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Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial

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Sildenafil in severe pulmonary hypertension associated with copd: a randomized controlled multicenter clinical trialSildenafil treatment for severe pulmonary hypertension in COPD

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SILDENAFIL IN SEVERE PULMONARY HYPERTENSION ASSOCIATED WITH COPD: A RANDOMIZED CONTROLLED MULTICENTER CLINICAL TRIAL

Short Title: Sildenafil treatment for severe pulmonary hypertension in COPD

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ABBREVIATIONS LIST

6MWT: 6-minute walk test

A-a O_2 gradient: alveolar-arterial O_2 gradient

ABG: arterial blood gases

CI: cardiac index

CO: cardiac output

COPD: chronic obstructive lung disease

DLCO: diffusing capacity of the lung for carbon monoxide

FEV1: forced expiratory volume in 1 second

FiO_2: fraction of inspired oxygen

FVC: forced vital capacity

HR: heart rate

mPAP: mean pulmonary artery pressure

O2 desat.6MWT : oxygen desaturation at the end of 6MWT

PAH: pulmonary arterial hypertension

$PaCO_2$: partial pressure of carbon dioxide

PaO_2: partial pressure of oxygen in arterial blood

PH: pulmonary hypertension

PH-COPD: pulmonary hypertension associated with COPD

PVR: pulmonary vascular resistance

PWP: pulmonary wedge pressure

QoL: quality of life questionnaire

RAP: right atrial pressure

RHC: right heart catheterization

RV: residual volume

sPAP: systolic pulmonary arterial pressure

SVR: systemic vascular resistance

SVI: stroke volume index

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TPVR: total pulmonary vascular resistance

TLC: total lung capacity

ABSTRACT

Background. Pulmonary hypertension (PH) is a well known independent prognostic factor in chronic obstructive pulmonary disease (COPD), and a sufficient criteria for lung transplant candidacy. Currently, there is little data available on the hemodynamic and clinical impact of phosphodiesterase 5 (PDE-5) inhibitors in patients with severe pulmonary hypertension associated with COPD (PH-COPD). The aim of the present study is to assess the effect of sildenafil on pulmonary hemodynamics and gas exchange in severe PH-COPD.

Methods. This is a multicenter, randomized, placebo-controlled double-blind trial. After the screening evaluation, patients were randomized to receive 20 mg sildenafil or placebo TID (ratio 2:1) for 16 weeks. The primary end-point was the reduction in pulmonary vascular resistance (PVR). Secondary end-points included BODE index, 6-minute walk test (6MWT), and quality of life questionnaire (QoL). PaO_2 changes were evaluated as a safety parameter.

Results. The final population included 28 patients, 18 in the sildenafil group and 10 in the placebo group. At 16 week, patients treated with sildenafil had a decrease in PVR (mean difference with placebo -1,4 WU; 95% CI ≤ -0.05, p=0.04). Sildenafil also improved the BODE index, DLCO% and QoL. Change from baseline in PaO_2 was not significantly different between the sildenafil and placebo groups.

Conclusions. In this pilot study, treatment with sildenafil reduced TPVR and improved the BODE index and QoL, without significal impact on gas exchange.

Keywords:
pulmonary hypertension, chronic obstructive pulmonary disease, sildenafil, BODE index, end stage lung disease, lung transplantation,

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INTRODUCTION

Pulmonary hypertension (PH) is a condition frequently observed in chronic obstructive pulmonary disease (COPD).[1,2,3] Usually, PH-COPD is mild/moderate (mPAP 25-35 mmHg), but in 3-5% of COPD patients a severe PH (mPAP >35 mmHg) occurs.[3,4]

The clinical impact of PH in COPD is relevant as it represents an independent predictor of poor prognosis and a sufficient criteria for lung transplant candidacy.[4,5,6]

The pathogenesis of severe PH in COPD is not completely explained by simple hypoxic vasoconstriction mechanism,[7] and recent data from the pathological analysis of COPD lungs explanted for transplantation showed a correlation between the type/extention of pulmonary vascular lesions and the severity of PH assessed by right heart catheterization (RHC)[8].

Despite the independent prognostic effect of PH in COPD, only few randomized controlled studies addressed the question if pulmonary arterial hypertension (PAH) drugs may be effective in the treatment of PH in COPD.[8,9,10,11] Generally the overall results were inconclusive, as their inclusion criteria varied widely (definition of PH, mPAP cut-off, severity of obstruction) and their study designs were incomparable. Moreover, a worsening of gas exchange was reported in COPD patients with mild PH treated with sildenafil.[13]

In the present prospective randomized controlled proof-of-concept study we investigate whether sildenafil improves rest pulmonary hemodynamic in severe PH-COPD without detrimental effect on gas exchange.

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METHODS

Study overview

The study is an investigator-driven trial (ISS) funded by Pfizer and sponsored by AIPO (Associazione Italiana Pneumologi Ospedalieri) performed in Italy. The funder donated sildenafil and identical tablets containing placebo, but took no part in the study design, in the accrual or analyses of data, and in the preparation of the manuscript. The study was conducted by seven Italian centers with expertise in the management of PH and COPD, most of which are also lung transplant centers. ISMETT (Istituto Mediterraneo per I Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy) served as data-coordinating center, and managed all aspects of the study, data management, and statistical analysis. The study was approved by the Institutional Review Boards of each center, and all the patients signed informed consent before enrolment. The trial was registered on the www.clinicaltrials.gov Web site (NCT0144193).

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Study patients

We included patients between the ages of 40 and 80 years, diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines.[14]

Patients were excluded if they had decompensated heart failure, severe mental disorder preventing appropriate judgment concerning study participation, known intolerance or formal contraindication for the use of sildenafil.

Patients with COPD referred for a suspicion of PH were screened with Doppler echocardiography: an estimated sPAP > 50 mmHg was the indication for the baseline RHC.

In order to identify patients with significant PH in respect to airflow limitation, we enrolled patients with mPAP ≥ 35 mmHg in the case of FEV1 < 30% of predicted value after bronchodilator, and mPAP ≥ 30 mmHg for a FEV1 > 30% of predicted value after bronchodilator.

