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Ocular safety of sildenafil citrate when administered chronically for pulmonary arterial hypertension: results from phase III, randomised, double masked, placebo controlled trial and open label extension

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Abstract

Objective To assess the ocular effects and safety profile of chronic sildenafil oral dosing in patients with pulmonary arterial hypertension.

Design 12 week, double masked, randomised, placebo controlled, phase III trial with open label extension.

Setting 53 institutions worldwide.

Participants 277 adults with idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension associated with connective tissue disease or after congenital heart disease repair (mean pulmonary artery pressure ≥ 25 mm Hg; pulmonary capillary wedge pressure ≤ 15 mm Hg at rest).

Interventions During the double masked study, oral sildenafil 20 mg, 40 mg, or 80 mg or placebo (1:1:1:1) three times daily for 12 weeks was added to baseline drug treatment. In the extension study, the placebo, 20 mg and 40 mg groups received 40 mg three times daily titrated to 80 mg three times daily at week 6. After unmasking, the dose was titrated according to clinical need.

Main outcome measure Ocular safety (ocular examinations, visual function tests, participants' reports of adverse events, and visual disturbance questionnaire completed by investigators) by treatment group at 12 weeks, 24 weeks, 18 months, and yearly.

Results Findings of the objective assessments—that is, intraocular pressure and visual function tests (visual acuity, colour vision, and visual field)—were similar across groups (20 mg, n=69; 40 mg, n=67; 80 mg, n=71; placebo, n=70). No clinically significant changes occurred between baseline and 12 weeks, except for an efficacy signal in contrast sensitivity for the sildenafil 40 mg three times daily group. In right eyes, changes in intraocular pressure from baseline to week 12 ranged from a mean of -0.5 (95% confidence interval -1.3 to 0.2) mm Hg with placebo, -0.2 (-0.9 to 0.5) mm Hg with sildenafil 40 mg, and -0.1 (-0.7 to 0.5) mm

Hg with 80 mg to 0.3 (-0.4 to 0.9) mm Hg with sildenafil 20 mg (the approved dose for pulmonary arterial hypertension). Mean changes from baseline to week 12 in contrast sensitivity in right eyes were -0.02 (SD 0.12) in the sildenafil 20 mg three times daily group compared with -0.05 (0.18) in the placebo group ($P=0.044$). Percentages of participants with deterioration in visual acuity (Snellen) from baseline to week 12 ranged from 10% (n=7) in the placebo group to 3% (n=2) in the sildenafil 20 mg three times daily group; the same percentages had visual field changes from normal to abnormal during the period in these two groups. The investigators did not deem any findings on colour vision assessment to be clinically significant. Findings of the objective assessments in the 40 mg and 80 mg three times daily sildenafil treatment groups and in left eyes were not substantially different, nor were any measures different throughout the open label extension compared with week 12. However, objective data were limited after month 18, as most participants had missing data or visual parameters were no longer collected by investigators. Incidence of ocular adverse events reported on the case report forms and assessed by the investigator was low with all doses, but a modest, dose related incidence of chromatopsia, cyanopsia, photophobia, and visual disturbance was reported with 80 mg three times daily consistent with the indicated dosing for erectile dysfunction. Retinal haemorrhages, captured on funduscopy, occurred in 2% (4/207) of sildenafil treated participants and none in the placebo group during the double masked study and in 4% (10/259) during the open label extension.

Conclusions Sildenafil dosing up to 80 mg three times daily is safe and well tolerated from an ocular perspective in patients with pulmonary arterial hypertension. Daily chronic dosing in this patient population was not associated with visual change and had no detrimental effect on best corrected visual acuity, contrast sensitivity, colour vision, or visual field, or on slit lamp examinations, funduscopy, or intraocular pressure during the duration of this study.

Trial registration Clinical trials NCT00644605 and NCT00159887.

Introduction

Orally administered selective phosphodiesterase type 5 inhibitors developed for the management of erectile dysfunction have been used more recently as a treatment for pulmonary arterial hypertension. Sildenafil citrate (Revatio, Pfizer Inc, New York) is approved in several countries worldwide, including the United States and Europe, for this indication. This class of vasodilators is capable of crossing the blood-retina barrier.¹

Phosphodiesterases produce vasoconstriction of smooth muscle cells through their ability to degrade cyclic nucleotides such as cyclic guanosine monophosphate. As nitric oxide acts to increase concentrations of cyclic guanosine monophosphate through stimulation of guanylate cyclase,^{2,3} and phosphodiesterase type 5 hydrolyses cyclic guanosine monophosphate, the combined effect of these changes is a significant lowering of cyclic guanosine monophosphate concentrations.^{1,4} Downstream effects of this reduction in cyclic guanosine monophosphate through phosphodiesterase type 5 activation include increases in intracellular calcium and potassium leading to vasoconstriction and the promotion of vascular smooth muscle cell proliferation and vascular fibrosis.⁵⁻⁷ By increasing cyclic guanosine monophosphate concentrations, phosphodiesterase type 5 inhibitors promote systemic arterial smooth muscle relaxation and vasodilatation while simultaneously preventing cellular proliferation; they thus offer the possibility of alleviating pulmonary arterial hypertension.⁶

Pulmonary arterial hypertension is characterised by restricted flow through the pulmonary circulation with resultant increase in pulmonary vascular resistance and, ultimately, right heart failure.⁸ Although the underlying pathophysiology is not completely understood, the key features are the decreased expression of nitric oxide synthase by endothelial cells together with increased expression of phosphodiesterase type 5 in smooth muscle cells of the pulmonary artery and right ventricular myocardium.^{5,6,9-12}

Owing to the widespread use of single dose sildenafil as a treatment for erectile dysfunction, clinical studies and case reports have focused on the possible systemic and ocular side effects (including those on visual function) associated with sildenafil and other phosphodiesterase type 5 inhibitors (for recent reviews, see Laties 2009¹ and Kerr and Danesh-Meyer 2009⁴). Phosphodiesterase type 5 is expressed on the retinal and choroidal vasculature (smooth muscle and endothelial cells) as well as on ganglion and bipolar cells. Concerns have been raised about potential ocular side effects of sildenafil that derive directly from its effect on ocular vasculature and from its concurrent crossover inhibition of phosphodiesterase type 6, which is expressed in the retinal photoreceptor layer (both rods and cones),¹³ with a potency approximately 10-fold less than that for phosphodiesterase type 5.^{13,14} The most common visual disturbance reported is a dose dependent reversible impairment of colour discrimination, principally in the blue-green to blue-purple range.^{1,15,16} Transient electroretinographic changes have been reported with sildenafil, including increases in light sensitivity,^{17,18} possibly reflecting inhibition of phosphodiesterase type 6,⁴ but no other effects on psychophysical measures of visual function have been found.^{4,19} A recent study in sheep showed increased intraocular pressure within one hour of a dose²⁰; however, in humans, clinically important adverse effects of sildenafil on intraocular pressure have not been reported.²¹⁻²³

Studies of the effects of sildenafil on ocular vasculature have not had consistent results. Several reports show little or no effect on various measures related to vessel diameter and ocular

circulation.²⁴⁻²⁷ By contrast, other studies have measured increases in one or both of these vascular properties after oral intermittent sildenafil treatment.^{13,28-33} The inconsistencies among these study results may reflect variations in experimental approaches, instrumentation, and length of dosing as well as the short lived and relatively modest amplitude of the changes measured.¹⁹ Rare vascular events that have been reported in case studies include non-arteritic anterior ischaemic optic neuropathy,¹ central serous chorioretinopathy,³⁴ branch retinal artery occlusions,^{35,36} and third nerve palsy.^{37,38}

To evaluate potential effects on visual function and the ocular safety profile of sildenafil during chronic oral use, the pivotal placebo controlled trial of sildenafil for the treatment of pulmonary arterial hypertension and its open label extension included ophthalmic examinations and assessments of visual function. During the double masked study, sildenafil doses of 20, 40, or 80 mg or placebo were administered orally three times daily for 12 weeks.³⁹ In the extension, doses were first up-titrated to a maximum of 80 mg three times daily at week 6 in a masked fashion while the 80 mg group had sham titration. After the last participant in the double masked study had completed 12 weeks of treatment, doses in the extension study were unmasked and then could be adjusted according to clinical need to a maximum of 80 mg three times daily or a minimum of 20 mg three times daily. We report here the ocular findings.

