

CONFIDENTIAL

Abstract:

Title: Open-label Phase 1 study to investigate drug - drug interactions between pulsed, inhaled nitric oxide (INO) and Sildenafil in healthy volunteers

Background: Inhaled Nitric Oxide (INO) has been approved for use in infants with hypoxic respiratory failure. Nitric oxide is a selective pulmonary vasodilator, whose action is mediated by the cyclic guanosine monophosphate (cGMP) pathway. Hence, studies are being conducted to assess the Efficacy and Safety of Inhaled Nitric Oxide for use in adults with Pulmonary Arterial Hypertension (PAH). Patients that have PAH may already be on 2-3 PAH specific drugs such as Sildenafil. Sildenafil is a selective inhibitor of cGMP- specific phosphodiesterase type 5, whose prescribing label has a warning against the use of nitrates due to the risk of hypotension, since both sildenafil and nitrates act via the cGMP pathway. However, no interaction studies have been done between Sildenafil and Nitric Oxide.

Aim: The objective of this study is to investigate the potential pharmacodynamic interaction between pulsed Inhaled Nitric Oxide and Sildenafil in healthy volunteers.

Methods: 5 healthy volunteers would receive Sildenafil for 24 hours prior to the addition of inhaled nitric oxide. Changes in pharmacodynamics parameters such as Heart Rate, Blood Pressure, and Oxygen Saturation after dosing with both drugs will be assessed for 27 hours and hourly for 4 hours post inhaled nitric oxide discontinuation.

Results: There was no further decline in the Systolic and Diastolic Blood Pressures at peak levels of nitric oxide metabolites, which corresponds to the 6th and 7th dose of Sildenafil, compared to the Blood Pressure values observed at first 3 doses of Sildenafil alone, and Sildenafil dose 4 and 5 which was given in combination with INO.

Conclusion: No synergistic adverse drug-drug interaction was observed between Inhaled Nitric Oxide and Sildenafil at peak levels of metabolites in all volunteers in this study.

- Authors:
 - Primary: Peter Fernandes
 - Co Author: Bobae Kim
 - Co Author: Rachel Pinto
 - Co Author: Parag Shah
 - Co Author: Deborah Quinn

Peter Fernandes, M. Pharm

VP/Chief Regulatory, Safety & Quality Officer

84 Liberty Corner Road, Suite 302 | Warren, NJ 07059

Cell: 973 856 2900

