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Completed

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Clinical Study to Compare the Efficacy and Safety of Macitentan and Tadalafil Monotherapies With the Corresponding Fixed-dose Combination Therapy in Subjects With Pulmonary Arterial Hypertension (PAH) (A DUE)

ClinicalTrials.gov ID

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 NCT03904693

Sponsor

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 Actelion

Information provided by

i

 Actelion (Responsible Party)

Last Update Posted

i

 2025-04-27

Study Details Tab

Study Overview

Brief Summary

Combination therapy in pulmonary arterial hypertension (PAH) has been the subject of active investigation for more than a decade, with the benefit of targeting different pathways known to be involved in the pathogenesis of the disease. Adherence to prescribed therapy has an impact on clinical outcomes. Reducing the pill/tablet count and frequency has a major impact on patients' adherence to therapies and therefore the observed clinical outcomes. One way to simplify treatment is to use fixed-dose combination (FDC) products that combine multiple treatments targeting different pathways into a single tablet.

This study aims to demonstrate that the FDC of macitentan and tadalafil is more effective than therapy with 10 mg of macitentan alone or 40 mg of tadalafil alone. This phase 3 study will evaluate the efficacy and safety at 16 weeks of an FDC (macitentan 10 mg and tadalafil 40 mg) against these two PAH-approved therapies given as monotherapy to further confirm the added value of the FDC.

Detailed Description

PAH is characterized by a progressive increase in pulmonary arterial pressure (PAP) and in pulmonary vascular resistance (PVR) potentially leading to right heart failure and death. Current PAH-specific therapeutic options include treatments that target the three pathways (endothelin, nitric oxide, and prostacyclin pathways). While combination treatment is common, FDC pills or tablets that combine two or more PAH-specific therapies are not available, thereby requiring participants to take multiple pills/tablets daily. An FDC is an attractive option for PAH participants because it simplifies the treatment regimen by combining two therapies (which would otherwise involve a total of three tablets: one macitentan 10 mg tablet and two tadalafil 20 mg tablets) into a single tablet. Macitentan is an orally active, non-peptide, potent dual endothelin receptor A and B antagonist. Tadalafil is a selective inhibitor of phosphodiesterase type-5 (PDE-5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). This study comprises the following consecutive periods: Screening period (lasts up to 30 days), Double-

blind treatment period (consists of the titration phase [the first 2 weeks] and the maintenance phase [Week 3 through Week 16]), Open-label treatment period, End-of-Treatment (EOT), Safety follow-up (S-FU) period, and End of Study (EOS). The total study duration for a participant will be up to 30 months. Study assessments like physical examinations, vital signs, right heart catheterization, 6-minute walk test will be performed. Safety will be assessed throughout the study.

Official Title

Prospective, Multi-center, Double-blind, Randomized, Active-controlled, Triple-dummy, Parallel-group, Group-sequential, Adaptive Phase 3 Clinical Study to Compare the Efficacy and Safety of Macitentan and Tadalafil Monotherapies With the Corresponding Fixed Dose Combination in Subjects With Pulmonary Arterial Hypertension (PAH), Followed by an Open-label Treatment Period With Macitentan and Tadalafil Fixed Dose Combination Therapy

Conditions

Pulmonary Arterial Hypertension (PAH) (WHO Group 1 PH)

Intervention / Treatment

- Drug: FDC macitentan/tadalafil
- Drug: Macitentan 10 mg
- Drug: Tadalafil 40 mg
- Drug: Placebo FDC
- Drug: Placebo macitentan
- Drug: Placebo tadalafil

Other Study ID Numbers

- AC-077A301
- 2014-004786-25 (EudraCT Number)
- AC-077A301 (Other Identifier) (OTHER: Actelion Pharmaceuticals Ltd)

Study Start (Actual)

2019-07-29

Primary Completion (Actual)

2022-08-23

Study Completion (Actual)

2024-09-27

Enrollment (Actual)

187

Study Type

Interventional

Phase

Phase 3

Resource links provided by the National Library of Medicine

[MedlinePlus Genetics](https://medlineplus.gov/genetics/) (<https://medlineplus.gov/genetics/>), related topics: [Pulmonary arterial hypertension](https://medlineplus.gov/genetics/condition/pulmonary-arterial-hypertension) (<https://medlineplus.gov/genetics/condition/pulmonary-arterial-hypertension>), [Hypertension](https://medlineplus.gov/genetics/condition/hypertension) (<https://medlineplus.gov/genetics/condition/hypertension>).