Methods

The initial 12 week, double masked, placebo controlled study of sildenafil citrate for pulmonary arterial hypertension was conducted in 53 centres in Australia, Belgium, Brazil, Canada, the Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Mexico, the Netherlands, Norway, the Philippines, Poland, Singapore, South Africa, South Korea, Spain, Sweden, the United Kingdom, and the United States between October 2002 and November 2003 (NCT00644605). Participants who completed the double masked study could enrol in an open label, optimised dose extension study (NCT00159887). All participants gave written informed consent. Sildenafil has been widely prescribed since it was introduced into the market in 2005, and recent data indicate that sildenafil 20 mg three times daily has more than 118 000 patient years of experience globally.

The methods and primary results of both the double masked study and the extension have been reported.³⁹ A summary of the methods and details of the ophthalmologic assessments follows.

Adult participants with pulmonary arterial hypertension, defined as a mean pulmonary artery pressure of at least 25 mm Hg and a pulmonary capillary wedge pressure of 15 mm Hg or lower at rest, were eligible. Participants could have idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with connective tissue disease, or pulmonary arterial hypertension following surgical repair of congenital systemic to pulmonary shunts at least five years previously. Patients with a six minute walking distance of less than 100 m or more than 450 m were excluded; intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost, or subcutaneous treprostinil, as well as supplementation with L-arginine, were prohibited. Warfarin, calcium channel blockers, digoxin, oxygen, and diuretics were allowed during the study. Entry criteria were unrelated to history of ocular pathology, macular degeneration, glaucoma, or ocular hypertension or to baseline intraocular pressure.

At baseline, participants were randomised (1:1:1:1) to 20, 40, or 80 mg of sildenafil or placebo administered three times daily. Participants randomised to receive 80 mg initially received 40 mg for one week and then were titrated to 80 mg. All other participants had a sham titration. Study drug was added to the participant's baseline drug treatment regimen and administered for 12 weeks.

The study used an automated interactive voice response system incorporating a central randomisation and drug supply scheme. The randomisation scheme was stratified by baseline walking distance (<325 m, ≥ 325 m) and cause (primary pulmonary arterial hypertension, pulmonary hypertension secondary to connective tissue disease, pulmonary hypertension with surgical repair). The interactive voice response system assigned numbers sequentially to the participants from the appropriate randomisation stratification group as they were determined to be eligible for treatment by the investigator. The drug supply scheme consisted of a list of pack numbers and corresponding treatment types. A unique pack number identified each drug pack. The interactive voice response system assigned participants a pack number from the list corresponding to the treatment assigned. At the start of the masked study, the study site was instructed on the method for unmasking, which was either a manual or an electronic process. Masking codes were broken only in emergency situations for reasons of participants' safety. The investigator was encouraged to contact the study sponsor before unmasking. When the code was broken, the reason was fully documented and entered on the study report form.

In the open label extension, the first pivotal portion involved a forced masked upward titration (figure 1). The participants originally randomised to receive placebo or sildenafil 20 or 40 mg in the double masked study received a starting dose of sildenafil 40 mg three times daily during the first six weeks, after which the dose was increased to 80 mg three times daily. Those randomised to 80 mg sildenafil three times daily in the double masked study remained on this dose for the first six weeks of the extension and had a sham dose escalation. One down-titration was permitted for tolerability during the first 12 weeks of the extension study. The open label extension study was unmasked after the last participant had completed at least three months of extension treatment. After unmasking, sildenafil was titrated according to clinical need as determined by the investigator and the participant to a maximum of 80 mg three times daily or to a minimum of 20 mg three times daily. Participants were to continue taking their optimised dose of sildenafil until the last enrolled patient had completed three years of treatment or until sildenafil was shown to be ineffective, poorly tolerated, or unsafe in the treatment of pulmonary arterial hypertension.

All doses were to be administered at least six hours apart. Participants were asked to record doses taken in their diary cards and took the first dose in the morning at the hospital at baseline and weeks 8 and 12. Participants were asked to return unused drug at each visit and were given sufficient supply for treatment until the next visit.

During the initial double masked portion of the study, ophthalmologists did ophthalmic examinations and visual function tests in both eyes at baseline and week 12. The ophthalmic examinations included external inspection of the eye, slit lamp biomicroscopy of the anterior portion, funduscopy to examine the posterior segment, and measurement of intraocular pressure by Goldmann applanation tonometry. Visual function was evaluated with best corrected visual acuity testing using a Snellen eye chart, the Farnsworth-Munsell D15 hue test

for colour, the Pelli-Robson test of contrast sensitivity, and the Humphrey visual field test. The timing of ocular examinations and assessments in relation to administration of oral sildenafil, diurnal intraocular pressure variability, or both was not pre-specified. Intraocular pressure changes of less than 4 mm Hg from baseline to week 12 were predefined as being clinically not significant. Investigators recorded all observed and volunteered adverse events, the severity (mild, moderate, or severe) of the events, and their opinion of the relation of the events to study treatment on case report forms. We coded adverse events centrally using the Medical Dictionary for Regulatory Activities. In addition, the investigator completed a four item visual disturbances safety questionnaire if a participant reported an ocular adverse event. The questionnaire included items reflecting the timing, duration, and impact of the event; most responses were recorded in check boxes, but the instrument also included an open ended question on the effect of the symptom on the participant's day to day life. In the open label portion of the extension study, once all participants had completed their first 12 weeks, the same ocular examinations including slit lamp, funduscopy, intraocular pressure, and visual function measurements were done in both eyes at week 12 (corresponding to week 24 of the overall trial), month 15 (corresponding to month 18 of the overall trial), and yearly thereafter. At the baseline visit, testing was done before the initial dose of sildenafil was administered, whereas evaluations at subsequent visits were done after the dose.

We summarised the results of the visual function assessments and the visual disturbance questionnaire by randomised treatment group. We did not analyse between group differences with statistical hypothesis testing owing to low power. Ocular adverse event data collected by the investigator and reported on the case report form are summarised per number (percentage) of participants and not per eye. For intraocular pressure and visual function assessments (such as visual acuity and contrast sensitivity), we report data for the right eye unless results for the left eye seemed to be clinically significantly different.

