Open-label Phase 1 Study to Investigate Drug-Drug Interactions between pulsed Inhaled Nitric Oxide (iNO) and Sildenafil in Healthy Volunteers

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Background: Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (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 studies have been done to date that investigate the interaction between pulsed iNO and Sildenafil.

Aim: The objective of this study was to investigate the potential pharmacodynamic interaction between pulsed iNO and Sildenafil in healthy volunteers.

Methods: 5 healthy volunteers received Sildenafil for 24 hours prior to the addition of iNO via the INOpulse® delivery system. Changes in pharmacodynamic parameters such as Heart Rate, Blood Pressure (BP), and Oxygen Saturation after dosing with both drugs were assessed for 27 hours and hourly for 4 hours post iNO discontinuation **(Figure 1).**

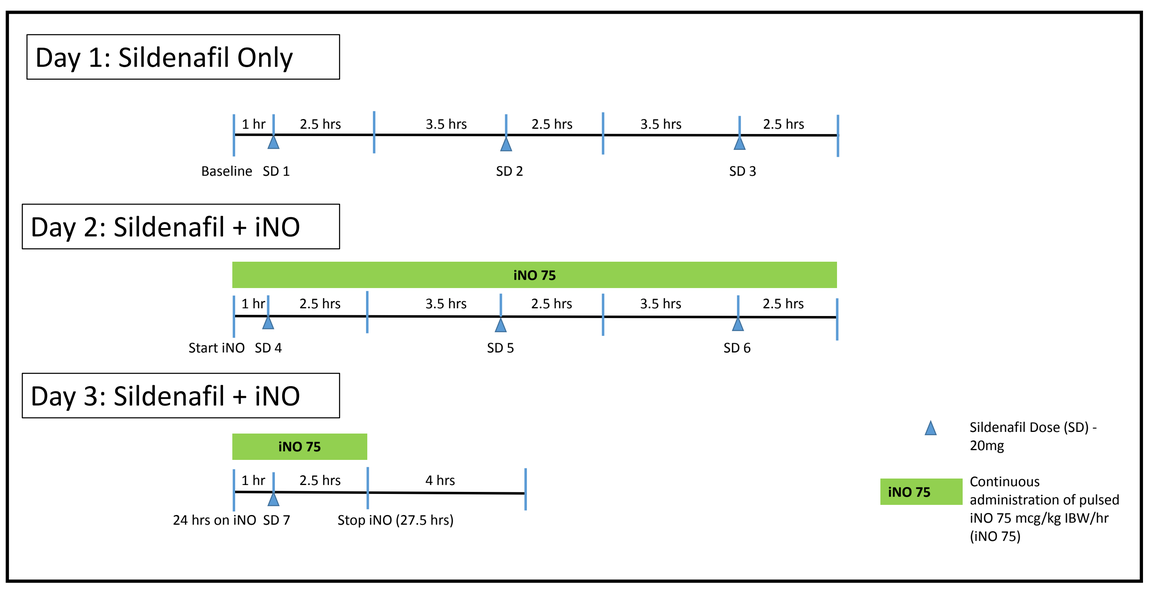

Figure 1: Dose Administration Schedule for Continuous, Pulsed iNO (iNO 75) and Sildenafil Dose (▲). On Day 1 (Sildenafil Only), vital sign assessments (I) were performed prior to and following each administered dose of Sildenafil (SD 1, SD 2 and SD 3) to confirm stable BP. On Day 2 (Sildenafil + iNO), iNO was continuously administered 1 hour before Sildenafil Dose 4 (SD 4) and discontinued 2.5 hours after reaching a peak dose of Sildenafil (SD 7). Vital sign assessments (I) were taken throughout Day 2 and 3 as indicated, with the last assessment performed 4 hours after iNO administration was terminated.

Results: There was no further decline in the average Systolic (**Figure 3**) and Diastolic BP of all subjects (**Figure 4**) when peak levels of nitric oxide (NO) metabolites were measured (**Figure 2**), which corresponds to the Sildenafil Dose 6 and 7 (SD 6 and SD 7), compared to BP values on Day 1 - Sildenafil alone (SD 1-3), and Day 2 - Sildenafil (SD 4; SD 5) given in combination with Continuous iNO. There was no other clinically relevant change in any of the other parameters tested.

