KAE609 represents a new class of potent, fast-acting, schizonticidal antimalarials. This study investigated the safety and pharmacokinetics of KAE609 in combination with the long-acting antimalarial piperquine (PPQ) in healthy volunteers. A two-way pharmacokinetic interaction was hypothesized for KAE609 and PPQ, as both drugs are CYP3A4 substrates and inhibitors. The potential for both agents to affect the QT interval was also assessed. This was an open-label, parallel-group, single-dose study with healthy volunteers. Subjects were randomized to four parallel dosing arms with five cohorts (2:2:2:2:1), receiving 75 mg KAE609 plus 320 mg PPQ, 25 mg KAE609 plus 1,280 mg PPQ, 25 mg KAE609 alone, 320 mg PPQ alone, or 1,280 mg PPQ alone. Triplicate electrocardiograms were performed over the first 24 h after dosing, with single electrocardiograms at other time points. Routine safety (up to 89 days) and pharmacokinetic (up to 61 days) assessments were performed. Of the 110 subjects recruited, 99 completed the study. Coadministration of PPQ had no overall effect on exposure to KAE609, although 1,280 mg PPQ decreased the KAE609 maximum concentration (C_{max}) by 17%. The group that received 25 mg KAE609 plus 1,280 mg PPQ showed a 32% increase in the PPQ area under the concentration-time curve from 0 to infinity (AUC_{inf}), while the group that received 75 mg KAE609 plus 320 mg PPQ showed a 14% reduction. Mean changes from baseline in the QT interval corrected by Fridericia’s method (QTcF) and the QT interval corrected by Bazett’s method (QTcB) with PPQ were consistent with its known effects. PPQ but not KAE609 exposure correlated with corrected QT interval (QTc) increases, and KAE609 did not affect the PPQ exposure-QTc relationship. The QTcF effect for PPQ (least-squares estimate of the difference in mean maximal changes from baseline of 7.47 ms [90% confidence interval, 3.55 to 11.4 ms]) was consistent with the criteria for a positive thorough QT study. No subject had QTcF or QTcB values of >500 ms. Both drugs given alone or in combination were well tolerated, with no deaths, serious adverse events (AEs), or severe AEs reported. Most AEs were mild; upper respiratory tract infections, headache, diarrhea, and oropharyngeal pain were most common. PPQ and KAE609 coadministration had no relevant effect on exposure to either agent, and KAE609 did not affect or potentiate the known effects of PPQ on cardiac conduction.
representing a different mode of action. One potential combination partner for KAE609 is piperaquine (PPQ). PPQ is an approved antimalarial that is currently available in fixed-dose combination with dihydroartemisinin under the label Eurartesim (Sigma-Tau and Medicines for Malaria Venture). Eurartesim is well tolerated (8), although PPQ is known to have effects on cardiac conduction, most notably in terms of exposure-related corrected QT interval (QTc) prolongation, with no plateau of effect described in the range examined and a duration of at least 24 h (9, 10). For KAE609, no significant changes in electrocardiographic (ECG) parameters have been observed in clinical studies conducted to date (7); however, preclinical studies (in vitro and in animals) have suggested a potential risk for QTc prolongation.

KAE609 is metabolized by CYP3A but does not appear to induce it, and it has the potential to inhibit CYP3A, based on in vitro data (unpublished Novartis data). PPQ is metabolized by CYP3A4 and can also inhibit the enzyme (9); hence, a two-way interaction during drug exposure was hypothesized. The primary objective of this study was to evaluate the safety and drug-drug interaction potential of KAE609 and PPQ. Triplicate ECG evaluations were conducted to evaluate possible QT interval changes in the presence of both drugs.

