Initial Exploration of Oral Pazopanib in Healthy Participants and Patients With Age-Related Macular Degeneration

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IMPORTANCE Neovascular age-related macular degeneration (AMD) is managed with intravitreal anti-vascular endothelial growth factor therapy; however, the burden of care is high and alternate approaches could be beneficial.

OBJECTIVE To identify an acceptable dose of oral pazopanib for investigation in AMD.

DESIGN, SETTING, AND PARTICIPANTS Fourteen-day, placebo-controlled, dose-rising study in 72 healthy participants and 28-day phase 2a open-label study in 15 patients with subfoveal choroidal neovascularization secondary to AMD at a clinical unit for healthy participants and outpatient for patients with AMD.

INTERVENTION Oral pazopanib tablets, 5 to 30 mg daily (healthy participants) and 15 mg daily (patients with AMD).

MAIN OUTCOMES AND MEASURES Safety, pharmacokinetics, best-corrected visual acuity, central retinal lesion thickness, and central retinal thickness at day 29.

RESULTS Oral pazopanib up to 30 mg daily in healthy participants and 15 mg daily in patients with AMD was well tolerated. Six of 15 patients received rescue therapy before day 29; all had the CFH Y402H CC "high-risk" genotype for AMD. Nine patients completed the study without rescue with improvements from baseline in best-corrected visual acuity (8 Early Treatment Diabetic Retinopathy Study letters), central retinal lesion thickness (~50.94 μm), and central retinal thickness (~50.28 μm). There was a trend for association between the CFH Y402H T allele ("low risk" for AMD, n = 6) and improvement.

CONCLUSIONS AND RELEVANCE Oral pazopanib (15 mg daily) was well tolerated and resulted in improvements in mean best-corrected visual acuity, central retinal lesion thickness, and central retinal thickness at day 29 in a per-protocol, nonrescued AMD population (n = 9). It is postulated that CFH Y402H genotype may help predict which patients respond to pazopanib.

The size and length limitations of this study warrant further investigation to determine if oral pazopanib may be an appropriate treatment for a subset of neovascular patients with AMD or as an adjunct to standard of care.

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Age-related macular degeneration (AMD) is the leading cause of acquired blindness in people older than 65 years in the developed world.1 The majority of significant vision loss caused by AMD is attributed to the aberrant blood vessel formation associated with the neovascular form of the disease characterized by choroidal neovascularization (CNV).2 Vascular endothelial growth factor (VEGF) is a major factor contributing to aberrant blood vessel formation in CNV.3,4

Drug treatment options for patients with neovascular AMD have advanced with the availability of therapies that target VEGF; however, they require frequent intravitreal administration.5-7 Opportunity exists for therapies with a lower burden of care.

Pazopanib (GW786034) is a potent antiangiogenic, multi-targeted tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3; platelet-derived growth factor receptors α and β; and the stem cell factor receptor, c-kit.8-10 Pazopanib inhibits the clinically validated VEGF pathway at the receptor tyrosine kinase level. Additional benefit may come from inhibition of platelet-derived growth factor receptors.9,10 Following oral administration, pazopanib has resulted in inhibition and regression of laser-induced CNV in mice.10

Clinical experience with pazopanib exists in oncology, where 800 mg once daily (Votrient) has been approved for use in certain cancers.11,12 Safety findings such as elevations in liver transaminase levels, hypertension, hypothyroidism, and proteinuria were reported in cancer patients, influencing the potential benefit-risk for use in the AMD population.

Preclinical data suggest lower oral doses of pazopanib may have therapeutic potential in AMD. In the mouse CNV model, oral administration of pazopanib, 4 mg/kg twice daily for 7 days, resulted in an average plasma concentration of approximately 1.3 μg/mL 18 hours after the final pazopanib dose.10 The mean steady-state trough plasma pazopanib concentration after administration of 50 mg once daily in cancer patients was 5.1 μg/mL.13 These results suggest that an oral dose of approximately 13 mg of pazopanib once daily will achieve plasma concentrations in humans similar to those that resulted in a positive effect in the laser-induced CNV mouse model. A 2-fold increase in plasma pazopanib has been observed with coadministration of strong cytochrome P4503A4 inhibitors.14 Therefore, a maximum dose of 30 mg was planned for the investigation to provide safety coverage for potential future use of oral pazopanib with concomitant medications.

