Cardiac Safety of MMV533, a new Antimalarial Drug Candidate: Concentration-QTc Analysis from the First-In-Human Study in Healthy Volunteers

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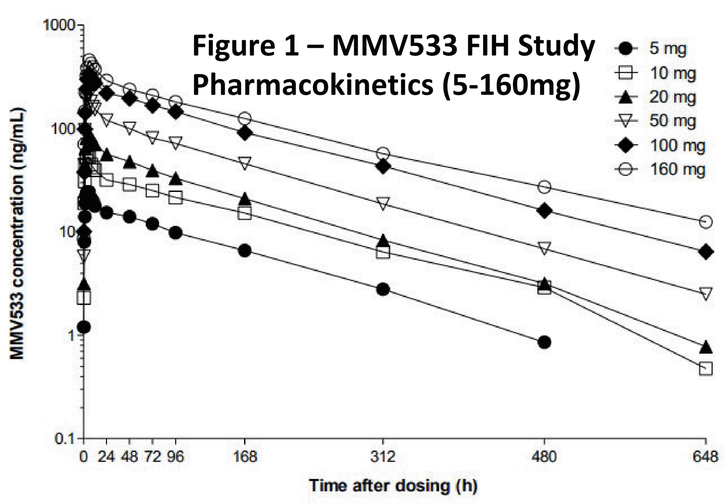
Introduction

MMV533 is a first in class, fast acting, blood stage inhibitor of all *Plasmodium* species, being developed for single dose oral treatment of uncomplicated malaria in adults and children. A First-In-Human (FIH) study recently reported (Kuemmerle et al. 2023) has shown a long $t_{1/2}$ (104-127h), a Tmax of 4-6h, an increase in exposure with doses, a good safety/tolerability profile and lack of clinically relevant QTc prolongation after categorical analysis. Two metabolites MMV893022 (Tmax 4-6h) and MMV893023 (Tmax up to 12h) were identified. Metabolite/parent ratios based on $AUC_{0-\infty}$ at the 160 mg dose were 8.5% for MMV893022 and 21.4% for MMV893023. Both metabolites showed $t_{1/2}$ values similar to those of MMV533. A concentration-QTc (C-QTc) exposure-response analysis was conducted to assess the impact of the parent drug and its two metabolites on changes from baseline in QTc .
[Clinicaltrials.gov-ID: NCT04323306].

Figure 1 – MMV533 FIH Study Pharmacokinetics (5-160mg)



Methods

Study Data. Healthy male and female volunteers (n = 50) were randomized in a double-blind, placebo-controlled, sequential-group FIH study (Part1) to a single fasting oral dose of MMV533 (5, 10, 20, 50, 100 and 160mg – Each dose 5-100mg: n=6; 160mg: n=8) or matching placebo (n=12). Eight participants enrolled in a pilot food effect Part2 (30mg – fasted period only) were also included in the analysis. Serial plasma samples for pharmacokinetic (PK) analysis of MMV533 and its two main metabolites and time-matched triplicate digitalized ECGs were obtained at baseline and 14 prespecified time-points over 96 hours, yielding a total of 811 QTc interval-plasma concentration time-matched pairs.

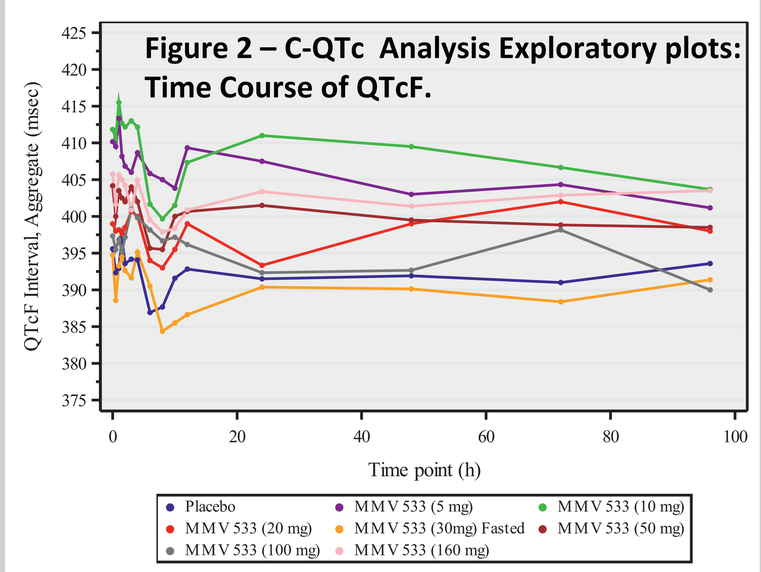
Concentration-Response Analysis. The model was based on the pre-specified mixed linear model as detailed by Garnett et al. (2018) and in line with the recent ICHE14/SB7 revisions (2022) considering ΔQTcF as dependent variable.