Discussion: In our study, we continuously administered pulsed iNO to subjects, after the administration of Sildenafil. None of the subjects experienced hypotension at peak levels of NO metabolites (**Figures 3 & 4**). Pulsed iNO has a local vasodilatory effect that preferentially targets the lung tissue, thus resulting in no systemic vasodilatory or hypotensive effects.[1] iNO when administered with PDE-5s, such as Sildenafil, does not have additive systemic hemodynamic effect when administered either acutely or chronically.

References: 1. Hajian, Bita, et al. "Unravelling The Mode Of Action Of Pulsed Inhaled Nitric Oxide In Severe IPF Using Functional Respiratory Imaging (fri)." *A42. NEW DEVELOPMENTS IN ILD RESEARCH*. American Thoracic Society, 2017. A1560-A1560.

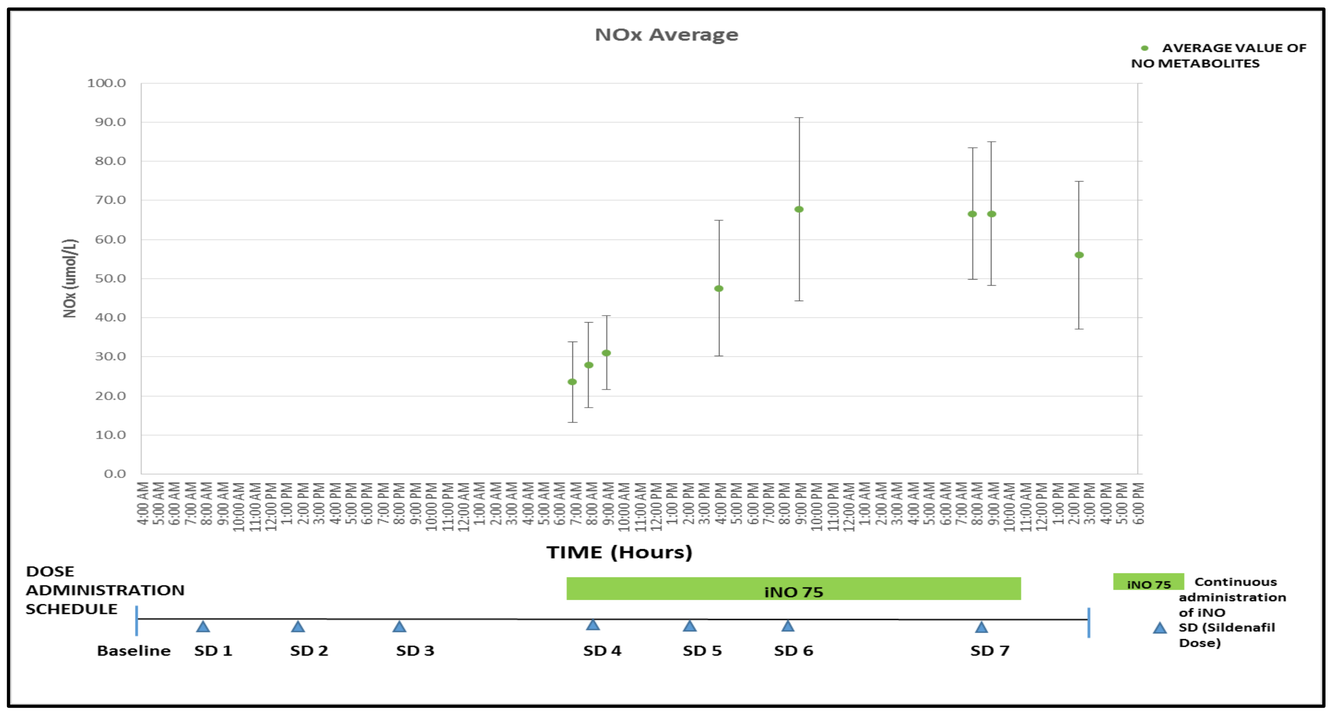

Figure 2 Average Value of Measured Nitric Oxide (NO) Metabolites Relative to Dose Administration with the standard deviation for all subjects. Samples were collected on Day 2, prior to iNO (iNO 75), just prior to Sildenafil (▲) Dose 4 and 1 hour post SD 4, 2 hours post SD 5, 1 hour post SD 6, just prior to and 1 hour post SD 7 and 4 hours post iNO discontinuation. Levels of NO metabolites measured show peak values correspond to the administration of SD 6 and SD 7.

