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**Please Contact:**  
**NHLBI Communications Office**  
**(301) 496-4236**  
[Nhlbi\\_news@nhlbi.nih.gov](mailto:Nhlbi_news@nhlbi.nih.gov)

## **NHLBI STOPS STUDY OF TREATMENT FOR PULMONARY HYPERTENSION IN PATIENTS WITH SICKLE CELL DISEASE DUE TO SAFETY CONCERNS**

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped a clinical trial testing a drug treatment for pulmonary hypertension in adults with sickle cell disease nearly one year early due to safety concerns. In an interim review of safety data from 33 participants who completed 16 weeks of treatment, researchers found that, compared to participants on placebo (dummy pill), participants taking sildenafil (Revatio) were significantly more likely to have serious medical problems. The most common problem was episodes of severe pain called sickle cell crises, which resulted in hospitalization. No deaths have been associated with the drug in the clinical trial.

Known as walk-PHaSST, the study was the first multicenter, randomized clinical trial to test the safety and effectiveness of sildenafil for pulmonary hypertension in patients with sickle cell disease, one of the most common genetic blood disorders in the United States. Pulmonary hypertension is a debilitating condition of high blood pressure in the arteries that carry blood to the lungs, which can lead to heart failure and death. Approximately 30 percent of sickle cell disease patients develop pulmonary hypertension, and even mild levels of pulmonary hypertension have been associated with sudden death in people with sickle cell disease.

"The increase in sickle cell medical problems is concern enough for us to stop this clinical trial to protect the safety of our participants," said NHLBI Director Elizabeth G. Nabel, M.D. "We will continue to look into the possible causes of these preliminary results. In the meantime, we encourage patients with sickle cell disease who are taking sildenafil for pulmonary hypertension to talk with their physicians about the potential risks and benefits of the medication and what actions they should consider, including whether to taper off this medication and how to best manage both sickle cell disease and pulmonary hypertension."

Because the medical problems experienced in walk-PHaSST were complications specific to sickle cell disease, "The findings of the walk-PHaSST study should not be applied to other groups of patients with pulmonary hypertension where the drug has been found to be safe and effective," Nabel added.

Researchers are conducting extensive analyses of the study results, which could contribute to recommendations for treating pulmonary hypertension in patients with sickle cell disease. They will prepare reports of their research for publication in peer-reviewed journals.

The NHLBI stopped the study on July 7, 2009, based on the unanimous recommendations of the Pulmonary Complications of Sickle Cell Disease Data and Safety Monitoring Board (DSMB), an independent advisory group that has been monitoring the study since it began. This DSMB is composed of experts in sickle cell disease, lung disease, statistics, and bioethics.

Participants in walk-PHaSST have discussed the preliminary findings of the study with their study clinicians. They have been instructed to taper sildenafil treatment over a period of three to seven days to minimize problems associated with immediate withdrawal from the drug, such as worsening of symptoms of pulmonary hypertension. Researchers will continue to monitor participants and conduct further analyses to assess the findings.

Walk-PHaSST was designed to determine whether sildenafil lessens the symptoms of pulmonary hypertension, such as shortness of breath, by improving heart and lung function, in individuals with sickle cell disease who develop pulmonary hypertension. The primary outcome measure was the results of a six-minute walk test, a standard indicator of a person's heart and lung function. Hence, the name walk-PHaSST reflects the primary test used to assess effectiveness of the treatment ("walk" test) for Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy. Researchers also evaluated the safety of the drug for sickle cell disease patients through reports of adverse effects and laboratory tests.

Sildenafil is approved by the Food and Drug Administration for use in patients with pulmonary hypertension. In general, the drug treats pulmonary hypertension by relaxing the blood vessels in the lungs to allow blood to flow more easily. Since sildenafil is not FDA-approved to treat pulmonary hypertension in patients with sickle cell disease, the walk-PHaSST study was conducted under an investigational new drug application. The FDA was notified of the termination of the study on July 14.

Walk-PHaSST began recruiting participants in July 2007 and enrolled 74 patients over the age of 19 (average age 45). Participants had sickle cell disease and mild to severe pulmonary hypertension. They were randomly assigned to receive sildenafil or placebo for 16 weeks. Participants could also receive other therapies as needed to manage sickle cell and related complications. After completing the study treatment (or placebo), participants could choose to be part of the open-label follow-up phase of the study and continue to be assessed for up to one year. In the open-label study, participants and clinicians knew that sildenafil was being taken. When the study was stopped, 33 participants had completed the clinical trial.

Researchers found that 38 percent of participants taking sildenafil had serious adverse effects -- primarily sickle cell pain crises -- compared to 8 percent of participants in the placebo group.