[Genetic and Rare Diseases Information Center](https://rarediseases.info.nih.gov/gard) (<https://rarediseases.info.nih.gov/gard>), resources: [Pulmonary arterial hypertension](https://rarediseases.info.nih.gov/?gard_id=0007501) (https://rarediseases.info.nih.gov/?gard_id=0007501).

[Drug Information](https://dailymed.nlm.nih.gov/dailymed/) (https://dailymed.nlm.nih.gov/dailymed/) available for: [Tadalafil](https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=human&query=Tadalafil) (https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=human&query=Tadalafil). [Macitentan](https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=human&query=Macitentan) (https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=human&query=Macitentan).

[FDA Drug and Device Resources](https://clinicaltrials.gov/fda-links) (https://clinicaltrials.gov/fda-links).

Contacts and Locations

This section provides contact details for people who can answer questions about joining this study, and information on where this study is taking place.

To learn more, please see the [Contacts and Locations section in How to Read a Study Record](https://clinicaltrials.gov/study-basics/how-to-read-study-record#contacts-and-locations) (https://clinicaltrials.gov/study-basics/how-to-read-study-record#contacts-and-locations).

This study has 148 locations

United States

California Locations

-  **Fullerton, California, United States, 92835**
Providence Medical Foundation
-  **Los Angeles, California, United States, 90033**
University of Southern California

Georgia Locations

-  **Atlanta, Georgia, United States, 30309**
Piedmont Healthcare
-  **Marietta, Georgia, United States, 30060**
WellStar Health System

Illinois Locations

-  **Peoria, Illinois, United States, 61614**
OSF HealthCare Cardiovascular Institute

Iowa Locations

-  **Iowa City, Iowa, United States, 52242**
University of Iowa Hospitals and Clinics

Kentucky Locations

-  **Louisville, Kentucky, United States, 40202-1332**
Norton Healthcare

Michigan Locations

-  **Lansing, Michigan, United States, 48912**
Sparrow Clinical Research Institute

Minnesota Locations

-  **Minneapolis, Minnesota, United States, 55407**
Minneapolis Heart Institute Foundation

Missouri Locations

-  **St Louis, Missouri, United States, 63110**
Washington University School Of Medicine

Nevada Locations

-  **Reno, Nevada, United States, 89509**
VA Sierra Nevada Health Care System

North Carolina Locations

-  **Chapel Hill, North Carolina, United States, 27514**
The University of North Carolina at Chapel Hill
-  **Greenville, North Carolina, United States, 27835**
Pitt County Memorial Hospital d/b/a Vidant Medical Center

North Dakota Locations

-  **Fargo, North Dakota, United States, 58122**
Sanford Health

Ohio Locations

-  **Cincinnati, Ohio, United States, 45267**
University of Cincinnati
-  **Youngstown, Ohio, United States, 44503**
St. Elizabeth Hospital Mercy Bon Secours

Oregon Locations

-  **Portland, Oregon, United States, 97210**
Legacy Hospital
-  **Portland, Oregon, United States, 97239**
Oregon Health and Science University

Pennsylvania Locations

-  **Philadelphia, Pennsylvania, United States, 19107**
Thomas Jefferson University Hospital
-  **Pittsburgh, Pennsylvania, United States, 15213**
University of Pittsburgh Medical Center

South Dakota Locations

-  **Sioux Falls, South Dakota, United States, 57105**
Sanford Health

Texas Locations

-  **Dallas, Texas, United States, 75390**
University of Texas Southwestern Medical Center
-  **Plano, Texas, United States, 75093**
Baylor Scott White - Plano

West Virginia Locations

-  **Morgantown, West Virginia, United States, 26506**
WVU Health Sciences Center

Wisconsin Locations

-  **Madison, Wisconsin, United States, 53792**
University of Wisconsin At Madison
-  **Milwaukee, Wisconsin, United States, 53226**
Medical College of Wisconsin Froedtert Hospital

Australia

-  **Adelaide, Australia, 5000**
Royal Adelaide Hospital
-  **Hobart, Australia, 7000**
Pulmonary Arterial Hypertension Clinic