Other potential causes of PH, such as chronic thromboembolic pulmonary hypertension or left heart disease were excluded, as was ischemic or cardiac valve disease. Patients in concomitant nitrate or

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PAH treatment or with liver/kidney dysfunction or suffering from a recent bronchial exacerbation (< 4 weeks) were excluded.

Study design

SPERIC-1 is a 16-week, double-blind, multicenter, randomized, placebo-controlled trial of oral sildenafil (20 mg) given three times a day. Patients who met the eligibility criteria were screened with transthoracic echocardiogram, and after the baseline evaluation including the confirmatory RHC, spirometry, arterial blood gas analysis and 6MWT they were randomized with a 2:1 ratio to receive sildenafil or matched placebo. The randomization was managed by a pharmacologist, not involved directly in the study, by means of an electronic system. At the end of study, after 16 weeks of treatment, a second clinical and hemodynamic assessment was made.

Outcome measures

The primary end-point was the improvement in pulmonary hemodynamics assessed by the change in pulmonary vascular resistances (PVR) at the end of the study, as compared with the baseline. Additional end-points included changes from baseline of the following parameters: PaO_2, BODE index, 6MWT distance, and quality of life (SF36 questionnaire).

Safety Evaluations

As sildenafil may worsen pulmonary gas exchange in COPD,[12] the candidates were evaluated for their arterial blood gases (ABG) in stable condition before randomization. Patients in long-term oxygen therapy (≤ 6 L/min flow) were accepted. The cut-off value of $PaCO_2$ for inclusion was set at ≤ 55 mmHg. For safety reason all subjects after taking the first dose of blind study medication underwent a second ABG: a drop of PaO_2 below 55 mmHg was considered inacceptable and the patient excluded from the study.

During the study peripheral SO_2% and ABG were repeated monthly at the same O_2 flow level of the screening assessment. We also recorded the number and severity of acute COPD exacerbation

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episodes, and recorded any adverse event.

Procedures

Echocardiographic screening was done according to the American Society of Echocardiography recommendations[15]. Systolic pulmonary arterial pressure was estimated by the measurement of the velocity of tricuspid regurgitant flow in a 4-chamber view, and the estimate of right atrial pressure from the dimension and collapsibility of the inferior vena cava.[15]

Hemodynamic evaluation was done with a standard technique. Pressures were measured after zeroing the system at mid-chest position with a fluid-filled catheter. All pressures were measured at end expiration. Cardiac output (CO) was measured in triplicate with the thermodilution technique, and pulmonary vascular resistance was calculated with the formula PVR=(mPAP - pulmonary capillary wedge pressure PWP)/CO.

Pulmonary function tests were done according to the European Respiratory Society standards.[16]Diffusing capacity for carbon monoxide was measured by the single breath technique. A specimen of arterial blood was taken with the patient seated and breathing room air or oxygen supplementation. The pH, $PaCO_2$ and PaO_2 were measured with a commercially available blood gas analyzer.

Exercise capacity was measured with the non-encouraged 6-minute walk test done in a 25-meter long corridor in the same environmental conditions and at about the same time of day (+2 h).[17]

Quality of life was analyzed using the SF-36 generic questionnaire (Medical Outcomes Study 36-item Short-Form Health Survey).[18]

STATISTICAL ANALYSIS

Categorical variables are described as frequencies and percentages, continuous variables as mean ± standard deviation or median and interquartile range, when appropriate.

To compare baseline values, Fisher's exact test was used for categorical variables, and two-sample t

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test, or the Wilcoxon rank-sum test was used for continuous variables, when appropriate. The level of statistical significance was set at 5%, and two-sided p-values and relative CI intervals were reported.

The primary efficacy analysis was done on the intention-to-treat (ITT) population. (Fig. 3). Safety analysis was done on the complete group of randomized patients.

For three patients with missing end-of-study RHC, a missing at random (MAR) mechanism was assessed.[20] The mixed-effects linear regression model with EM imputation method[21]was applied in order to assess the efficacy of sildenafil over placebo. The EM method leads to unbiased estimate with the MAR mechanism.[20] Last observation carried forward (LOCF) imputation method was not applied because, even under the unrealistically strong assumption of completely missing at random mechanism (MCAR), it was demonstrated that the bias in the LOCF estimator typically does not vanish and, even more importantly, the bias can be positive or negative.[21-24] The same regression method was applied for the secondary outcome measures. In order to assess the efficacy of sildenafil over placebo, the level of statistical significance was set at 5%, and one-sided p-values and CI intervals were reported. All analyses were done using the statistical software STATA version 13.1 (STATA StataCorp. College Station, Texas, US).

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RESULTS

Study population

The study lasted 12 months from March 2012 to March 2013. Thirty-one patients were recruited. Three patients did not receive the first dose of sildenafil/placebo and were excluded from the final analysis. Twenty-eight patients completed the study: 18 on sildenafil and 10 on placebo. Three patients did not perform the end-of-study RHC for refuse or technical reasons and were included in the ITT analysis. Fig.1 shows the patients disposition.

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Baseline demographic characteristics were similar between the two groups (Tab. 1): patients had moderate airway obstruction but severely impaired DLCO, mean PaO_2 was > 70 mmHg with low flow oxygen requirement, $PaCO_2$ was close to the normal range. The sildenafil group had a trend towards a shorter distance at the 6MWT (229.2±101.4 vs. 308.5±99.6 meters, p= 0.06). Both groups at baseline had severe pre-capillary hypertension (19 patients (68%) had mPAP ≥ 35 mmHg and 11 (39%) ≥ 40 mmHg (Tab. 1 and Fig. 2) with preserved cardiac index and right atrial pressure.