Results

In all, 278 participants were randomly assigned to receive sildenafil in doses of 20 mg ($n=69$), 40 mg ($n=68$), or 80 mg ($n=71$) or to receive placebo ($n=70$), and 277 participants took at least one dose of study drug. A total of 265 participants completed the 12 week randomised study, and 259 entered the extension. The median length of treatment during the extension was 1171 (range 1-1442) days, and 222 participants completed one year of treatment with sildenafil monotherapy.³⁹ However, data reflecting the results of the visual function assessments after month 18 were limited given that most participants had data missing or the visual parameters were no longer collected by investigators. Subjective adverse event data (that is, reports by participants) were collected throughout the double masked and open label studies.

Baseline characteristics were similar across treatment groups (table 1). About three quarters of participants were female, and the overall mean age was approximately 49 years. Between 60% and 65% of participants in each group were diagnosed as having idiopathic pulmonary arterial hypertension, and 58% overall were classified as World Health Organization functional class III. Only six participants had pre-existing glaucoma or ocular hypertension. Across treatment groups, the mean baseline intraocular pressure was approximately 15 mm Hg, and 71% of participants had normal visual fields at baseline as assessed by clinical investigators.

At baseline ophthalmic examinations, the most prevalent ocular finding reported was dilated episcleral vessels (right eye: 44/260, 17%; table 2^{||}). Conjunctival injection and abnormal blood vessels were also relatively common, with incidences of 13% (34/260) and 12% (32/260). Retinal vein engorgement and conjunctival oedema were relatively rare at baseline. The baseline incidence of dilated episcleral blood vessels, conjunctival injection, and abnormal blood vessels was somewhat higher in participants with primary pulmonary arterial hypertension than in those with pulmonary arterial hypertension associated with connective tissue disease (table 2^{||}). For example, conjunctival injection was present in the right eye of 22/164 (13%) participants with primary pulmonary arterial hypertension and in 7/81 (9%) with pulmonary arterial hypertension associated with connective tissue disease. The baseline incidence of retinal vein engorgement was lower in participants taking warfarin (right eye: 2/114, 2%) than in those not taking warfarin (right eye: 8/146, 6%), whereas the incidence of dilated episcleral vessels was higher in participants taking warfarin (right eye: 21/114, 18%) than in those not taking warfarin (right eye: 23/146, 16%).

12 week, randomised, double masked pivotal study

In all treatment groups, findings of the ophthalmic examinations (external inspection, slit lamp, funduscopy, and intraocular pressure) and visual function tests were little changed from baseline to week 12 in the double masked study. No clinically significant changes from baseline to week 12 in mean intraocular pressure occurred in either eye in any treatment group. In right eyes, the modest changes in intraocular pressure that did occur ranged from a mean change of -0.5 (95% confidence interval -1.3 to 0.2) mm Hg with placebo, -0.2 (-0.9 to 0.5) mm Hg with sildenafil 40 mg, and -0.1 (-0.7 to 0.5) mm Hg with 80 mg, to a mean change of 0.3 (-0.4 to 0.9) mm Hg with sildenafil 20 mg. Most participants in all groups had “clinically non-significant” changes in intraocular pressure (<4 mm Hg) from baseline to week 12.

We found no change in log contrast sensitivity (<0.15) at week 12 relative to baseline in most participants in any treatment group (table 3^{||}). The percentages of participants showing deterioration in log contrast sensitivity from baseline to week 12 were similar in the 80 mg sildenafil and placebo groups and were somewhat lower in the other sildenafil dose groups. In the right eye, the mean change from baseline to week 12 was -0.02 (SD 0.12), 0.02 (0.14), and -0.02 (0.14) in the sildenafil 20, 40, and 80 mg groups, compared with -0.05 (0.18) in the placebo group ($P=0.044$, $P<0.001$, and $P=0.093$ versus placebo). In right eyes, proportions of responders (positive change in log contrast sensitivity ≥ 0.15) in the sildenafil treatment groups compared with placebo were 5% versus 3% ($P=0.638$) for 20 mg three times daily, 12% versus 3% ($P=0.044$) for 40 mg three times daily, and 8% versus 3% ($P=0.222$) for 80 mg three times daily. In left eyes, the corresponding proportions of responders in the sildenafil treatment groups compared with placebo were 5% versus 2% ($P=0.305$), 11% versus 2% ($P=0.026$), and 5% versus 2% ($P=0.290$).

Treatment with sildenafil for 12 weeks did not seem to alter visual acuity at any dose tested. Most participants in all treatment groups showed no change or indeterminable change in the number of lines read on the Snellen chart from baseline to week 12 (table 3^{||}). The percentage of participants who showed an algebraic negative change from baseline in visual correction or deterioration in either eye, defined as a decrease of one or more lines read in those with a baseline assessment

between 6/6 and 6/60, was also similar across groups. Most participants with normal visual fields at baseline continued to have normal visual fields at week 12 (table 4^{||}). We found no apparent differences among treatment groups in the overall frequency of visual field changes.

We plotted results of colour vision assessments manually for each participant. One of the authors (AML) assessed all abnormal findings and changes from baseline. We made queries to investigators for all identified adverse events, and they said that no clinically significant findings occurred. We then archived the plots.

The incidence of reported and observed ocular adverse events was low (table 5^{||}). Ocular adverse events that did occur were of mild to moderate severity in all cases, with the exception of one participant in the sildenafil 80 mg group who developed severe photophobia 72 days after the start of the study. We saw a modest, dose related increase in the incidence of phosphodiesterase type 6 mediated effects consistent with the known ocular profile of single dose sildenafil for erectile dysfunction, including chromatopsia, cyanopsia, photophobia, visual brightness, and visual disturbance; the incidence of each of these effects was 7% or lower with sildenafil 80 mg and less than 5% with sildenafil 40 mg. For the sildenafil 20 mg three times daily group, which received the clinically approved dose, as well as for those receiving placebo, these incidences were less than 2%. Four cases of retinal haemorrhage were observed in participants receiving warfarin, one each in the sildenafil 20 mg and 80 mg groups (incidence=1%) and two in the sildenafil 40 mg group (incidence=3.0%).

Overall, the frequency of characteristic ocular anatomical findings seen in right heart failure/pulmonary arterial hypertension at baseline and at week 12 seemed not to differ among treatment groups for right eyes (table 6^{||}). No cases of serous retinal or choroidal detachment were observed in either eye in any treatment group at baseline, but both conditions were detected at week 12 in the left eye of one participant with pulmonary arterial hypertension associated with connective tissue disease in the sildenafil 40 mg group (incidence for each=2%). The upward drift in conjunctival injection was somewhat greater in participants treated with sildenafil relative to those treated with placebo; however, we found no evidence of a significant dose-response relation. We noted a modest increase in the incidence of conjunctival oedema in sildenafil treated participants between baseline and week 12, but we found no evidence of a dose-response relation. A slight increase in dilated episcleral vessels occurred in both sildenafil and placebo treated groups between baseline and week 12; the magnitude of the increase seemed similar in the active treatment and placebo groups, and the increase was not dose dependent in the sildenafil groups. The incidence of abnormal blood vessels remained fairly constant from baseline to week 12 in the placebo group as well as in all the sildenafil dose groups. The incidence of retinal vein engorgement was relatively low in all groups both at baseline and at week 12. For each of these measures, we saw a similar pattern in participants with primary pulmonary arterial hypertension and in those with pulmonary arterial hypertension associated with connective tissue disease.