 **Milton, Australia, 4064**
Core Research Group

Brazil

-  **Belo Horizonte, Brazil, 30130-100**
Universidade Federal De Minas Gerais - Hospital das Clínicas
-  **Belo Horizonte, Brazil, 30441-070**
Instituto das Pequenas Missionárias de Maria Imaculada - Hospital Madre Teresa
-  **Botucatu, Brazil, 18618-686**
Fundacao para o Desenvolvimento Medico Hospitalar (UNESP Botucatu)
-  **Fortaleza, Brazil, 60840-285**
Secretaria da Saude do Estado do Ceara - Hospital Doutor Carlos Alberto Studart Gomes
-  **Goiânia, Brazil, 74605-020**
Universidade Federal de Goias - Hospital das Clinicas da UFG
-  **Porto Alegre, Brazil, 90035-007**
Hospital das Clinicas de Porto Alegre
-  **Porto Alegre, Brazil, 90035-074**
Irmandade Santa Casa de Misericordia de Porto Alegre
-  **Porto Alegre, Brazil, 90610-000**
Uniao Brasileira de Educacao e Assistencia Hospital Sao Lucas da PUCRS
-  **São Paulo, Brazil, 04024-002**
SPDM - Associacao Paulista para o Desenvolvimento da Medicina - Hospital Sao Paulo
-  **São Paulo, Brazil, 05403-000**
Hospital Das Clinicas Da Faculdade De Medicina Da USP

Bulgaria

-  **Sofia, Bulgaria, 1309**
National Heart Hospital
-  **Sofia, Bulgaria, 1750**
University Multiprofile Hospital for Active Treatment- UMHAT Sveta Anna AD

Canada

Alberta Locations

-  **Calgary, Alberta, Canada, T1Y 6J4**
Alberta Health Services
-  **Edmonton, Alberta, Canada, T6G 2G3**
University of Alberta

British Columbia Locations

-  **Vancouver, British Columbia, Canada, V5Z 1M9**
Vancouver General Hospital

Ontario Locations

-  **London, Ontario, Canada, N6A 5W9**
London Health Sciences Centre

China

-  **Beijing, China, 100029**
Beijing Anzhen Hospital
-  **Changsha, China, 410011**

The Second Xiangya Hospital of Central South Hospital

 Guangzhou, China, 510120

The First Affiliated Hospital of Guangzhou Medical University

 Nanjing, China

Jiangsu Province Hospital

 Shanghai, China, 200433

Shanghai Pulmonary Hospital

 Shenyang, China, 110000

The General Hospital of Northern Theater Command

 Tianjin, China, 300052

Tianjin Medical University General Hospital

 Xi'an, China, 710061

The First Affiliated Hospital of Xian Jiaotong University

Czechia

 Prague, Czechia, 128 08

General University Hospital II.department of Internal Medicine-
cardiology and angiology