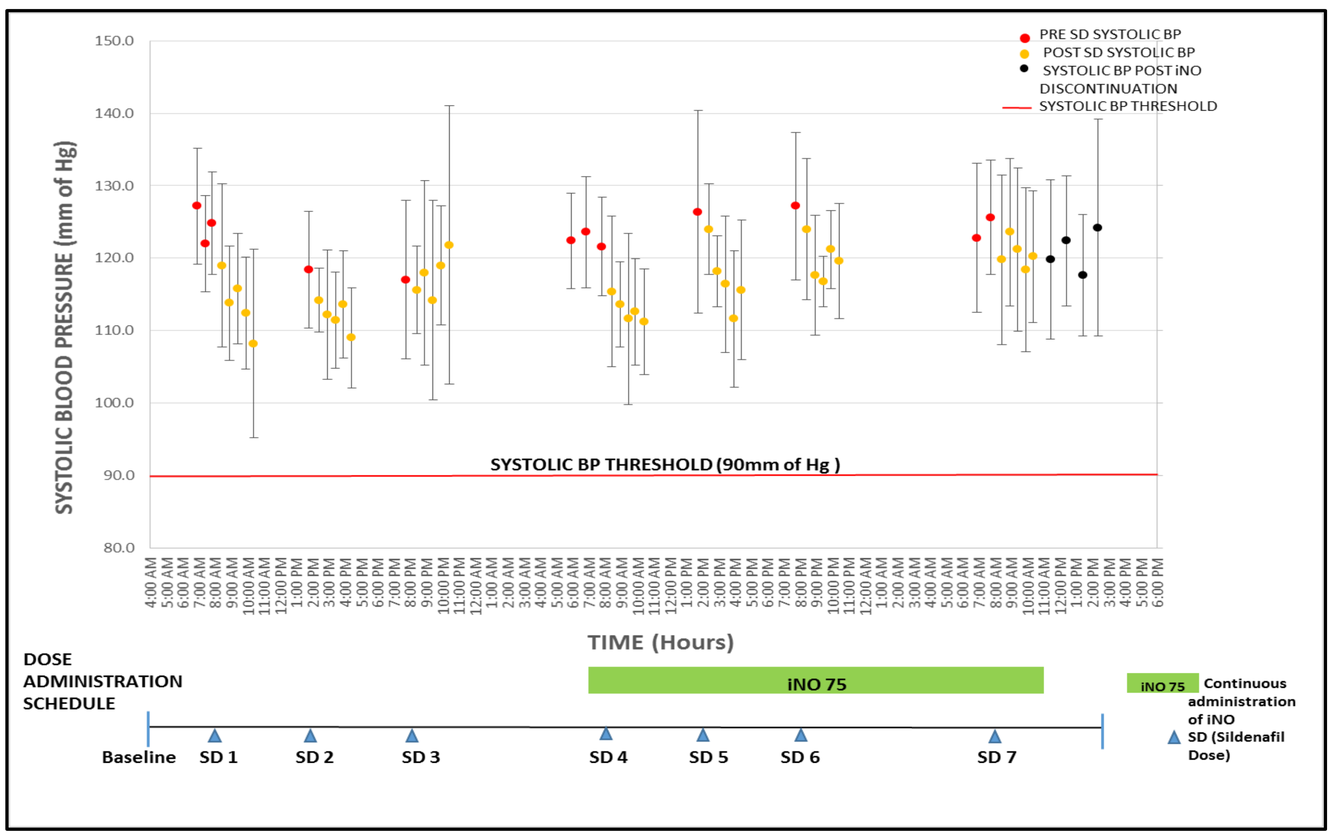

Figure 3 Average of Changes in Systolic Blood Pressure for all Subjects. There were no notable BP drops relative to the threshold level of Systolic BP (— 90mm of Hg). The average systolic BP of all subjects with standard deviation bars are shown in the figure above where drops were seen post sildenafil dose administration (● POST SD SYSTOLIC BP) compared to the systolic BP prior to sildenafil dose administration (● PRE SD SYSTOLIC BP). At peak levels of NO metabolites corresponding to Sildenafil Dose SD 6 and SD 7, there was no further relevant decrease in BP. Systolic BP was also monitored 4 hours post iNO (iNO 75) discontinuation (● SYSTOLIC BP POST iNO DISCONTINUATION) and no rebound was observed post iNO discontinuation.

