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# Modified-Release Sildenafil Reduces Raynaud's Phenomenon Attack Frequency in Limited Cutaneous Systemic Sclerosis

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***Objective.*** **To examine the effect of sildenafil in patients with Raynaud's phenomenon (RP) secondary to limited cutaneous systemic sclerosis (lcSSc).**

***Methods.*** **In this double-blind, placebo-controlled study, 57 patients with RP secondary to lcSSc were randomized to receive modified-release sildenafil 100 mg once daily for 3 days followed by modified-release sildenafil 200 mg once daily for 25 days or placebo. The primary assessment was the percentage change in the number of RP attacks per week in the per-protocol population. Secondary end points included Raynaud's Condition Score, duration of attacks, RP pain score, endothelial dysfunction assessed by a peripheral arterial tonometric (PAT) device, and serum biomarker levels.**

***Results.*** **The mean percentage reduction from baseline to day 28 in attacks per week was greater for modified-release sildenafil than for placebo (−44.0% versus −18.1%, $P = 0.034$); the mean number of attacks per week improved from 25.0 at baseline to 19.3 after placebo treatment and from 30.5 to 18.7 after modified-release sildenafil treatment ($P = 0.244$). Decreases from baseline in Raynaud's Condition Score, duration of attacks, and RP pain score were not significantly different between groups. Mean values and changes from baseline in PAT responses and serum biomarker levels were similar between groups. The most frequent adverse events were headache and dyspepsia; the majority of adverse events were mild or moderate.**

***Conclusion.*** **Our findings indicate that modified-release sildenafil reduced attack frequency in patients with RP secondary to lcSSc and was well tolerated. Modified-release sildenafil may be a treatment option in this patient population.**

Raynaud's phenomenon (RP) is a cardinal feature of systemic sclerosis (SSc) and occurs in almost all cases (1). Associated structural vasculopathy makes this a particularly troublesome symptom (2,3) and, combined with intermittent vasospasm, is responsible for the serious digital vascular complications of SSc, including digital ulceration, soft tissue or bone infection, and critical ischemia or gangrene (3,4). In addition, symptoms of RP attacks themselves are an important morbidity in SSc.

The pathologic process in SSc is not fully understood. Reduction in the production and release of nitric oxide and up-regulated endothelin production by dysfunctional endothelium may result in a tendency toward vasoconstriction and reduced vasodilatory capacity (2). Endothelial cell dysfunction and altered vascular tone may directly contribute to the SSc disease process (4). The hyperemic response, thought to be an indicator of endothelial cell (dys)function (5), can be measured noninvasively by a peripheral arterial tonometric (PAT) device and has been used to identify patients with early coronary atherosclerosis (6) and to predict late cardiovascular events (7). Elevated levels of adhesion molecules, including soluble vascular cell adhesion molecule

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(VCAM), intercellular adhesion molecule (ICAM), and N-terminal type I procollagen propeptide (PINP), are found in patients with SSc relative to healthy controls and, although not validated biomarkers, may be useful for tracking disease progress (8–13), and so may be included for exploratory analysis in studies of treatment response.

Secondary RP, such as that occurring with SSc, is typically more severe and thus more difficult to treat than primary idiopathic RP (14). Prostacyclin and prostacyclin analogs are effective when given intravenously but require hospitalization (15,16). Vasodilator drugs have proved variably effective in clinical trials but many have significant adverse effects (17).

Sildenafil and other phosphodiesterase type V (PDE V) inhibitors are attractive candidates for therapy in patients with RP secondary to SSc. Vascular smooth muscle relaxation and vasodilation occur when nitric oxide diffuses through the endothelial cell layer and activates guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), which provides the signal leading to smooth muscle relaxation. Because PDE V breaks down cGMP in endothelial cells, its inhibition by sildenafil increases the level of cGMP available to promote vascular smooth muscle relaxation and consequently improves local blood flow. Some encouraging results have emerged from case studies and limited clinical trials of PDE V inhibitors in RP (14,18); however, the inclusion of patients with idiopathic primary disease and those with disease secondary to non-SSc connective tissue diseases restricts applicability to patients with limited cutaneous SSc (lcSSc). Therefore, in this randomized, double-blind, placebo-controlled study, we examined the effect of sildenafil specifically in patients with RP secondary to lcSSc. A modified-release formulation was used to permit once-daily dosing.

