Effects of the Selective α_{1A}-Adrenoceptor Antagonist Silodosin on ECGs of Healthy Men in a Randomized, Double-Blind, Placebo- and Moxifloxacin-Controlled Study

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In order to determine the effects of therapeutic and supratherapeutic doses of silodosin on QT interval, healthy men (*N* = 186; aged 18–45 years) were randomized to receive silodosin (8 or 24 mg) or placebo for 5 days or moxifloxacin 400 mg (positive control, known to prolong QT) once on day 5. At baseline and on day 5, five ECGs were recorded 0.25 h before dosing and 1, 1.5, 2, 3, 4, 6, 8, 10, and 23.5 h after dosing. Adjusted mean differences (analysis of covariance) between silodosin and placebo in the change in individual heart rate–corrected QTc (QTcI) from baseline to day 5 were <5 ms at all times (all 90% confidence interval (CI) upper limits <10 ms). The QTcI difference for moxifloxacin compared with placebo often exceeded 5 ms, establishing assay sensitivity. For silodosin, no statistically or clinically significant correlation was seen between plasma concentration and QTcI, and no clinically important effects on heart rate, PR segment, QRS complex, or morphologic ECG data were observed.

The QT interval recorded by a surface electrocardiogram (ECG) is a measure of the time from ventricular depolarization to repolarization, and QT prolongation is an indicator of delayed myocardial repolarization. Drug-induced QT prolongation is associated with increased risk of developing lethal polymorphic ventricular tachyarrhythmias such as torsade de pointes.[1]

In order to minimize the incidence of drug-induced torsade de pointes,[2] the US Food and Drug Administration, through the International Conference on Harmonisation E14 guidance, recommended in 2005 that all new drugs with systemic exposure submitted for marketing approval be evaluated for effects on heart rate–corrected QT interval (QTcI).[3] The guidance established prolongation by 5 ms as the threshold for regulatory concern. To provide reasonable assurance that the mean QTc prolongation caused by a study drug is below this 5-ms threshold, a "thorough QT/QTc study" in healthy volunteers should demonstrate that the upper limit of the 95% one-sided confidence interval (CI) of the largest time-matched mean effect is <10 ms for clinical and supratherapeutic doses. To ensure the validity of the results, the study should be adequately powered and include negative and positive controls.[3]

Silodosin is a highly selective α_{1A}-adrenergic receptor antagonist (α-blocker) that is approved in the United States for the treatment of patients with urinary symptoms secondary to benign prostatic hyperplasia. Silodosin has been shown to provide rapid and sustained relief of moderate to severe urinary symptoms and to rapidly increase peak urinary flow rates in patients with symptomatic benign prostatic hyperplasia.[4] *In vitro* and animal studies suggest that, compared with other α-blockers used to treat this condition, silodosin has a low affinity for α_{1B}-adrenoceptors located in vascular tissue.[5–7] This receptor subtype selectivity may contribute to the favorable cardiovascular safety profile of silodosin—in two phase III, randomized, controlled clinical studies, the percentage of patients receiving silodosin who had treatment-emergent orthostatic hypotension was low (2.6%) and was similar to that noted in patients receiving placebo (1.5%).[4]

Drug-induced delay of myocardial repolarization is generally the result of inhibition of the rapidly activating component of the delayed potassium current (I_{Kr}), which is mediated by the $hK_v11.1$ (hERG, KCNH2) potassium channel.[1,8,9] *In vitro* studies in transformed human embryonic kidney-293 cells transfected with $hK_v11.1$ showed that silodosin inhibited $hK_v11.1$ tail current with

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a half maximal inhibitory concentration (IC_{50}) of 8,910 nmol/l.[10] This concentration is >2,000 times the maximum plasma concentration (~4 nmol/l) of unbound silodosin in subjects who received a single therapeutic dose (8 mg; 16.1 μmol) of silodosin.[11]

In accordance with the International Conference on Harmonisation E14 guidance, we conducted a thorough double-blind, placebo-controlled study in healthy men to evaluate the effects of silodosin on QT prolongation and other ECG parameters. The primary objective was to determine whether therapeutic or supratherapeutic doses of silodosin cause QTc prolongation.