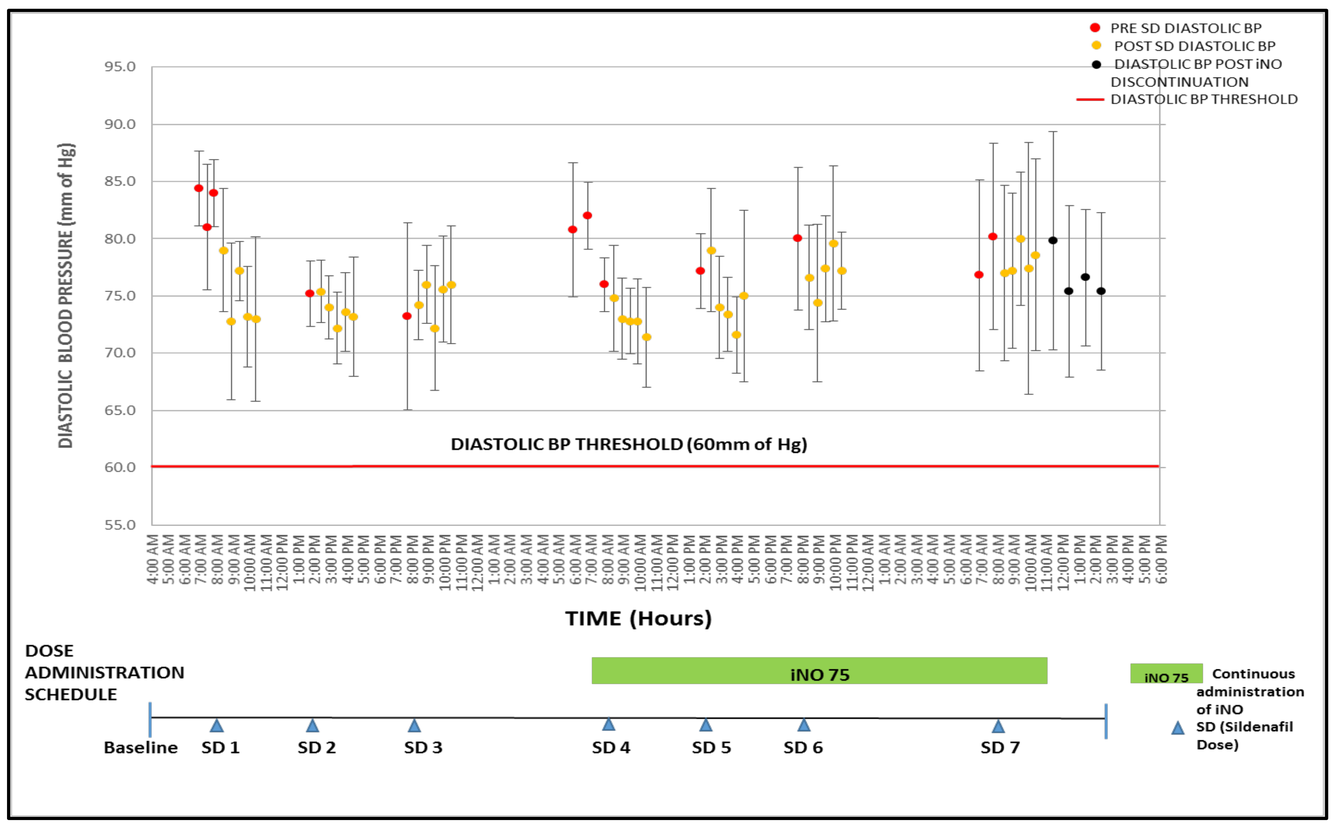

Figure 4 Average of Changes in Diastolic Blood Pressure for all Subjects there were no notable BP drops relative to the threshold level of Diastolic BP (—60mm of Hg). The average diastolic BP of all subjects with standard deviation bars are shown in the figure above. Diastolic BP drops were seen post sildenafil dose administration (● POST SD DIASTOLIC BP) compared to the diastolic BP prior to sildenafil dose administration (● PRE SD DIASTOLIC BP). At peak levels of NO metabolites corresponding to Sildenafil Dose SD 6 and SD 7, there was no further relevant decrease in BP. Diastolic BP was also monitored 4 hours post iNO (iNO 75) discontinuation (● DIASTOLIC BP POST iNO DISCONTINUATION) and no rebound observed post iNO discontinuation.

Conclusion: No potential DDI (hypotension) was seen in subjects when iNO (at peak iNO metabolites) was added to sildenafil (at peak), and results were consistent across all subjects.