Improved power for TB Phase IIa trials using a model-based pharmacokinetic–pharmacodynamic approach compared with commonly used analysis methods

Robin J. Svensson1, Stephen H. Gillespie2 and Ulrika S. H. Simonsson1*

1Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; 2The School of Medicine, University of St Andrews, St Andrews KY169TF, UK

*Corresponding author. Tel: +46-18-471-4685; Fax: +46-18-471-4003; E-mail: ulrika.simonsson@farmbio.uu.se

Received 1 February 2017; accepted 5 April 2017.

Background: The demand for new anti-TB drugs is high, but development programmes are long and costly. Consequently there is a need for new strategies capable of accelerating this process.

Objectives: To explore the power to find statistically significant drug effects using a model-based pharmacokinetic–pharmacodynamic approach in comparison with the methods commonly used for analysing TB Phase IIa trials.

Methods: Phase IIa studies of four hypothetical anti-TB drugs (labelled A, B, C and D), each with a different mechanism of action, were simulated using the multistate TB pharmacometric (MTP) model. cfu data were simulated over 14 days for patients taking once-daily monotherapy at four different doses per drug and a reference (10 mg/kg rifampicin). The simulated data were analysed using t-test, ANOVA, mono- and bi-exponential models and a pharmacokinetic–pharmacodynamic model approach (MTP model) to establish their respective power to find a drug effect at the 5% significance level.

Results: For the pharmacokinetic–pharmacodynamic model approach, t-test, ANOVA, mono-exponential model and bi-exponential model, the sample sizes needed to achieve 90% power were: 10, 30, 75, 20 and 30 (drug A); 30, 75, 245, 75 and 105 (drug B); 70, 1250, 315, 1250 and 1250 (drug C); and 30, 110, 710, 170 and 185 (drug D), respectively.

Conclusions: A model-based design and analysis using a pharmacokinetic–pharmacodynamic approach can reduce the number of patients required to determine a drug effect at least 2-fold compared with current methodologies. This could significantly accelerate early-phase TB drug development.

Introduction

The currently recommended treatment for drug-susceptible TB consists of rifampicin, isoniazid, pyrazinamide and ethambutol.1 Under trial conditions the regimen provides a cure rate of approximately 95%.2–4 For MDR TB, however, cure rates are much lower5 and few drugs have been developed for use in these patients. Although bedaquiline6 and delamanid7 have recently reached the market through conditional approval there remains a paucity of candidates in early clinical development. Thus, there is a pressing need for the development of new agents to address this gap in our therapeutic armamentarium.

The primary endpoint for Phase III TB trials is relapse-free cure after treatment.2 The choice of Phase III combinations is guided by the results of Phase IIb trials where drug combinations are studied for the first 8 weeks of treatment.8 These late-stage clinical trials are preceded by a Phase IIa methodology adapted to TB when a novel drug is given to TB patients alone or in combination. This is designed to provide information on the bactericidal effects9–11 and may aid in dose selection for Phase IIb.12

Phase IIa TB studies are usually monotherapy trials analysed by comparing the changes in mycobacterial load in sputum for 7–14 days of treatment compared within or between dose arms. A traditional approach used to analyse such trials is by calculating the early bactericidal activity (EBA) defined as the faill in log10 cfu/day.13 The EBA is non-model-based and is obtained using only two timepoints, such as the first and last cfu measurements in a patient. The mean EBA is compared between drugs and doses by ANOVA or t-test.14 Conventionally, an empirical model approach is also used which gives model-based estimates of the change in cfu.

© The Author 2017. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

2311
using simple empirical models including mono- and bi-exponential regression models.\textsuperscript{15,16} These empirical models are simultaneously fitted to all available data points from a patient. The model-based estimates of change in cfu are compared between drugs and doses. Phase IIa TB studies typically include 10-15 patients per dose arm and many fail to demonstrate statistically significant differences between drugs and between different doses of the same drug.\textsuperscript{13,17} Model-based analysis using a pharmacokinetic–pharmacodynamic approach has been shown to increase the power of Phase II studies in indications such as HIV, acute stroke and diabetes when compared with traditional statistical analyses.\textsuperscript{18,19} Thus, in this study, we adapt this approach to TB to evaluate the power of a pharmacokinetic–pharmacodynamic approach using the multistate TB pharmacometric (MTP) model\textsuperscript{20–22} in comparison with traditional statistical analyses including empirical model approaches (mono- and bi-exponential regression) and traditional approaches (t-test and ANOVA).