RESULTS

Study participants

Of 188 subjects assigned to treatment, 2 were not treated and were therefore excluded from further analysis. One subject who received silodosin 8 mg and one who received silodosin 24 mg voluntarily withdrew from the study. Of the 184 subjects who completed the study, there were evaluable data for 183. Patient baseline characteristics were similar across treatment groups (Table 1). Subjects ranged in age from 18 to 45 years (mean age, 28 years); 67% were white and 29% were black. No subject used a concomitant medication during the study.

Effect on QTc prolongation

Comparison of time-matched QTcI changes from baseline between subjects receiving moxifloxacin and those receiving placebo revealed a maximal least-squares mean (LSM) difference (LSM baseline- and placebo-corrected QTcI values) of >5 ms 3, 4, 6, 8, and 10 h after dosing (Table 2, Figure 1). This demonstration of clinically significant QTc prolongation by moxifloxacin indicated that the QTcI assay used in this study was sufficiently sensitive to assess the effects of silodosin treatment on QTc prolongation.

LSM differences for time-matched QTcI changes from baseline (LSM baseline- and placebo-corrected QTcI values) between each of the silodosin dose groups and the placebo group were <5 ms at all times; LSM differences ranged from −0.2 to 3.4 ms for silodosin 8 mg and from −2.9 to 1.6 ms for silodosin 24 mg. The LSM baseline- and placebo-corrected QTcI values for both silodosin dose groups were associated with 90% CI upper limits of <10 ms at all times (Table 2, Figure 2). These results demonstrate that silodosin did not cause clinically important QTc prolongation.

Effect on other ECG parameters

Time-averaged heart rates at baseline (mean ± SD, range (beats/min)) were similar among patients randomized to placebo (68.9 ± 9.1, 51.6–90.9), silodosin 8 mg (68.3 ± 7.6, 52.0–95.7),

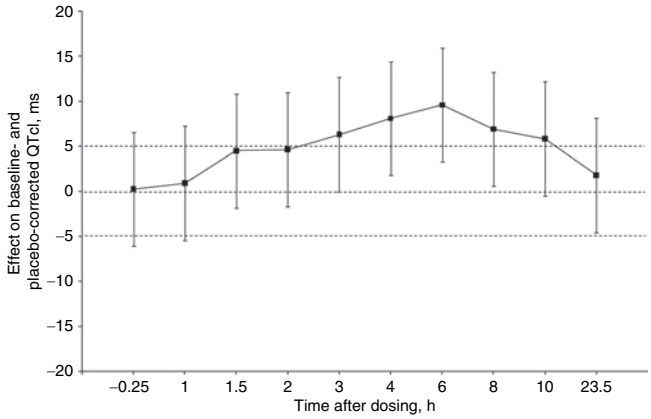

Figure 1 Effect of moxifloxacin on QTc prolongation. Time-matched least-squares mean baseline- and placebo-corrected QTcI values are shown. Differences were determined by analysis of covariance. Error bars indicate 90% confidence intervals. QTcI, individual heart rate–corrected QT interval.

Table 1 Patient baseline characteristics (safety population[a])

	Placebo ($n = 46$)	Silodosin 8 mg ($n = 48$)	Silodosin 24 mg ($n = 45$)	Moxifloxacin ($n = 47$)
Age, years				
Mean (SD)	25.6 (6.1)	26.8 (7.5)	30.0 (7.9)	27.7 (7.3)
Median (range)	23.5 (18–45)	24 (18–45)	30 (18–45)	26 (18–45)
Race, n (%)				
White	32 (69.6)	32 (66.7)	30 (66.7)	30 (63.8)
Black	12 (26.1)	15 (31.3)	13 (28.9)	13 (27.7)
Other	2 (4.3)	1 (2.1)	2 (4.4)	4 (8.5)
Height, cm				
Mean (SD)	177.5 (6.9)	175.4 (6.7)	175.1 (6.5)	175.9 (7.2)
Median (range)	177 (164–194)	175 (161–188)	175 (159–186)	175 (163–200)
Weight, kg				
Mean (SD)	82.5 (11.9)	80.1 (13.9)	81.4 (11.5)	77.8 (12.4)
Median (range)	79.4 (60.3–108.6)	78.3 (55.8–111.5)	83.3 (59.0–104.1)	79.9 (68.2–84.9)
BMI, kg/m^2				
Mean (SD)	26.1 (3.1)	26.0 (3.7)	26.6 (3.4)	25.1 (3.3)
Median (range)	25.9 (19.6–32.1)	26.1 (19.8–33.0)	26.5 (24.2–29.5)	24.9 (18.0–31.8)

[a]All randomized subjects who received at least one dose of study drug.