MATERIALS AND METHODS

Subjects. Eligible subjects were healthy male and female subjects, 18 to 45 years of age and weighing at least 50 kg. Vital signs measured at screening and baseline had to be within normal ranges (oral body temperature, 35.0 to 37.5°C; systolic blood pressure, 90 to 140 mm Hg; diastolic blood pressure, 50 to 90 mm Hg; pulse rate, 40 to 90 beats/min). Women of childbearing potential were excluded from this study. Other exclusion criteria included a history or the presence of clinically significant ECG abnormalities or arrhythmias (PR interval of >200 ms, QRS interval of >120 ms, or QT interval corrected by Fridericia’s method [QTcF] of >430 ms [male] or >440 ms [female]) and a family history or the presence of long QT syndrome. Subjects were excluded if they had hypersensitivity to any of the study drugs or similar chemical classes, food allergies, or a history of malignancy, autonomic dysfunction, bronchospastic disease, conditions that might alter drug absorption, distribution, metabolism, or excretion, or pancreatic, liver, or renal dysfunction. Subjects with hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, or other immunodeficiency diseases were excluded. Subjects were excluded if they had recently used other investigational drugs, and they were not allowed to ingest grapefruit juice, St. John’s wort, or agents that can interact with either KAE609 or PPQ for at least 7 days prior to dosing and during the study. All patients provided written informed consent, and the study was approved by the ethics committee at each participating site.

Study design. This was an open-label, parallel-group, single-dose, randomized study in healthy volunteers. The dose of KAE609 currently being evaluated for use in malaria is 75 mg. The highest approved dose of PPQ used clinically in Eurartesim is 1,280 mg once a day (fasting) for 3 days. Prior to study initiation, SimCYP (Certara) simulations using midazolam as a surrogate for PPQ (substrate for CYP3A4) suggested that KAE609 could potentially increase the exposure to PPQ by up to 2-fold (as a worst-case scenario). Based on the in vitro data, an increase in KAE609 exposure by PPQ of up to 4-fold (worst-case scenario) was predicted (DDI Predict version 1.7; Aureus Sciences, France). As PPQ has known exposure-related effects on the QT interval and there was concern regarding potential additional pharmacodynamic (PD) effects on the QT interval, the doses of KAE609 and PPQ were reduced in the arms evaluating each as the subject of the potential drug-drug interaction (see below). The long elimination half-life of PPQ (~22 days) and the potential for further prolongation of the half-life with coadministration with KAE609 made a crossover design nonfeasible, because of the long washout periods that would be required. Therefore, the parallel-group design was selected for this study, to address the pharmacokinetic interactions and safety evaluations for the two study drugs singly and in combination.

The study consisted of four treatment arms, which were conducted in parallel. Arms A through C included one cohort each, whereas arm D included two cohorts. Approximately 108 eligible subjects were randomly assigned to the 5 cohorts in the four dosing arms, in a 24:24:24:24:12 ratio. Arm A (cohort 1) received a single morning dose of 75 mg KAE609 plus a single dose of 320 mg PPQ. Arm B (cohort 2) received a single morning dose of 25 mg KAE609 and a single dose of 1,280 mg PPQ. Arm C (cohort 3) received a single morning dose of 25 mg KAE609 only. In cohort 4 in arm D, subjects received a single morning dose of 320 mg PPQ only; in cohort 5 in arm D, subjects received a single morning dose of 1,280 mg PPQ only. Subjects who met the inclusion criteria at screening were admitted to baseline evaluations at the trial sites (day -1). Eligible subjects fasted overnight, were dosed on day 1, and then were domiciled at the site from baseline until 24 h postdosing. Subjects then returned to the site at defined times for an 8-week period (arms A, B, and D) or for an 11-day period (arm C), to undergo safety evaluations and PK sampling. Study completion evaluations were conducted after the last PK sampling on day 61 (end of study). The total study duration for subjects in arms A, B, and D was 89 days. Arm C (KAE609 monotherapy) had a shorter study duration (39 days) than arms A, B, and D due to the shorter half-life of KAE609 (~22 to 25 h) compared to PPQ (~22 days).

Pharmacokinetic assessments. Sampling for pharmacokinetic analysis in arms A, B, and D occurred at times 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 144, 192, 240, 336, 504, 672, 1,008, and 1,440 h. In arm C (KAE609 alone), pharmacokinetic samples were obtained only to 240 h, using the aforementioned schedule. KAE609 was analyzed in samples to the 240-h time point, and piperaquine was analyzed in samples to 1,440 h. Plasma was isolated within 30 min after blood collection, and tubes were kept frozen at or below -70°C until analysis. KAE609 and PPQ in plasma samples were analyzed separately, using validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) methods.

For the KAE609 assay, a 10-μl aliquot of the reconstituted extract was analyzed by HPLC-MS/MS in multiple reaction monitoring (MRM) mode, using electrospray ionization (ESI) as the ionization technique. KAE609[M6] was used as the internal standard.

