the influence of selexipag versus placebo on kidney function as indicated by eGFR slope; assess the extent to which changes in kidney function mediate clinical response to selexipag treatment; and evaluate selexipag and metabolite levels stratified by baseline kidney function.

**Study Design:**
This study is a post hoc analysis of the GRIPHON randomized trial of selexipag versus placebo in people with PAH.

**Participants:**
The study will include all 1156 participants of the GRIPHON trial.

**Primary and Secondary Outcome Measures:**
The primary outcome for objective 1 is eGFR slope. For objective 2, we will assess the composite of death and PAH complication, death, PAH complication, PAH-related death and adverse events. The outcomes for objective 3 include selexipag and active metabolite (ACT-333679) plasma levels.

**Statistical Analysis:**
To assess eGFR slope, we will use linear mixed models with eGFR as a continuous variable, a random intercept for subject, and a random slope for time to calculate eGFR slopes for each participant. To analyze the association between treatment and eGFR slope, we will use linear regression with eGFR slope as the dependent variable, treatment group as the independent variable, and baseline eGFR as a covariate. We will apply a mediation analysis framework to determine the extent to which eGFR slope during the course of the study mediates the influence between selexipag treatment and clinical outcomes. To evaluate how baseline kidney function influences selexipag drug levels, we will use linear regression modeling with peak selexipag drug level as the dependent variable and baseline eGFR as the independent variable. We will repeat this approach to analyze the end-of-study selexipag level and levels of the active metabolite, ACT-333679.

**Brief Project Background and Statement of Project Significance:**
Kidney dysfunction is common in people with pulmonary arterial hypertension (PAH) and closely tied to clinical outcomes in this population. The core treatments for PAH include pulmonary vasodilators that target the endothelin, nitric oxide, and prostacyclin pathways. Despite this bidirectional relationship between kidney disease and PAH, the influence of some of the most common therapies for PAH on kidney function remains unclear.

Selexipag is an oral prostacyclin receptor agonist approved to treat PAH. In the phase 3 GRIPHON randomized trial of selexipag versus placebo in people with PAH, selexipag significantly reduced the incidence of death or PAH complication. In addition to its pulmonary vasodilatory and potent antiplatelet effects, prostacyclin plays an integral role in kidney injury and repair through its actions to mitigate kidney fibrosis. Prostacyclin-deficient mice also develop sequelae of ischemic kidney
injury. While the influence of selexipag on kidney function remains unknown, the limited data from prostacyclin analogues report a wide range of potential kidney effects. For example, a phase 2 randomized trial of a prostacyclin analog, beraprost, demonstrated favorable changes in creatinine compared to placebo in people with chronic kidney disease. However, infusion of a different prostacyclin analog, iloprost, to patients with severe peripheral arterial disease was associated with a higher risk of acute kidney injury in a small retrospective study. Given these disparate findings from small studies and the importance of kidney function on outcomes in PAH, an analysis of the influence of selexipag on kidney function in a large population with PAH is clearly needed.

To address this clinical need, we propose a secondary analysis of the GRIPHON phase 3 trial of selexipag versus placebo in people with PAH with three primary objectives. First, we will analyze the influence of selexipag versus placebo on kidney function as indicated by eGFR slope over the duration of the study period (median of 64 weeks). We will also assess the extent to which changes in kidney function during the study mediate the clinical response to selexipag treatment, specifically time to death or complication related to PAH. Lastly, we will evaluate drug levels of selexipag and its metabolite stratified by baseline kidney function.

Specific Aims of the Project:

1. Analyze the influence of selexipag versus placebo on kidney function as indicated by eGFR slope
2. Assess the extent to which changes in kidney function mediate clinical response to selexipag treatment
3. Evaluate selexipag and metabolite levels stratified by baseline kidney function

Study Design:

Individual trial analysis

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

All 1156 participants with PAH enrolled in the GRIPHON trial will be included. Only patients with missing baseline data on kidney function will be excluded.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Objective 1: eGFR slope stratified by treatment group
Objective 2: Mediation analysis with eGFR slope as the mediator, treatment group as the exposure, and composite of death and PAH complication as the outcome; we will similarly evaluate the associations with death, PAH complication, PAH-related death, and adverse events individually
Objective 3: Peak and end-of-study selexipag and active metabolite (ACT-333679) plasma levels stratified by baseline eGFR

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Objective 1: The main independent variable will be treatment group (selexipag vs placebo)
Objective 2: The main independent variable will be treatment group with eGFR slope as a mediator
Objective 3: The main independent variable will be baseline eGFR (= 60 ml/min/1.73m²)

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

Demographics and Baseline Characteristics:
Sex
Age
Geographic region (Asia, Eastern Europe, Latin America, North America, Western Europe, and Australia)
Time since diagnosis of Pulmonary Arterial Hypertension (PAH)

PAH Classification:
Idiopathic
Heritable
Associated with connective tissue disease
Associated with corrected-congenital shunts
Associated with Human Immunodeficiency Virus (HIV) infection
Associated with drug or toxin exposure

Medication Use at Baseline:
PAH Therapy (none, ERAs, PDE-5 inhibitors, combo therapy)
Diuretics

Laboratory Data:
Creatinine
eGFR
BUN
Sodium
Potassium
Hemoglobin
Platelet count
NT-proBNP

Right Heart Catheterization:
mPAP
PVR
PCWP
LVEDP
RAP
Cardiac output/index

Physical Assessment/Functional Status:
6MWD
Borg dyspnea index
WHO Class
Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire (select sites)

Vital Signs:
Systolic blood pressure
Diastolic blood pressure
Heart rate
Height
Weight
BMI

**Statistical Analysis Plan:**
Objective 1
To assess eGFR slope, we will calculate eGFR from creatinine data using the revised 2021 Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration definition.11 We will use linear mixed models with eGFR as a continuous variable, a random intercept for subject, and a random slope for time to calculate eGFR slopes for each participant. We will window time as a proportion of 12 months to yield an eGFR slope in units of ml/min per 1.73 m2 per year. To analyze the association between treatment and eGFR slope, we will use linear regression with eGFR slope as the dependent variable, treatment group as the independent variable, and baseline eGFR as a covariate.

Objective 2
We will apply a mediation analysis framework to determine the extent to which eGFR slope during the course of the study mediates the influence between selexipag treatment and clinical outcomes. First, we will assess the direct effect of selexipag treatment on each respective outcome using a Cox proportional hazards model. To evaluate mediation, we will incorporate eGFR slope as a mediator in the model to determine if changes over time account for a portion of the treatment effect on the clinical outcome. We will then assess the indirect effect of selexipag treatment on the outcome through change in eGFR.

Objective 3
To evaluate how baseline kidney function influences selexipag drug levels, we will use linear regression modeling with peak selexipag drug level as the dependent variable and baseline eGFR as the independent variable. We will repeat this approach to analyze the end-of-study selexipag level and levels of the active metabolite, ACT-333679.

Software Used:
R

Project Timeline:
Projected start date: 7/1/24.
Projected analysis completion date: 10/1/24
Projected manuscript draft/submission: 11/1/24
Projected report back to YODA: 7/1/25

Dissemination Plan:
The goal of the project is publication of the results in a journal targeted to either pulmonary hypertension providers or nephrologists.

Bibliography:


