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Geneva, Switzerland

RE: CPMT-08-011 "Pharmacokinetic Analyses of Fixed-Dose Drug Combinations for Pediatric Tuberculosis"

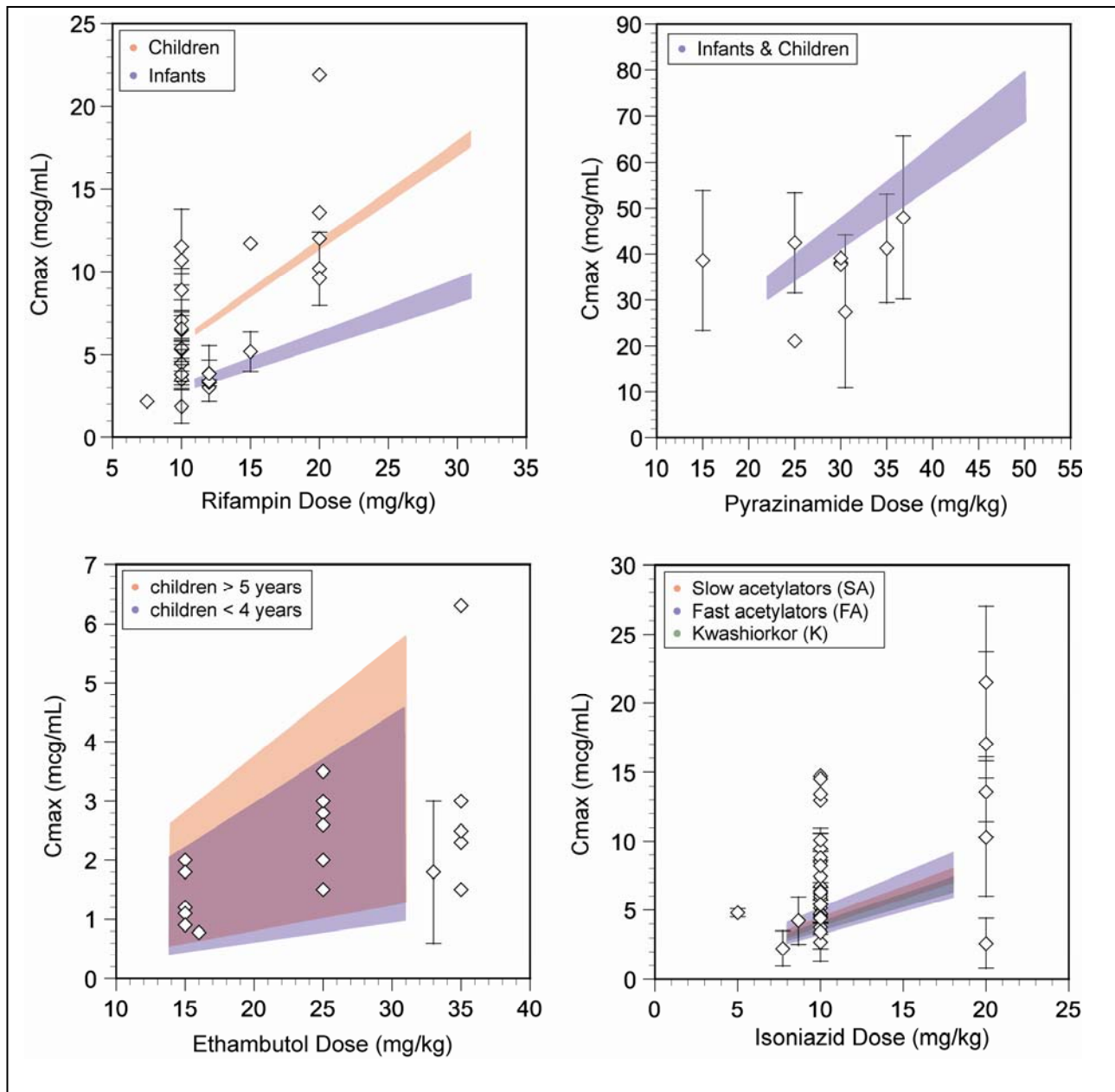
Dear Dr. Hill,

We appreciate the opportunity to respond to the thoughtful comments on the aforementioned study report that were submitted by reviewers from the Gates Foundation [Richard Elliott, Michael Kimerling and Jan Gheuens as provided via electronic communication from Saul Morris]. The sections that follow represent our response to these comments/queries.