"Although these preliminary results are disappointing, we expect that the study's results, once fully analyzed, will provide important insights into the role of pulmonary hypertension in sickle cell disease," said Mark Gladwin, M.D., lead investigator of walk-PHaSST and director of the Vascular Medicine Institute at the University of Pittsburgh. Gladwin is also a special volunteer for the NHLBI and was formerly a senior investigator with the Critical Care Medicine Department at the NIH Clinical Center and chief of the NHLBI Pulmonary and Vascular Medicine Branch.

The design of the walk-PHaSST study was based on extensive evidence that sildenafil improves pulmonary hypertension regardless of its cause and on results of a small, open-label, nonrandomized pilot study led by Gladwin while he was at the NIH. The pilot study evaluated 12 sickle cell patients with mild or moderate pulmonary hypertension who were being treated with sildenafil and with hydroxyurea, a drug known to help reduce the numbers of episodes of sickle cell pain crises and acute chest syndrome, as well as hospitalizations and blood transfusions needed. In 2005, Gladwin and his colleagues reported that after about 6 months, sildenafil was well tolerated, decreased pulmonary blood pressure, and increased exercise capacity.

"Walk-PHaSST emphasizes the importance of multi-site, blinded, randomized clinical trials to increase our understanding of both the benefits and the potential risks of specific treatments," noted Jonathan C. Goldsmith, M.D., NHLBI project officer of walk-PHaSST. "As with all clinical studies, patient safety is paramount."

Walk PHaSST was conducted at the following locations:

- Children's Hospital, Oakland, Calif.
- University of Colorado, Denver
- Howard University Hospital, Washington, D.C.
- University of Illinois at Chicago
- Johns Hopkins Medical Institutions, Baltimore • NIH Clinical Center, Bethesda, Md.
- Albert Einstein College of Medicine, New York City • Columbia University, New York City • Children's Hospital, Pittsburgh • Imperial College London and Hammersmith Hospital, London, England

Rho Inc. of Chapel Hill, N.C., serves as the data coordinating center. Pfizer provided the treatment drug and placebo for the study.

Sickle cell anemia affects millions of people worldwide. An estimated 70,000 to 100,000 people in the United States have sickle cell disease, primarily African Americans and, to a lesser degree, people whose families come from South or Central America. Patients with this disease have abnormal hemoglobin molecules in their red blood cells. The abnormal molecules deform the red blood cells, causing them to clump together and block blood flow through blood vessels, leading to painful sickle cell crises, organ damage, and anemia. Life-threatening complications include infections, acute chest syndrome, stroke, and pulmonary hypertension. Painful crises are the leading cause of emergency room visits and hospitalizations of people who have sickle cell anemia.

There are currently no established guidelines for treating pulmonary hypertension in patients with sickle cell disease. Pulmonary hypertension can lead to heart failure and death as the heart must work harder to push blood into the lungs. In general, intensive management of sickle cell disease through hydroxyurea, blood transfusions, and/or bone marrow transplantation may be indicated. Other treatment options may include blood-thinning medicines, diuretics, and oxygen therapy.

"As new treatments have evolved over the past several years, sickle cell patients are living longer than in previous decades, presenting new challenges for managing chronic problems and complications such as pulmonary hypertension," noted Susan Shurin, MD, NHLBI deputy director and a hematologist. "The NHLBI continues to maintain a strong commitment to supporting research in adults as well as in children to discover new and better ways to improve quality of life and survival for patients with sickle cell disease."

Further information about this trial (NCT00492531) can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)<<http://www.clinicaltrials.gov>>. To arrange an interview with an NHLBI spokesperson or Dr. Gladwin, please contact the NHLBI Communications Office at (301) 496-4236 or email [nhlbi\\_news@nhlbi.nih.gov](mailto:nhlbi_news@nhlbi.nih.gov)<[mailto:nhlbi\\_news@nhlbi.nih.gov](mailto:nhlbi_news@nhlbi.nih.gov)>. Dr. Gladwin can also be reached at [gladwinmt@upmc.edu](mailto:gladwinmt@upmc.edu)<<mailto:gladwinmt@upmc.edu>>.

Part of the National Institutes of Health, the National Heart, Lung, and Blood Institute (NHLBI) plans, conducts, and supports research related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, and blood diseases; and sleep disorders. The Institute also administers national health education campaigns on women and heart disease, healthy weight for children, and other topics. NHLBI press releases and other materials are available online at [www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)<<http://www.nhlbi.nih.gov>>.

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Resources:

Sickle cell disease<[http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA\\_WhatIs.html](http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_WhatIs.html)>  
([http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA\\_WhatIs.html](http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_WhatIs.html)).

Pulmonary hypertension ([http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah\\_what.html](http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah_what.html))

Report of the National Heart, Lung, and Blood Advisory Council Subcommittee Review of the NHLBI Sickle Cell Disease Program, February 29, 2008  
([http://www.nhlbi.nih.gov/resources/docs/scd\\_program.htm](http://www.nhlbi.nih.gov/resources/docs/scd_program.htm))