**Methods**

To explore the impact of different analysis techniques we postulated four drugs (labelled A, B, C and D) with different mechanisms of action, but similar pharmacokinetics. Firstly, individual cfu versus time data were simulated using a previously described pharmacokinetic–pharmacodynamic model for pre-clinical and clinical TB, the MTP model.\textsuperscript{20–22} As a second step, the simulated data were analysed using the different approaches in order to determine the statistical power for each respective approach for drugs A–D.

**Study design**

The Phase IIa study design included four study arms receiving 100, 200, 300 or 400 mg of the putative drugs and 10 mg/kg rifampicin (reference arm) administered orally once daily as monotherapy for 14 consecutive days. Subjects were divided equally across arms. We simulated sputum collections at baseline and days 1–7, 9 and 14 after start of treatment\textsuperscript{23} between 8 p.m. and 8 a.m. with assumed sputum volumes of 10 mL. As patients were assumed to have established infections, all treatments were started 150 days after time of infection.\textsuperscript{22} Patients were assumed to weigh 56 kg and to be smear-positive, newly diagnosed adults with uncomplicated previously untreated pulmonary TB taking no other medications.

**Phase IIa cfu simulations**

The MTP model\textsuperscript{20–22} was linked to a pharmacokinetic model in addition to exposure–response parameters and was used to simulate individual cfu data over time for four different drugs (A, B, C and D). The MTP model parameters described cfu without drug, the pharmacokinetic model parameters described exposure and the exposure–response parameters described the drug effect (Table 1).\textsuperscript{22} The model described three mycobacterial states including fast-, slow- and non-multiplying states with growth present on the fast-multiplying state. The numbers in the different states at any timepoint were defined by the following differential equations:

\[
\frac{dN}{dt} = k_{SN} \cdot S + k_{FN} \cdot F - k_{NS} \cdot N
\]

where

\[k_{SN} = k_{FS,_{1}} \cdot t\]

where \(F\), \(S\) and \(N\) are the model-predicted bacterial numbers in fast-, slow- and non-multiplying states, respectively. Rate constants \((k)\) with two-letter subscripts describe transfer rates between fast \((F)\), slow \((S)\) and non-multiplying \((N)\) states; the first letter indicates the transfer origin and the second letter the destination. The parameter \(k_{SN}\) describes a time-dependent transfer from fast- to slow-multiplying state. Time \((t)\) is in days after infection, \(k_{0}\) is the fast-multiplying bacterial growth rate and \(B_{\text{max}}\) is the system carrying capacity.

We assumed that only the fast- and slow-multiplying bacteria are detectable as cfu and those in the non-multiplying state are not. The sputum sampling compartment method was included representing the clinical sampling procedure performed over a given time interval. For the sputum sampling compartment method, bacteria accumulate in a sputum sample compartment \((\text{Sample})\) during the sampling interval described by:

\[
\frac{d\text{Sample}}{dt} = k_{\text{prod}} \cdot (F + S)
\]

where

\[k_{\text{prod}} = \frac{V_{\text{sample}}}{D_{\text{sample}}}\]

where \(k_{\text{prod}}\) is the sputum production rate.\textsuperscript{22} The parameter \(V_{\text{sample}}\) is the sputum sample volume (mL) and \(D_{\text{sample}}\) is the sampling duration (h). The cfu in the sample compartment was calculated by:

\[\text{cfu} = \frac{\text{Sample}}{V_{\text{sample}}}\]

at the end of each sampling period to get cfu (mL\textsuperscript{-1}).

The drug pharmacokinetic parameters for drugs A–D were set to the same hypothetical values, reflecting a drug with one-compartment disposition with first-order absorption and rapid elimination (Table 1 and Figure 1). The pharmacokinetics of rifampicin were generated using a previously developed population pharmacokinetic model.\textsuperscript{24} Rifampicin was assumed to inhibit growth of the fast-multiplying bacteria in addition to killing the slow- and non-multiplying bacteria.\textsuperscript{22} Drugs A and B had the same mechanism of action as rifampicin, i.e. inhibition of fast-multiplying bacterial growth and killing of the slow- and non-multiplying bacteria (Figure 1). Drug C was defined as being able to kill non-multiplying bacteria and drug D was assumed to kill slow-multiplying bacteria. The different mechanisms of action for drugs A–D are shown in Figure 1.