## PATIENTS AND METHODS

**Study design.** This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that took place between January and June 2003. Patients with RP secondary to lcSSc were randomized in a 1:1 ratio to receive either modified-release sildenafil 100 mg once daily for 3 days followed by modified-release sildenafil 200 mg once daily for 25 days or placebo for 28 days. The 2-step dosing was used to enhance tolerability. Modified-release sildenafil uses a swellable core technology, with expected overall exposure for 200 mg of modified-release sildenafil once daily similar to that of 50 mg of immediate-release sildenafil 3 times daily (19).

Each patient had 5 visits: a screening visit (days −14 to −7), a baseline visit (day 1), 2 visits while receiving treatment (days 14 and 28), and a followup visit (7–14 days following day 28). Patients completed a daily diary during the 7–14 days before baseline and during the 28-day treatment phase. Clinical and other outcome measures and pharmacokinetic and laboratory safety samples were obtained at screening, baseline, on days 14 and 28, and at the followup visit.

The protocol was approved by an independent ethics committee or institutional review board at each study center, and the study was conducted in compliance with the ethics principles of the Declaration of Helsinki. All patients provided written informed consent before initiating study procedures.

**Patients.** The study included men and women ages 18–75 years with a diagnosis of RP secondary to lcSSc confirmed by the investigator. Patients had at least 7 RP attacks per week with attacks on 5 or more days per week as determined from the daily diaries. RP was defined as episodic digital pallor followed by cyanosis and/or erythema in response to cold or emotion; lcSSc was defined using the criteria of LeRoy et al (1), with skin involvement limited to hands, forearms, feet, and face. Patients with diffuse cutaneous SSc (dcSSc) were excluded. Other key exclusion criteria included hemodynamic instability or systolic arterial pressure <95 mm Hg; a history of stroke, myocardial infarction, severe cardiac failure, unstable angina, or life-threatening arrhythmia within the previous 6 months; creatinine clearance <30 ml/minute; impaired hepatic function (Child-Pugh class C); untreated proliferative retinopathy; diabetes mellitus; vibration-induced RP; therapy with nitrates or nitric oxide donors, alpha blockers, iloprost, bosentan, calcium-channel blockers, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, corticosteroids (except stable doses), aspirin >325 mg/day, dipyridamole, or antiplatelet agents 14 days before beginning the study; current smoking or use of smoking cessation treatments.

**Efficacy assessments.** The primary assessment was the number of RP attacks per week. Secondary assessments were Raynaud's Condition Score, RP pain score, mean duration of RP attacks, PAT-reactive hyperemic response, serum levels of biomarkers (VCAM, ICAM, and PINP), and plasma sildenafil concentration.

**Clinical evaluation.** The number and duration of RP attacks were recorded in patient diaries throughout the study. The Raynaud's Condition Score was a number selected by the patient to best indicate the difficulty the patient had that day with RP on an 11-point scale, where 0 = no difficulty and 10 = extreme difficulty, and is a validated outcome measure (20). The RP pain score was a number selected by the patient to best describe the pain caused by their RP during the past 24 hours on an 11-point scale, where 0 = no pain and 10 = worst possible pain.

Serum samples for biomarker tests were collected at baseline and 4–6 hours after dosing on days 1, 14, and 28. Blood samples (5 ml) for pharmacokinetic sampling of sildenafil were collected before administration of the first dose of study drug (baseline only) and 4–6 hours after the study drug doses taken at baseline and on days 14 and 28.