Complement factor H (CFH) is a major inhibitor of the alternative complement pathway. The CFH Y402H variant has been shown to be strongly associated with risk for AMD.15,16 Recent studies have suggested that this CFH polymorphism may also be associated with treatment response to anti-VEGF agents in patients with neovascular AMD; treatment response with respect to visual acuity was reported to be better for patients with the TT genotypes (low risk for AMD) compared with those with the CC genotype (high risk for AMD).17,18 A previous exploratory pharmacogenetics analysis of phase 2a data showed that pazopanib eye drops may be more efficacious for patients with neovascular AMD carrying the T allele than those with the CC genotype. Therefore, the treatment effects of low-dose oral pazopanib were assessed by the CFH Y402H genotype in the study of patients with AMD.

This article reports the findings of 2 studies identifying a dose of oral pazopanib with an acceptable safety profile in healthy participants that was further explored in a small study in patients with subfoveal CNV secondary to AMD.

Methods

Study Design and Objectives

The studies were conducted in accordance with the guiding principles of the Declaration of Helsinki. Institutional review boards approved the study protocols before the clinical trials were initiated. All participants provided written informed consent.

MDI113555 (clinicaltrials.gov identifier NCT01051700) was a 2-part phase 1 study: (1) an open-label single dose and (2) a single-masked, randomized, placebo-controlled, 14-day repeated dose–rising part to evaluate the safety, tolerability, and pharmacokinetics in healthy participants. The objective was to identify a dose of pazopanib to support the investigation in patients with AMD.

MDI114155 (clinicaltrials.gov identifier NCT01154062) was a multicenter, open-label, 28-day pilot study in patients with subfoveal CNV secondary to neovascular AMD, with a follow-up visit approximately 2 weeks after the last dose of pazopanib. The objective was to characterize the safety, tolerability, pharmacokinetics, and exploratory efficacy and pharmacodynamics of 15 mg of oral pazopanib administered daily for 28 days.

Participants

The healthy participant study included men or women of non-childbearing potential, 18 years or older for part 1 and 50 years or older for part 2. Participants returned for a follow-up visit 7 to 10 days following the final dose.

Participants in the patient study were treatment naive, were 50 years or older, and had minimally classic or occult subfoveal CNV. Patients were included if they had CNV of 50% or more of the lesion area, a lesion size no greater than 12 disc areas, less than 50% of their lesion area with blood, 25% or less of the lesion area with fibrosis, center subfield thickness of more than 320 μm (Spectralis spectral-domain optical coherence tomography [SD-OCT]; Heidelberg Engineering), and a best-corrected visual acuity (BCVA) between 27 and 73 letters (approximately Snellen equivalent of 20/320-20/32). Patients were excluded if they were using systemic steroids, had additional eye disease that could compromise BCVA, or were women of childbearing potential.

At any time during the study including the follow-up period, rescue treatment (standard of care) was given based on the clinical judgment of the ophthalmologist. Rescue treatment was to be strongly considered for patients whose center subfield thickness had increased by 50 μm from the lowest value during the study or BCVA decreased by more than 5 letters compared with baseline and who also had persistent fluid by SD-OCT. Patients requiring rescue treatment continued receiving study medication and were followed up for the remainder of the study.
For both studies, prestudy screening included medical and medication histories; physical examination; medical and laboratory evaluations; blood pressure evaluation; 12-lead electrocardiogram; a urinary drug screen; and eye examinations. Participants receiving stable monotherapy (≥3 months duration before screening) for well-controlled medical conditions such as hypertension, hypercholesterolemia, depression, anxiety, or acid reflux were allowed into the study at the discretion of the investigator. The use of multivitamins or low-dose aspirin or occasional use of aspirin, ibuprofen, and acetaminophen at doses of 1 g/d or less were also permitted.

Sample size for both studies was based on feasibility, which was deemed sufficient to initially evaluate the primary objectives.