BMI, body mass index.

Table 2 LSM baseline- and placebo-corrected QTcI values for silodosin and moxifloxacin (evaluable population)

Time after dosing, h	Placebo ($n = 46$)	Silodosin 8 mg ($n = 46$)		Silodosin 24 mg ($n = 44$)		Moxifloxacin[a] ($n = 47$)	
	CFB LSM	CFB LSM	Difference vs. placebo LSM (90% CI)	CFB LSM	Difference vs. placebo LSM (90% CI)	CFB LSM	Difference vs. placebo LSM (90% CI)
−0.25[b]	0.9	2.4	1.5 (−4.8, 7.9)	2.25	1.4 (−5.1, 7.8)	1.1	0.3 (−6.1, 6.6)
1	−3.9	−4.0	−0.4 (−6.4, 6.3)	−4.45	−0.5 (−6.9, 5.9)	−3.0	0.9 (−5.4, 7.2)
1.5	−5.2	−3.0	2.2 (−4.2, 8.6)	−3.65	1.6 (−4.8, 8.0)	−0.7	4.5 (−1.8, 10.8)
2	−3.7	−1.7	2.0 (−4.3, 8.4)	−5.97	−2.2 (−8.7, 4.2)	0.9	4.6 (−1.7, 11.0)
3	−1.0	−1.2	−0.2 (−6.6, 6.2)	−1.19	−0.2 (−6.6, 6.2)	5.3	6.3 (−0.1, 12.6)
4	0.5	1.5	0.9 (−5.4, 7.3)	0.15	−0.4 (−6.8, 6.1)	8.6	8.1 (1.8, 14.4)
6	−0.2	3.2	3.4 (−2.9, 9.8)	1.21	1.4 (−5.0, 7.8)	9.4	9.6 (3.3, 15.9)
8	−2.8	−2.5	0.3 (−6.1, 6.6)	−5.63	−2.9 (−9.3, 3.6)	4.1	6.9 (0.6, 13.2)
10	−0.3	−0.1	0.2 (−6.2, 6.6)	−0.60	−0.3 (−6.7, 6.2)	5.5	5.8 (−0.5, 12.2)
23.5	2.0	3.3	1.3 (−5.1, 7.6)	1.44	−0.6 (−7.0, 5.8)	3.8	1.8 (−4.5, 8.2)

CFB, change from baseline; CI, confidence interval; LSM, least-squares mean (ms); QTcI, individual heart rate–corrected QT interval.

[a]Moxifloxacin is a positive control known to cause mild QTc prolongation. [b]ECG recorded 0.25 h before dosing.

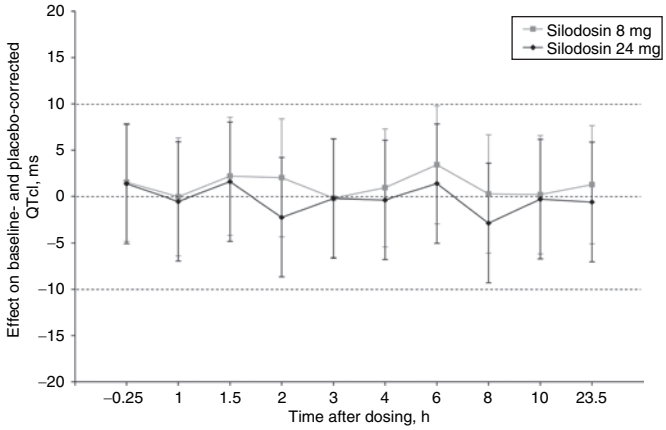

Figure 2 Effects of silodosin 8 and 24 mg on QTc prolongation. Shown are time-matched least-squares mean baseline- and placebo-corrected QTcI values. The upper bounds of the 90% confidence intervals do not exceed 10 ms at any time point. Differences were determined by analysis of covariance. Error bars indicate 90% confidence intervals. QTcI, individual heart rate–corrected QT interval.