The PAT test was performed at 4 of the 11 study sites. PAT, as stated above, is thought to indicate endothelial dysfunction; the device measured the magnitude and time course of changes in arterial pulsatile blood flow in the fingertip. Patients were in a temperature-controlled environment (22–24°C ± 0.5°C) for at least 30 minutes before and during the test. A PAT finger probe was applied to each hand and recordings began. A cuff was inflated on the nondependent arm to 60 mm Hg greater than the systolic pressure for 5

minutes. The cuff was deflated; recordings continued for an additional 5 minutes. The ratio between the preocclusion PAT and the postocclusion PAT constituted the hyperemic response.

All reported adverse events were recorded at every visit during treatment (including up to 7 days after drug discontinuation); investigators assessed seriousness and relation to treatment (deemed treatment related if no causality was noted or if the event was described as having probable, possible, or uncertain relationship to study treatment). Exacerbations of illnesses recorded at baseline or abnormal test findings that resulted in a change in study drug dosage or study discontinuation were recorded as adverse events.

Additional safety measures included sitting blood pressure and heart rate and clinical laboratory tests (hematology, clinical chemistry, and electrocardiogram [EKG]). Sitting blood pressure and heart rate were recorded at screening, baseline (before and after first dose), on days 14 and 28, and at followup. A 12-lead EKG recording was obtained at screening, on day 28, and at followup.

**Statistical analysis.** The sample size was calculated using the primary end point and assuming a mean ± SD difference from baseline of 9 ± 12 attacks per week between patients receiving modified-release sildenafil and patients receiving placebo. Thirty patients per group were required to detect a difference with 80% power at a 2-sided significance level of 5%.

The intent-to-treat (ITT) population included all randomized patients who received ≥1 dose of study drug and had a baseline and a postbaseline efficacy assessment. The per-protocol population included all randomized patients who received all planned treatments, were compliant with diary completion, and completed the study without a serious protocol violation.

*Primary analysis.* For the primary efficacy assessment, the number of RP attacks per week, the percentage change from baseline (day −6 to day 0) to week 4 (day 21 to day 27) was analyzed in the per-protocol population. An analysis of covariance (ANCOVA) with treatment as a factor and baseline as a covariate was used in the per-protocol population.

*Secondary analyses.* The change from baseline to week 4 in the number of RP attacks per week was analyzed with an ANCOVA with treatment as a factor, baseline and randomization date as continuous covariates, and center as a discrete covariate. It was thought that center and randomization date might reflect changes in temperature that might affect the results; randomization date was coded as a whole number describing the day from a fixed baseline.

Additionally, the change from baseline to week 4 in the square root transformed number of RP attacks per week and the change from baseline to week 4 in the number of RP attacks per week with or without influential observations were analyzed with an ANCOVA with treatment as a factor and baseline as a covariate. To examine robustness, these analyses were also performed on the ITT population. Model assumptions underlying these analyses were examined in a series of diagnostic plots.

Mean Raynaud's Condition Score, mean RP pain score, and mean duration of RP attacks were analyzed as changes from baseline to week 4. End points were analyzed for the per-protocol population with an ANCOVA using treatment as a factor and baseline as a covariate.

PAT-reactive hyperemic response and serum levels of biomarkers for VCAM, ICAM, and PINP were summarized as absolute values and changes from baseline by treatment at each study visit with no statistical analysis. Plasma sildenafil concentrations were plotted against other efficacy end points to assess pharmacokinetic and pharmacodynamic relationships. All volunteered or observed adverse events were recorded, and the findings were summarized.

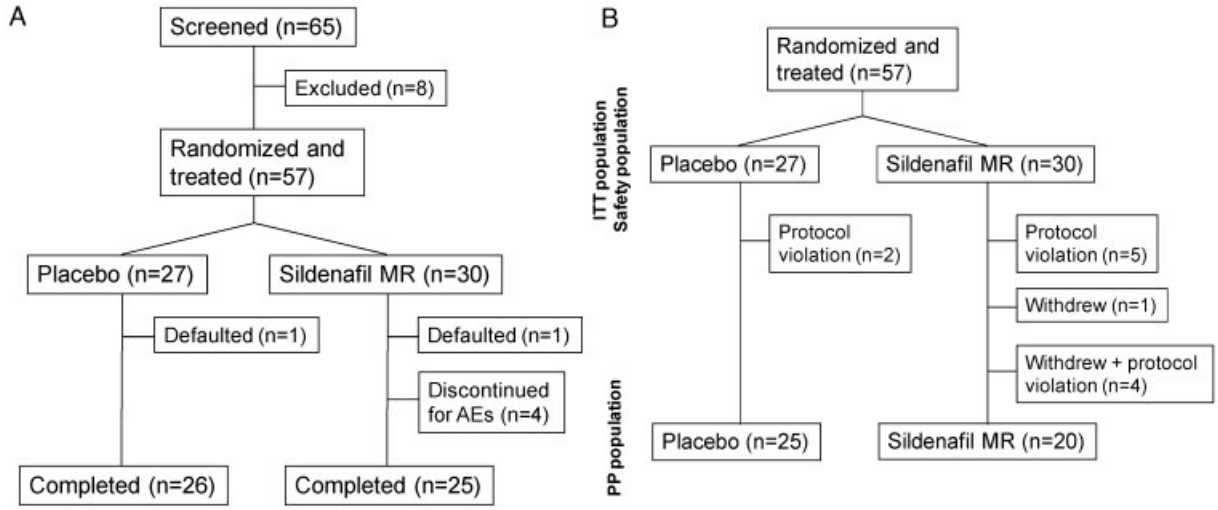


**Figure 1.** Disposition of the patients (**A**) and patient populations (**B**). Patients treated with placebo were excluded from the per-protocol (PP) population for unstable steroid dosing (n = 1) and Raynaud's phenomenon (RP) attacks <5 days per week at baseline (n = 1). Patients treated with modified-release (MR) sildenafil were excluded for RP attacks <5 days per week at baseline (n = 4), insufficient diary entries (n = 2), concomitant nonsteroidal antiinflammatory drug use (n = 1), unstable steroid dosing (n = 1), and insufficient diary entry combined with <7 RP attacks per week at baseline (n = 1). AEs = adverse events; ITT = intent to treat.

**Table 1.** Demographic characteristics of the patients with RP secondary to SSc*

| | Placebo | | Modified-release sildenafil 200 mg | |
|---|---|---|---|---|
| | Men (n = 3) | Women (n = 24) | Men (n = 3) | Women (n = 27) |
| Age, years | 53.7 (38–64) | 50.3 (34–73) | 49.3 (34–62) | 51.4 (31–72) |
| Weight, kg | 79.0 (61–102) | 64.9 (49–99) | 77.4 (71–82) | 64.4 (45–111) |
| Height, cm | 174.7 (172–176) | 161.9 (149–181) | 174.7 (173–176) | 163.6 (153–172) |

* Values are the mean (range). The mean (range) duration since Raynaud's phenomenon (RP) diagnosis was 16.3 (3.0–57.0) years in the placebo group and 14.3 (2.6–40.2) years in the modified-release sildenafil 200 mg group. The mean (range) duration since systemic sclerosis (SSc) diagnosis was 8.8 (0.3–22.0) years in the placebo group and 7.6 (0.3–23.0) years in the modified-release sildenafil 200 mg group.

## RESULTS

**Patient characteristics.** Patient progress through the study is shown in Figure 1A. Demographic characteristics were similar for both treatment groups (Table 1). The median duration of treatment in both groups was 29 days. The ITT and per-protocol populations are shown in Figure 1B.

**Primary end point.** The percentage change from baseline to week 4 in the number of RP attacks per week was significantly greater for modified-release sildenafil than for placebo in the per-protocol population ($P$ = 0.034) (Figure 2). The number of RP attacks per week improved from baseline in both the placebo group (from 25.0 to 19.3) and the modified-release sildenafil group (30.5 to 18.7) ($P$ = 0.244 for modified-release sildenafil versus placebo). Adjusting for center and randomization date (as surrogates for outdoor temperature) appeared to have no significant effect on the number of attacks.