The different mechanisms of action were represented by three different exposure–response models:

\[EFG = 1 - FG_{\text{on/off}}\]

\[ESD = SD_{k} \cdot C_{p}\]
where $EFG$, $ESD$ and $END$ are drug effects, namely inhibition of fast-multiplying growth and killing of slow- and non-multiplying bacteria, respectively. The parameter $FG_{on/off}$ is the fractional inhibition of growth of the fast-multiplying state, where the drug effect is present once the drug concentration ($C_p$) is above 0. The parameters $SD_k$ and $ND_k$ are the death rates of the slow- and non-multiplying states, respectively. Different values of the exposure–response parameters ($FG_{on/off}$, $SD_k$ and $ND_k$) were assumed for drugs A–D (Table 1). Drug A was 20% more potent than rifampicin, except for inhibition of fast-multiplying growth which was similar to rifampicin, i.e. 100%. Drug B was 50% less potent than drug A. Drug C had the same potency as drug A for killing of the non-multiplying state. Drug D had the same potency as drug A for killing of slow-multiplying bacteria. The drug effects were included in the differential equations for the MTP model as follows:

$$
\frac{dF}{dt} = k_G \cdot \log\left( \frac{B_{\text{max}}}{F + S + N} \right) \cdot EFG \cdot F + k_{SF} \cdot S - k_{FS} \cdot F - k_{FN} \cdot F
$$

$$
\frac{dS}{dt} = k_{FS} \cdot F + k_{NS} \cdot N - k_{SN} \cdot S - ESD \cdot S
$$

$$
\frac{dN}{dt} = k_{SN} \cdot S + k_{FN} \cdot F - k_{NS} \cdot N - END \cdot N
$$

### Power analysis

A large cfu dataset was simulated and subsets of the dataset were sampled repeatedly at several sample sizes. Each subset was analysed using five different methods: pharmacokinetic–pharmacodynamic model

---

**Table 1.** Pharmacokinetic and MTP model parameters used in the simulations of cfu versus time after different doses of drugs A, B, C and D for different study sample sizes (1000 replicates per sample size)

| Parameter Description | Value | Interindividual variability (%CV) |
|-----------------------|-------|-----------------------------------|
| **MTP model parameters** | | |
| $k_G$ (days$^{-1}$) fast-multiplying bacterial growth rate | 0.206 | — |
| $k_{FN}$ (days$^{-1}$) transfer rate from fast- to non-multiplying state | 8.98 × 10$^{-7}$ | — |
| $k_{SN}$ (days$^{-1}$) transfer rate from slow- to non-multiplying state | 0.186 | — |
| $k_{SF}$ (days$^{-1}$) transfer rate from slow- to fast-multiplying state | 0.0145 | — |
| $k_{NS}$ (days$^{-1}$) transfer rate from non- to fast-multiplying state | 0.00123 | — |
| $k_{FS\text{lin}}$ (days$^{-1}$) time-dependent transfer rate from fast- to slow-multiplying state | 0.00166 | — |
| $F_0$ (mL$^{-1}$) initial bacterial number of fast-multiplying state | 4.11 | — |
| $S_0$ (mL$^{-1}$) initial number of slow-multiplying state | 9770 | — |
| $B_{\text{max}}$ (mL$^{-1}$) system carrying capacity per mL of sputum | 2.61 × 10$^9$ | 152 |
| **Drug pharmacokinetic parameters** | | |
| $CL/F$ (L h$^{-1}$) oral clearance | 8.00 | 30.7 |
| $V/F$ (L) apparent volume of distribution | 60.0 | — |
| $k_a$ (h$^{-1}$) absorption rate constant | 1.00 | — |
| **Exposure–response parameters** | | |
| $FG_{on/off}$ fractional inhibition of growth of fast-multiplying state | | |
| drug A | 1.00 | — |
| drug B | 0.50 | — |
| drug C | — | — |
| drug D | — | — |
| $SD_k$ (L mg$^{-1}$ days$^{-1}$) second-order slow-multiplying state death rate | | |
| drug A | 0.240 | 60 |
| drug B | 0.120 | 60 |
| drug C | — | — |
| drug D | 0.240 | 60 |
| $ND_k$ (L mg$^{-1}$ days$^{-1}$) second-order non-multiplying state death rate | | |
| drug A | 0.127 | 75 |
| drug B | 0.064 | 75 |
| drug C | 0.127 | 75 |
| drug D | — | — |
| **Residual error parameters** | | |
| $\varepsilon$ (CV%) additive residual error on log scale | 110 | — |
| $\varepsilon_{\text{repl}}$ (CV%) additive residual error on log scale | 23.1 | — |

CV, coefficient of variation.