Investigational Product
Healthy participants received either a single dose of 5, 10, 20, or 30 mg of oral pazopanib (n = 6 per cohort) or repeated doses of 5, 10, 20, or 30 mg of oral pazopanib (n = 9 per cohort) or placebo (n = 3 per cohort), once daily for 14 days. In the repeated-dose portion, participants were assigned to pazopanib or placebo in a 3:1 ratio in accordance with the randomization schedule, prior to the start of the study. Patients with AMD received oral pazopanib, 15 mg once daily for 28 days.

Assessments
Efficacy
Spectral-domain optical coherence tomography and BCVA using electronic Early Treatment Diabetic Retinopathy Study visual acuity were performed in patients at screening, baseline, and weekly during the 28-day treatment period and follow-up. Fluorescein angiography and color fundus photography were assessed at the screening and day 29 visits. Final SD-OCT interpretations, as well as interpretation of fluorescein angiography and color fundus photography, were performed by a central reading center (Digital Angiography Reading Center, New York, New York). Best-corrected visual acuity certification was performed by the EMMES Corporation.

Safety
Adverse events (AEs), serious AEs, concomitant medications, clinical chemistry findings, urinalysis results, vital signs, and ophthalmic assessments were studied. Adverse events were coded by preferred term and primary system organ class according to the Medical Dictionary for Regulatory Activities.

Pharmacokinetics
Serial blood samples were collected over 72 hours postdose on day 1 in the single-dose part and over 24 hours postdose on day 1 and day 14 in the repeated-dose part in healthy participants. Sparse blood samples were collected over 8 hours in patients. Plasma pazopanib concentrations were measured using a validated high-performance liquid chromatography tandem mass spectrometry analytical method.

Statistical Analyses
Changes from baseline in BCVA and SD-OCT measures were analyzed by fitting an analysis of covariance model by visit, with visit as the fixed-effect term and baseline value as the covariate. This analysis was performed using observed cases, last observation carried forward (LOCF), and per-protocol population. In the observed cases analysis, a missing assessment or assessment after rescue was not included in the data set. In the LOCF analysis, a missing assessment or assessment after rescue was replaced by the last nonmissing assessment before rescue. The per-protocol population comprised patients who completed 28 days of pazopanib treatment without rescue during the study.

Pharmacogenetic Analysis
An exploratory investigation of the relationship between treatment response and CFH Y402H (rs1061170) genotype was conducted in patients. DNA was extracted from venous blood and genotyping was conducted using a TaqMan single-nucleotide polymorphism genotyping assay (Applied Biosystems). No formal pharmacogenetics statistical test was performed because of limited sample size.

Pharmacokinetic Analysis
Pharmacokinetic parameters were calculated by standard noncompartmental methods. Population pharmacokinetic analysis was performed using NONMEM version 7 (ICON) to estimate pharmacokinetic parameters for patients in whom the sparse blood sample scheme was used. Pharmacokinetic parameters were summarized using descriptive statistics for each dose level.

Results
Study Population
We enrolled a total of 87 participants into the oral pazopanib studies: 72 in the healthy participants study (January-May 2010) and 15 in the patient study (August 2010-April 2011). All participants completed both studies. There were no deviations during study conduct that would affect the results in either study. Patient demographics for the 2 studies are described in Table 1 and Table 2. Figure 1 describes the participant deposition for the patient study.

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Demographics in the Patient Study</th>
</tr>
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<tbody>
<tr>
<td><strong>Age, y, mean (range)</strong></td>
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<tr>
<td><strong>Sex, No. (%)</strong></td>
</tr>
<tr>
<td><strong>F</strong></td>
</tr>
<tr>
<td><strong>M</strong></td>
</tr>
<tr>
<td><strong>BCVA, letters, mean (SD)</strong></td>
</tr>
<tr>
<td><strong>Approximate Snellen equivalent</strong></td>
</tr>
<tr>
<td><strong>CRT, μm, mean (SD)</strong></td>
</tr>
<tr>
<td><strong>Total lesion size, mm², mean (SD)</strong></td>
</tr>
<tr>
<td><strong>CNV size, mm², mean (SD)</strong></td>
</tr>
<tr>
<td><strong>CNV type, No. (%)</strong></td>
</tr>
<tr>
<td><strong>Classic</strong></td>
</tr>
<tr>
<td><strong>Occult</strong></td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness.
Efficacy Findings