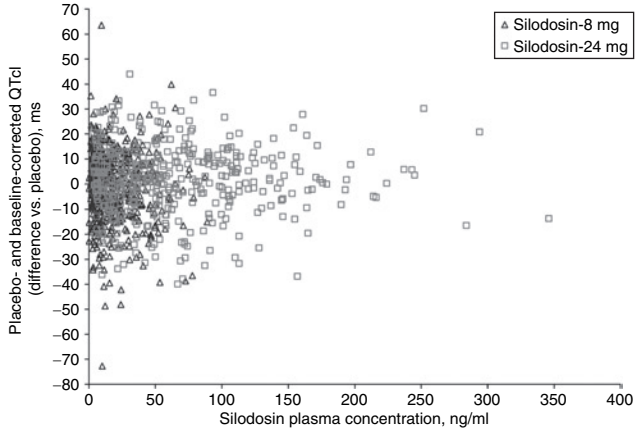

Figure 3 Correlation between plasma concentration of silodosin and the effect of silodosin on QTcI values. Plasma concentrations are plotted against time-matched mean baseline- and placebo-corrected QTcI values. QTcI, individual heart rate–corrected QT interval.

and silodosin 24 mg (72.4 ± 7.0, 59.6–87.6). Time-averaged mean changes ± SD (beats/min) from baseline in heart rate were similar for the placebo (−0.8 ± 7.0), silodosin 8 mg (1.3 ± 7.2), and silodosin 24 mg groups (0.1 ± 5.8). Similarly, changes from baseline in the PR segment (placebo, 4.4 ± 6.0 ms; silodosin 8 mg, 2.5 ± 6.4 ms; silodosin 24 mg, 2.9 ± 5.1 ms) and the QRS complex (placebo, 2.7 ± 4.7 ms; silodosin 8 mg, 0.9 ± 3.8 ms; silodosin 24 mg, 0.4 ± 4.2 ms) were similar for the three treatment groups. No clinically significant differences in ECG morphology were observed among subjects in different treatment groups (data not shown).

Pharmacokinetics/pharmacodynamics correlation

Figure 3 illustrates the relationship between plasma concentration of silodosin and time-matched placebo- and baseline-corrected QTcI. In a model without the intercept, the correlation analysis generated a slightly negative slope of −0.057 (90% CI, −0.108 to −0.006) for silodosin 8 mg, but the result was neither statistically significant ($P = 0.068$) nor clinically meaningful. For silodosin 24 mg, no correlation was observed (slope = 0.002; 90% CI, −0.014 to 0.018; $P = 0.852$). No significant correlation was observed between plasma concentrations of silodosin and placebo- and baseline-corrected QTcI values, irrespective of whether the models used included intercepts or were based on separate or pooled analysis of silodosin doses (Table 3). Similarly, no statistically significant or clinically meaningful correlation was observed between plasma concentrations of silodosin metabolites and placebo- and baseline-corrected QTcI (data not shown).

Safety and tolerability

A total of 156 adverse events (AEs) occurred in 81 subjects; 61 subjects experienced only mild events. The only severe AE (orthostatic hypotension) occurred in a subject who received silodosin 8 mg.

Table 3 Correlation analyses of silodosin plasma concentration and baseline- and placebo-corrected QTcI values

Analysis	Intercept	*P* value (intercept)	Slope	90% Confidence interval	*P* value (slope)
Models without intercept					
8 mg only	N/A	N/A	−0.057	−0.108, −0.006	0.068
24 mg only	N/A	N/A	0.002	−0.014, 0.018	0.852
Pooled	N/A	N/A	−0.005	−0.020, 0.011	0.625
Models with intercept					
8 mg only	−0.637	0.7192	−0.052	−0.107, 0.003	0.118
24 mg only	1.648	0.2769	−0.004	−0.022, 0.014	0.745
Pooled	0.045	0.9686	−0.005	−0.021, 0.012	0.634

N/A, not applicable.

In subjects who received silodosin 8 mg ($n = 48$), the most common drug-related AEs (with number of subjects) were retrograde ejaculation (8), nasal congestion (5), headache (4), fatigue (3), dizziness (2), nausea (2), orthostatic hypotension (2), and palpitations (2). In subjects who received silodosin 24 mg ($n = 45$), the most common drug-related AEs (with number of subjects) were headache (6), retrograde ejaculation (5), fatigue (4), orthostatic hypotension (4), diarrhea (2), and dyspepsia (2). No serious AEs and no AEs of QT prolongation occurred.