*The pharmacokinetic parameters were the same for all four different drugs.*
approach (MTP model), traditional approaches (t-test and ANOVA) and empirical model approaches (mono- and bi-exponential regression). The proportion of the subsets at each sample size where a drug effect was detected was defined as the power. Statistical significance was accepted at the 5% significance level. An additional criterion for clinical significance was included for each approach (outlined below). The approaches are described briefly below. For a detailed description see Appendix S1 (available as Supplementary data at JAC Online).

**Pharmacokinetic–pharmacodynamic model approach using the MTP model**

For the pharmacokinetic–pharmacodynamic model approach using the MTP model, the Monte Carlo mapped power (MCMP) method was applied. For each drug a reduced model without drug effect corresponded to $H_0$ and a full model including drug effect corresponded to $H_1$. The clinical significance criterion was included as a constraint on the exposure–response parameters $SD_k$ and $ND_k$; only positive values were allowed for these parameters. Negative values would mean that the drug directly increases the bacterial number.

**Empirical model approaches**

For the empirical approaches the power to find a drug effect was obtained using mono- and bi-exponential regression models applied to the highest (400 mg) dose group. Both models assumed that cfu changed over time and in order to test if these changes were statistically significant the mono- and bi-exponential regression models were compared with a reduced empirical model assuming no change in cfu over time. Testing was done using an $F$-test under the null hypothesis that the mono- or bi-exponential model did not provide a better fit than the reduced empirical model ($H_0$). The clinical significance criterion was implemented to only allow declines in cfu.

**Traditional statistical approaches**

For the traditional approaches using t-test or ANOVA, the EBA between days 0 and 14 (EBA0–14) was used as the test statistic. The power to detect a drug effect was determined using a two-sided t-test under the null hypothesis that the mean EBA0–14 from patients in the highest dose group (400 mg) did not differ from 0 ($H_0$). A clinical significance criterion was introduced where only positive values for EBA0–14 contributed to the power since negative EBA0–14s represent drugs that increase cfu over time, which was considered a clinically irrelevant drug effect. The power was also calculated for finding differences in EBA0–14 between study arms using ANOVA under the null hypothesis that there was no difference in EBA0–14 between study arms ($H_0$).

**Software**

Simulations were performed in NONMEM [version 7.3; Icon Development Solutions (http://www.iconplc.com/innovation/nonmem/), Ellicott City, MD, USA] using MCMP within PsN (version 4.5.2; Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden). Power calculations for the traditional approaches were performed in R.
Figure 2. Typical simulated log$_{10}$ cfu change from baseline versus time after start of treatment of four hypothetical anti-TB drugs (drugs A–D) following 100, 200, 300 and 400 mg (black continuous lines) and 10 mg/kg rifampicin (grey broken lines) given orally once daily (OD).
Table 2. Total sample size required for finding a drug effect at 90% power and 5% significance level for drugs A, B, C and D using a pharmacokinetic-pharmacodynamic model approach with the MTP model, traditional statistical approaches and empirical model approaches

| Analysis                                           | Total sample size (ratio compared with pharmacokinetic–pharmacodynamic model approach) |
|----------------------------------------------------|---------------------------------------------------------------------------------------|
| Pharmacokinetic–pharmacodynamic                    |                                                                                       |
| model approach                                     |                                                                                       |
| MTP model                                          | 10 (---)                                                                               |
| Traditional statistical approaches                 |                                                                                       |
| t-test                                             | 30 (3.0)                                                                               |
| ANOVA                                              | 75 (7.5)                                                                               |
| Empirical model approaches                         |                                                                                       |
| mono-exponential model                             | 20 (2.0)                                                                               |
| bi-exponential model                               | 30 (3.0)                                                                               |
| bi-exponential model                               | 75 (2.5)                                                                               |
| Empirical model approaches                         |                                                                                       |
| Empirical model approach                           |                                                                                       |
| mono-exponential model                             | >1250 (>17.9)                                                                           |
| Empirical model approach                           |                                                                                       |
| Empirical model approach                           | 170 (5.7)                                                                               |
| Empirical model approach                           |                                                                                       |
| Empirical model approach                           | 185 (6.2)                                                                               |

°90% power was not reached at the maximal sample size of 1250.