The results of sensitivity analyses supported the primary end point: the change from baseline to week 4 in the square root transformed number of RP attacks per week and the number of attacks excluding influential observations (n = 3) favored modified-release sildenafil over placebo ($P$ = 0.047 and $P$ = 0.050, respectively). For robustness, the same primary and secondary analyses were conducted on the ITT population; results were consistent with those for the per-protocol population.

**Secondary end points.** Decreases relative to baseline in Raynaud's Condition Score and the mean duration of attacks were greater for the modified-release sildenafil group than for the placebo group, but did not reach statistical significance (Table 2). Changes in the RP pain score were similar in the 2 groups. Mean values and changes from baseline in PAT hyperemic responses and serum levels of biomarkers (soluble VCAM, soluble ICAM, and PINP) showed similar results for the modified-release sildenafil and placebo groups (Table 3). No apparent pharmacokinetic or pharmacodynamic relationships with sildenafil were observed for any end points (data not shown).

**Safety.** The number of patients with all-cause and treatment-related adverse events and the total number of adverse events were greater in the modified-release sildenafil group than in the placebo group. In the modified-release sildenafil group, 28 patients reported 76 adverse events of all causes and 21 patients reported

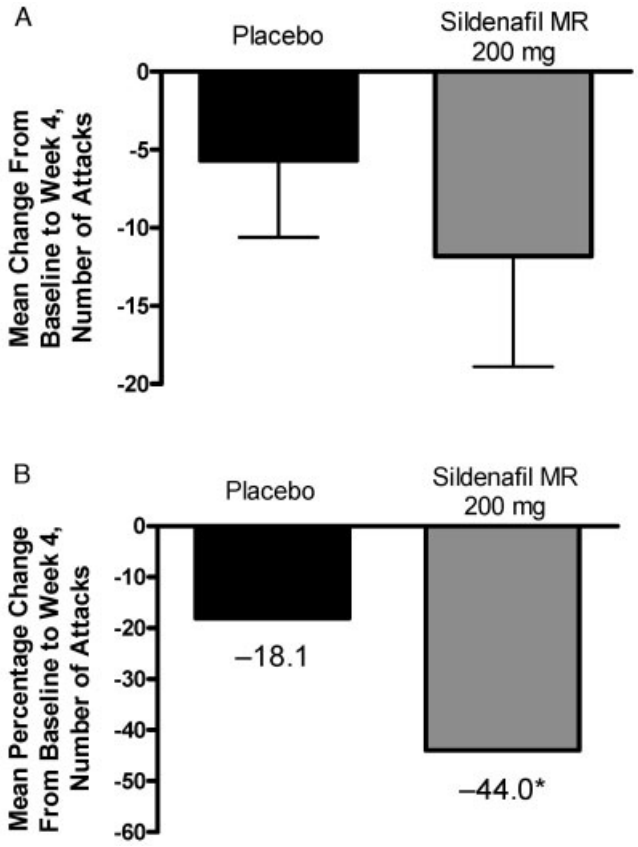


**Figure 2. A,** Mean change from baseline to week 4 in the number of Raynaud's phenomenon (RP) attacks per week in the per-protocol population. Error bars show 95% confidence intervals. **B,** Mean percentage change from baseline to week 4 in the number of RP attacks per week in the per-protocol population. * = $P$ = 0.034 versus adjusted mean in the placebo group. MR = modified release.