In subjects who received placebo ($n = 46$), the most common drug-related AEs (with number of subjects) were headache (3) and orthostatic hypotension (2). In subjects who received the single dose of moxifloxacin 400 mg ($n = 47$), the most common drug-related AEs (with number of subjects) were orthostatic hypotension (2) and somnolence (2).

DISCUSSION

In this study, silodosin had no clinically important effects on any ECG parameter. Specifically, no effect was observed on myocardial repolarization, as determined by baseline- and placebo-corrected QTcI, in healthy men aged 18–45 years; the largest time-matched mean effect of silodosin did not exceed 5 ms, and the upper limit of the corresponding 90% two-sided CI did not exceed 10 ms. Silodosin was well tolerated, even at three times the therapeutic dose. Overall, the findings are consistent with data from two large clinical studies that found no adverse cardiac effects of silodosin in patients with symptomatic benign prostatic hyperplasia over a period of up to 1 year.[4]

Moxifloxacin was used as a positive control because it is known to cause mild QTc prolongation and has been used previously in a number of thorough QT/QTc studies, including a study of the α-blocker alfuzosin.[12–15] In our study, time-matched means of baseline- and placebo-corrected QTcI exceeded 5 ms at multiple time points after dosing with moxifloxacin. The moxifloxacin data demonstrate that the assay used in our study was sufficiently sensitive to detect 5-ms QTc prolongation after dosing with an agent known to have such an effect and therefore to validate the negative QTc results obtained for silodosin.

Blockade of α_{1B}-adrenoceptors is believed to explain the propensity of some α-blockers to promote orthostatic hypotension.[16] The excellent cardiovascular safety profile of silodosin has been attributed, at least in part, to its α_1-adrenoceptor subtype selectivity, which is characterized by low affinity for α_{1B}-adrenoceptors and, consequently, low pharmacologic activity in vascular tissue.[5–7] The relationship between α_1-adrenoceptor subtype selectivity and risk for QTc prolongation is currently unknown because alfuzosin is the only α-blocker for which QTc data have been reported.[8]

Silodosin, a new, highly selective α_{1A}-adrenoceptor antagonist, had no effect on ECG parameters in this thorough QT study, which was conducted according to the International Conference on Harmonisation E14 guidance. No statistically significant or clinically meaningful correlation was observed between plasma concentrations of silodosin (or its metabolites) and cardiac repolarization. The findings of this study provide evidence of the cardiac safety of silodosin.

METHODS

Study participants. Study participants were healthy men aged 18–45 years with body mass indexes of 18–33 kg/m^2. Subjects were excluded if they were hypersensitive to the study medication, had a first-degree relative with long QT syndrome, or had 12-lead ECG findings that indicated a clinically significant abnormality in heart rate, rhythm, or conduction. Use of pharmacologic agents and consumption of foods that might pose a safety risk or confound the interpretation of ECG data were not permitted during the study. Moderate and potent inhibitors of cytochrome P450 3A4 were not allowed during screening or study periods.

Study design. This double-blind, placebo-controlled, parallel-group study (SI05014) was conducted at a single US center (NW Kinetics, Tacoma, WA). Subjects were randomly assigned to one of the following four treatments: silodosin at its therapeutic dose (8 mg) or at a supratherapeutic dose (24 mg) once daily, with breakfast, for 5 days; placebo once daily for 5 days; or moxifloxacin 400 mg once on day 5. The multiple dosing schedule was designed to achieve steady-state concentrations of silodosin and its metabolites. Moxifloxacin, which is known to cause mild QT prolongation,[12] served as a positive control to assess assay sensitivity. Randomization was preceded by a screening period of up to 28 days and was followed by a confinement period of ~6 days. Study medication was administered by clinic staff from subject-specific, blinded medication kits. For moxifloxacin, no blinding occurred at the treatment site, but staff members at the central ECG laboratory (COResearch, Durham, NC) were blinded to treatment. The study protocol was approved by the Aspire Independent Review Board (La Mesa, CA). The study complied with the Declaration of Helsinki and followed the guidelines for good clinical practice described in the US Code of Federal Regulations.