Outcome measures

Primary end-point and hemodynamic variables (see Table 2 and Fig 3)

Changes from baseline to week 16 in the PVR were different in the two treatment groups, with a mild increase in the placebo arm, and a decrease in the sildenafil arm. In the intention-to-treat population, the placebo-corrected difference in PVR and TPVR after 16 weeks of sildenafil was statistically significant (PVR -1.4 WU, 95% CI ≤.-0.05; p 0.044; TVPR -1.8 WU, 95% CI ≤-0.21, p 0.032). In the treated group cardiac index (CI) increased significantly (placebo corrected change +0.42 l/min/m^2, 95% CI ≥ 0.16; p 0.0036), as well as stroke volume index (SVI) (+ 8 mL/m^2, 95% CI ≥ 4; p 0.0007) without significant reduction in mPAP (placebo corrected change -1.44 mmHg, , 95% CI ≤ 4.44; p 0.3). Right atrial pressure (RAP) remained unchanged.

Secondary end-points (see Table 3-4 and Fig 3-4)

In the treatment group, no significant differences were observed in lung function from baseline to week 16 except for DLCO%, which increased in the sildenafil group and decreased in the placebo treated patients. The alveolar-arterial (A-a) O_2 gradient and PaO_2 did not change significantly. No significant decrease in SpO2 at rest at each visit during the double-blind phase (Fig.4). At the end-of-study 6MWT we did not find any difference in SpO2 desaturation between the sildenafil and placebo group (Tab.3). $PaCO_2$ slightly increased in the sildenafil group, while it decreased in the placebo group, though remaining in the normal range. We observed a trend towards an improvement in 6MWT distance; the BODE index, MMRC scale, and SF-36 general health domain improved

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significantly in the sildenafil group compared with placebo.

Adverse events

Adverse events were observed in 5 patients, all in the sildenafil arm. The events were mild to moderate and included headache, diarrhea, flushing, limb pain, dyspnea, myalgia, and peripheral edema. None interrupted the study treatment because of adverse events. No significant adverse effects were reported in the placebo arm.

DISCUSSION

To our knowledge, SPHERIC-1 is the first randomized controlled trial providing data on the safety and the efficacy of chronic administration of sildenafil 20 mg TID in severe PH-COPD. Our results show that sildenafil decreased pulmonary vascular resistance, with improvement in cardiac index, stroke volume, MMRC score, BODE index, and quality of life, with no detrimental effects on gas-exchange.

Previous studies showed conflictual results due to the presence of bias in the selection of population. In a small population of COPD patients, bosentan, a dual endothelin receptor antagonist, failed to improve exercise capacity after 12 weeks of treatment, and caused a considerable deterioration in gas exchange and functional status:[9] most of the subjects had modest PH which was diagnosed only by means of transthoracic Doppler ultrasound.

Experiences with PDE-5 inhibitors showed similar results. Lederer and coll. carried out a small study in COPD patients with mild PH comparing sildenafil with placebo in a cross-over design over 4 weeks.[10] Blanco compared the effect of sildenafil and placebo in a population of COPD patients with mild PH who were enrolled in a rehabilitation program.[11] In both studies, sildenafil did not show any effect on effort tolerance compared with placebo, but worsened gas exchange. In a more recent paper, Goudie and coll. studied a larger COPD population, using tadalafil, a different PDE-5 inhibitor. After 12 weeks of treatment tadalafil did not improve exercise capacity or quality of life compared to placebo.[12] The main limitation in the majority of these studies is that the selected COPD cohorts had borderline or mildly elevated pulmonary pressure. Therefore it is not surprising that pulmonary

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vasodilator drugs did not have positive effect, as those patients had mostly ventilatory limitation to exercise rather than reduced circulatory reserve.[25]

In the present study, we included only subjects with COPD in GOLD stage II or III and severe pre-capillary hypertension matching the definition of severe PH-COPD as suggested in the recent ESC/ERS guidelines.[26]

In the present study, PH-COPD patients treated with sildenafil showed a placebo-corrected decrease in PVR similar to that obtained in the SUPER-1 study for PAH. As the pathophysiology of right ventricular dysfunction in severe PH is mainly due to an excessive increase in the afterload, a reduction in one component of the afterload (PVR) causes an increase in the RV stroke volume and cardiac output, with trivial decrease in mPAP.

Pulmonary pressure is a well known independent prognostic factor in COPD[2-5]. As our study was not designed to address the impact of hemodynamic changes on prognosis of PH-COPD patients, we can not infer any conclusion about this important issue, but the significant increase in cardiac index mainly due to the increase in stroke volume is a very favorable hemodynamic improvement.

The hemodynamic improvement does not confer an improvement in effort capacity as we did not observe a statistically significant improvement of exercise capacity evaluated by 6MWT. This result is different compared to what observed in the SUPER-1 study for PAH patients,[19] and could be explained by some confounding conditions such as the older age of examined population, the more severe exercise deconditioning, the higher number of comorbidities and by some degree of ventilatory limitation due to the airways disease in PH-COPD population.

Notably, the changes in 6MWT distance and in the MRC dyspnea score resulted in a statistically significant improvement of BODE score, a validated composite prognostic index in COPD.[27]

A considerable finding of our investigation is the absence of detrimental effect of sildenafil on gas-exchange (A-a O_2 gradient and PaO_2). The reduction in PaO_2 was slight in both groups as observed acutely in other studies,[13] without clinical impact as no patients required a FiO_2 up-titration. Moreover, the increase in cardiac index observed during sildenafil treatment had likely a favorable impact on oxygen delivery.

We describe for the first time a significant improvement in the DLCO% in the treated group. This

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finding and the absence of peripheral SpO2 desaturation at rest suggest that in severe PH-COPD the impact of sildenafil on V/Q ratio may be beneficial.

All these results are in agreement with the improvement in SF-36 general health domain.

Limitation of the study

The main limitation of the study is the small patient sample size. Nevertheless, it is the largest RCT on sildenafil in COPD patients with severe PH ever performed. Moreover, as a pilot study, it would give robust proof-of-concept data useful for the design of larger randomized controlled trials.

The study did not provide information on sildenafil dose-titration, since a fixed dose of sildenafil (20 mg TID) was administered. As a positive dose-effect relationship has been described in PAH, we don't know if an increased dose may imply better results or more pronounced side effects.