Open label, optimised dose extension

Doses of 12 (5%) participants were titrated downward from sildenafil 80 mg three times daily during the first 12 weeks of open label treatment. Table 7^{||} shows a cross tabulation of the double masked study dose groups by dose during the open label study. As in the double masked pivotal study, sildenafil

maintained a favourable ocular safety profile throughout the open label phase of the optimised dose extension. In both eyes, we found no clinically significant changes in the results of the ophthalmic examinations and or visual function tests. At week 24, three quarters (163/218) of participants showed no change in intraocular pressure, defined as a change of less than 4 mm Hg relative to baseline. Among those who did show a change of 4 mm Hg or more, intraocular pressure was more likely to decrease than to increase. Likewise, findings with regard to contrast sensitivity, visual acuity, colour vision, and visual field measurements were not substantially different at week 24 compared with week 12.

The incidence of reported and observed ocular adverse events was low. As expected, a modest incidence of phosphodiesterase type 6 mediated effects was noted at the last visit (table 8^{||}). The incidence of retinal haemorrhage remained low during open label treatment, with a total of 11 (4%) cases, which included three participants who were receiving warfarin. Fifty per cent of the noted ocular haemorrhages, including retinal haemorrhages, that occurred as adverse events in participants taking warfarin were noted to have resolved at the time of each participant's last visit.

After 24 weeks and 18 months of total follow-up, the incidence of characteristic ocular anatomical findings seen in participants with right heart failure pulmonary arterial hypertension was generally similar to that noted after 12 weeks of double masked treatment. At week 24, serous retinal detachment and choroidal detachment were observed in both eyes of the participant who had shown these abnormalities in the left eye only at week 12; choroidal detachment was observed in the right eye of one additional participant. Thus, at week 24, the incidence of serous retinal detachment was 0.4% (1/239) for both left and right eyes, and the incidence of choroidal detachment was 0.4% (1/239) for left eyes and 0.8% (2/239) for right eyes. Both conditions subsequently resolved in these two participants, and no cases of either serous retinal detachment or choroidal detachment were reported at month 18 (incidence: either eye=0%). The incidence of conjunctival injection was consistent across the open label extension treatment (about 17%), and that of conjunctival oedema was low at week 12 and decreased moderately at week 24 and month 18 (right eye: 2% (4/256), 1% (3/239), and 1% (1/117), respectively). The incidence of dilated episcleral blood vessels was higher at week 12 than at week 24 or month 18 (right eye: 22% (56/256), 18% (44/239), and 15% (17/117), respectively). The incidence of abnormal blood vessels decreased slightly from week 12 to week 24 but was similar to the baseline level at month 18 (right eye: 12% (31/256), 8% (20/239), and 13% (15/117), respectively), whereas the incidence of retinal vein engorgement was lowest at month 18 (right eye: 6% (15/256), 6% (15/239), and 3% (4/117)).

Discussion

The principal finding of both the pivotal trial and its open label extension is that chronic oral sildenafil treatment did not lead to any significant ocular safety signals on ocular examination, on assessment of visual function, or through visual disturbance questionnaires. With respect to changes in subjective visual function, the only effect was a low, dose dependent, and in many cases reversible incidence of the transient phosphodiesterase type 6 mediated effects that have been reported from clinical experience with single use sildenafil in the treatment of erectile dysfunction.¹⁴ Moreover, in the pivotal trial, treatment with the clinically approved dose, 20 mg three times daily, resulted in a frequency of these effects that was indistinguishable from that

with placebo treatment. Similarly, we found no evident adverse effect of chronic sildenafil on visual acuity or contrast sensitivity. Notably, sildenafil 40 mg three times daily improved log contrast sensitivity compared with placebo over 12 weeks. Although it is a functional test associated with variability and noise, contrast sensitivity provides an objective measure of retinal/neuronal/photoreceptor function that can be affected by microvascular changes.^{40 41}

In addition to having no significant effect on measures of visual function, chronic sildenafil treatment in this study was not associated with an increased incidence of reported and observed ocular adverse events, and the incidences of retinal haemorrhage, conjunctival oedema, and serous retinal and choroidal detachment were low, with no evident effect on intraocular pressure in objective ophthalmic examinations. However, the trial was not adequately powered to detect significant differences between groups for ocular events occurring at low frequency, and a true causality cannot be determined. Retinal haemorrhage is an ocular finding that has been described in patients with pulmonary arterial hypertension and in those with connective tissue disease.⁴²⁻⁴⁵ Risk factors for retinal haemorrhage are numerous and include sudden changes in ocular or vascular pressures, such as those that occur during vomiting, trauma, or violent exercise. They also are seen at both extremes of vascular perfusion pressure, either arterial or venous, being noted both in acute systemic hypertension and in chronic venous insufficiency. Anticoagulants, which are commonly used by patients with pulmonary arterial hypertension, are associated with an increased risk of ocular and retinal haemorrhages. In virtually all cases, responsibility lies with the risk imposed by the prolonged coagulation time brought about by warfarin treatment. Moreover, in large general population surveys, microvascular abnormalities, including small retinal haemorrhages, are consistently noted in 2-4% of people surveyed.⁴⁶ Commonly, retinal haemorrhages can be incidental clinical findings that resolve without sequelae.

In this study, we also saw the low incidence of serous retinal and choroidal detachments that is implied from case reports of untreated pulmonary arterial hypertension.^{42 43 47-49} Those that occurred were most likely due to the underlying systemic pathology, possibly resulting from alterations in choroidal blood flow, such as increased choroidal pressure, venous stasis, and uveal effusions.⁵⁰ Dilated episcleral veins and conjunctival injection were the most common observed ocular anatomical findings in both untreated and treated participants with pulmonary arterial hypertension in this study. With respect to the incidence of dilated episcleral vessels and retinal engorgement, these were similar in both sildenafil and placebo groups during the double masked study and actually declined during the open label extension. Whether these decreases were treatment associated effects due to changes in the ocular vascular stasis, vascular changes associated with the severity and chronicity of the underlying pulmonary arterial hypertension,^{49 50} or the result of attrition of participants is, however, unclear. The upward drift in the incidence of conjunctival injection in both treatment groups at 12 weeks seemed to be slightly greater in participants receiving sildenafil. However, across the 15 months of the open label extension, the incidence was consistent across treatment groups. As conjunctival oedema is a less specific ocular manifestation of pulmonary arterial hypertension, this finding is difficult to assess.