Results
Simulated typical cfu versus time after treatment with different doses of drugs A–D in monotherapy are shown in Figure 2. The required sample sizes to reach 90% power for finding a statistically significant drug effect (P ≤ 0.05) for treatment with drugs A–D using different analysis approaches, including a pharmacokinetic–pharmacodynamic model approach (MTP model), empirical approaches (mono- and bi-exponential regression) and traditional approaches (t-test and ANOVA), are shown in Table 2 with corresponding power curves in Figure 3.

The required sample size to achieve 90% power for finding a statistically significant drug effect for Phase IIa TB trials was at least two times lower for the pharmacokinetic–pharmacodynamic model approach (MTP model) in comparison with other tested approaches for all drugs. The ANOVA approach required higher sample sizes for all drugs compared with all other analyses except drug C, where all other analyses except the ANOVA and pharmacokinetic–pharmacodynamic approaches failed to reach 90% power. Mono-exponential regression required lower sample sizes compared with bi-exponential regression for all drugs except drug C where all approaches except the pharmacokinetic–pharmacodynamic model approach and the ANOVA approach failed to reach 90% power at the studied sample size range. The t-test required lower sample sizes than the empirical approaches for drug D whilst it performed similarly to bi-exponential regression for drug A and similarly to mono-exponential regression for drug B.

Discussion
This work shows the advantage of adopting a pharmacokinetic–pharmacodynamic model approach when designing and analysing Phase IIa TB trials. For all the hypothetical drugs studied here the sample size required to achieve a significant result at 90% power was smaller using the MTP model than all of the other approaches investigated. The reasons for this sample size reduction are that a pharmacokinetic–pharmacodynamic analysis includes all longitudinal data simultaneously, including data from all dose groups. The empirical approaches (mono- and bi-exponential regression) are less informative as they include longitudinal data only from the highest dose group. The traditional approaches (t-test and ANOVA) only include the difference between cfu at day 0 and day 14.

Phase IIa trials within TB typically include 10–15 patients per arm; hence the five arms used in the current study design correspond to a total study size of 50–75 patients. For drugs A–D, most analysis methods except the pharmacokinetic–pharmacodynamic model approach failed to attain 90% power at total sample sizes of 50–75 patients, in line with the known difficulty of finding statistically significant drug effects for Phase IIa TB trials and the even more difficult to detect differences between dose arms (i.e. exposure–response) which is assessed using ANOVA. Defining exposure–response is crucial for Phase IIa in general, but is not feasible for TB when using traditional methods and including 10–15 patients per arm. The pharmacokinetic–pharmacodynamic model approach also assesses differences between arms by estimating exposure–response parameters. By using the MTP model, the sample size needed to reach 90% power was reduced several-fold (Table 2) compared with the other approaches studied, enabling detection of exposure–response when including as few as 10–15 patients per arm. This allows for more robust dose selection for future trials based on exposure–response defined in Phase IIa.

The empirical approaches (mono- and bi-exponential regression) are expected to have higher power than traditional approaches since the empirical approaches include more data. However, when comparing the empirical approaches with the t-test approach, our results do not favour one over the other. Regression-based methods are expected to have higher power if the tested model fits the data well. In contrast, low power is likely to be seen for a model which is unable to describe the data. The cause of the unexpectedly low powers for the empirical analyses seen in this work is unknown, but our analysis shows that the relative power of empirical versus traditional approaches appears drug dependent.
The ANOVA approach had lower power than the t-test approach except for drug C (increased killing of non-multiplying bacteria) where ANOVA had higher power than the t-test (Figure 3c). The reason is that cfu increased in the highest dose group for day 14 compared with day 0 (Figure 2c) which was not considered clinically significant for the t-test analysis and therefore did not contribute to the power. The ANOVA approach also had higher power than the mono- and bi-exponential analyses due to the criterion for clinical significance only allowing a decrease in cfu. The criterion for clinical significance was implemented as constraints on the rate constant parameters for bacterial elimination to only allow decrease in cfu which stopped the mono- or bi-exponential models from describing the increases in cfu well, resulting in low power. The ANOVA approach only looks at statistical significance.