Germany

 Bonn, Germany, 53105

Universitätsklinikum Bonn

 Dresden, Germany, 01307

Universitätsklinikum Carl Gustav Carus Dresden

 Giessen, Germany, 35392

Universitätsklinikum Giessen

 Greifswald, Germany, 17475

Universität Greifswald

 Hamburg, Germany, 20246

Universitätsklinikum Hamburg Eppendorf

 Heidelberg, Germany, 69126

Thoraxklinik am Universitätsklinikum Heidelberg

 Papenburg, Germany, 26871

Kardiologische Praxis Papenburg

 Regensburg, Germany, 93053

Universitätsklinikum Regensburg

 Würzburg, Germany, 97074

Klinikum Würzburg Mitte gGmbH Standort Missioklinik

Hungary

 Budapest, Hungary, 1083

Semmelweis Egyetem,Pulmonológiai Klinika

 Budapest, Hungary, 1096

Gottsegen György Országos Kardiológiai Intézet, Felnőtt kardiológiai
osztály

 Pécs, Hungary, 7624

Pecsi Tudományegyetem Klinikai Központ

 Szeged, Hungary, 6725

Szegedi Tudományegyetem

Italy

 Bari, Italy, 70124

Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari

 Brescia, Italy, 25123

Cardiologia c/o Spedali Civili

 Milan, Italy, 20122

Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico

 Monza, Italy, 20090

Azienda Ospedaliera San Gerardo

 Nuoro, Italy, 08100

Ospedale San Francesco

 Pavia, Italy, 27100

IRCCS Policlinico San Matteo, Università degli studi di Pavi

 Roma, Italy, 00161

Policlinico Umberto I

Japan

 Bunkyo City, Japan, 113-8655

The University of Tokyo Hospital

 Chiba, Japan, 260 8677

Chiba University Hospital

 Fukuoka, Japan, 812 8582

Kyushu University Hospital

 Fukushima, Japan, 960 1295

Fukushima Medical University Hospital

 Gunma, Japan, 371-0034

Gunma University Hospital

 Hiroshima, Japan, 737-8505

Kure Kyosai Hospital

 Isehara, Japan, 259-1193

Tokai University Hospital

 Kagoshima, Japan, 890-8544

Kagoshima University Hospital

 Kanazawa, Japan, 920 8641

Kanazawa University Hospital

 Kobe, Japan, 650 0017

Kobe University Hospital

 Kumamoto, Japan, 860-8556

Kumamoto University Hospital

 Kurume, Japan, 830-0011

Kurume University Hospital

 Kyoto, Japan, 602-8566

University Hospital Kyoto Prefectural University of Medicine

 Kyoto, Japan, 606 8507

Kyoto University Hospital

 Matsumoto, Japan, 390 8621

Shinshu University Hospital

 Mitaka, Japan, 181-8611

Kyorin University Hospital

 Nagasaki, Japan, 852-8501

Nagasaki University Hospital

 Okayama, Japan, 700 8558

Okayama University Hospital

 Okayama, Japan, 701-1192

National Hospital Organization Okayama Medical Center

 Sapporo, Japan, 060-8543

Sapporo Medical University Hospital

 Sapporo, Japan, 060-8648

Hokkaido University Hospital

 Sendai, Japan, 980 8574

Tohoku University Hospital

-  **Suita-Shi, Japan, 564-8565**
National Cerebral and Cardiovascular Center
-  **Tokyo, Japan, 113-8431**
Juntendo University Hospital
-  **Tsu, Japan, 514 8507**
Mie University Hospital
-  **Tsukuba, Japan, 305 8576**
University of Tsukuba Hospital

Malaysia

-  **Kuala Lumpur, Malaysia, 50400**
Institut Jantung Negara (National Heart Institute)
-  **Kuching, Malaysia, 94300**
Sarawak Heart Center

Mexico

-  **México, Mexico, 14080**
Instituto Nacional de Cardiología Dr. Ignacio Chavez
-  **Monterrey, Mexico, 64718**
Unidad de Investigacion Clinica en Medicina S.C. (UDICEM)

Poland

-  **Bialystok, Poland, 15 276**
Klinika Kardiologii Z Oddziałem Intensywnego Nadzoru
Kardiologicznego UM W Białymstoku
-  **Bydgoszcz, Poland, 85-168**
Szpital Uniwersytecki nr 2 im dr Jana Biziela w Bydgoszczy, Klinika
Kardiologii
-  **Gdansk, Poland, 80 214**
Uniwersyteckie Centrum Kliniczne
-  **Katowice, Poland, 40 635**
GCM SUM I Oddział Kardiologii
-  **Lodz, Poland, 91 347**
Oddział Kardiologii Wojewodzki Szpital Specjalistyczny im W
Bieganskiego
-  **Lublin, Poland, 20-718**
Wojewodzki Szpital Specjalistyczny im. Stefana Kardynała
Wyszynskiego SPZOZ, Oddział Kardiologii
-  **Otwock, Poland, 05-400**
ECZ Otwock Klinika Kardiologii Klinika Krazenia Plucnego Chorob
Zakrzepowo Zatorowych i Kardiologii
-  **Szczecin, Poland, 70 111**
Uniwersytecki Szpital Kliniczny nr 2 PUM Klinika Kardiologii
-  **Wroclaw, Poland, 51 124**
Wojewodzki Szpital Specjalistyczny Oddział Kardiologiczny

Russia

-  **Barnaul, Russia, 656055**
Altay Regional Cardiological Dispensary
-  **Kemerovo, Russia, 650002**
Scientific and Research Institution of Cardiovascular Diseases Complex
Problems
-  **Moscow, Russia, 121552**
National Medical Research Center of Cardiology of MoH of Russian
Federation
-  **Moscv, Russia, 129090**

GU Moscow Regional Research Clinical Institute n.a. M.F.Vla

-  **Saint Petersburg, Russia, 197341**
National medical Research Center n.a. V.A.Almazov of MoH of Russian Federation
-  **Samara, Russia, 443070**
Samara Regional Clinical Cardiological Dispensary

South Africa

-  **Durban, South Africa, 4001**
Abdullah, IA
-  **Lenasia, South Africa, 1820**
Dr Kalla