Relation to other studies

As discussed above, the findings of this study are in accord with existing reports in the literature of the short term effects of single

use sildenafil on measures such as colour discrimination and visual sensitivity.^{4 19} Moreover, a recent study examining long term use of sildenafil in healthy people found no significant difference from placebo in such measures of visual function as visual acuity, static perimetry, or colour discrimination or in key electroretinographic variables,²³ whereas a study of five patients with pulmonary arterial hypertension taking high doses, up to 225 mg/day for one to four years, also found only modest electroretinographic changes in cone function and no evidence of serious visual toxicity.⁵¹

One visual disorder, non-arteritic anterior ischaemic optic neuropathy, has been reported as a rare event (18 instances in all) after single use sildenafil.¹ Although no definitive link exists between these occurrences and the drug, the product label includes advice to discontinue use of sildenafil in the event of sudden loss of vision.^{1 14} Optic nerve heads that are relatively small with small cup to disc ratios have been reported to be at risk of non-arteritic anterior ischaemic optic neuropathy.⁵² Estimates of the overall incidence of non-arteritic anterior ischaemic optic neuropathy in the United States range from 2.52 to 11.8 men and from 2.14 to 9.2 women per 100 000 of the population aged over 50^{53 54}; the comparable estimate in China for adults aged over 40 is six per 100 000.⁵⁵ With intermittent usage of sildenafil, however, the estimated incidence of non-arteritic anterior ischaemic optic neuropathy is only 2.8 per 100 000 patient years of use.^{1 56} Moreover, many of the risk factors for non-arteritic anterior ischaemic optic neuropathy, such as diabetes, hypertension, hypercholesterolaemia, atherosclerosis, ischaemic heart disease, stroke, pro-thrombotic factors, raised homocysteine concentrations, sleep apnoea, and nocturnal hypotension, are also risk factors for erectile dysfunction,¹ so that assessing whether occurrences of non-arteritic anterior ischaemic optic neuropathy should be attributed to the drug or to the underlying systemic vascular pathology is difficult. Although the potential for inducing non-arteritic anterior ischaemic optic neuropathy in patients with pulmonary arterial hypertension cannot be discounted,⁵⁷ on the basis of this study of chronic sildenafil use, it seems likely that in patients with similar characteristics, no increased risk of non-arteritic anterior ischaemic optic neuropathy exists for at least 18 months.

Strengths and limitations

A decision was made during the design of this double blind study and open label extension not to do electroretinographic testing for several reasons. Firstly, in preclinical studies with two species, no evidence existed of general ocular toxicity or of specific retinal structural changes with long term, high dose sildenafil administration.⁵⁸ Furthermore, the results from a series of electroretinographic studies in humans receiving sildenafil are similarly reassuring, showing either no effect at all or modest, fully reversible, transient electroretinographic changes that do not translate into significant effects on visual performance.⁵⁹⁻⁶¹ Finally, the risk of retinal toxicity seems to be exceedingly small, whereas the constraints on and limitations of clinical electroretinographic testing at multiple sites are considerable. Transportation of these seriously ill patients to certified centres for electroretinographic testing would be necessary, and the underlying systemic disease and ocular manifestations could contribute to technical difficulties with administration and interpretation of the test.

Several limitations to the study should be noted. Firstly, because ocular safety, including visual function, was not the primary objective of this phase III study, the sample size calculation was not based on ocular end points. We believe that the large amount

of data available is generally sufficient for assessment of ocular safety with sildenafil use in patients with pulmonary arterial hypertension, although the power to detect rare, serious events was lacking. Other limitations were associated with the timing of the ocular assessments, the number of examinations/tests done, and the omission of diagnostic procedures such as electroretinographic and standardised digital fundus photos that would have provided additional information about vascular or optic nerve effects. For example, the fact that only one intraocular pressure measurement was taken was reasonable, but the timing of this measurement in relation to diurnal intraocular pressure variability should have been pre-specified. Also, several measurements of intraocular pressure should have been taken at each sitting (right eye, followed by left) and the mean presented. In addition, the Humphrey visual field examination has many limitations in itself, such as reproducibility, between visit variability, a lack of standardisation as to what constitutes a normal or abnormal field, the need for three examinations averaged as a baseline to assess the average mean deviation and decibel loss over time, and the occurrence of false positives and negatives which support the performance of repeat tests. Finally, findings from this study should not be extrapolated to the use of sildenafil for erectile dysfunction or for other reasons.⁶²

Conclusions

The main purpose of the pivotal study and its open label extension was to investigate the overall efficacy and systemic safety of sildenafil in patients with pulmonary arterial hypertension during short term and long term chronic daily exposure. The ocular safety and visual function evaluation was an additional component based on newly emerging ocular safety signals with the use of sildenafil on an as needed basis for the indication of erectile dysfunction. The data show that sildenafil, taken three times daily at doses up to four times the usual recommended dose for erectile dysfunction, is not associated with compromised visual function or ocular adverse events.

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Competing interests: All authors have completed the ICMJE unified disclosure form at www.icmje.org/coi_disclosure.pdf and declare that BMW, previously an employee of Pfizer Inc, had support from Pfizer Inc for the submitted work; CT, L-JH, and GB, currently employees of Pfizer Inc, had support from Pfizer Inc for the submitted work; and AML,

What is already known on this topic

The phosphodiesterase type 5 inhibitor sildenafil citrate has an established safety profile for intermittent use in the management of erectile dysfunction

It is approved in the United States and Europe as daily oral therapy for the chronic treatment of pulmonary arterial hypertension, a progressive debilitating disease

Relevant literature suggests a low incidence of minor, transient ocular effects mediated by partial inhibition of phosphodiesterase type 6 (PDE6), and a recent study in sheep showed intraocular pressure elevated within one hour post-dose

What this study adds

This phase III study allowed objective assessment of visual function parameters for most patients through 18 months of treatment and collection of subjective reports of ocular adverse events

A dose related increase in transient ocular adverse events mediated by PDE6, such as chromatopsia, cyanopsia, photophobia, visual brightness, and visual disturbances, was seen

Chronic oral dosing of sildenafil for treating patients with pulmonary arterial hypertension did not have a detrimental effect on any aspect of visual function or ocular safety evaluated

as a consultant for Pfizer Inc in the study conduct and in data analysis and interpretation, had support from Pfizer Inc for the submitted work.

Ethical approval: Local institutional review boards or independent ethics committees approved the study protocol. All participants gave written informed consent.

Data sharing: No additional data are available.

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Tables

Table 1 | Participants' demographics and baseline characteristics. Values are numbers (percentages) unless stated otherwise

Characteristic	Placebo (n=70)	Sildenafil		
		20 mg (n=69)	40 mg (n=67)	80 mg (n=71)
Female sex	57 (81)	49 (71)	47 (70)	56 (79)
Mean (SD) age (years)	49 (17)	47 (14)	51 (15)	48 (15)
Racial/ethnic background:				
White	61 (87)	59 (86)	58 (87)	58 (82)
Black	1 (1)	0	4 (6)	1 (1)
Asian	2 (3)	6 (9)	2 (3)	9 (13)
Other	6 (9)	4 (6)	3 (5)	3 (4)
Mean (SD) weight (kg)	74 (19)	71 (17)	75 (17)	71 (17)
WHO functional class:				
I	1 (1)	0	0	0
II	32 (46)	24 (35)	23 (34)	28 (39)
III	34 (49)	40 (58)	44 (66)	42 (59)
IV	3 (4)	5 (7)	0	1 (1)
Cause of pulmonary arterial hypertension:				
Idiopathic	42 (60)	44 (64)	43 (64)	46 (65)
Connective tissue disease	22 (31)	21 (30)	20 (30)	21 (30)
Repaired congenital systemic to pulmonary shunts	6 (9)	4 (6)	4 (6)	4 (6)
History of glaucoma or ocular hypertension	0	1 (1)	5 (8)	0
Mean (95% CI) intraocular pressure, right eye (mm Hg)	15.2 (14.0 to 16.4)	14.8 (14.0 to 15.6)	14.9 (14.2 to 15.6)	14.4 (13.7 to 15.1)
Normal visual field, right eye*	52/68 (77)	48/67 (72)	43/66 (65)	47/66 (71)
Mean (SD) contrast sensitivity, right eye	1.58 (0.20) (n=62)	1.63 (0.17) (n=58)	1.61 (0.16) (n=61)	1.60 (0.19) (n=63)
Visual acuity (Snellen), right eye:				
20/20	44 (63)	51 (74)	48 (72)	51 (72)
20/30	15 (21)	12 (17)	13 (19)	11 (16)
20/40	4 (6)	1 (1)	1 (2)	3 (4)
20/60	0	1 (1)	0	2 (3)
20/120	1 (1)	0	0	0
Missing	6 (9)	4 (6)	5 (8)	4 (6)

*Data missing for two participants in placebo and sildenafil 20 mg groups, one in sildenafil 40 mg group, and five in sildenafil 80 mg group.