For the piperaquine assay, a 50-μl aliquot of internal standard (15.0 ng/ml 3H2-piperaquine) and 400 μl of methanol were added to a 100-μl plasma sample. The mixture was vortex mixed and centrifuged, the supernatant was dried at 40°C until analysis. KAE609 and PPQ in plasma samples were analyzed separately, using validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) methods. For the KAE609 assay, a 10-μl aliquot of the reconstituted extract was analyzed by HPLC-MS/MS in multiple reaction monitoring (MRM) mode, using electrospray ionization (ESI) as the ionization technique. KAE609[M6] was used as the internal standard.

For the piperaquine assay, a 50-μl aliquot of internal standard (15.0 ng/ml 3H2-piperaquine) and 400 μl of methanol were added to a 100-μl plasma sample. The mixture was vortex mixed and centrifuged, the supernatant was dried at 40°C. KAE609 and PPQ in plasma samples were analyzed separately, using validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) methods. A mass spectrometer in MRM mode was used as the detector, with ESI.

The lower limits of quantitation (LLOQs) for KAE609 and PPQ are 1 ng/ml and 0.5 ng/ml, respectively. The Linearity ranges for KAE609 and PPQ are 1 to 5,000 ng/ml and 0.5 to 250 ng/ml, respectively. Accuracy and precision for both KAE609 and PPQ were within acceptable limits for study validation. For KAE609, at different concentrations of quality control samples, the coefficient of variation (CV) (precision) and bias (accuracy) were as follows: 2 ng/ml, CV, 10.3%; bias, 4.5%; 5 ng/ml, CV, 4.0%; bias, 5.0%; 400 ng/ml, CV, 5.6%; bias, -2.3%; 2,000 ng/ml, CV, 4.2%; bias, -4.0%; 4,000 ng/ml, CV, 4.6%; bias, -5.8%. Similarly, for PPQ, the values were as follows: 1.5 ng/ml, CV, 7%; bias, -0.7%; 15 ng/ml, CV, 4.8%; bias, -1.3%; 75 ng/ml, CV, 3.7%; bias, -1.9%; 200 ng/ml, CV, 4.2%; bias, -4.0%. Concentrations below the limit of quantification were treated as zero in summary statistics and for the calculation of PK parameters. No formal imputation for missing data was performed. PK parameters of KAE609 and PPQ were determined from the plasma concentration-time data using the recorded sampling times and noncom-

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PK parameters for KAE609 in plasma in the presence and absence of PPQ. KAE609 concentration-time profiles according to treatment group are shown in Fig. 1 (arithmetic means) and Fig. 2 (medians). The apparent flattening of the semilogarithmic curve in Fig. 1 for the group that received 25 mg KAE609 plus 1,280 mg piperazine was due to a single outlier (subject 1002 00051). This subject had a KAE609 concentration at 192 h of 45.1 ng/ml, with corresponding concentrations for the other subjects in this treatment group ranging from 0 to 3.14 ng/ml. Semilogarithmic plots of median KAE609 concentrations (which minimized the effects of outliers) did not show flattening of the curve for the group that received 25 mg KAE609 plus 1,280 mg piperazine (Fig. 2).

All KAE609 PK parameters measured for the group that received 25 mg KAE609 plus 1,280 mg PPQ were similar to those observed for the group that received 25 mg KAE609 (Table 1). Calculation of the geometric mean ratios (GMRs) for the primary KAE609 PK parameters for the two treatment groups indicated
that exposure to KAE609 was not affected by coadministration of PPQ, i.e., for $C_{\text{max}}$, the GMR was 1.03 (90% CI, 0.87 to 1.22), and for $AUC_{\text{last}}$, the GMR was 1.02 (90% CI, 0.86 to 1.20). There was, however, a 17% decrease in the KAE609 $C_{\text{max}}$ in the presence of 1,280 mg PPQ (GMR, 0.83 [90% CI, 0.73 to 0.94]).

**PK parameters for PPQ in plasma in the presence and absence of KAE609.** Exposure to PPQ was influenced by coadministration of KAE609, but the effects with increasing KAE609 doses were inconsistent. Figure 3 presents a semilogarithmic plot of mean PPQ concentrations over time according to treatment group.