Spain

-  **Barcelona, Spain, 08036**
Hosp Clinic de Barcelona
-  **Barcelona, Spain, 8035**
Hosp Univ Vall D Hebron
-  **Madrid, Spain, 28034**
Hosp. Univ. Ramon Y Cajal
-  **Madrid, Spain, 28040**
Hosp Univ Fund Jimenez Diaz
-  **Madrid, Spain, 28046**
Hosp. Univ. La Paz
-  **Salamanca, Spain, 37007**
Hosp Clinico Univ de Salamanca
-  **Santander, Spain, 39011**
Hosp. Univ. Marques de Valdecilla
-  **Toledo, Spain, 45004**
Hosp. Virgen de La Salud
-  **Valencia, Spain, 46014**
Hosp. Gral. Univ. Valencia

Taiwan

-  **Kaohsiung City, Taiwan, 813**
Kaohsiung Veterans General Hospital
-  **Tainan City, Taiwan, 704**
National Cheng Kung University Hospital
-  **Taipei, Taiwan, 10002**
National Taiwan University Hospital
-  **Taipei, Taiwan, 10449**
Mackay Memorial Hospital
-  **Taipei, Taiwan, 112**
Taipei Veterans General Hospital
-  **Taoyuan District, Taiwan, 333**
Chang-Gung Memorial Hospital, LinKou Branch

Turkey (Türkiye)

-  **Adana, Turkey (Türkiye), 01790**
Cukurova University Medical Faculty
-  **Ankara, Turkey (Türkiye), 6100**
Hacettepe University Medical Faculty
-  **Ankara, Turkey (Türkiye), 6500**
Ankara University Medical Faculty
-  **Bursa, Turkey (Türkiye), 16310**
Bursa Yuksek Ihtisas Training and Research Hospital

-  **Istanbul, Turkey (Türkiye), 34096**
Istanbul University - Cerrahpasa Cardiology Institution
-  **Istanbul, Turkey (Türkiye), 34096**
Istanbul University Cerrahpasa Medical Faculty
-  **Istanbul, Turkey (Türkiye), 34899**
Marmara University Medical Faculty
-  **Izmir, Turkey (Türkiye), 35100**
Ege University School of Medicine
-  **Izmir, Turkey (Türkiye), 35340**
Dokuz Eylul University Hospital
-  **Kartal Istanbul, Turkey (Türkiye), 34865**
Kartal Kosuyolu Yuksek Ihtisas Egitim Ve Arastirma Hastanesi
-  **Konya, Turkey (Türkiye), 42131**
Konya Selcuk University Medical Faculty
-  **Mersin, Turkey (Türkiye), 33110**
Mersin University Medical Faculty

Participation Criteria

Researchers look for people who fit a certain description, called [eligibility criteria](#). Some examples of these criteria are a person's general health condition or prior treatments.

For general information about clinical research, read [Learn About Studies \(https://clinicaltrials.gov/study-basics/learn-about-studies\)](https://clinicaltrials.gov/study-basics/learn-about-studies).

Eligibility Criteria

Description

Inclusion Criteria:

- Signed and dated informed consent form (ICF)
- Confirmed diagnosis of symptomatic PAH in WHO FC II or III
- Symptomatic PAH belonging to one of the following subgroups of WHO Group 1 pulmonary hypertension:
 - Idiopathic
 - Heritable
 - Drug- or toxin-induced
 - Associated with connective tissue disease, HIV infection, portal hypertension or congenital heart disease with simple systemic-to-pulmonary shunt with persistent pulmonary hypertension documented by a right heart catheterization (RHC) ≥ 1 year after surgical repair
- PAH diagnosis confirmed by hemodynamic evaluation at rest (through central reading), evaluated within 5 weeks prior to randomization:
 - Mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, AND
 - Pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg, AND
 - Pulmonary vascular resistance (PVR) ≥ 3 WU (i.e., ≥ 240 dyn·sec·cm⁻⁵)
- Negative vasoreactivity test in idiopathic, heritable, and drug/toxin-induced PAH. (Participants for whom no vasoreactivity test was performed at diagnosis can be eligible if currently treated with PAH therapy for more than 3 months and PAH diagnosis confirmed by hemodynamic evaluation at least 3 months after introduction of their PAH therapy).
- Currently receiving a stable dose of ERA or PDE-5i monotherapy for at least 3 months prior to baseline RHC, within the prespecified doses in the study protocol or no history of PAH-specific treatment
- Participant able to perform the 6MWT with a minimum distance of 100 m and maximum distance of 450 m at Screening
- A woman of childbearing potential must:
 - have negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization
 - agree to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation
 - agree to follow the contraception scheme from Screening up to at least 30 days after study treatment discontinuation

