Malaria is an infectious disease that threatens half of the world’s population and is caused mainly by two protozoan parasites: Plasmodium falciparum and Plasmodium vivax. P218 is being developed for chemoprevention against Plasmodium falciparum resistant strains. P218 is a selective inhibitor of Plasmodium falciparum dihydrofolate reductase (DHFR) inhibit, an enzyme which catalyses the reduction of folates to tetrahydrofolates, which are essential for DNA biosynthesis in the malarial parasite [1].

This First-in-Human study evaluated the effect of P218 following single escalating doses on the QT interval in healthy subjects, using the effect of a meal on QTcF to demonstrate assay sensitivity.

For the primary model, predictions were made at the geometric mean C$_{\text{max}}$ of P218-OH combined with the arithmetic mean of the concentrations of 218-OH glucuronide seen at the individual t$_{\text{max}}$ of P218-OH as well as at the geometric mean C$_{\text{max}}$ of P218-OH glucuronide combined with the arithmetic mean of the concentrations of P218-OH seen at the individual t$_{\text{max}}$ of P218-OH glucuronide.

For the model based on P218 only, the geometric mean concentrations of this moiety were used. None of the models shown in Table 1 predict a QTcF prolongation larger than 0.6 ms.

Table 1: Predictions based on the primary model and the one based on P218 only and based the concentration seen in the two highest dose groups.

<table>
<thead>
<tr>
<th>Dose [mg]</th>
<th>Concentrations [ng/ml]</th>
<th>Predictions [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>P218</td>
<td>P218-OH</td>
<td>218-OH glucuronide</td>
</tr>
<tr>
<td>750</td>
<td>C$_{\text{max}}$ = 144</td>
<td>at t$_{\text{max}}$ = 4618</td>
</tr>
<tr>
<td>1000</td>
<td>C$_{\text{max}}$ = 193</td>
<td>at t$_{\text{max}}$ = 6847</td>
</tr>
<tr>
<td>1000</td>
<td>C$_{\text{max}}$ = 196</td>
<td>at t$_{\text{max}}$ = 6570</td>
</tr>
</tbody>
</table>

Cohort 3: 30 mg P218  
Cohort 4: 500 mg P218  
Cohort 5: 1000 mg P218  
Cohort 6: 750 mg P218  
Cohort 7: 1000 mg P218

Plasma concentration data were available from all completed cohorts for P218 (parent) as well as for the three primary metabolites: P218 β acyl glucuronide, P218-OH and P218-OH β acyl glucuronide. Concentrations for subjects having received placebo were set to zero.

The placebo corrected change from baseline in heart rate was well below 5 ms, confirming the appropriateness of Friederica’s correction for heart rate.

There were no signs of an effect of P218 on QTcF (Fig 1) and no indication of hysteresis. This verified the validity of the choice of a model assuming a direct effect of at least one of the moieties.

Conclusions

1. This study established the cardiac safety of P218. The study met the criteria for a negative QT study, with the upper bound of a 2-sided 90% confidence interval falling below 10 ms with respect to the doses tested.
2. Concentration-QTcF analysis showed the absence of any clinical significant effect of P218 on QTcF.
3. The sensitivity of the study to detect small changes in the QTcF interval was confirmed by demonstrating a significant shortening of QTcF after a standardised meal.