Table 2| Baseline incidence of characteristic ocular abnormalities seen in right heart failure by cause and warfarin treatment, right eye. Values are numbers (percentages)

Abnormality	All participants* (n=260)	Cause of pulmonary arterial hypertension†		Warfarin treatment	
		Primary (n=164)	Associated with connective tissue disease (n=81)	Yes (n=114)	No (n=146)
Dilated episcleral blood vessels	44 (17)	29 (18)	12 (15)	21 (18)	23 (16)
Conjunctival injection	34 (13)	22 (13)	7 (9)	17 (15)	17 (12)
Abnormal blood vessels	32 (12)	23 (14)	8 (10)	12 (11)	20 (14)
Retinal vein engorgement	10 (4)	7 (4)	3 (4)	2 (2)	8 (6)
Conjunctival oedema	3 (1)	2 (1)	1 (1)	2 (2)	1 (1)

*Includes all participants with visual assessment data.

†Data missing for 15 participants.

Table 3| Changes from baseline to week 12 in contrast sensitivity and best corrected visual acuity (spherical equivalent) in right eye during 12 week, double masked study*

Measure of visual function	Placebo (n=68)	Sildenafil		
		20 mg (n=67)	40 mg (n=66)	80 mg (n=65)
Contrast sensitivity†:				
Improvement	2 (3)	3 (5)	8 (12)	5 (8)
No change	44 (65)	44 (66)	40 (61)	41 (63)
Deterioration	9 (13)	5 (8)	5 (8)	9 (14)
Missing	13 (19)	15 (22)	13 (20)	10 (15)
Visual acuity‡:				
Improvement	7 (10)	5 (8)	1 (2)	2 (3)
No change	46 (68)	50 (75)	53 (80)	53 (82)
Deterioration	7 (10)	2 (3)	3 (5)	5 (8)
Missing	8 (12)	10 (15)	9 (14)	5 (8)

*Data are numbers (percentages) and include all participants with week 12 visit.

†Improvement=increase of ≥ 0.15 in log contrast sensitivity; no change=change of < 0.15 in log contrast sensitivity; deterioration=decrease of ≥ 0.15 in log contrast sensitivity; and missing=not possible to calculate owing to missing data; $P=0.039$ for comparison in contrast sensitivity improvement between sildenafil 40 mg and placebo groups.

‡Improvement=increase of ≥ 1 line read versus baseline (baseline assessment 6/60, 6/36, 6/24, 6/18, 6/12, or 6/9); no change=no change in number of lines read compared with baseline or change within last three lines of chart (6/6, 6/5, or 6/4); deterioration=decrease of ≥ 1 line compared with baseline (baseline assessment 6/60, 6/36, 6/24, 6/18, 6/12, 6/9, or 6/6); and missing=not possible to calculate owing to missing data.

Table 4| Overall frequency of visual field changes in right eye during 12 week, double masked study*

Treatment	Result at week 12	Result at baseline		
		Normal	Abnormal	Missing†
Placebo (n=68)	Normal	39 (57)	4 (6)	4 (6)
	Abnormal	7 (10)	2 (3)	1 (2)
	Missing†	6 (9)	0	5 (7)
Sildenafil 20 mg (n=67)	Normal	43 (64)	5 (8)	2 (3)
	Abnormal	2 (3)	4 (6)	0
	Missing†	3 (5)	3 (5)	5 (8)
Sildenafil 40 mg (n=66)	Normal	34 (52)	7 (11)	6 (9)
	Abnormal	1 (2)	3 (5)	1 (2)
	Missing†	8 (12)	4 (6)	2 (3)
Sildenafil 80 mg (n=66)	Normal	38 (58)	3 (5)	2 (3)
	Abnormal	3 (5)	8 (12)	2 (3)
	Missing†	6 (9)	1 (2)	3 (5)

*Data are numbers (percentages) and include all participants with week 12 visit.

†Not possible to calculate owing to missing assessment.

Table 5| Incidence of all causality eye disorder adverse events reported during 12 week, double masked study, either eye. Values are numbers (percentages, 95% CI)

Adverse event (MedDRA preferred term)	Placebo (n=70)	Sildenafil		
		20 mg (n=69)	40 mg (n=67)	80 mg (n=71)
Abnormal sensation in eye	0	2 (2.9, 0.35 to 10.08)	1 (1.5, 0.04 to 8.04)	0
Accommodation disorder	1 (1.4, 0.04 to 7.70)	0	0	0
Blepharitis	1 (1.4, 0.04 to 7.70)	1 (1.4, 0.04 to 7.81)	0	0
Cataract bilateral NOS	1 (1.4, 0.04 to 7.70)	0	1 (1.5, 0.04 to 8.04)	0
Cataract unilateral	0	0	1 (1.5, 0.04 to 8.04)	0
Chromatopsia	1 (1.4, 0.04 to 7.70)	1 (1.4, 0.04 to 7.81)	1 (1.5, 0.04 to 8.04)	3 (4.2, 0.88 to 11.86)
Conjunctival haemorrhage	0	0	0	1 (1.4, 0.04 to 7.60)
Conjunctival hyperaemia	0	1 (1.4, 0.04 to 7.81)	1 (1.5, 0.04 to 8.04)	0
Conjunctivitis	1 (1.4, 0.04 to 7.70)	0	1 (1.5, 0.04 to 8.04)	1 (1.4, 0.04 to 7.60)
Cyanopsia	0	0	1 (1.5, 0.04 to 8.04)	3 (4.2, 0.88 to 11.86)
Diplopia	0	1 (1.4, 0.04 to 7.81)	1 (1.5, 0.04 to 8.04)	1 (1.4, 0.04 to 7.60)
Dry eye NOS	0	1 (1.4, 0.04 to 7.81)	0	0
Episcleral hyperaemia	2 (2.9, 0.35 to 9.94)	0	0	0
Eye haemorrhage NOS	1 (1.4, 0.04 to 7.70)	1 (1.4, 0.04 to 7.81)	1 (1.5, 0.04 to 8.04)	1 (1.4, 0.04 to 7.60)
Eye inflammation NOS	1 (1.4, 0.04 to 7.70)	0	0	0
Eye irritation	0	2 (2.9, 0.35 to 10.08)	0	2 (2.8, 0.34 to 9.81)
Eye oedema	1 (1.4, 0.04 to 7.70)	0	0	0
Eye pain	1 (1.4, 0.04 to 7.70)	1 (1.4, 0.04 to 7.81)	0	3 (4.2, 0.88 to 11.86)
Eye pruritus	1 (1.4, 0.04 to 7.70)	0	1 (1.5, 0.04 to 8.04)	0
Eye redness	1 (1.4, 0.04 to 7.70)	0	1 (1.5, 0.04 to 8.04)	0
Eyelid oedema	1 (1.4, 0.04 to 7.70)	1 (1.4, 0.04 to 7.81)	0	0
Halo vision	1 (1.4, 0.04 to 7.70)	0	0	2 (2.8, 0.34 to 9.81)
Lacrimation increased	0	0	1 (1.5, 0.04 to 8.04)	0
Lenticular opacities	1 (1.4, 0.04 to 7.70)	0	1 (1.5, 0.04 to 8.04)	0
Macular oedema	0	1 (1.4, 0.04 to 7.81)	0	0
Ocular discomfort	0	0	1 (1.5, 0.04 to 8.04)	0
Ocular hyperaemia	0	1 (1.4, 0.04 to 7.81)	0	0
Ocular vascular disorder	0	0	0	1 (1.4, 0.04 to 7.60)
Photophobia	0	0	0	4 (5.6, 1.56 to 13.80)
Photophobia aggravated	0	0	0	1 (1.4, 0.04 to 7.60)
Retinal disorder	0	0	1 (1.4, 0.04 to 8.04)	0
Retinal haemorrhage	0	1 (1.4, 0.04 to 7.81)	2 (3.0, 0.36 to 10.37)	1 (1.4, 0.04 to 7.60)
Retinal pigment epitheliopathy	0	0	0	1 (1.4, 0.04 to 7.60)
Vision blurred	4 (5.7, 1.58 to 13.99)	3 (4.3, 0.91 to 12.18)	2 (3.0, 0.36 to 10.37)	4 (5.6, 1.56 to 13.80)
Visual acuity reduced	0	0	2 (3.0, 0.36 to 10.37)	1 (1.4, 0.04 to 7.60)
Visual brightness	0	0	0	2 (2.8, 0.34 to 9.81)
Visual disturbance NOS	0	0	3 (4.5, 0.93 to 12.53)	5 (7.0, 2.33 to 15.67)
Xanthopsia	0	0	0	1 (1.4, 0.04 to 7.60)

MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified.

Table 6| Overall frequency of ocular findings based on slit lamp and funduscopy examinations in right eye at baseline and week 12 during 12 week, double masked study*

Treatment	Result at week 12	Result at baseline		
		Normal	Abnormal	Missing†
Serous retinal detachment				
Placebo (n=70)	Normal	60 (86)	–	4 (6)
	Abnormal	–	–	–
	Missing†	5 (7)	–	–
Sildenafil 20 mg (n=69)	Normal	57 (83)	–	8 (12)
	Abnormal	–	–	–
	Missing†	4 (6)	–	–
Sildenafil 40 mg (n=67)	Normal	56 (84)‡	–	6 (9)
	Abnormal	–	–	–
	Missing†	4 (6)	–	–
Sildenafil 80 mg (n=71)	Normal	61 (86)	–	7 (10)
	Abnormal	–	–	–
	Missing†	2 (3)	–	–
Choroidal detachment				
Placebo (n=70)	Normal	60 (86)	–	4 (6)
	Abnormal	–	–	–
	Missing†	5 (7)	–	–
Sildenafil 20 mg (n=69)	Normal	57 (83)	–	8 (12)
	Abnormal	–	–	–
	Missing†	4 (6)	–	–
Sildenafil 40 mg (n=67)	Normal	56 (84)‡	–	6 (9)
	Abnormal	–	–	–
	Missing†	4 (6)	–	–
Sildenafil 80 mg (n=71)	Normal	61 (86)	–	7 (10)
	Abnormal	–	–	–
	Missing†	2 (3)	–	–
Conjunctival injection				
Placebo (n=70)	Normal	47 (67)	4 (6)	3 (4)
	Abnormal	–	8 (11)	2 (3)
	Missing†	5 (7)	–	–
Sildenafil 20 mg (n=69)	Normal	49 (71)	4 (6)	7 (10)
	Abnormal	2 (3)	2 (3)	1 (1)
	Missing†	3 (4)	1 (1)	–
Sildenafil 40 mg (n=67)	Normal	43 (64)	6 (9)	6 (9)
	Abnormal	2 (3)	6 (9)	–
	Missing†	4 (6)	–	–
Sildenafil 80 mg (n=71)	Normal	47 (66)	3 (4)	7 (10)
	Abnormal	2 (3)	9 (13)	–
	Missing†	1 (1)	1 (1)	–
Conjunctival oedema				
Placebo (n=70)	Normal	56 (80)	1 (1)	5 (7)
	Abnormal	1 (1)	1 (1)	–
	Missing†	5 (7)	–	–
Sildenafil 20 mg (n=69)	Normal	55 (80)	1 (1)	8 (12)
	Abnormal	–	1 (1)	–
	Missing†	4 (6)	–	–
Sildenafil 40 mg (n=67)	Normal	56 (84)	1 (2)	6 (9)

Table 6 (continued)

Treatment	Result at week 12	Result at baseline		
		Normal	Abnormal	Missing†
Sildenafil 80 mg (n=71)	Abnormal	–	–	–
	Missing†	4 (6)	–	–
	Normal	60 (85)	1 (1)	7 (10)
	Abnormal	–	–	–
	Missing†	2 (3)	–	–
Dilated episcleral blood vessels				
Placebo (n=70)	Normal	45 (64)	4 (6)	3 (4)
	Abnormal	2 (3)	8 (11)	2 (3)
	Missing†	4 (6)	1 (1)	–
Sildenafil 20 mg (n=69)	Normal	44 (64)	5 (7)	5 (7)
	Abnormal	2 (3)	6 (9)	3 (4)
	Missing†	3 (4)	1 (1)	–
Sildenafil 40 mg (n=67)	Normal	46 (69)	5 (8)	5 (8)
	Abnormal	1 (2)	5 (8)	1 (2)
	Missing†	3 (4)	1 (2)	–
Sildenafil 80 mg (n=71)	Normal	43 (61)	6 (9)	5 (7)
	Abnormal	4 (6)	8 (11)	2 (3)
	Missing†	–	2 (3)	–
Abnormal blood vessels				
Placebo (n=70)	Normal	48 (69)	3 (4)	4 (6)
	Abnormal	3 (4)	6 (9)	–
	Missing†	4 (6)	1 (1)	–
Sildenafil 20 mg (n=69)	Normal	47 (68)	2 (3)	7 (10)
	Abnormal	2 (3)	5 (7)	1 (1)
	Missing†	2 (4)	1 (1)	–
Sildenafil 40 mg (n=67)	Normal	50 (75)	1 (2)	6 (9)
	Abnormal	–	6 (9)	–
	Missing†	4 (6)	–	–
Sildenafil 80 mg (n=71)	Normal	51 (72)	3 (4)	5 (7)
	Abnormal	3 (4)	4 (6)	2 (3)
	Missing†	2 (3)	–	–
Retinal vein engorgement				
Placebo (n=70)	Normal	55 (79)	4 (6)	4 (6)
	Abnormal	–	1 (1)	–
	Missing†	4 (6)	1 (1)	–
Sildenafil 20 mg (n=69)	Normal	53 (77)	–	8 (12)
	Abnormal	–	4 (6)	–
	Missing†	4 (6)	–	–
Sildenafil 40 mg (n=67)	Normal	51 (76)‡	1 (2)	6 (9)
	Abnormal	1 (2)	3 (5)	–
	Missing†	4 (6)	–	–
Sildenafil 80 mg (n=71)	Normal	59 (83)	1 (1)	7 (10)
	Abnormal	–	1 (1)	–
	Missing†	2 (3)	–	–
No of participants with ocular abnormalities				
Placebo (n=70)	Normal	36 (51)	4 (6)	1 (1)
	Abnormal	1 (1)	19 (27)	3 (4)

