Expediting MIDD evidence generation to support quizartinib approval in newly diagnosed AML patients

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Objectives

- To summarize how MIDD evidence contributed to support the proposed dosing regimen
- To illustrate a workflow that can be used to accelerate the generation of submission-ready MIDD evidence

Conclusions

- The MIDD evidence supported a positive benefit-risk profile for the proposed quizartinib dosing regimens in adult patients with newly diagnosed AML.
- When pharmacometric analyses are on the critical path to submission, timelines can be optimized by parallelizing hands-on work, frontloading analyses as well as reports, and using reproducible reporting systems.

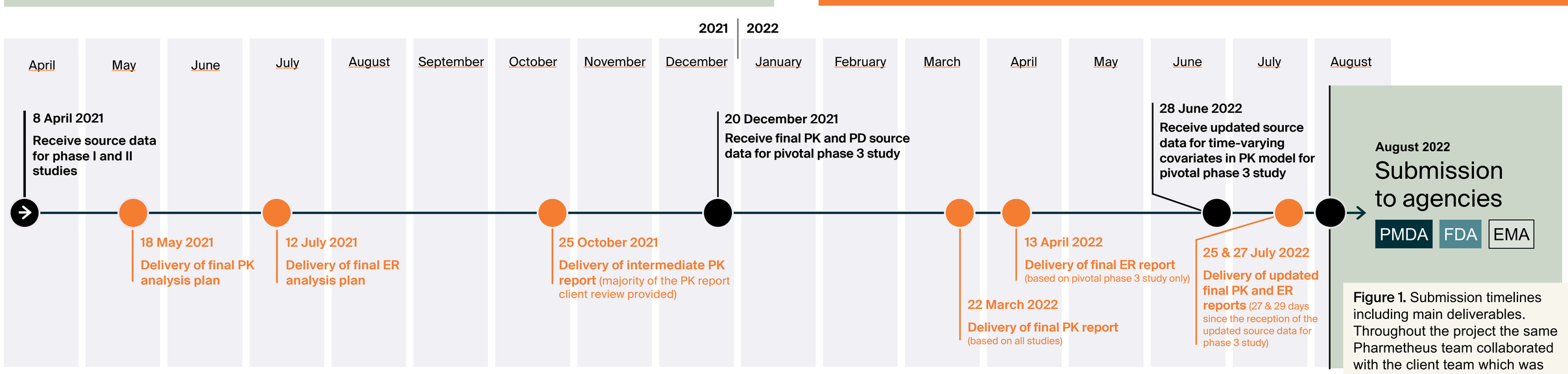

Figure 1. Submission timelines including main deliverables. Throughout the project the same Pharmetheus team collaborated with the client team which was continuously engaged.

Background

Quizartinib is a highly potent type II FMS-like receptor tyrosine kinase 3 (FLT3) inhibitor. The Phase 3 QuANTUM-First trial demonstrated that the addition of quizartinib to standard induction and consolidation chemotherapy in newly diagnosed FLT3-ITD-positive acute myeloid leukemia (AML) patients, followed by continuation with quizartinib monotherapy for up to 3 years, resulted in improved survival compared to placebo[1].

Speedy and high-quality submissions including pharmacometrics analyses following the completion of pivotal trials are crucial to faster access to new medicines for patients and return of investment for applicants. Because of their complexity, pharmacometric analyses often lie on the critical path to submission.

Data and methods

Endpoints: the population PK of quizartinib and its exposure-response (ER) relationship with 6 efficacy and 11 safety endpoints that were carefully selected were characterized.

Data: the PK analysis included data from 13 studies[2], while the ER analyses were based on data from the pivotal phase 3 study QuANTUM-First.

C-QTcF: the relationship between quizartinib exposure and Fridericia corrected QT (QTcF) interval was of particular interest due to the known QT interval prolongation by quizartinib[3].

Workflow: to increase efficiency in the pharmacometric analyses, from dataset preparation to report writing, the measures described in **Figure 2** were adopted. Independent quality control (QC) checkpoints combined with scientific peer reviews were included to ensure that the quality level of the generated MIDD evidence met regulatory standards.

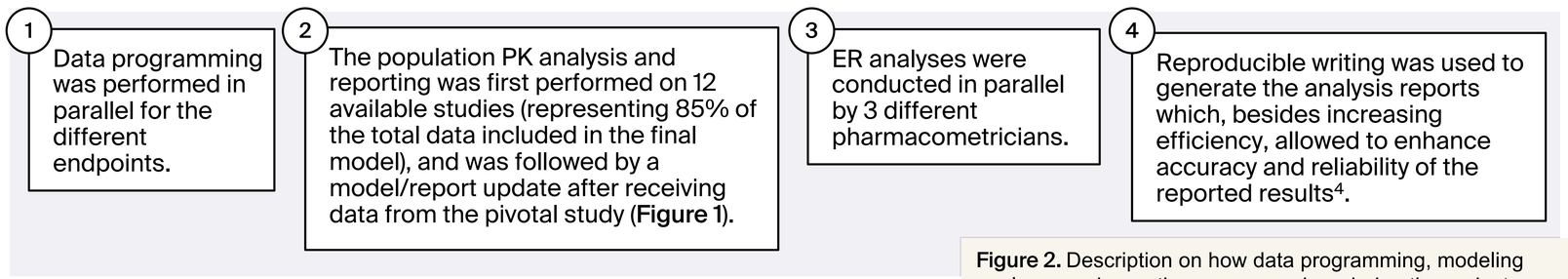

Figure 2. Description on how data programming, modeling analyses and reporting were speed-up during the project. This includes QC and peer-reviews.