1. [How predictive is this model if you perform \*in silico\* modeling for adults and compared with real clinical PK data \(e.g. Cmax; AUC, %time>desirable conc.\)?](#)

Data detailing maximum plasma concentrations (Cmax) were extracted from pediatric pharmacokinetic studies and overlaid on the relevant figures provided in the aforementioned technical study report [symbols represent individual data or mean data with or without the standard deviation as reflected in the original studies]. To minimize complexity, we have not segregated the data based on the nature of the study; however, these data derive from studies of varied design (e.g. single-dose vs. steady state, drug alone vs. in combination) with widely varying subject populations. Furthermore, it should be noted that numerous data points were extracted from studies utilizing a sparse sampling design thus they may represent a close approximation to, but not the actual, Cmax. Finally, it should be noted that the analytical methods used to generate the data in the original studies varied from simple microbiological assays to traditional chromatographic techniques.

Upon review of the figure, several observations can be made. The most notable is that there exists a substantial degree of inter-individual variability in the observed exposure estimates for the anti-tubercular agents that were simulated. In all cases, the predicted estimates (shaded regions) are reflected in, but do not wholly encompass, the observed values. Ethambutol serves as the exception where the predicted concentrations fully encompass the observed values. Notably, many of the observed ethambutol concentrations derive from the singular study that was robust enough to provide pharmacokinetic parameter estimates used in the simulations (thus, this would be expected via circular reasoning). In contrast, isoniazid concentrations markedly exceed the bounds defined in the simulations. This is not unexpected based on the multitude of factors that influence the biodisposition of the compound (including the well described polymorphism in *N*-acetyltransferase). In this case, the number of existing studies that



provide adequate information on the impact of development, genetics and pathophysiology on isoniazid pharmacokinetics is strikingly limited. Highly predictive simulations would require parameter estimates generated from well designed studies that simply do not exist. Similarly, the paucity of comprehensive pediatric trials on pyrazinamide pharmacokinetics results in observed values that appear to indicate the absence of a dose-exposure relationship in children despite the fact that this relationship is reasonably well established in adults.

Apart from the limitations to the data used to drive the simulations, the simplistic nature of the simulations, as set forth by the scope of work, accounts for models with varying predictive power. Our commission was to perform an initial set of steady-state

simulations for each drug as a singular entity (absent consideration for drug-drug interactions) based on information in the primary medical literature and contained in WHO technical reports.

2. What would the data look like if you modeled twice a day dosing. Would the advantages outweigh the inconvenience?

The ad hoc working group on paediatric tuberculosis constituted by WHO developed the initial drug/dosing table which was used as the basis for our simulations. It was the conclusion of this working group that a once-daily dosing regimen for a multi-drug formulation afforded the greatest chance for treatment adherence, especially in the developing world. Thus, for these initial, preliminary simulations, WHO suggested that we evaluate a once daily dosing regimen. Certainly, in silico approaches can be used to simulate twice daily dosing regimens which have the potential to improve inter-dose systemic exposure relative to expected pharmacodynamic surrogates. This could ostensibly improve therapeutic efficacy if adherence rates were 100%. Given many of the challenges associated with directly supervised TB treatment in the developing world, we can not reliably address whether any potential benefit associated with treatment regimens employing twice daily dosing outweigh convenience.

3. Page 2: Figure 1: may want to put units on Y axis (mcg/mL)

Any aspect of the technical report can be amended at the request of the sponsor. We concur that clarity for each illustration in the technical report is important.