Another limitation is the lack of mortality and time to clinical worsening among the study end-points due to the short observation time.[28] However, the BODE index is a surrogate composite end-point of prognostic significance[27], with indirect implications on mortality giving additional data on the benefit of specific PAH drugs in this particular settings.

CONCLUSION

The results of this pilot study suggest that sildenafil 20 mg TID has a favorable hemodynamic effect in severe PH-COPD, with no significant impact on gas exchange and with a good safety profile. Specific composite end-points such as the BODE index may be more appropriate than 6MWT in the assessment of the efficacy of PAH drugs and should be included in larger trials.

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Disclosures –

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REFERENCES

1. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. Chest 1998;113:576-83.
2. Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest 2005;127:1531-1536.
3. Chaouat A, Bugnet AS, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172:189-194.
4. Andersen KH, Iversen M, Kjaergaard J, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. J Heart Lung Transplant 2012; 31:373-80.
5. Weitzenblum E, Hirth C, Ducolone A, et al. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. Thorax 1981;36:752-758.
6. Weill D, Benden C, Corris P, et al. A consensus document for the selection of lung transplant candidates: 2014- An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. JHeart Lung Transplant 2015; 34: 1-15

7. Weill D, Benden C, Corris P, et al. A consensus document for the selection of lung transplant candidates: 2014- An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. JHeart Lung Transplant 2015; 34: 1-15
8. Barberà JA. Mechanisms of development of chronic obstructive pulmonary disease-associated pulmonary hypertension. Pulm Circ 2013;3:160-4.
9. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. Eur Respir J 2008;32:619-628.
10. Lederer DJ, Bartels MN, Schluger NW, et al. Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. COPD 2012;9:268-275.
11. Blanco I, Santos S, Gea J, et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. Eur Respir J 2013;42:982-92.
12. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD. Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial. Lancet Respir Med 2014;2:293-300.
13. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am J Respir Crit Care Med 2010;181:270-8.
14. Global Initiative for Chronic Obstructive Lung Disease (GOLD 2014) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: Updated 2014. Global Initiative for Chronic Obstructive Lung Disease; 2014. [Accessed June 18, 2014]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf.
15. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.
16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European

Accepted manuscript

Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993; 6:Suppl.16, s5-s40.

17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-117.
18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
19. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148-57.
20. Little RJA, Rubin DB. 2002. Statistical Analysis with Missing Data, 2nd Edition. Wiley.
21. Molenberghs G, Kenward MG. 2007. Missing Data in Clinical Studies. Wiley.
22. European Medicines Agency (2011). Guideline on Missing Data in Confirmatory Clinical Trials. Committee for Medicinal Products for Human Use (CHMP). EMA/CPMP/EWP/1776/99 Rev. 1
23. Michael G., Kenward & Geert Molenberghs (2009) Last Observation Carried Forward: A Crystal Ball, J of Biopharmaceutical Statistics, 19:5, 872-888,
24. Zhu, X.P. (2014) Comparison of Four Methods for Handing Missing Data in Longitudinal Data Analysis through a Simulation Study. Open Journal of Statistics, 4, 933-944.
25. Boerrigter BG, Bogaard HJ, Trip P, et al. Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. Chest 2012;142:1166-74.
26. Galiè N, Humbert M et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: : The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015 Aug 29. pii: ERJ-01032-2015. doi: 10.1183/13993003.01032-2015. [Epub ahead of print] PMID: 26318161
27. Celli BR. Predictors of mortality in COPD. Respir Med 2010;104:773-9.
28. Peacock AJ, Naeije R, N Galiè, Rubin L. End-points and clinical trial design in pulmonary arterial hypertension: have we made progress?. Eur Respir J 2009;34:231-42.

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Fig. 1 Patient disposition

Fig. 2 Plot of mPAP against FEV1 of the patients at baseline RHC

Fig. 3 Primary and secondary end-point variables significantly varied in patients treated with sildenafil (see also Tab 2-4)

Fig.4 Trend of rest SpO2 at the scheduled visits

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Table 1. Demographics, pulmonary function test, and functional capacity of patients who assumed at last 1 dose of sildenafil/placebo: comparison at baseline.

	Placebo n=10	**Sildenafil n=18**	**p-value**
Gender, male (%)	80.0	72.2	ns
Age, years	64.1 ± 11.0	66.4 ± 6.5	ns
BMI	24.9 ± 4.8	27.2 ± 6.2	ns
FiO_2,%	26.3 ± 7.1	28.3 ± 7.2	ns
PaO_2, mmHg	74.4 ± 14.9	74.2 ± 14.3	ns
$PaCO_2$, mmHg	44.5 ± 9.0	40.3 ± 5.2	ns
AaO_2 Gradient, mmHg	57.5 ± 55.0	77.1 ± 54.1	ns
Pulmonary Function Test			
FEV_1,% predicted	48.4 ± 25.3	54.4 ± 22.4	ns
FEV_1/FVC, %	0.53 ± 0.17	0.52 ± 0.13	ns
TLC,% predicted	97.1 ± 17.8	101.2 ± 25.1	ns
DLCO%, predicted	34.6 ± 23.0	32.8 ± 12.2	ns
Functional Capacity			
6MWT, m	308.5 ± 99.6	229.2 ± 101.4	0.06
BODE INDEX, units	4.7 ± 2.0	5.2 ± 2.5	ns
MRC scale, units	2.3 ± 0.7	3.0 ± 0.9	0.07
Hemodynamics			
RAP, mmHg	9.0 ± 2.6	7.3 ± 3.9	ns
mPAP, mmHg	39.1 ± 12.5	39.3 ± 7.6	ns
PCWP, mmHg	12.2 ± 2.9	10.9 ± 2.9	ns
CI, L/min/m^2	2.5 ± 0.7	2.4 ± 0.5	ns
SVI, mL/m^2	33.2 ± 9.9	29.4 ± 7.6	ns
TPVR, WU	9.2 ± 3.3	9.7 ± 3.1	ns
PVR, WU	6.3 ± 3.1	7.0 ± 2.6	ns
SVR, WU	23.7 ± 8.5	21.4 ± 5.7	ns
HR, b/m	77.8 ± 15.8	82.0 ± 10.9	ns
SF-36, General Health, units	44.6 ± 18.6	36.5 ± 16.1	ns