Coadministration of 25 mg KAE609 with 1,280 mg PPQ modestly increased PPQ exposure, whereas coadministration of 75 mg KAE609 with 320 mg PPQ appeared to yield similar PPQ exposure (Fig. 3 and Table 2). Geometric means for $C_{\text{max}}$, $AUC_{\text{last}}$, and $AUC_{\text{inf}}$ were compared for the different cohorts (25 mg KAE609 plus 1,280 mg PPQ versus 1,280 mg PPQ, and 75 mg KAE609 plus 320 mg PPQ versus 320 mg PPQ). This analysis indicated that coadministration of 75 mg KAE609 with 320 mg PPQ led to a 10% decrease in $AUC_{\text{inf}}$ (GMR, 0.86 [90% CI, 0.70 to 1.07]) for PPQ, whereas coadministration of 25 mg KAE609 with 1,280 mg PPQ modulated the rates of AEs, but there were no obvious patterns and the differences are difficult to interpret, given the small numbers of AEs.

**Safety and tolerability.** In this study, 54.5% of subjects experienced at least one adverse event (AE). None of the AEs was serious, none was graded 3 or 4, and all resolved by the end of the study; no patient discontinued due to an AE. The highest overall rate of AEs was observed in the group that received 1,280 mg PPQ. The most common AEs in all treatment groups were classified as infections and infestations, nervous system disorders, and gastrointestinal disorders; no other system or organ class showed AEs affecting more than 10% of the total safety set. There were no AEs affecting the cardiovascular system. The most common AE overall was upper respiratory tract infection, followed by headache in all groups except the group that received 75 mg KAE609 plus 320 mg PPQ (for which oropharyngeal pain was the second most common AE) (Table 3). In addition to upper respiratory tract infections, headache, and oropharyngeal pain, other AEs that occurred in more than one subject were diarrhea, gastritis, abdominal pain, and dry skin. The treatment groups showed some differences in the rates of AEs, but there were no obvious patterns and the differences are difficult to interpret, given the small numbers of AEs.

**KAE609 does not affect QTc.** PPQ is known to increase the rate of AEs affected more than 10% of the total safety set. There were no AEs affecting the cardiovascular system. The most common AE overall was upper respiratory tract infection, followed by headache in all groups except the group that received 75 mg KAE609 plus 320 mg PPQ (for which oropharyngeal pain was the second most common AE) (Table 3). In addition to upper respiratory tract infections, headache, and oropharyngeal pain, other AEs that occurred in more than one subject were diarrhea, gastritis, abdominal pain, and dry skin. The treatment groups showed some differences in the rates of AEs, but there were no obvious patterns and the differences are difficult to interpret, given the small numbers of AEs. **KAE609 does not affect QTc.** PPQ is known to increase the rate of AEs.

**Table 1** Plasma PK parameters for KAE609 in the presence and absence of piperaquine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for treatment group receiving:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg KAE609 + 320 mg PPQ (n = 25)$^a$</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mean ± SD [%CV]) (ng/ml)</td>
<td>760 ± 176 (23.2)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (median [range]) (h)</td>
<td>3.00 (1.00–46.5)</td>
</tr>
<tr>
<td>$AUC_{0-24}$ (mean ± SD [%CV]) (µg · h/ml)</td>
<td>9.33 ± 1.90 (20.4)</td>
</tr>
<tr>
<td>$AUC_{\text{last}}$ (mean ± SD [%CV]) (µg · h/ml)</td>
<td>18.6 ± 5.33 (29.8)</td>
</tr>
<tr>
<td>$AUC_{\text{inf}}$ (mean ± SD [%CV]) (µg · h/ml)</td>
<td>18.6 ± 5.55 (29.8)</td>
</tr>
<tr>
<td>$t_{1/2}$ (mean ± SD [%CV]) (h)</td>
<td>24.4 ± 6.82 (28.0)</td>
</tr>
<tr>
<td>$V_{F}$ (mean ± SD [%CV]) (liters)</td>
<td>149 ± 46.4 (31.2)</td>
</tr>
<tr>
<td>$CL/F$ (mean ± SD [%CV]) (liters/h)</td>
<td>4.34 ± 1.16 (26.6)</td>
</tr>
</tbody>
</table>

$^a$ n = 23 for $AUC_{\text{inf}}$, $AUC_{\text{last}}$, $t_{1/2}$, and $V_{F}$.