Figure 3. Predicted power at 5% significance level versus total sample size for four hypothetical anti-TB drugs (drugs A–D) using a pharmacokinetic–pharmacodynamic model approach (MTP model), mono-exponential regression, t-test, ANOVA and bi-exponential regression.
and not clinical significance, resulting in higher power for drug C. Exposure–response parameters were also constrained to be positive (i.e. only allowed to increase bacterial killing) for the pharmacokinetic–pharmacodynamic model approach, but the pharmacokinetic–pharmacodynamic model approach included disease-specific parameters governing bacterial growth ($k_c$ and $b_{max}$) which could allow an increase in cfu as an indirect consequence of drug exposure. The $b_{max}$ parameter acts to constrain growth at high bacterial densities, resulting in stationary phase growth. Drugs that kill bacteria reduce the bacterial density, resulting in growth proportional to the reduction in bacterial density, which caused regrowth for drug C (Figure 2c). It was only possible using a pharmacokinetic–pharmacodynamic approach to support statistically and clinically significant exposure–response relationships despite regrowth since this approach includes disease-specific parameters governing growth. If monotherapy data from drugs that increase cfu over time (due to regrowth as seen for drug C) are analysed using traditional or empirical approaches, this will lead to the conclusion that the drug is clinically insignificant, although this might not always be the case according to our results. It should be noted that the risk of this happening is low for drugs that either cause substantial inhibition of growth such as rifampicin or for drugs that strongly kill growing bacteria, effectively preventing regrowth. This finding is interesting in the context of the Phase IIa trial of SQ109 where daily monotherapy doses of 75 mg resulted in a greater decline in cfu over 14 days than doses of 150 and 300 mg. If SQ109 kills only the non-multiplying bacteria it would not be expected that the highest dose necessarily results in the greatest reduction in cfu over 14 days due to the regrowth phenomenon seen for drug C (Figure 3c). Although it would mean that if SQ109 acts to kill non-multiplying bacteria it would most likely enhance decline of cfu in combination with other drug(s) able to inhibit growth or otherwise prevent regrowth. Interestingly, SQ109 was combined with rifampicin in Phase IIa and an enhanced decline in cfu was seen when rifampicin was combined with 150 mg of SQ109 compared with rifampicin monotherapy. We speculate that if the Phase IIa trial of SQ109 had been designed and analysed using a pharmacokinetic–pharmacodynamic approach, SQ109 might have been interpreted as a drug that only kills non-multiplying bacteria. If this speculation is true SQ109 has potential for treating TB efficiently. But further refinement of the dose of SQ109 and choice of companion drugs are required as the reported efficacy after 12 weeks of treatment with 300 mg SQ109 combined with 10 or 20 mg/kg rifampicin, 5 mg/kg isoniazid and 25 mg/kg pyrazinamide was not better than the standard regimen consisting of 10 mg/kg rifampicin, 5 mg/kg isoniazid, 25 mg/kg pyrazinamide and 15–20 mg/kg ethambutol.

In conclusion, a pharmacokinetic–pharmacodynamic model approach using the MTP model was able to reduce the sample sizes required to reach 90% power to find statistically significant drug effects for Phase IIa TB trials compared with traditional and empirical approaches. This has the potential to make early TB drug development less expensive and more robust as fewer patients are required to show a statistically significant drug effect.

**Acknowledgements**

Some of the results presented here have been presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, 2015 (Abstract F278) and at the International Workshop on Clinical Pharmacology of Tuberculosis Drugs, 2015 (Abstract 22).

**Funding**

The research leading to these results has received funding from the Swedish Research Council (grant number 521-2011-3442) in addition to the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement no. 115337, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007–2013) and European Federation of Pharmaceutical Industries and Associations (EFPIA) companies’ in kind contribution.

**Transparency declarations**

None to declare.

**Supplementary data**

Appendix S1 is available as Supplementary data at JAC Online.

**References**

1. WHO. Treatment of Tuberculosis Guidelines. Geneva, 2010. http://www.who.int/tb/publications/2010/9789241547833/en/.

2. Gillespie SH, Crook AM, McHugh TD et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 2014; 371: 1577–87.

3. Merle CS, Fielding K, Sow OB et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med 2014; 371: 1588–90.

4. Jindani A, Harrison TS, Nunn AJ et al. High-dose rifampicin with moxifloxacin for pulmonary tuberculosis. N Engl J Med 2014; 371: 1599–606.