6MWT: 6-minute walk test; *AaO_2 Gradient*: alveolar-arterial gradient; *BMI*: body mass index; *CI*: cardiac index; *DLCO*: diffusing capacity of the lung for carbon monoxide; *FEV1*: forced expiratory volume in 1 second; *FiO_2*: fraction of inspired oxygen; *FVC*: forced vital capacity; *HR*: heart rate; *mPAP*: mean pulmonary arterial pressure; *MRC*: Medical Research Council scale; *$PaCO_2$*: partial pressure of carbon dioxide in arterial blood; *PaO_2*: partial pressure of oxygen in arterial blood; *PCWP*: pulmonary capillary wedge pressure; *PVR*: pulmonary vascular resistance; *RAP*: right atrial pressure; *SVR*: systemic vascular resistance; *TLC*: total lung capacity; *TPVR*: total pulmonary vascular resistance.

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Table 2. Primary end-point and hemodynamics of patients who assumed at last 1 dose of sildenafil/placebo (ITT analysis).

		Mean (SE)			
		Placebo (n=10)	**Sildenafil (n=18)**	**Difference in Change (95% CI)**	**p-value**
PVR, WU	Baseline	6.27 (0.79)	7.01 (0.59)		
	Follow up	6.36 (0.79)	5.72 (0.62)		
	Change	0.09	-1.29	-1.38 (≤ -0.05)	0.04
TPVR, WU	Baseline	9.21 (0.95)	9.70 (0.70)		
	Follow up	9.34 (0.95)	8.03 (0.74)		
	Change	0.13	-1.67	-1.80 (≤ -0.21)	0.03
RAP, mmHg	Baseline	9.00 (1.24)	7.28 (0.92)		
	Follow up	8.20 (1.24)	8.56 (1.00)		
	Change	-0.80	1.28	2.08 (≥ -0.86)	ns
mPAP, mmHg	Baseline	39.10 (2.85)	39.33 (2.13)		
	Follow up	36.70 (2.85)	35.49 (2.28)		
	Change	-2.40	-3.84	-1.44 (≤ 4.44)	ns
CI, l/min/m^2	Baseline	2.5 (0.2)	2.4 (0.1)		
	Follow up	2.3 (0.2)	2.6 (0.1)		
	Change	-0.2	0.2	0.4 (≥ 0.2)	0.004
SVI, ml/m^2	Baseline	33.2 (2.3)	29.4 (1.7)		
	Follow up	30.3 (2.3)	34.1 (1.8)		
	Change	-2.9	4.7	7.6 (≥ 3.7)	0.0007
SVR, WU	Baseline	2.89 (0.41)	2.73 (0.31)		
	Follow up	3.33 (0.42)	2.48 (0.33)		
	Change	0.44	-0.25	-0.69 (≤ -0.24)	0.006
HR, b/m	Baseline	77.8 (3.3)	82.0 (2.4)		
	Follow up	76.5 (3.3)	75.3 (2.6)		
	Change	-1.3	-6.7	-5.4 (≤ 1.13)	0.09

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CI: cardiac index; *HR*: heart rate; *ITT*: intention-to-treat; *mPAP*: mean pulmonary arterial pressure; *PVR*: pulmonary vascular resistance; *RAP*: right atrial pressure; *SVI*: stroke volume index; *SVR*: sistemic vascular resistance; *TPVR*: total pulmonary vascular resistance.

Table 3. Secondary end-points of patients who assumed at last 1 dose of sildenafil/placebo (ITT analysis).

		Mean (SE)			
		Placebo (n=10)	**Sildenafil (n=18)**	**Difference in Change (95% CI)**	**p-value**
FiO_2	Baseline	26.30 (2.25)	28.35 (1.73)		
	Follow up	26.10 (2.25)	28.65 (1.74)		
	Change	-0.20	0.30	0.50 (≥ -0.97)	ns
PaO_2	Baseline	74.40 (4.00)	74.23 (2.98)		
	Follow up	70.24 (4.00)	69.05 (3.26)		
	Change	-4.16	-5.18	- 1.02 (≤ 10.58)	ns
$PaCO_2$	Baseline	44.50 (2.02)	40.29 (1.51)		
	Follow up	41.24 (2.02)	42.22 (1.55)		
	Change	-3.26	1.94	5.20 (≥ 2.89)	0.0001
$D_{A\text{-}aO2}$	Baseline	57.49 (16.66)	77.10 (12.85)		
	Follow up	64.30 (16.66)	82.64 (12.95)		
	Change	6.81	5.54	-1.27 (≤ 11.77)	ns
FEV_1/FVC	Baseline	0.53 (0.04)	0.52 (0.03)		
	Follow up	0.57 (0.04)	0.51 (0.03)		
	Change	0.04	-0.01	-0.05 (≤ 0.02)	ns
DLCO %	Baseline	34.62 (5.22)	32.84 (4.01)		
	Follow up	31.27 (5.28)	35.02 (4.16)		
	Change	-3.35	2.18	5.53 (≥ 0.26)	0.04
Delta O_2 6MWT	Baseline	- 8.90 (1.65)	- 9.78 (1.23)		
	Follow up	- 8.12 (1.70)	- 10.18 (1.32)		
	Change	+0.78	-0.40	1.18 (≥ -1.64)	ns
General Health (SF36)	Baseline	44.6 (5.20)	36.5 (3.87)		
	Follow up	42.3 (5.20)	44.1 (4.08)		
	Change	-2.30	7.55	9.85 (≥ 0.78)	0.04

FiO_2: fraction of inspired oxygen; *$PaCO_2$*: partial pressure of carbon dioxide in arterial blood; *PaO_2*: partial pressure of oxygen in arterial blood;.*$D_{A\text{-}a\ O2}$*: alveolar-arterial O_2 gradient; *FEV_1/FVC*: forced expiratory volume in 1 second/ forced vital capacity; *DLCO*: diffusing capacity of the lung for carbon monoxide; Delta O2 6MWT: oxygen desaturation during six-minute walk-test; General Health(SF36): general health domain SF36 quality of life questionnaire

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Table 4. BODE score with individual components of patients who assumed at least 1 dose of sildenafil/placebo (ITT analysis).