- For each participant, MMV533 and its two main metabolites concentrations matching the ECG records were included in the analysis datasets.
- The scatter plots of changes in QTcF vs concentrations did not show any trend between MMV533, MMV893022 or MMV893023 concentration and ΔQTcF.
- The fixed effect parameters of the pre-specified model were intercept, slope for MMV533 concentrations, influence of baseline (centered on mean) and nominal time on intercept, and a treatment specific intercept.
- Quality of the QT correction to heart rate change was assessed.
- Subject specific random effects (between subject variability) were added on intercept and slope parameters.
- Hypotheses underlying the linear model and lack of hysteresis were assessed using preliminary graphical exploration.
- The quality of the final model was evaluated using goodness of fit and diagnostic plots and validated using decile plots and visual predictive checks.
- Placebo-corrected changes from baseline in QTcF (ΔΔQTcF) were predicted from final model parameters at each dose Cmax geometric mean.

Results

The C-QTc analysis was performed on a total of 58 study participants (50/Part 1 and 8/Part 2) and included the 12 placebo volunteers.

Figure 2 – C-QTc Analysis Exploratory plots: Time Course of QTcF.



All prerequisites for applying the direct linear mixed model (adequacy of the QT correction, linear and direct relationship) were met and the pre-defined model was used.

Moreover, the diagnostic plots (Figures not shown) showed no relationship between the residuals and the two metabolites of MMV533 assayed in this FIH, confirming that no effects attributable to the metabolites were omitted from the model.

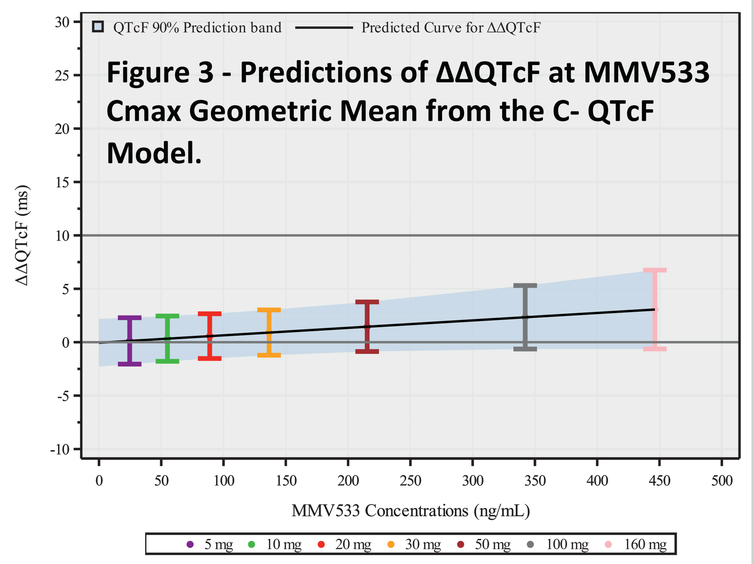
Between-subject random effects were supported on intercept and MMV533 concentrations slope. The intercept (mean off-drug effect) was estimated at -4.75 msec and was statistically not null. The treatment-specific intercept for MMV533 was estimated at -0.05 msec and was not statistically significant. This confirmed that the same overall mean decrease from baseline was observed during the study for placebo and MMV533 participants.

The slope for linear MMV533 concentrations contribution was estimated at 0.007 msec per ng/mL and was not statistically different from 0.

Overall, the diagnostic and goodness of fit plots did not reveal any trend suggesting model misspecification or potential impact of the two metabolites. This was confirmed by the validation plots.

Placebo-corrected changes from baseline in QTcF (ΔΔQTcF) with their 90% confidence intervals were computed from the model for each dose level at their Cmax geometric mean. Due to the weak albeit positive slope for MMV533 concentrations achieved after 5-160mg single doses, the ΔΔ QTcF increased with dose but remained far below the threshold of regulatory concern. The largest ΔΔ QTcF was estimated for the highest MMV533 single dose of 160 mg (Cmax = 446.31 ng/mL) at + 3.06 msec with a 90% CI of (-0.628; 6.75). The upper bound of the 90% CI for ΔΔQTcF at 160mg was <10 msec indicating the absence of a concerning QTc prolonging effect related to the MMV533 or its two metabolites.

Figure 3 - Predictions of ΔΔQTcF at MMV533 Cmax Geometric Mean from the C- QTcF Model.



Conclusion

While further studies in malaria patients in combination with a partner drug will support identification of the therapeutic dose and clinically relevant plasma concentrations of MMV533, this FIH C-QTc model suggests that MMV533 has a low risk for prolonging the QT interval and is unlikely to produce any proarrhythmic effects after single dose administration of up to 160mg.

References

- **Kuemmerle A et al.** 72nd Meeting, American Society for Tropical Medicine and Hygiene. October 18-22, 2023. Hyatt Regency Chicago, Chicago, IL, USA.
- **ICH E14/S7B Implementation Working Group** (2022) Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential. Questions & answers.
- **Garnett C et al.** J Pharmacokin Pharmacodyn 2018; 45: 383-397.

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PhinC Development

MMV Medicines for Malaria Venture 25 YEARS