Table 6 (continued)

Treatment	Result at week 12	Result at baseline		
		Normal	Abnormal	Missing†
Sildenafil 20 mg (n=69)	Missing†	3 (4)	2 (3)	1 (1)
	Normal	34 (49)	7 (10)	4 (6)
	Abnormal	4 (6)	12 (17)	4 (6)
	Missing†	2 (3)	2 (3)	–
Sildenafil 40 mg (n=67)	Normal	31 (46)	7 (10)	5 (8)
	Abnormal	2 (3)	17 (25)	1 (2)
	Missing†	3 (5)	1 (2)	–
Sildenafil 80 mg (n=71)	Normal	31 (44)	8 (11)	4 (6)
	Abnormal	5 (7)	17 (24)	3 (4)
	Missing†		2 (3)	1 (1)

*Data are numbers (percentages) and include all participants with week 12 visit.

†Not possible to calculate change owing to missing assessment.

‡Assessment not done for 1 participant.

Table 7 | Cross tabulation of double masked study dose groups by dose during open label extension study

Open label extension study		Double masked study			
Visit	Sildenafil dose (mg tid)	Placebo (n=67)	Sildenafil 20 mg tid (n=65)	Sildenafil 40 mg tid (n=63)	Sildenafil 80 mg tid (n=64)
Week 12	40	67 (100)	65 (100)	63 (100)	
	80				64 (100)
Week 18	20	2 (3)		1 (2)	
	40	23 (34)	16 (25)	20 (32)	1 (2)
	80	39 (58)	49 (75)	42 (67)	63 (98)
Week 24	20	2 (3)	1 (2)	1 (2)	
	40	1 (2)	1 (2)		2 (3)
	80	56 (84)	62 (95)	62 (98)	62 (97)
Month 9	20	2 (3)		1 (2)	
	40	1 (2)	1 (2)		2 (3)
	80	54 (81)	61 (94)	61 (97)	61 (95)
Month 12	20	2 (3)		1 (2)	
	40	1 (2)	1 (2)		2 (3)
	80	49 (73)	60 (92)	56 (89)	58 (92)
Month 15	20	1 (2)			
	40	1 (2)	1 (2)		2 (3)
	80	36 (54)	38 (59)	45 (71)	41 (64)
Month 18	40	1 (2)			1 (2)
	80	17 (25)	22 (34)	26 (41)	21 (33)
Month 21	40	1 (2)			1 (2)
	80	4 (6)	4 (6)	8 (13)	4 (6)
Month 33	20	1 (2)		1 (2)	
	40	1 (2)	1 (2)		2 (3)
	80	47 (70)	55 (85)	56 (89)	54 (84)

tid=three times daily.

Table 8| Incidence of all causality eye disorder adverse events reported by participants by last visit,* either eye. Values are numbers (percentages, 95% CI)

Adverse event (MedDRA preferred term)	Sildenafil (n=259)
Abnormal sensation in eye	1 (0.4, 0.01 to 2.13)
Cataract	2 (0.8, 0.09 to 2.76)
Cataract bilateral NOS	1 (0.4, 0.01 to 2.13)
Cataract cortical	1 (0.4, 0.01 to 2.13)
Cataract nuclear	1 (0.4, 0.01 to 2.13)
Cataract unilateral	2 (0.8, 0.09 to 2.76)
Choroidal detachment	1 (0.4, 0.01 to 2.13)
Chromatopsia	7 (2.7, 1.09 to 5.49)
Conjunctival hyperaemia	12 (4.6, 2.42 to 7.95)
Conjunctival oedema	1 (0.4, 0.01 to 2.13)
Conjunctivitis	2 (0.8, 0.09 to 2.76)
Conjunctivitis allergic	1 (0.4, 0.01 to 2.13)
Cyanopsia	4 (1.5, 0.42 to 3.91)
Diplopia	2 (0.8, 0.09 to 2.76)
Dry eye NOS	2 (0.8, 0.09 to 2.76)
Episcleral hyperaemia	10 (3.9, 1.87 to 6.99)
Episcleritis NOS	1 (0.4, 0.01 to 2.13)
Eye disorder NOS	2 (0.8, 0.09 to 2.76)
Eye haemorrhage NOS	6 (2.3, 0.85 to 4.97)
Eye inflammation NOS	1 (0.4, 0.01 to 2.13)
Eye irritation	3 (1.2, 0.24 to 3.35)
Eye pain	3 (1.2, 0.24 to 3.35)
Eye pruritus	1 (0.4, 0.01 to 2.13)
Eye redness	3 (1.2, 0.24 to 3.35)
Eye swelling	1 (0.4, 0.01 to 2.13)
Eyelid disorder NOS	1 (0.4, 0.01 to 2.13)
Eyelid oedema	1 (0.4, 0.01 to 2.13)
Eyelid ptosis	2 (0.8, 0.09 to 2.76)
Glaucoma NOS	1 (0.4, 0.01 to 2.13)
Halo vision	2 (0.8, 0.09 to 2.76)
Iris vascular disorder NOS	1 (0.4, 0.01 to 2.13)
Keratitis	2 (0.8, 0.09 to 2.76)
Keratoconjunctivitis sicca	1 (0.4, 0.01 to 2.13)
Lacrimation increased	2 (0.8, 0.09 to 2.76)
Lenticular opacities	4 (1.5, 0.42 to 3.91)
Macular degeneration	2 (0.8, 0.09 to 2.76)
Macular oedema	1 (0.4, 0.01 to 2.13)
Ocular discomfort	5 (1.9, 0.63 to 4.45)
Ocular vascular disorder	2 (0.8, 0.09 to 2.76)
Papilloedema	1 (0.4, 0.01 to 2.13)
Photopsia	5 (1.9, 0.63 to 4.45)
Presbyopia	1 (0.4, 0.01 to 2.13)
Punctate keratitis	2 (0.8, 0.09 to 2.76)
Refractive errors NOS	4 (1.5, 0.42 to 3.91)
Retinal exudates	1 (0.4, 0.01 to 2.13)
Retinal haemorrhage	10 (3.9, 1.87 to 6.99)
Retinal microaneurysms	1 (0.4, 0.01 to 2.13)
Retinal pigmentation	3 (1.2, 0.24 to 3.35)

Table 8 (continued)

Adverse event (MedDRA preferred term)	Sildenafil (n=259)
Retinal tear	2 (0.8, 0.09 to 2.76)
Vision blurred	21 (8.1, 5.09 to 12.13)
Visual acuity reduced	3 (1.2, 0.24 to 3.35)
Visual brightness	4 (1.5, 0.42 to 3.91)
Visual disturbance NOS	15 (5.8, 3.28 to 9.37)

MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified.

*Counts of adverse events include data up to seven days after last dose of study drug.

Figure

Treatment allocation schedule during open label extension study. During first six weeks, participants who did not tolerate initial sildenafil three times daily dose were allowed to down-titrate to half dose; participants were also allowed to down-titrate once during first 12 weeks