		Mean (SE)			
		Placebo (n=10)	**Sildenafil (n=18)**	**(95% CI)**	**p-value**
BODE Index	Baseline	4.29 (0.74)	5.22 (0.55)		
	Follow up	4.80 (0.73)	4.82 (0.56)		
	Change	0.51	-0.40	-0.92 (≤ -0.20)	0.02
6MWT, m	Baseline	308.5 (31.7)	229.2 (23.6)		
	Follow up	297.3 (32.0)	237.3 (24.2)		
	Change	-11.2	8.1	-19.3 (≥ -8.99)	ns
BMI, Kg/m^2	Baseline	24.93 (1.71)	27.22 (1.27)		
	Follow up	25.64 (1.71)	27.47 (1.28)		
	Change	0.71	0.25	-0.46 (≤ 0.11)	0.09
MRC scale	Baseline	2.31 (0.28)	3.00 (0.20)		
	Follow up	2.40 (0.27)	2.49 (0.21)		
	Change	0.09	-0.51	-0.60 (≤ -0.31)	0.03
FEV_1, % predicted	Baseline	48.41 (7.11)	54.38 (5.30)		
	Follow up	45.63 (7.11)	54.60 (5.35)		
	Change	-2.78	0.21	2.99 (≥ -1.58)	ns

6MWT: 6-minute walk test; *BMI*: body mass index; *FEV_1*: forced expiratory volume in 1 second; *ITT*: intention-to-treat; *MRC*: Medical Research Council scale.

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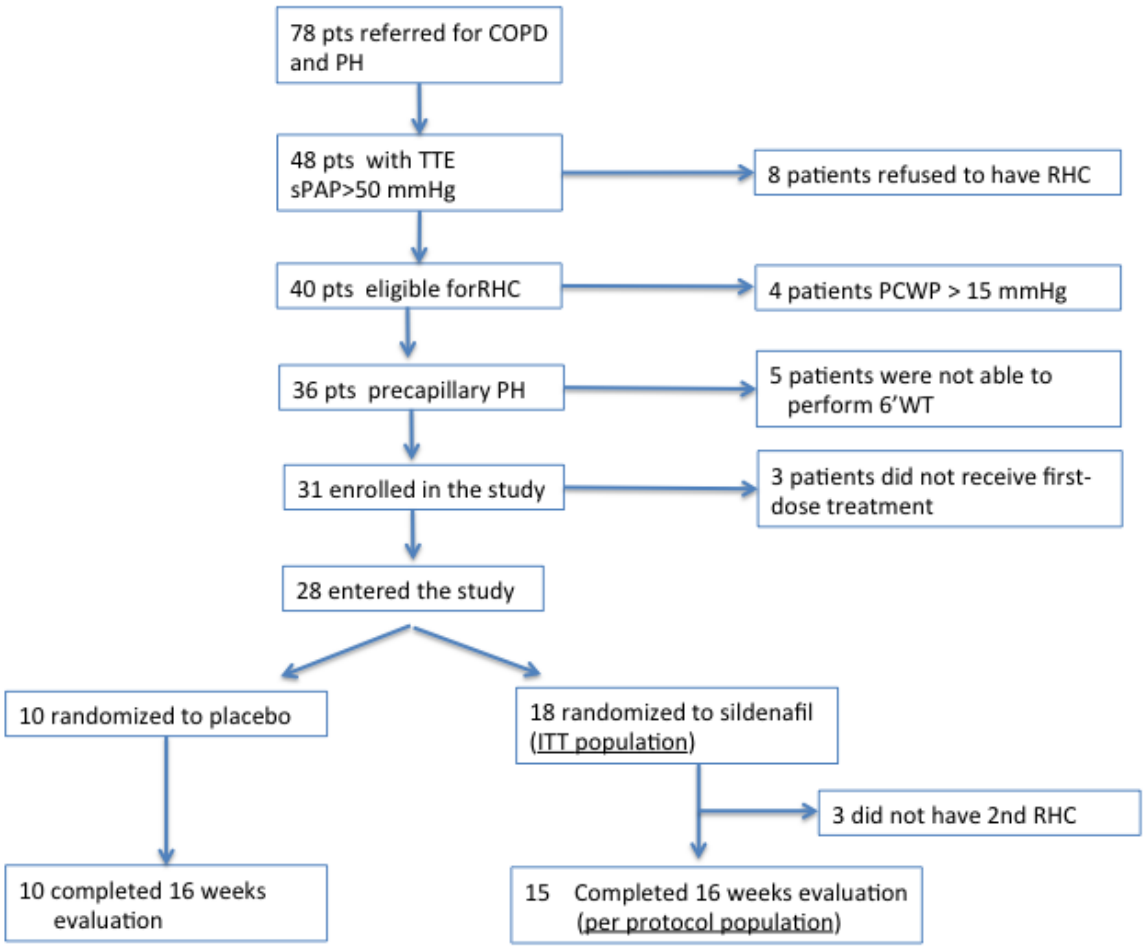
78 pts referred for COPD and PH
48 pts with TTE sPAP>50 mmHg
8 patients refused to have RHC
40 pts eligible forRHC
4 patients PCWP > 15 mmHg
36 pts precapillary PH
5 patients were not able to perform 6'WT
31 enrolled in the study
3 patients did not receive first-dose treatment
28 entered the study
10 randomized to placebo
18 randomized to sildenafil (ITT population)
3 did not have 2nd RHC
10 completed 16 weeks evaluation
15 Completed 16 weeks evaluation (per protocol population)

