CLINICAL TRIAL RESULTS

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medicine works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer, Inc.

Medicine(s) Studied: Revatio® (sildenafil)

Protocol Number: A1481316

Dates of Trial: 05 August 2013 to 31 December 2019

Title of this Trial: A Randomized Trial of Sildenafil in Babies with Breathing Problems [A Multi-Centre, Randomized, Placebo-Controlled, Double-Blind, Two-Armed, Parallel Group Study To Evaluate Efficacy And Safety Of IV Sildenafil In The Treatment Of Neonates With Persistent Pulmonary Hypertension Of The Newborn (PPHN) Or Hypoxic Respiratory Failure And At Risk For PPHN, With A Long Term Follow-Up Investigation Of Developmental Progress 12 And 24 Months After Completion Of Study Treatment]

Date of this Report: 20 December 2019

– Thank You –

Pfizer, the Sponsor, would like to thank you for your participation in this clinical trial and provide you a summary of results representing everyone who participated. If you have any questions about the study or results, please contact the doctor or staff at your study site.

WHY WAS THIS STUDY DONE?

"Persistent pulmonary hypertension of the newborn" (PPHN) is a serious condition that can affect the breathing of newborn infants and prevent them from getting enough "oxygen". Oxygen is a gas that is present in the air and all human and animals need this gas to live and grow. The main symptoms of PPHN includes fast breathing and increased heart rate as well as a blue tint to the skin, flaring of the nostrils in the nose, and sometimes the baby can make a grunting noise. PPHN is seen in about 2 births in every 1000 births, and around 1 in 10 babies who have breathing problems will have PPHN.

The normal treatment for PPHN is to give babies nitric oxide gas to breathe. This inhaled nitric oxide only helps 2 out of every 3 babies to get enough oxygen. If the inhaled nitric oxide doesn't help the baby, the next step for doctors is to try "extracorporeal membrane oxygenation" or ECMO. ECMO is a way of getting oxygen into the baby's blood with a machine and can help if the "lungs" and/or heart aren't working properly. The lungs are air sacs that fill with oxygen-containing air and the lungs are used to get oxygen into the blood.

Sometimes babies with PPHN will pass away even if they receive treatment with inhaled nitric oxide and/or ECMO. Other babies will survive, but they may have developmental problems that make it hard for them to grow, learn things, and hear sounds. New treatment options are needed to help the heart and lungs get enough oxygen into the baby's blood.

Revatio® (sildenafil citrate) is a medicine that can help blood vessels in the lungs relax. By doing this, the amount of blood that can flow to and from the lungs in these blood vessels is increased, which may help get oxygen to where it is needed. The researchers did this study to see if sildenafil given by "infusion" along with inhaled nitric oxide was able to help improve breathing in babies with PPHN or babies with hypoxic respiratory failure (HRF) who are likely to get PPHN. In an infusion, the medicine is slowly dripped from a bag into a tube that is connected to a needle, which has been "injected" or pushed through a patient's skin into a vein. The vein then carries the medicine in the blood around the body.

WHAT HAPPENED DURING THE STUDY?

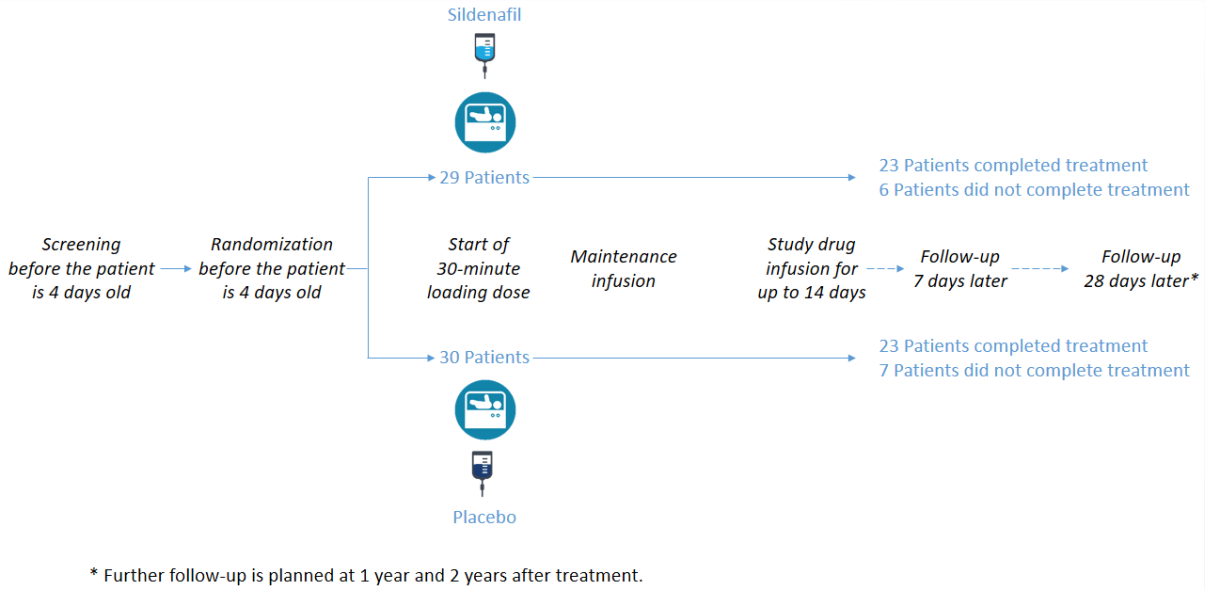
This study compared 2 groups of patients to find out if patients with PPHN or at risk of getting PPHN who received an infusion of sildenafil compared with patients given "placebo" had:

- A lower "treatment failure rate", and
- Inhaled nitric oxide therapy for a shorter amount of time.