Administration of oral pazopanib, 15 mg, for 28 days resulted in statistically significant mean (95% CI) improvements of 8 (0.11 to 15.89) Early Treatment Diabetic Retinopathy Study letters and −50.28 μm (−100.41 to −0.41) in central retinal thickness (CRT) and −50.94 μm (−98.87 to −3.02) in central retinal lesion thickness (CRLT) in the 9 patients in the observed-cases and per-protocol analyses. No significant changes were found in these parameters for the LOCF analysis. Efficacy findings at day 29 are described in Table 3.

The 9 patients who demonstrated improvement did not receive rescue therapy. At the discretion of the investigators, 6 participants received anti-VEGF medications as rescue treatment prior to the day 29 assessments (Table 4).

Safety Findings

The majority of the AEs in both studies were reported by a single participant and were mild to moderate. In healthy participants, abdominal discomfort (10-mg dose, n = 1), fatigue (20-mg and 30-mg doses, n = 1 each), and headache (10-mg and 30-mg doses, n = 1 each) were reported as drug related. Two participants had aberrant values in alanine aminotransferase and aspartate aminotransferase. One participant had elevated aspartate aminotransferase levels (5.2 times the upper limit of normal) at the follow-up visit after receiving a single dose of pazopanib, 5 mg. The second participant, who had received 14 days of repeated doses of pazopanib, 20 mg, had elevated alanine aminotransferase and aspartate aminotransferase levels up to 2.5 times the upper limit of normal during the 14-day dosing period, which returned to baseline levels during the follow-up period. Asymptomatic elevations in thyrotropin values (more than the upper limit of normal) were reported for 1 participant in the single-dose cohort group (pazopanib, 5 mg) and 5 participants in the repeated-dose cohort group with pazopanib (5 mg, n = 2; 20 mg, n = 1) and placebo (n = 2).

Seven of 15 participants in the patient study reported ocular AEs. Five reported single events (eye hemorrhage, macular degeneration, retinal exudates, retinal edema, and reduction in visual acuity). All were mild to moderate. Two participants experienced more than 1 mild ocular AE (retinal hemorrhage, metamorphopsia, and vitreous floaters and macular edema and vitreous floaters, respectively). All were consistent with the natural history of AMD or administration of the anti-VEGF rescue therapy. The most frequently reported nonocular AEs were intermittent headache (n = 2) and upper respiratory tract infection (n = 2). One case of a mild headache was considered drug related by the investigator. One participant experienced an AE of hypertension (without reported abnormal study blood pressure measurements) and an increase in urine protein-creatinine ratio from normal at screening (range, 0.11-0.25) to 0.31 at day 29, returning to normal at follow-up.

No withdrawals due to AEs and no deaths were reported in either study. One participant in the healthy participants study (58 years of age, 10-mg repeated dosing) reported a serious AE of severe atrial flutter in the follow-up period that was not considered pazopanib related. No clinically significant changes in ophthalmic examination or laboratory findings were reported in either study.

Exploratory Pharmacogenetic Findings

Among the 15 patients, 1 had the CFH Y402H TT genotype, 5 had the CT genotype, and 9 had the CC genotype. Mean vision at baseline was similar for the CC and T (CT and TT) allele subgroups (58 and 60 Early Treatment Diabetic Retinopathy Study letters, respectively). Patients with the CC genotype on average had thicker CRT values than those in the T allele subgroup (407 and 355 μm, respectively). There was a trend for an association between the presence of the CFH Y402H T allele and improvement following oral pazopanib (Figure 2).
RetinopathyStudy; IVT, intravenous transfusion. CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravenous transfusion.

None of the participants carrying a CFH T allele lost any vision or required rescue therapy by the day 29 assessment. Five of the 6 participants carrying a T allele had a decrease in macular edema from baseline after receiving pazopanib. All 6 patients who were rescued carried the CC genotype. Consistent with these observations, comparing with baseline, CRT did not improve in patients with the CC genotype (n = 9) (LOCF analysis) and patients with CT or TT genotypes (n = 6) showed improvement (Table 3).