**Table 2.** Secondary end point results in the per-protocol population*

| | Raynaud's Condition Score | | RP Pain Score | | Duration of attacks, minutes | |
|---|---|---|---|---|---|---|
| | Placebo (n = 25) | Modified-release sildenafil (n = 20) | Placebo (n = 25) | Modified-release sildenafil (n = 20) | Placebo (n = 25) | Modified-release sildenafil (n = 20) |
| Baseline | 3.2 | 4.1 | 2.9 | 3.5 | 21.0 | 22.2 |
| Week 4 | 2.6 | 2.8 | 2.2 | 2.5 | 18.4 | 15.0 |
| Adjusted mean change from baseline to week 4 | −0.7 | −1.2 | −0.9 | −0.8 | −2.8 | −7.0 |

* Values are the mean. The difference between adjusted means (95% confidence interval) between the placebo and modified-release sildenafil groups was −0.5 (−1.5, 0.5) for Raynaud's Condition Score ($P = 0.347$), 0.0 (−1.0, 1.1) for Raynaud's phenomenon (RP) pain score ($P = 0.983$), and −4.2 (−9.3, 1.0) for mean duration of attacks ($P = 0.112$).

43 treatment-related adverse events. In the placebo group, 16 patients reported 33 adverse events of all causes and 8 patients reported 17 treatment-related adverse events.

The most frequent adverse events were headache and dyspepsia (Table 4); the majority of adverse events were mild or moderate. At baseline, 5 patients in each group had dyspepsia, a frequent symptom in patients with RP secondary to SSc; more patients in the modified-release sildenafil group (n = 9) than the placebo group (n = 5) had dyspepsia on day 28.

Treatment-related adverse events leading to discontinuation of treatment in 4 patients in the modified-release sildenafil group included allergic reaction (n = 1), headache and myalgia (n = 1), headache, chest pain, and facial edema (n = 1), and headache, palpitations, and non–treatment-related arthralgia (n = 1). Two patients in the modified-release sildenafil group discontinued temporarily because of adverse events that were not considered to be related to treatment (muscle hypertonia and gastroenteritis; n = 1 each).

No deaths or serious adverse events were reported. Laboratory test data showed no evidence of a relationship between modified-release sildenafil administration and test abnormalities (i.e., hematology or clinical chemistry). Mean changes from baseline to last observation in blood pressure and heart rate were small; similarly, mean changes from baseline in EKG parameters were small in both groups (≤1.5% of baseline for heart rate; ≤2.8% of baseline for PR interval; ≤2.5% of baseline for QRS width; ≤0.8% of baseline for QT interval).

## DISCUSSION

We examined the efficacy of modified-release sildenafil as a treatment for RP in patients with lcSSc. We observed a statistically significant reduction in percentage change in attack frequency in patients receiving

**Table 3.** PAT and serum biomarker results in the per-protocol population*

| | PAT-reactive hyperemic responses | | Soluble VCAM, ng/ml | | Soluble ICAM, ng/ml | | PINP, ng/ml | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (n = 9)† | Modified-release sildenafil (n = 9)‡ | Placebo (n = 22)§ | Modified-release sildenafil (n = 17)¶ | Placebo (n = 22)# | Modified-release sildenafil (n = 18)** | Placebo (n = 24)†† | Modified-release sildenafil (n = 18)‡‡ |
| Baseline predose | 1.5 | 1.6 | 620 | 610 | 338 | 344 | 48.5 | 42.0 |
| Baseline postdose | 1.0 | 1.8 | 610 | 583 | 336 | 329 | 47.1 | 39.2 |
| Day 28 | 1.1 | 1.5 | 581 | 600 | 328 | 329 | 45.8 | 39.8 |
| Change from baseline predose to day 28 (95% CI) | −0.3 (−1.1, 0.5) | 0.0 (−1.2, 1.1) | −41.0 (−84.3, 2.2) | 39.0 (−59.6, 137.6) | −5.0 (−19.0, 9.0) | −2.1 (−19.3, 15.0) | −1.5 (−5.3, 2.3) | 1.1 (−3.2, 5.3) |