A placebo does not have any medicine in it, but looks just like the medicine. Treatment failure was said to have occurred if the patient needed additional treatment for their PPHN or if they needed ECMO, or if the patient passed away.

The study included patients who were 4 days old or younger and who had PPHN or HRF and who were at risk of getting PPHN. The PPHN could be of no known cause or could be due to "meconium aspiration syndrome" (breathing in fecal matter produced by the baby while in the womb), "sepsis" (blood poisoning caused by bacteria) or "pneumonia" (infection in the lungs caused by bacteria or a virus).

The patients and researchers did not know who was given sildenafil and who was given placebo. This is known as a "blinded" study. Volunteers were assigned to each group by chance alone. This is done to make the groups more similar, which makes comparing the groups more fair.



While patients were only in the main study for up to 6 weeks, this part of the study took over 5 and a half years to complete. Follow-up is continuing for an additional 1 and 2 years and this phase of the study is ongoing .The sponsor ran this study at 25 locations in 11 countries in Europe and North America. It began on 05 August 2013 and ended on 31 December 2019. A total of 33 boys and 26 girls participated. All patients were 4 days old or younger.

Patients were to be treated for up to 14 days. Of the 59 patients who started the study, 46 finished the treatment phase. A total of 13 patients did not complete the treatment phase and this was their parent's choice, because a doctor decided it was best for a patient to stop the study, or the patient passed away. Some of the patients who left the study still took part in the follow-up.

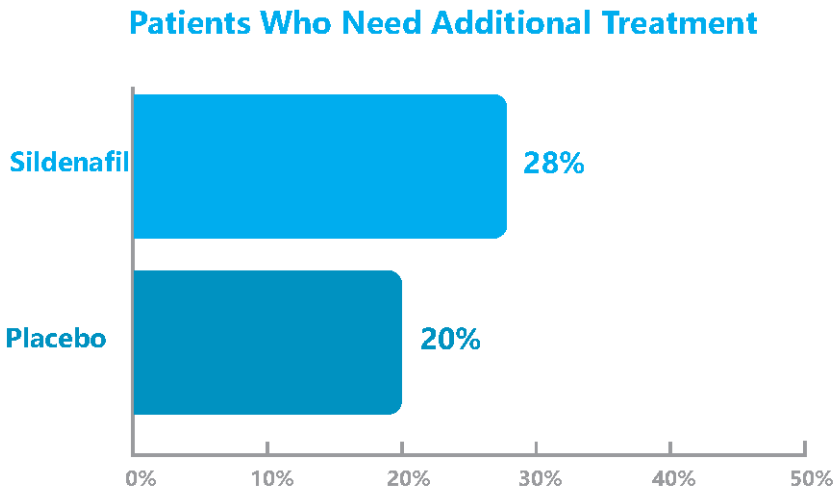
As of 31 January 2019 (the data cutoff date for the main report), the Sponsor began reviewing the information collected. The Sponsor then created a main report of the results. This is a summary of that report.

WHAT WERE THE RESULTS OF THE STUDY?

What was the treatment failure rate in patients given sildenafil compared with those given placebo?

Treatment failure was said to happen if a patient needed additional treatment for their PPHN, if ECMO was needed, or if the patient passed away. The researchers looked at the number of patients who needed additional treatment, ECMO, or who passed away in the group given sildenafil and compared this with the group given placebo. This gave the researchers the treatment failure rate for sildenafil and placebo.

Treatment failure by Day 14 was seen in 8 patients in the sildenafil group (28%, or 8 out of 29 patients) and in 6 patients in the placebo group (20%, or 6 out of 30 patients). The researchers did not think there was any real difference in the treatment failure rate between the 2 groups (see figure).



The reasons for treatment failure were similar between groups and these are shown in the following table.

Number of Patients With Each Type of Treatment Failure by Day 14		
Type of Treatment Failure	**Sildenafil (29 Patients treated)**	**Placebo (30 Patients treated)**
Additional PPHN treatment	**4 (14%)**	**3 (10%)**
Need for ECMO treatment	**3 (10%)**	**3 (10%)**
Patient died	**1 (3%)**	**0**

Based on these results, the researchers thought that sildenafil was no different to placebo when given with inhaled nitric oxide treatment in patients with PPHN or HRF and at risk of PPHN. Any differences between the groups were most likely a result of chance.