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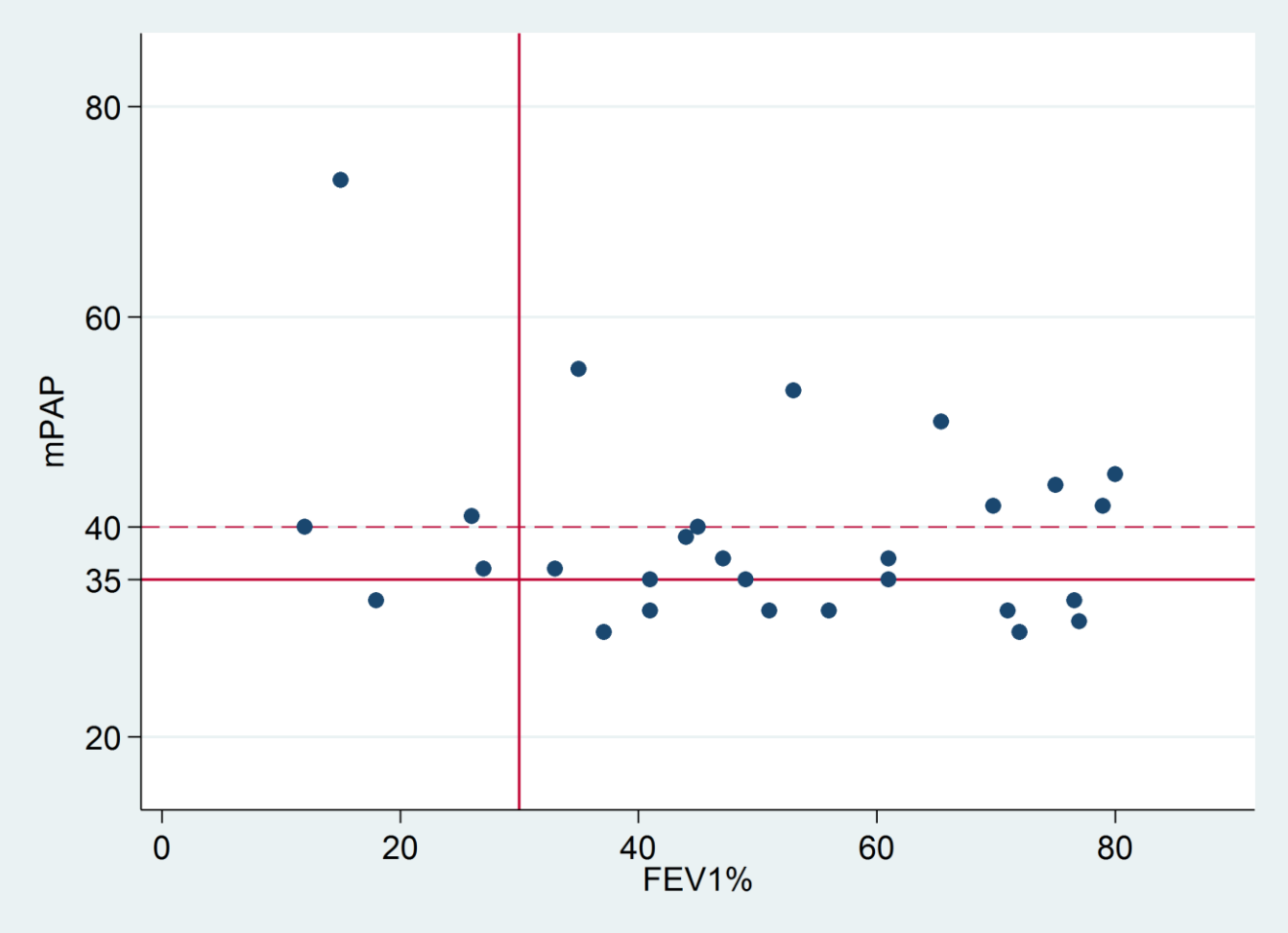

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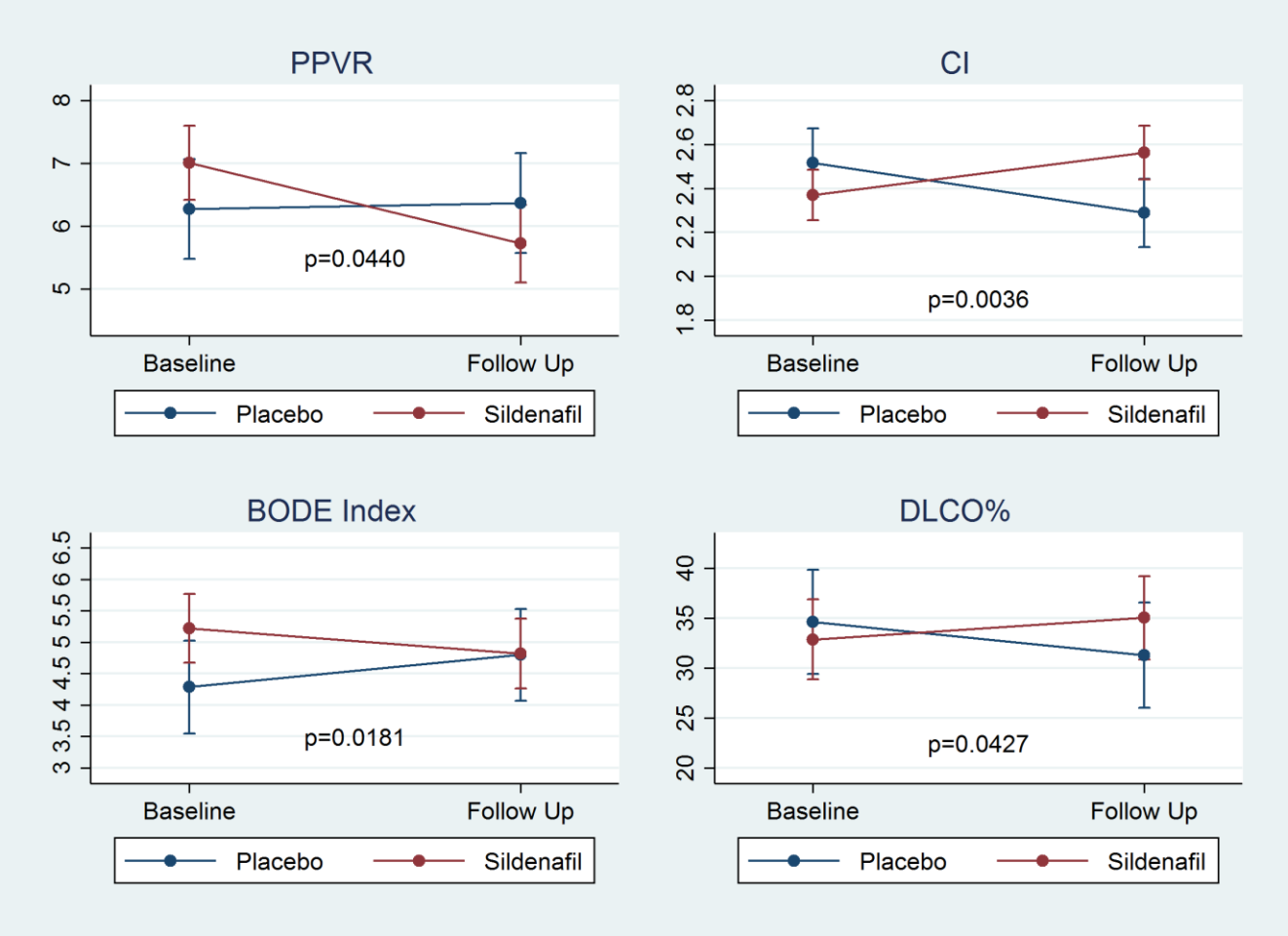
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Follow Up
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Sildenafil
CI
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2.2
2
1.8
p=0.0036
Baseline
Follow Up
Placebo
Sildenafil
BODE Index
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5.5
5
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4
3.5
3
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Baseline
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Baseline
Follow Up
Placebo
Sildenafil