* Values are the mean. PAT = peripheral arterial tonometric; VCAM = vascular cell adhesion molecule; ICAM = intercellular adhesion molecule; PINP = N-terminal type I procollagen propeptide; 95% CI = 95% confidence interval.
† Except for baseline predose (n = 10) and day 28 (n = 11).
‡ Except for day 28 (n = 10).
§ Except for baseline postdose (n = 23) and day 28 (n = 23).
¶ Except for baseline postdose (n = 18), day 28 (n = 16), and change from baseline predose to day 28 (n = 15).
# Except for baseline predose (n = 23) and day 28 (n = 23).
** Except for day 28 (n = 17) and change from baseline predose to day 28 (n = 15).
†† Except for day 28 (n = 22) and change from baseline predose to day 28 (n = 21).
‡‡ Except for day 28 (n = 17) and change from baseline predose to day 28 (n = 15).

**Table 4.** Adverse events occurring in ≥3 patients in any treatment group*

| | Placebo (n = 27) | Modified-release sildenafil (n = 30) |
|---|---|---|
| Headache | 8/6 | 15/12 |
| Dyspepsia | 3/2 | 7/5 |
| Flatulence | 1/0 | 3/1 |
| Arthralgia | 0/0 | 3/0 |
| Myalgia | 3/1 | 2/2 |
| Respiratory tract infection | 1/0 | 3/0 |

* Values are the number of adverse events/number of treatment-related adverse events.

modified-release sildenafil compared with patients receiving placebo but no significant difference in the absolute number of attacks per week. Although other key clinical outcome measures favored modified-release sildenafil treatment, none reached statistical significance. Modified-release sildenafil was well tolerated, with the majority of adverse events being mild or moderate and not unexpected for treatment with PDE V inhibitors.

The effect of sildenafil on RP attacks has been investigated in previous trials. A double-blind, placebo-controlled, crossover study included 14 patients with SSc, 2 with mixed connective tissue disease, and 2 with primary RP. In the 16 patients with secondary RP, the number of attacks was significantly reduced when patients received 4 weeks of sildenafil treatment (50 mg twice daily) compared with placebo; however, because patients correctly guessed their order of treatment, the study was not truly blinded (21). In contrast, attacks were not significantly improved after 2 weeks of treatment with sildenafil 50 mg twice daily in a prospective, double-blind, crossover pilot study in patients with primary RP (22). This discrepancy could reflect important differences between primary and secondary RP cases, especially because of the obstructive vasculopathy characteristic of SSc-associated RP.

A difference in trial duration (2 weeks versus 4 weeks) also may have contributed to the discrepancy in findings; in some cases of PDE V inhibitor treatment, improvement was noted after a longer period (23–26). In a study by Brueckner et al (26), after a mean duration of 5.2 months of treatment with maximally tolerated doses of sildenafil, 16 patients with SSc (7 with lcSSc and 9 with dcSSc) reported significant improvement in RP ($P = 0.003$) (26). The primary end point in that study was digital ulcer healing, but improvement in RP was measured with a visual analog scale (26). Although the use of different methodologies makes direct comparison difficult, the significant improvements observed in RP and pain after sildenafil treatment in the study by Brueckner et al support our findings.

Other trials of PDE V inhibitors have examined patients with RP secondary to autoimmune disease. Mean RP frequency, mean RP duration, and mean Raynaud's Condition Score were not significantly reduced after treatment with tadalafil compared with placebo in a randomized, double-blind, crossover study in women with RP secondary to SSc (27). In contrast, a preliminary report showed that tadalafil reduced attack frequency relative to baseline in 9 male patients with RP secondary to unspecified autoimmune disease (25). Attack frequency was reduced in half of 40 patients (33 of whom had secondary RP) receiving vardenafil; however, exact numbers were not reported, nor was significance (28).