Exclusion Criteria:

- Treatment with a soluble guanylate cyclase stimulator, L-arginine, any form of prostanoids or prostacyclin-receptor agonists (including oral, inhaled, or infused routes) in the 3-month period prior to start of treatment
- Treatment with combination therapy of ERA and PDE-5i in the 3-month period prior to start of treatment or history of intolerance to ERA and PDE-5i combination therapy
- Hypersensitivity to any of the study treatments or any excipient of their formulations
- Treatment with a strong cytochrome P450 3A4 (CYP3A4) inducer in the 1-month period prior to start of treatment
- Treatment with a strong CYP3A4 inhibitor or a moderate dual CYP3A4/CYP2C9 inhibitor or co-administration of a combination of moderate CYP3A4 and moderate CYP2C9 inhibitors in the 1-month period prior to start of treatment
- Treatment with doxazosin
- Treatment with any form of organic nitrate, either regularly or intermittently
- Diuretic treatment initiated or dose changed within 1 week prior to the RHC or start of treatment
- Treatment with another investigational drug in the 3-month period prior to start of treatment
- Body mass index (BMI) > 40 kg/m² at Screening
- Known presence of three or more of the following risk factors for heart failure with preserved ejection fraction at Screening:
 - BMI > 30 kg/m²
 - Diabetes mellitus of any type
 - Essential hypertension (even if well controlled)
 - Coronary artery disease, i.e. history of stable angina or known more than 50% stenosis in a coronary artery or history of myocardial infarction or history of or planned coronary artery bypass grafting and/or coronary artery stenting

- Known presence of moderate or severe obstructive lung disease any time prior to Screening as specified in study protocol
- Known presence of moderate or severe restrictive lung disease any time prior to Screening as specified in study protocol
- Clinically significant aortic or mitral valve disease; pericardial constriction; restrictive or congestive left-sided cardiomyopathy; life-threatening cardiac arrhythmias; significant left ventricular dysfunction; or left ventricular outflow obstruction, in the opinion of the investigator
- Known permanent atrial fibrillation, in the opinion of the investigator
- Known or suspected uncontrolled thyroid disease (hypo- or hyperthyroidism)
- Documented pulmonary veno-occlusive disease
- Hemoglobin < 100 g/L (<10 g/dL) at Screening
- Known severe hepatic impairment as specified in study protocol
- Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 × upper limit of normal (ULN) at Screening
- Severe renal impairment at Screening as specified in study protocol
- Systemic hypotension at Screening or Randomization and systemic hypertension at Screening as specified in study protocol
- Acute myocardial infarction or cerebrovascular event (e.g., stroke) within the last 26 weeks prior to Screening
- Known bleeding disorder, in the opinion of the investigator
- Loss of vision in one or both eyes because of non-arteritic anterior ischemic optic neuropathy
- Hereditary degenerative retinal disorders, including retinitis pigmentosa
- History of priapism, conditions that predispose to priapism (example, sickle cell anemia, multiple myeloma, or leukemia) or anatomical deformation of the penis (example, angulation, cavernosal fibrosis, or Peyronie's disease)
- Difficulty swallowing large pills/tablets that would interfere with the ability to comply with study treatment regimen
- Any planned surgical intervention (including organ transplant) during the double-blind treatment period, except minor interventions
- Exercise training program for cardiopulmonary rehabilitation in the 12-week period prior to start of treatment, or planned to be started during the double-blind period of the study
- Pregnant, planning to become pregnant or lactating
- Any known factor or disease that might interfere with treatment adherence, full participation in the study or interpretation of the results as judged by the investigator (e.g., drug or alcohol dependence etc.)
- Known concomitant life-threatening disease with a life expectancy less than (<) 12 months
- Calcium channel blocker treatment initiated, or dose changed within 3 months prior to right heart catheterization (RHC) at screening

Ages Eligible for Study ⓘ

18 Years and older (Adult, Older Adult)

Sexes Eligible for Study ⓘ

All

Accepts Healthy Volunteers ⓘ

No

Study Plan

This section provides details of the study plan, including how the study is designed and what the study is measuring.

How is the study designed?