5. WHO. Global Tuberculosis Report 2015. Geneva: WHO Press, 2015.

6. Diacon AH, Pym A, Grabusch M et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009; 360: 2397–405.

7. Gler MT, Skripconoka V, Sanchez-Garavita E et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012; 366: 2151–60.

8. Mitchison DA, Davies GR. Assessment of the efficacy of new anti-tuberculosis drugs. Open Infect Dis J 2008, 2: 59–76.

9. Diacon AH, Dawson R, von Grote-Biddingmaier F et al. 14-Day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. Lancet 2012; 380: 986–93.

10. Heinrich N, Dawson R, du Bois J et al. Early phase evaluation of SQ109 alone and in combination with rifampicin in pulmonary TB patients. J Antimicrob Chemother 2015; 70: 1558–66.

11. Diacon AH, Dawson R, von Grote-Biddingmaier F et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. Am J Respir Crit Care Med 2015; 191: 943–53.

12. Diacon AH, Donald PR. The early bactericidal activity of antituberculosis drugs. Expert Rev Anti Infect Ther 2014; 12: 223–37.

13. Donald PR, Diacon AH. The early bactericidal activity of anti-tuberculosis drugs: a literature review. Tuberculosis (Edinb) 2008; 88 Suppl 1: S75–83.

14. Donald PR, Sirgel FA, Botha FJ et al. The early bactericidal activity of isoniazid related to its dose size in pulmonary tuberculosis. Am J Respir Crit Care Med 1997; 156: 895–900.

15. Jindani A, Aber VR, Edwards EA et al. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980; 121: 939–49.
16 Jindani A, Doré CJ, Mitchison DA. Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. *Am J Respir Crit Care Med* 2003; **167**: 1348–54.

17 Gosling RD, Helfets L, Gillespie SH. A multicentre comparison of a novel surrogate marker for determining the specific potency of anti-tuberculosis drugs. *J Antimicrob Chemother* 2003; **52**: 473–6.

18 Rekić D, Röshammar D, Simonsson USH. Model based design and analysis of phase II HIV-1 trials. *J Pharmacokinet Pharmacodyn* 2013; **40**: 487–96.

19 Karlsson KE, Vong C, Bergstrand M et al. Comparisons of analysis methods for proof-of-concept trials. *CPT Pharmacomet Syst Pharmacol* 2013; **2**: e23.

20 Clewe O, Aulin L, Hu Y et al. A multistate tuberculosis pharmacometric model: a framework for studying anti-tubercular drug effects in vitro. *J Antimicrob Chemother* 2016; **71**: 964–74.

21 Chen C, de Knegt GJ, de Steenwinkel JEM et al. Application of the multistate tuberculosis disease model for studying pharmacokinetics and pharmacodynamics in a chronic tuberculosis mouse model. In: Abstracts of the Annual Meeting of the Population Approach Group in Europe, Crete, Greece, 2015. Abstract 3511. PAGE, UK.

22 Svensson RJ, Simonsson USH. Application of the multistate tuberculosis pharmacometric model in patients with rifampicin-treated pulmonary tuberculosis. *CPT Pharmacomet Syst Pharmacol* 2016; **5**: 264–73.

23 Boeree MJ, Diacon AH, Dawson R et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015; **191**: 1058–65.

24 Smythe W, Khandelwal A, Merle C et al. A semimechanistic pharmacokinetic-enzyme turnover model for rifampin autoinduction in adult tuberculosis patients. *Antimicrob Agents Chemother* 2012; **56**: 2091–8.

25 Vong C, Bergstrand M, Nyberg J et al. Rapid sample size calculations for a defined likelihood ratio test-based power in mixed-effects models. *AAPS J* 2012; **14**: 176–86.

26 Beal S, Sheiner LB, Boeckmann A et al. NONMEM User’s Guides (1989-2009). Ellicott City, MD: Icon Development Solutions, 2009.

27 Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. *CPT Pharmacomet Syst Pharmacol* 2013; **2**: e50.

28 http://psn.sourceforge.net/.

29 Gillespie SH, Gosling RD, Charalambous BM. A reiterative method for calculating the early bactericidal activity of antituberculosis drugs. *Am J Respir Crit Care Med* 2002; **166**: 31–5.

30 Boeree MJ, Heinrich N, Aarnoutse R et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017; **17**: 39–49.