Assessments. ECGs were obtained using a Mortara Instruments H-12+ ECG continuous 12-lead digital recorder (Mortara Instruments, Milwaukee, WI). ECG data for the primary analysis were reviewed only after processing by staff at the central ECG laboratory. At least three complexes from lead II (the primary lead) were used for QT assessment. If QT assessment could not be completed on lead II, then v5, v2, or any other available ECG lead was used. At baseline (day −1) and on day 5, ECGs were extracted with the patient in the supine position 0.25 h before dosing and 1, 1.5, 2, 3, 4, 6, 8, 10, and 23.5 h after dosing. Five replicate ECGs were extracted within 1–3 min at each time point.

Daily safety evaluations during treatment included assessment of vital signs (measurements of supine blood pressure and heart rate) and recording of AEs reported spontaneously by subjects or observed by investigators.

Blood samples for pharmacokinetic evaluation were taken from all subjects on day 5 of treatment, but only samples from subjects who had received silodosin were analyzed. Samples were collected within 2 min of the nominal time of ECG extraction.*Statistical analyses*. The safety of silodosin was analyzed in all randomized subjects who received at least one dose of the drug. The primary analysis evaluated results for randomized subjects who received all doses of the study drug for whom time-matched ECG data were available at baseline and at day 5 (the evaluable population). The pharmacokinetic population comprised randomized subjects who received all doses of the study drug and had evaluable pharmacokinetic data on day 5 for at least one analyte.

QT intervals were corrected for variations in heart rate using an individual correction method[17] based on the parabolic model $QT = \beta \cdot RR^{\alpha}$ (where RR is the interval between adjacent QRS complexes in the ECG, and α and β are subject-specific correction parameters). The model was fitted with data from all 50 baseline ECGs (five for each of 10 time points) obtained for each subject. Silodosin or moxifloxacin had no clinically significant effect on heart rate (data not shown). The resulting correction factors were applied to all QT values in order to generate individual QTcI values.

The primary end point was time-matched change from baseline to day 5 in placebo-corrected QTcI. The delta–delta approach was used for each subject: mean QTcI values obtained at each time point at baseline were first subtracted from time-matched values obtained on day 5 to calculate changes from baseline in QTcI (individual baseline-corrected QTcI values). Individual baseline-corrected QTcI values were corrected further by subtracting the time-matched mean change in QTcI for the entire placebo population, to yield individual time-matched baseline- and placebo-corrected QTcI values. Time-averaged analyses of changes from baseline for additional ECG parameters were based on ECG data obtained on day 5.

Mixed-model analysis of covariance, with treatment group and corresponding baseline values as covariates, was used for pairwise comparison of treatment groups to determine LSM differences in QTcI change from baseline between active treatment and placebo (LSM baseline- and placebo-corrected QTcI). By definition, lack of treatment effect of silodosin on QTcI would result in an LSM baseline- and placebo-corrected QTcI of 0 ms. In accordance with US Food and Drug Administration recommendations,[3] QTc prolongation was considered to be not clinically significant if the upper limit of the 90% two-sided CI (equivalent to a 95% one-sided CI) for the effect of silodosin treatment on QTcI was <10 ms at all time points. Assay sensitivity was considered adequate if the mean effect of moxifloxacin treatment (LSM baseline- and placebo-corrected QTcI) was >5 ms at any time point.

It was estimated that a sample size of 45 subjects per group, with five replicate ECGs per time point, would provide at least 80% power to demonstrate that the upper limit of the 90% CI was <10 ms. The correlation of plasma concentrations of silodosin with individual baseline- and placebo-corrected QTcI was analyzed using a linear mixed-effects model.

Data from both silodosin dose groups were used to analyze the correlation between baseline- and placebo-corrected QTcI and plasma concentration of silodosin. Linear mixed-effects models with or without the intercept were used to estimate the slope and slope SE. Models were analyzed in two ways: (i) with dose groups included in a single model and (ii) with dose groups analyzed separately. Because the results showed only minor differences between the two methods, the results of the separate analyses were pooled in a single presentation (**Figure 3**).

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CONFLICT OF INTEREST

J.M. serves as a consultant for Watson Pharmaceuticals and is an employee of eResearch Technology, Inc. H.L. is a consultant and a member of the Speakers' Bureau for Watson Pharmaceuticals. L.A.H., W.V., and G.H. are employees of Watson Pharmaceuticals.

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