4. Figure 4. Are calculated values for infants or children?

Both infants and children are considered in the pyrazinamide simulations as the pharmacokinetic parameters derived from available studies that did not segregate children by age.

5. Might be nice to put in a (adult) toxicity line for the Cmax plots for each drug (where known), so can put exposure predictions in context with safety.
6. What is known about the safety in infants/children for the doses used in these calculations? Should cut-off values be added?

These simulations were in no way intended to infer safety. Moreover, the number of existing studies detailing the relationship between concentration and toxicity are, in our opinion, insufficient to demarcate a specific threshold plasma concentration that can be reliably associated with the production of adverse events from any of the drugs administered in "normal" therapeutic doses. This notwithstanding, the plasma concentration illustrations contained within the technical report are constructed in such a fashion to enable reviewers to visually interpolate any plasma concentrations that they might feel are associated with adverse events / toxicity.

7. Questions around some of the assumptions:
  - Assumptions 1 & 2: Do these assumptions take into account differential hepatic function of infants/children compared to adults? Have these assumptions proven to be true in any real life examples?

- Assumption 3: What about Rif induction of CYP2D6 and CYP3A4? I see on bottom of page 15 some reference to CYP induction, but seems like one should be able to use whatever is known from adult Rif induction and, for a first approximation, build that into the model. May not be perfect, but will be a little closer to reality.
- Assumption 5: Is this true in adults?
- Assumptions 6-8: Any evidence for this assumption?

Assumptions are employed out of necessity when the existing medical literature are unavailable or incomplete. As is the case for any pharmacokinetic simulation of plasma drug concentrations, one must assume that pharmacokinetic parameter estimates derived from a particular, generally small population can be generalized to represent the majority of individuals in that population. To that end we were careful to identify pharmacokinetic parameters that most closely reflected the population of interest (where available). Drug-drug interactions were not considered given the absence of relevant data from pediatric populations where the intersection of developmental and constitutive expression of drug metabolizing enzyme / transporter activity can determine the direction and magnitude of any drug-drug interaction. In children, this undertaking is far more complex than would be the case for adults where constitutive enzyme expression is established and relatively static. As indicated in the report, the validity of selected assumptions remains questionable as for the case of rifampin absorption. Previous experimental data appear to indicate that selected rifamycins may undergo active transport at the level of the intestine but the extent and magnitude to which this occurs in humans has not been established.

8. How well do these simulations predict what is known in the literature? Are there other variables (e.g. GI volumes, liver function, GI tract permeability differences) that could be incorporated into the model for improved predictivity?

Known developmental differences in drug disposition have been previously summarized (Kearns GL, et al. *N Engl J Med* 2003;349:1157-1167) and certainly, have the ability to impact the biodisposition of antitubercular drugs. With the possible exception of developmental “road maps” for renal function and some of the major drug metabolizing enzymes, existing developmental physiology literature does not afford the degree of granularity necessary to effectively parameterize a pharmacokinetic/pharmacodynamic model in a quantitative fashion. At best, one can incorporate “directional” changes which, in the case of several of the simulations contained in this report, have been incorporated when possible (ie. afforded by some existing information). In the absence of clear data, introducing hypothetical “differences” in the model could serve to compound variability in an artificial manner and thereby, further compromise any predictive value in the simulations.

Importantly, the limitations of the simulations discussed herein illustrate the gaps that need to be filled before we can reliably identify the ideal formulation for use in children. These initial simulations as performed are intended to provide a starting point in the development of a multi-drug formulation of conventional antitubercular drugs that are currently recommended by WHO for the management of TB in paediatric patients. As such, they provide a necessary framework upon which to further build strategies for dose selection and ultimately, the prospective study of such drug formulations in patients who receive them as treatment. Given the urgency to ensure the availability of effective treatments that can be reliably used in developing countries, it is hoped that these

simulations, all of which are based on fundamental clinical pharmacology principles, will provide the insight necessary to move the paediatric TB initiative forward.

Kind regards,

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