### Pharmacokinetic Findings

In healthy participants, following single and repeated doses of pazopanib, 5 to 30 mg, the median pazopanib t\textsubscript{max} value was observed 2 hours postdose and plasma concentrations declined with a mean t\textsubscript{1/2} of 30.3 to 33.7 hours (Figure 3). Steady-state plasma pazopanib concentrations were attained by day 10 of repeated-dose administration.

Following once-daily oral administration of 15 mg of pazopanib, plasma concentrations of pazopanib in patients with AMD were similar to those that prevented progression of CNV in a mouse model,\textsuperscript{10} as suggested by the geometric mean C\textsubscript{max} (4.14 μg/mL), C\textsubscript{s} (2.35 μg/mL), and area under the curve to−t\textsubscript{1/2} (73.4 μg × h/mL).

### Discussion

This investigation of oral pazopanib in patients was limited to occult and minimally classic CNV. The MARINA trial of ranibizumab in a similar population demonstrated a BCVA increase of 4.5 letters at month 1 in the overall study population and a CRT decrease of 105 μm in the subset of patients who had CRT determined.\textsuperscript{5,19} Administration of 15 mg of oral pazopanib for 28 days did not result in any significant changes in BCVA or SD-OCT CRT and CLRT in the LOCF analysis (n = 15). However, administration of 15 mg of oral pazopanib resulted in a statistically significant mean improvement from baseline of 8 letters and 50 μm in CRT in 9 of 15 patients in the per-protocol population. These 9 patients did not receive rescue therapy.

The study is small and the exploratory analysis should be interpreted with caution. A trend for an association between CFH Y402H genotype and response to oral pazopanib was observed. None of the participants carrying a CFH T allele lost any vision or required rescue therapy during the 28 days of pazopanib therapy and this subset had a 9-letter mean increase in BCVA and a 63-μm decrease in CRT. In contrast, the CFH CC genotype group lost 5 letters during the study and had no mean decrease in macular edema. This trend is consistent with our observation in a phase 2a study of pazopanib eye drops, in which patients with AMD and the T allele showed better improvement in visual acuity than those with the CC genotypes. Furthermore, the observed association between CFH genotype and treatment response to pazopanib is consistent with at least 6 reports for intravitreal anti-VEGF agents.\textsuperscript{17,18} However, there were recent conflicting reports regarding the effect of CFH Y402H genotype on response to anti-VEGF therapy, suggesting that further investigation of the pharmacogenetic effect on treatment response is warranted.\textsuperscript{17}

### Table 3. Mean Change From Baseline in BCVA and CRT at Day 29

<table>
<thead>
<tr>
<th>Population</th>
<th>Sample Size</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCF</td>
<td>15</td>
<td>0.67 (14.3) -24.50 (89.92)</td>
</tr>
<tr>
<td>PP</td>
<td>9</td>
<td>8.00 (10.0) -50.28 (63.27)</td>
</tr>
<tr>
<td>CFH CC genotype*</td>
<td>3</td>
<td>5.7 (15.1) -24.33 (60.1)</td>
</tr>
<tr>
<td>CFH CT+TT genotype*</td>
<td>6</td>
<td>9.2 (8.1) -63.3 (60.8)</td>
</tr>
<tr>
<td>CFH CC genotype*</td>
<td>9</td>
<td>-5.0 (15.4) 1.3 (102.3)</td>
</tr>
</tbody>
</table>