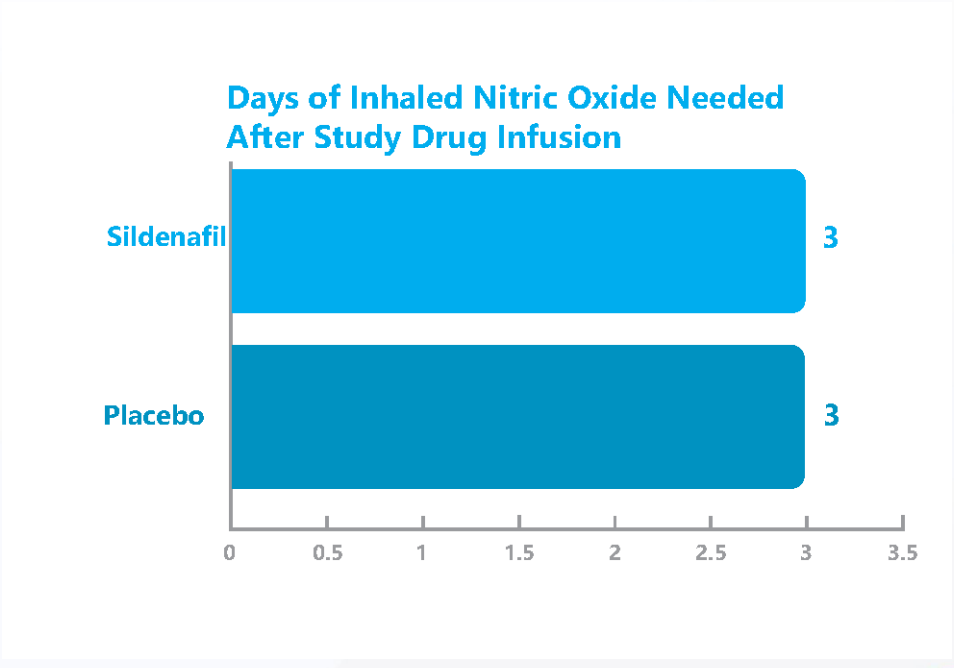
How long did patients need inhaled nitric oxide treatment after being given sildenafil or placebo?

A total of 21 patients in the sildenafil group (72%, or 21 out of 29 patients) and 24 patients in the placebo group (80%, or 24 out of 30 patients) did not experience treatment failure.

The researchers then counted the number of days of treatment with inhaled nitric oxide that patients were given before and after the sildenafil or placebo infusion. The researchers took the result (in the number of days) and put the values in order from the smallest to the largest. They then looked at the middle number, or "median", to help them answer this question.

Inhaled nitric oxide treatment was given for a median of 1 day to all patients in both treatments groups before the infusion of sildenafil or placebo was started. After the sildenafil or placebo infusion was given, inhaled nitric oxide treatment was continued for a median of 3 days in both groups (see figure).

These results show there was no difference between groups in the number of days of inhaled nitric oxide treatment given to patients without treatment failure.



This does not mean that everyone in this study had these results. Other studies may produce different results, as well. These are just some of the main findings of the study, and more information may be available at the websites listed at the end of this summary.

WHAT MEDICAL PROBLEMS DID PATIENTS HAVE DURING THE STUDY?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment, or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what the side effects of an experimental drug might be.

A total of 41 out of the 59 patients in this study had at least 1 medical problem and 8 patients did not finish the study treatment because of medical problems. This included 14%, or 4 out of 29 patients in the sildenafil group and 13%, or 4 out of 30 patients in the placebo group. The most common medical problems are listed in the following table.

Most Common Medical Problems (Reported by More Than 2 of Patients in Any Group)		
Medical Problem	**Sildenafil (29 Patients Treated)**	**Placebo (30 Patients Treated)**
Low blood pressure	8 (28%)	3 (10%)
Low levels of potassium in the blood	7 (24%)	0
Low numbers of red blood cells in the blood	4 (14%)	3 (10%)
Drug withdrawal	4 (14%)	0
Collapsed lung	2 (7%)	4 (13%)
Low heart rate	3 (10%)	1 (3%)
Swelling	1 (3%)	3 (10%)
High levels of the protein bilirubin in the blood, which can mean red blood cells are being broken down	1 (3%)	3 (10%)
Increased levels of C-reactive protein, which can mean inflammation is present	0	3 (10%)

WERE THERE ANY SERIOUS MEDICAL PROBLEMS?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

During this study, 9 patients had serious medical problems; 7 patients in the sildenafil group (24%, or 7 out of 29 patients) and 2 patients in the placebo group (7%, or 2 out of 30 patients). Only 1 of these serious medical problems was thought by the doctors to be related to treatment. This was a report of low blood pressure and this was seen in a patient given sildenafil. Treatment with sildenafil was stopped because of this serious medical problem.

There were 3 patients who passed away during this study (2 patients in the sildenafil group and 1 patient in the placebo group). The doctors did not think any of these deaths were due to the study treatment.

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT01720524***
www.clinicaltrialsregister.eu	Use the study identifier **2012-002619-24**
www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **A1481316**

* Results expected to be available soon

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!