Design Details**Primary Purpose** ⓘ : Treatment**Allocation** ⓘ : Randomized**Interventional Model** ⓘ : Parallel Assignment

Interventional Model Description: In total, approximately 170 subjects are planned to be randomized into study to receive either FDC macitentan/tadalafil or macitentan 10 mg or tadalafil 40 mg given once daily and will also receive matching placebos for two other study treatments. Treatment allocation will be stratified based on prior PAH therapy (i.e., treatment-naïve or treated by an Endothelin receptor antagonist or a Phosphodiesterase type-5 inhibitor as a monotherapy) at baseline. Sample size will be re-estimated at interim analysis if study is not terminated early for efficacy/futility up to sample size of 150-250. After completion of double-blind treatment period, subjects will continue study in an open-label treatment (OLT) period for 24 months, which may be prolonged beyond 24 months until macitentan and tadalafil are accessible at required doses, through other options according to local regulations. All assessments at end of double-blind treatment must be completed before subject enters OLT period.

Masking ⓘ : Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Arms and Interventions

Participant Group/Arm ¹	Intervention/Treatment ¹
<p>Experimental: FDC therapy + Placebo macitentan + Placebo tadalafil</p> <p>Subjects to receive FDC macitentan/tadalafil (macitentan 10 mg and tadalafil 40 mg) plus matching placebos for the two other study treatments.</p>	<p>Drug: FDC macitentan/tadalafil</p> <ul style="list-style-type: none"> Film-coated tablet with 10 mg macitentan and 40 mg tadalafil, to be administered orally once daily. Other Names: <ul style="list-style-type: none"> ACT-064992D <p>Drug: Placebo macitentan</p> <ul style="list-style-type: none"> Matching placebo not containing any active substance but otherwise identical in appearance to the respective active drug tablet, to be administered orally once daily. <p>Drug: Placebo tadalafil</p> <ul style="list-style-type: none"> Matching placebo not containing any active substance but otherwise identical in appearance to the respective active drug tablet, to be administered orally once daily.
<p>Active Comparator: Macitentan mono-therapy + Placebo tadalafil + Placebo FDC</p> <p>Subjects to receive macitentan 10 mg plus matching placebos for the two other study treatments.</p>	<p>Drug: Macitentan 10 mg</p> <ul style="list-style-type: none"> Film-coated tablet with 10 mg macitentan, to be administered orally once daily. Other Names: <ul style="list-style-type: none"> ACT-064992 <p>Drug: Placebo FDC</p> <ul style="list-style-type: none"> Matching placebo not containing any active substance but otherwise identical in appearance to the respective active drug tablet, to be administered orally once daily. <p>Drug: Placebo tadalafil</p> <ul style="list-style-type: none"> Matching placebo not containing any active substance but otherwise identical in appearance to the respective active drug tablet, to be administered orally once daily.
<p>Active Comparator: Tadalafil mono-therapy + Placebo macitentan + Placebo FDC</p> <p>Subjects to receive tadalafil 40 mg (2 x 20 mg) plus matching placebos for the two other study treatments.</p>	<p>Drug: Tadalafil 40 mg</p> <ul style="list-style-type: none"> Film-coated tablet with 40 mg tadalafil (2 x 20 mg tablets), to be administered orally once daily. <p>Drug: Placebo FDC</p> <ul style="list-style-type: none"> Matching placebo not containing any active substance but otherwise identical in appearance to the respective active drug tablet, to be administered orally once daily. <p>Drug: Placebo macitentan</p>

- Matching placebo not containing any active substance but otherwise identical in appearance to the respective active drug tablet, to be administered orally once daily.

What is the study measuring?

Primary Outcome Measures 1

Outcome Measure	Measure Description	Time Frame
Change in Pulmonary Vascular Resistance (PVR) Expressed as the Ratio of Geometric Means of End of Double-blind Treatment (EDBT) to Baseline	Change in PVR expressed as the ratio of geometric means of EDBT to baseline were reported.	Baseline, EDBT (up to 16 weeks)

Secondary Outcome Measures 1

Outcome Measure	Measure Description	Time Frame
Change From Baseline in 6-minutes Walking Distance (6MWD) to EDBT		Baseline, EDBT (up to 16 weeks)
Change From Baseline in Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) in Cardiopulmonary Symptom Domain Scores to EDBT		Baseline, EDBT (up to 16 weeks)
Change From Baseline in Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) in Cardiovascular Symptom Domain Scores to EDBT		Baseline, EDBT (up to 16 weeks)
Percentage of Participants With Absence of Worsening		Baseline, EDBT (up to 16 weeks)

in World Health Organization (WHO)			
Functional Class (FC)			
From Baseline to EDBT			

Collaborators and Investigators

This is where you will find people and organizations involved with this study.