Results

No dose adjustments were necessary for various patient groups based on age, sex, body weight or race groups. It confirmed the need to reduce the quizartinib dose during concomitant treatment with strong cytochrome P450 3A (CYP3A) inhibitors[2] (**Figure 3**).

The concentration-QTcF analysis (**Figure 4**) supported the dose-modification algorithm used in the QuANTUM-First trial, basing dose adjustments on observed QTcF prolongation and/or concomitant administration of strong CYP3A inhibitors[5].

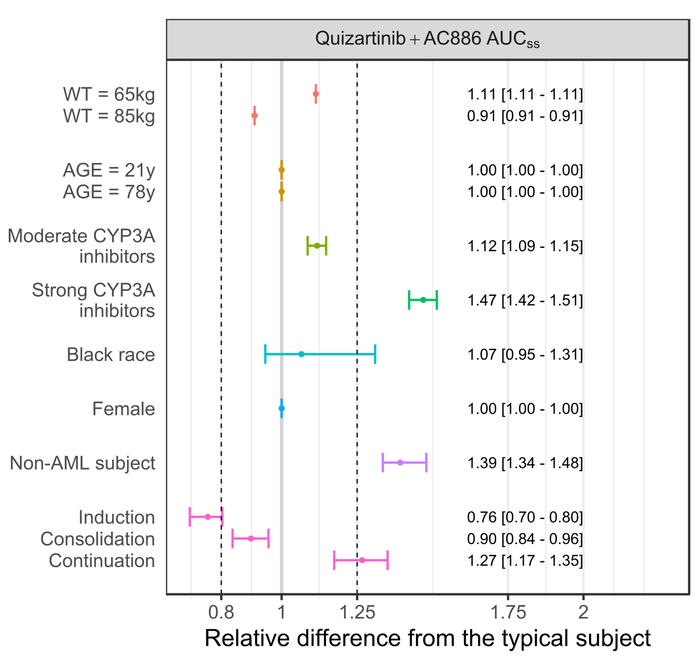

Figure 3. Forest plot of covariate effects for the sum of quizartinib and AC886 AUCss. The dots represent the median of the relative difference from the typical subject and the whiskers represent the confidence interval for the sum of quizartinib and AC886 AUCss. The dotted lines indicate the margins relative to the typical subject represented by the grey line.

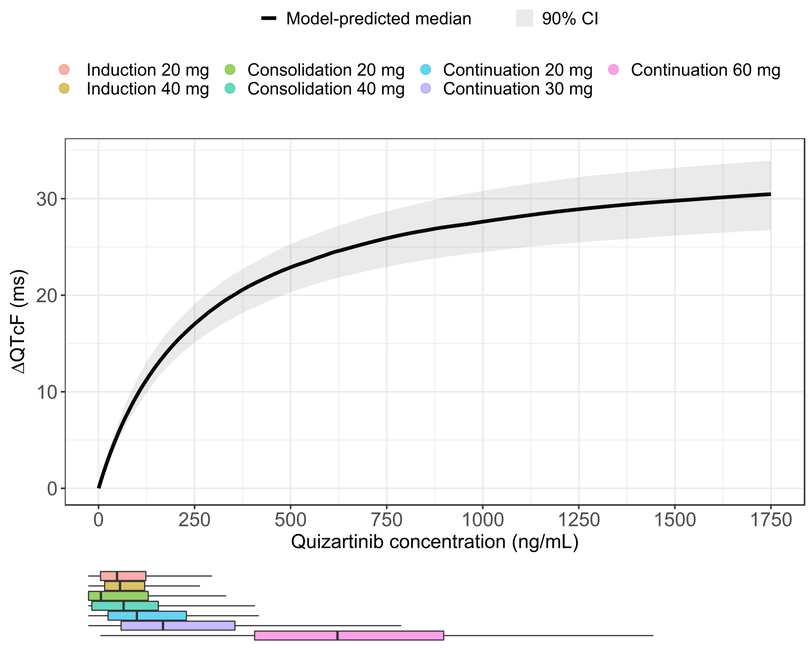

Figure 4. Predicted ΔQTcF versus quizartinib concentrations. The shaded area represents the 90% CI for the prediction in newly diagnosed subjects obtained from simulations with uncertainty (n=250). The horizontal boxplots depict the distribution of the observed quizartinib concentrations in study QuANTUM-First, colored by phase and dose.

Overall, the analyses supported the successful approval of quizartinib by the European Medicines Agency, the US Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency.

References

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