$^b$ n = 24 for $AUC_{\text{inf}}$, $AUC_{\text{last}}$, $t_{1/2}$, and $V_{F}$.
QTc (9, 10). Therefore, ECG evaluations were performed for all cohorts using QTcF values in the primary analysis. No mean increase in QTcF was seen except for the two treatment groups that received 1,280 mg PPQ (Fig. 4). There appeared to be little difference in ECG results between the group that received 1,280 mg PPQ alone and the group that received 25 mg KAE609 plus 1,280 mg PPQ or between the group that received 320 mg PPQ alone and the group that received 320 mg PPQ plus 75 mg KAE609. The group that received 25 mg KAE609 did not show an increase in QTcF at any time point.

A statistical analysis of treatment comparisons for maximal changes in QTcF from baseline for the first 24 h postdose is presented in Table 4; it uses a linear fixed-effects model with treatment as a fixed effect and the PPQ concentration at maximal exposure effects of KAE609 or PPQ alone or in combination on cardiac effects of PPQ when given in combination.

No mean increase in QTcF was seen except for the two treatment groups that received 1,280 mg PPQ (Fig. 4). There appeared to be little difference in ECG results between the group that received 1,280 mg PPQ alone and the group that received 25 mg KAE609 plus 1,280 mg PPQ or between the group that received 320 mg PPQ alone and the group that received 320 mg PPQ plus 75 mg KAE609. The group that received 25 mg KAE609 did not show an increase in QTcF at any time point.

A statistical analysis of treatment comparisons for maximal changes in QTcF from baseline for the first 24 h postdose is presented in Table 4; it uses a linear fixed-effects model with treatment as a fixed effect and the PPQ concentration at maximal exposure effects of KAE609 or PPQ alone or in combination on cardiac effects of PPQ when given in combination.

Data were pooled across treatment groups to investigate the exposure effects of KAE609 or PPQ alone or in combination on the change in QTcF from baseline. There was no apparent relationship between KAE609 concentrations and changes in QTcF from baseline; this was the case for KAE609 alone and in the pres-
ence of PPQ (Fig. 5). The $R^2$ for KAE609 plus PPQ was 0.0273 ($P = 0.01$), and that for KAE609 alone was 0.0003 ($P = 0.8365$).

For PPQ, there was an indication of a concentration-dependent effect on changes in QTcF from baseline, but this response was not affected by the presence of KAE609 (Fig. 6). The $R^2$ for KAE609 plus PPQ was 0.0709 ($P < 0.0001$), and that for PPQ alone was 0.0693 ($P = 0.0004$).

**DISCUSSION**

The current study assessed the safety, tolerability, and drug-drug interaction potential of KAE609 and PPQ administered alone or in combination to healthy subjects. Both drugs, when administered alone or coadministered, appeared to be well tolerated by the study volunteers. There were no serious adverse events, severe adverse events, or adverse events that led to discontinuation from the study. The most commonly reported AEs were upper respiratory tract infections, headache, diarrhea, and oropharyngeal pain. There were no consistent differences between the treatment groups, and there were no obvious increases in the rates of specific AEs when PPQ and KAE609 were coadministered, compared with administration of PPQ alone.

The ability of KAE609 and PPQ to affect cardiac conduction when given alone or in combination was also tested. PPQ is known to be associated with QTc prolongation in human studies (9, 10) and, although no significant changes in ECG parameters were observed in clinical studies of KAE609 (7), preclinical evaluations indicated this as a potential risk (unpublished Novartis data). The data from this study indicated that the mean maximal changes in QTcF and QTcB from baseline following a single PPQ dose were consistent with the known effects of the drug. A difference in QTcF of 7.47 ms (90% CI, 3.55 to 11.4 ms) was found for PPQ plus KAE609 versus KAE609 alone. The labeling for Eurartesim indicates a much greater QTcF increase after 3 days of dosing, which achieves approximately 3 times the PPQ exposure of a single dose. The magnitude of the change observed in this study and the Eurartesim labeling would be consistent with a positive thorough QTc study according to ICH E14 guidelines. In contrast, a single dose of KAE609 administered alone did not show an effect on the QTc, and QTcF and QTcB changes showed no correlation with KAE609 concentrations. Furthermore, coadministration of KAE609 did not potentiate the effects of PPQ on QTc. No cardiovascular AEs were reported for any subject.