The significant reduction in RP attack frequency in the present study was not accompanied by statistically significant reductions in mean changes from baseline to week 4 in Raynaud's Condition Score, RP pain score, or duration of attacks. Improvements or reductions in attack frequency accompany changes in duration, perception of pain or severity, and Raynaud's Condition Score in most case reports and clinical trials of newer agents. The Raynaud's Condition Score is a validated outcome measure for RP (20) that was sensitive to changes in other attack end points in previous clinical trials (21,22,27,28). Decreases in Raynaud's Condition Score and in duration of attacks in the modified-release sildenafil group tended to be greater than those in the placebo group in our study, which was not powered to detect clinically meaningful differences in secondary end points. Frequency of attacks was chosen as the primary outcome measure as this was thought to be the most objective measure recorded in the patient diary.

It is possible that the short duration of treatment, which was comparable to that of other studies examining PDE V inhibitors in the treatment of RP (21,22), contributed to the observed lack of effect in secondary end points; treatment effects have been delayed in other studies of RP treatment (23–26). Disease heterogeneity may also result in the lack of effect noted in this study. Small numbers of patients make it difficult to assess factors such as severity of disease that might predict which patients could most benefit from treatment. Although outdoor temperature had no significant effect on RP attacks, the large number of centers and short recruitment period for this limited patient set resulted in low power to test an effect. Additionally, although smokers were excluded from the study, those with a history of smoking were not analyzed separately;

both current and past smoking are associated with digital vascular disease in patients with SSc (29).

Mean values and changes from baseline in PAT hyperemic responses and serum levels of biomarkers were similar between the modified-release sildenafil and placebo groups. The lack of improvement in PAT response was disappointing. In a previous double-blind trial of sildenafil in 16 patients with RP secondary to connective tissue disease (14 with SSc) and resistant to previous vasodilatory therapy (21), blood flow increased significantly after treatment ($P = 0.0004$), confirming the effects seen in smaller, uncontrolled studies (30–32). Serum biomarkers were selected based on their increased expression in SSc. The 3 serum biomarkers chosen (VCAM, ICAM, and PINP) all relate to key aspects of disease, and previous studies (9,12,13) have suggested that although there is a wide variation in levels between patients, these levels may be useful in monitoring treatment response. However, individual biomarkers might be more useful in patients with dcSSc than in the patients with lcSSC examined in this trial (33,34) or may not be definitively up-regulated in lcSSc (35). Alternatively, the length of treatment with modified-release sildenafil in this trial may not have been sufficient to alter endothelial function.

Dyspepsia is a common manifestation of RP in patients with SSc because of upper gastrointestinal involvement in the disease (36) and can also occur as an adverse effect of sildenafil treatment (37,38), as noted in this study. Therefore, physicians must consider whether an exacerbation of dyspepsia in SSc patients treated with sildenafil might be treatment related.

There are several limitations to this study. The study was small and not powered to detect changes in secondary efficacy end points. Raynaud's Condition Score and attack duration showed greater improvements in the modified-release sildenafil group compared with placebo, and statistical significance might have occurred if patients were given a longer duration of treatment. Also, 33% of the patients treated with sildenafil were excluded from the per-protocol population (including those excluded due to protocol violations and withdrawals) assessed for efficacy end points compared with 7% of patients treated with placebo, perhaps resulting in a bias toward sildenafil "responders." The modified-release formulation of sildenafil was used and may not have provided the most effective dose. The average maximum plasma concentration of 100 mg of the modified-release formulation was 10-fold lower than that of 100 mg of the immediate-release formulation in a fasting state in healthy volunteers (52.3 versus 549 ng/ml, respectively); average area under the curve values were also lower for the modified-release formulation (1,021 versus 1,830 ng·hour/ml) (19).

In conclusion, modified-release sildenafil successfully reduced attack frequency in patients with RP secondary to lcSSc and was well tolerated. These results, taken together with the well-characterized safety profile of sildenafil in non-SSc patient populations (39), suggest that modified-release sildenafil may be of benefit as a treatment option in patients with RP secondary to lcSSc.

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### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Herrick had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Analysis and interpretation of data.** Herrick, van den Hoogen, Gabrielli, Tamimi, Reid, O'Connell, Vázquez-Abad, Denton.

### ROLE OF THE STUDY SPONSOR

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