Sponsor ⓘ

Actelion

Investigators ⓘ

- Study Director: Hany Rofael, MD, Janssen, LP

Publications

From PubMed

These publications come from PubMed, a public database of scientific and medical articles. This list is automatically created by ClinicalTrials.gov Identifier (NCT Number), and these articles may or may not be about the study.

- Grunig E, Jansa P, Fan F, Hauser JA, Pannaux M, Morganti A, Rofael H, Chin KM. Randomized Trial of Macitentan/Tadalafil Single-Tablet Combination Therapy for Pulmonary Arterial Hypertension. J Am Coll Cardiol. 2024 Jan 30;83(4):473-484. doi: 10.1016/j.jacc.2023.10.045. (https://pubmed.ncbi.nlm.nih.gov/38267108)

Study Record Dates

These dates track the progress of study record and summary results submissions to ClinicalTrials.gov. Study records and reported results are reviewed by the National Library of Medicine (NLM) to make sure they meet specific quality control standards before being posted on the public website.

Study Registration Dates	
First Submitted ⓘ	2019-04-04
First Submitted that Met QC Criteria ⓘ	2019-04-04
First Posted ⓘ	2019-04-05
Results Reporting Dates	
Results First Submitted ⓘ	2023-10-19
Results First Submitted that Met QC Criteria ⓘ	2023-10-19

Results First Posted ⓘ
2023-11-13
Study Record Updates
Last Update Submitted that met QC Criteria ⓘ
2025-04-25
Last Update Posted ⓘ
2025-04-27
Last Verified ⓘ
2025-04

More Information

Terms related to this study
Keywords Provided by Actelion
Pulmonary Arterial Hypertension
PAH
macitentan
tadalafil
fixed dose combination therapy
Additional Relevant MeSH Terms
Hypertension, Pulmonary
Lung Diseases
Respiratory Tract Diseases
Pulmonary Arterial Hypertension
Carbolines
Pyridines
Heterocyclic Compounds, 1-Ring
Heterocyclic Compounds
Indole Alkaloids
Indoles
Heterocyclic Compounds, 2-Ring
Heterocyclic Compounds, Fused-Ring
Heterocyclic Compounds, 3-Ring
Tadalafil
macitentan

Plan for Individual Participant Data (IPD)
Plan to Share Individual Participant Data (IPD)?
Yes

IPD Plan Description

The data sharing policy of the Janssen Pharmaceutical Companies of Johnson & Johnson is available at www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at yoda.yale.edu.

IPD Sharing Url

<https://www.janssen.com/clinical-trials/transparency>. (<https://www.janssen.com/clinical-trials/transparency>).

Drug and device information, study documents, and helpful links

Studies a U.S. FDA-Regulated Drug Product

Yes

Studies a U.S. FDA-Regulated Device Product

No

Study Documents Provided by Actelion

- [Study Protocol](https://cdn.clinicaltrials.gov/large-docs/93/NCT03904693/Prot_000.pdf) (https://cdn.clinicaltrials.gov/large-docs/93/NCT03904693/Prot_000.pdf) [PDF, 2.37MB, 2022-11-21]
- [Statistical Analysis Plan](https://cdn.clinicaltrials.gov/large-docs/93/NCT03904693/SAP_001.pdf) (https://cdn.clinicaltrials.gov/large-docs/93/NCT03904693/SAP_001.pdf) [PDF, 1.22MB, 2023-01-31]

Helpful Links Provided by Actelion

[RRF KOM slides](https://filehosting-v2.pharmacm.com/api/Attachment/Download?tenantId=80217051&parentIdentifier=AC-077A301&attachmentIdentifier=6a92fb9d-e152-4929-aa6b-06238109e9a5&fileName=AC-077A301_-_RRF_KOM.pptx&versionIdentifier=) (https://filehosting-v2.pharmacm.com/api/Attachment/Download?tenantId=80217051&parentIdentifier=AC-077A301&attachmentIdentifier=6a92fb9d-e152-4929-aa6b-06238109e9a5&fileName=AC-077A301_-_RRF_KOM.pptx&versionIdentifier=).