Preclinical data also suggested a potential risk for phototoxicity from KAE609 exposure. Three light-related AEs were reported. All were of mild intensity and they did not exhibit a pattern suggesting a dose-response relationship for either KAE609 or PPQ. Two of these AEs were suspected by the investigators to be related to a study drug (one on day 2 in the group that received 75 mg KAE609 plus 320 mg PPQ, and one on day 3 in the group that

**TABLE 4 Statistical analysis of comparisons for mean maximal changes in QTcF from baseline**

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>LS mean maximal change from baseline (ms)</th>
<th>LS estimate of difference (90% CI) (ms)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg KAE609 + 320 mg PPQ vs 320 mg PPQ</td>
<td>5.04</td>
<td>−0.86 (−4.41 to 2.68)</td>
<td>0.6864</td>
</tr>
<tr>
<td>25 mg KAE609 + 1,280 mg PPQ vs 1,280 mg PPQ</td>
<td>9.50</td>
<td>2.37 (−2.08 to 6.82)</td>
<td>0.3775</td>
</tr>
<tr>
<td>25 mg KAE609 + 1,280 mg PPQ vs 25 mg KAE609</td>
<td>11.20</td>
<td>7.47 (3.55–11.4)</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

At predosing and 2, 4, 8, 12, and 24 h postdosing, triplicate ECG assessments were available. Averages of triplicate assessments were calculated, and the values for baseline and changes from baseline were derived accordingly. The repeated measurements were not taken into account for the calculation of statistics. The maximal changes from baseline for ECG intervals of less than 24 h were analyzed using a linear fixed-effects model with treatment as a fixed effect and KAE609 and PPQ concentrations at maximal changes as covariates. LS, least-squares.
received 25 mg KAE609). The investigators’ interpretation was that these subjects had increased vision sensitivity to light. The subject in the group that received 25 mg KAE609 reported a long history of intermittent similar symptoms. The third case involved a subject in the group that received 25 mg KAE609. This was not suspected by the investigators to be related to a study drug, as the subject had experienced sunburn after falling asleep on a beach.

This study evaluated the effects of combination treatment on exposure to each drug. Both KAE609 and PPQ are substrates for CYP3A4. PPQ is also a CYP3A inhibitor, based on the approved label for Eurartesim (9), while in vitro studies (unpublished Novartis data) have shown that KAE609 does not induce CYP3A but has a low potential to inhibit the enzyme. Prior to study initiation, SimCYP simulations using midazolam (a well-characterized high-clearance CYP3A4 substrate) as a surrogate for PPQ (CYP3A4 substrate) suggested that KAE609 could potentially increase the exposure to PPQ by up to 2-fold (as a worst-case scenario). Based on the in vitro interaction data and limited clinical data, an increase in KAE609 exposure of up to 4-fold (worst-case scenario) with PPQ was predicted (DDI Predict). The results from this study indicated a low degree of interaction, as coadministration of PPQ was found to have no overall effect on exposure to KAE609 in healthy subjects, although the KAE609 $C_{\text{max}}$ was decreased by 17% in the group that received 75 mg KAE609 plus 320 mg PPQ, compared with the group that received 320 mg PPQ. Coadministration of KAE609 had inconsistent and nonsignificant effects on exposure to PPQ. The reasons for this observation are unknown, but both comparisons had high variability, as shown by the wide confidence intervals. The study was designed to have at least 80% power to detect differences in AUC or $C_{\text{max}}$ in geometric mean $\pm$ H9252 0.0693 for PPQ.

**REFERENCES**


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D.S.S., J.P.J., M.K., G.L., and S.M. are employees of Novartis and/or shareholders of Novartis stock. P.G. and J.L. conducted the study and reviewed the data. D.S.S. was responsible for the overall study. All authors reviewed and approved the manuscript.

**FIG 6** Piperaquine concentration effects on changes in QTcF from baseline for piperaquine alone and in the presence of KAE609. ○, KAE609 plus PPQ; ▲, PPQ. Solid line, regression for KAE609 plus PPQ; dotted line, regression for PPQ. $R^2 = 0.0709$ for KAE609 plus PPQ; $R^2 = 0.0693$ for PPQ.