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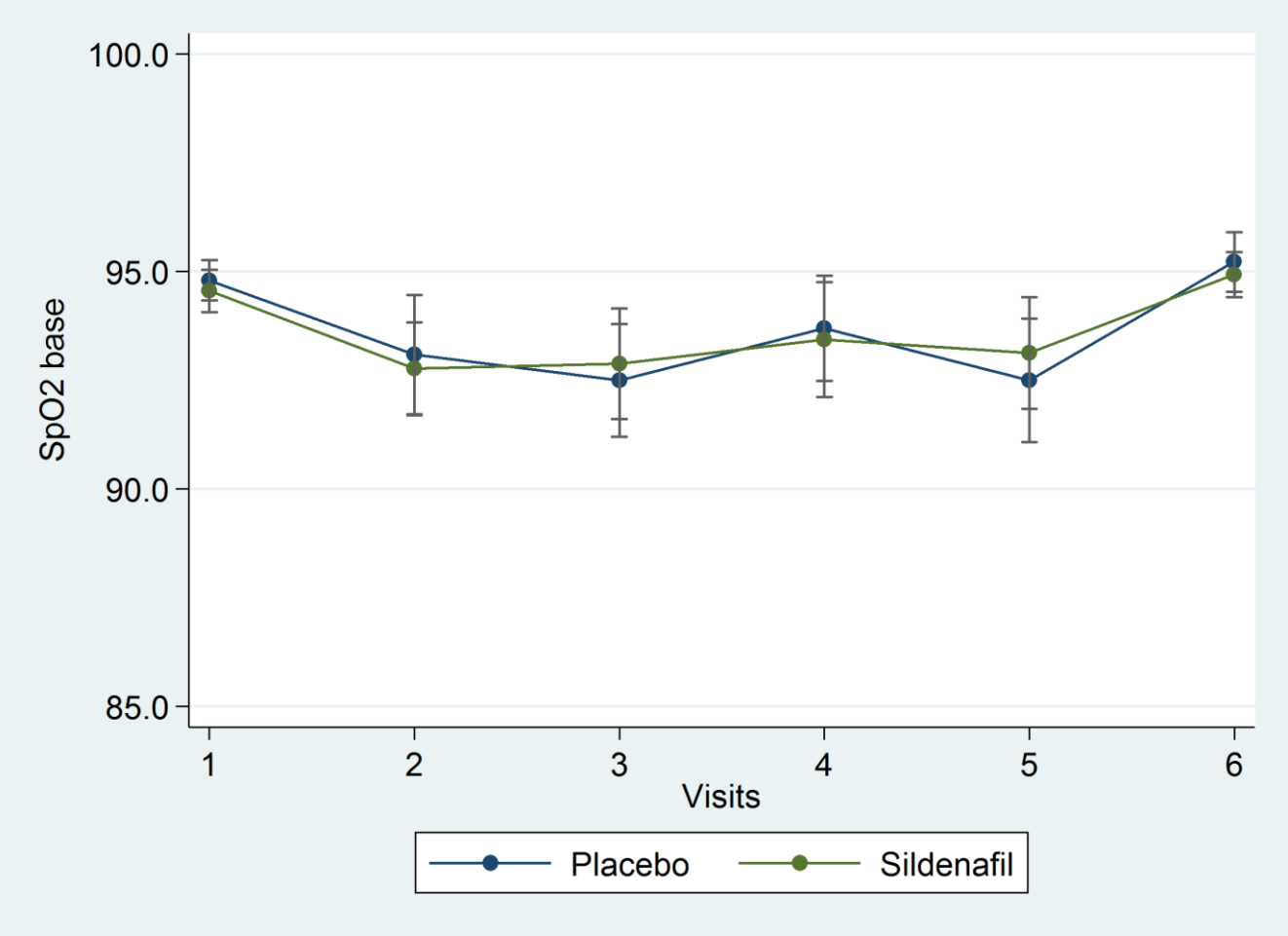
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SpO2 base
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Visits
Placebo
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