### Table 4. CNV Type, Vision, and Center Subfield for Rescued Participants*

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>CNV Type</th>
<th>Baseline BCVA, ETDRS Letters</th>
<th>Baseline Center Subfield, μm</th>
<th>Day of Rescue</th>
<th>BCVA (ΔBL on Day of Rescue), ETDRS Letters</th>
<th>Center Subfield (ΔBL on Day of Rescue), μm</th>
<th>Rescue Medication and Subsequent IVT</th>
<th>Follow-up BCVA, ETDRS Letters</th>
<th>Follow-up Center Subfield, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>Occult</td>
<td>66</td>
<td>576</td>
<td>15</td>
<td>55 (~11)</td>
<td>749 (173)</td>
<td>Ranibizumab</td>
<td>68</td>
<td>251</td>
</tr>
<tr>
<td>203</td>
<td>Classic Occult</td>
<td>44</td>
<td>561</td>
<td>8</td>
<td>14 (~30)</td>
<td>606 (45)</td>
<td>Ranibizumab and between day 29 follow-up</td>
<td>32</td>
<td>585</td>
</tr>
<tr>
<td>404</td>
<td>Occult</td>
<td>69</td>
<td>422</td>
<td>22</td>
<td>77 (8)</td>
<td>445 (23)</td>
<td>Bevacizumab</td>
<td>82</td>
<td>314</td>
</tr>
<tr>
<td>406</td>
<td>Occult</td>
<td>67</td>
<td>442</td>
<td>15</td>
<td>67 (0)</td>
<td>489 (47)</td>
<td>Bevacizumab</td>
<td>76</td>
<td>309</td>
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<tr>
<td>408</td>
<td>Classic Occult</td>
<td>32</td>
<td>538</td>
<td>15</td>
<td>12 (~20)</td>
<td>471 (~67)</td>
<td>Bevacizumab</td>
<td>28</td>
<td>421</td>
</tr>
<tr>
<td>701</td>
<td>Occult</td>
<td>68</td>
<td>540</td>
<td>8</td>
<td>59 (~9)</td>
<td>509 (~31)</td>
<td>Bevacizumab</td>
<td>66</td>
<td>276</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; ΔBL, change from baseline; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravenous transfusion.

*If any prior to follow-up.
The current studies demonstrated that oral pazopanib was generally safe and well tolerated up to 30 mg daily for 14 days in healthy participants and 15 mg once daily for 28 days in patients with AMD. In phase 3 clinical trials of 800 mg of daily pazopanib in cancer patients, hypertension, hepatic toxicity, hypothyroidism, and proteinuria were observed. Low-dose oral pazopanib did not have a clinically relevant effect on blood pressure or liver function. There were no values of potential clinical importance in vital signs and there were no transaminase elevations more than 3 times the upper limit of normal. Hypothyroidism, confirmed based on a simultaneous rise of thyrotropin and a decline of T4 and proteinuria, was not reported in the current studies.

Administration of pazopanib, 15 mg once daily, resulted in a mean steady-state trough plasma concentration similar to that which prevented progression of CNV in a preclinical model. Plasma pazopanib concentrations following 15 mg daily in patients with AMD were much lower in comparison with the 800-mg daily dose approved for cancer. The geometric mean area under the curve (AUC) value of 73.4 μg × h/mL was approximately 14-fold lower and most likely contributed to a more favorable safety profile of low-dose pazopanib in participants with AMD compared with that observed in cancer patients.

Based on safety and preliminary efficacy, these studies identified a dose of oral pazopanib that may be appropriate for further investigation in patients with neovascular AMD. Because of the highly effective standard of care, the preliminary efficacy observed in this small patient study suggests that pazopanib monotherapy in the overall AMD population would not be appropriate; however, the potential exists to study it adjuvantly. Alternatively, pazopanib studies in patients with AMD carrying a T allele of CFH, representing approximately 70% of white individuals and 99% of East Asian individuals, may be warranted to further investigate these preliminary findings of potential benefit in that subset.

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Study concept and design: McLaughlin, Paglione, Slakter, Ye, Xu, Suttle, Kim.
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Analysis and interpretation of data: McLaughlin, Paglione, Slakter, Ye, Xu, Suttle, Kim.
Drafting of the manuscript: McLaughlin, Paglione, Tolentino, Ye, Xu, Suttle, Kim.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ye.
Obtained funding: McLaughlin.
Administrative, technical, or material support: Paglione, Tolentino.
Study supervision: McLaughlin, Paglione, Xu, Kim.

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McLaughlin and Ye and Drs Paglione, Xu, Suttle, and Kim are employees of GlaxoSmithKline.

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