Increased bactericidal activity but dose-limiting intolerability at 50 mg·kg^{-1} rifampicin

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Lindsey H.M. te Brake[1], Veronique de Jager[2], Kim Narunsky[3], Naadira Vanker[2], Elin M. Svensson[1,4], Patrick P.J. Phillips[5], Stephen H. Gillespie[6], Norbert Heinrich[7,8], Michael Hoelscher[7,8], Rodney Dawson[3], Andreas H. Diacon[2], Rob E. Aarnoutse[1] and Martin J. Boeree[9] on behalf of the PanACEA Consortium

[1]Dept of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. [2]TASK Applied Science, Cape Town, South Africa. [3]UCT Lung Institute, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa. [4]Dept of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. [5]UCSF Center for Tuberculosis, University of California San Francisco, San Francisco, CA, USA. [6]School of Medicine, Medical and Biological Sciences, University of St Andrews, St Andrews, UK. [7]Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich, Munich, Germany. [8]German Center for Infection Research (DZIF), Munich, Germany. [9]Dept of Lung Diseases, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands.

Corresponding author: Lindsey H.M. te Brake (lindsey.tebrake@radboudumc.nl)

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While bactericidal activity continues to increase with dose, for the first time we identified dose-limiting intolerability for rifampicin dosed at 50 mg·kg^{-1}; 40 mg·kg^{-1} seems the optimal tolerable dose for evaluation in TB treatment-shortening trials https://bit.ly/37dUIuB

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Abstract

Background Accumulating data indicate that higher rifampicin doses are more effective and shorten tuberculosis (TB) treatment duration. This study evaluated the safety, tolerability, pharmacokinetics, and 7- and 14-day early bactericidal activity (EBA) of increasing doses of rifampicin. Here we report the results of the final cohorts of PanACEA HIGHRIF1, a dose escalation study in treatment-naive adult smear-positive patients with TB.

Methods Patients received, in consecutive cohorts, 40 or 50 mg·kg^{-1} rifampicin once daily in monotherapy (day 1–7), supplemented with standard dose isoniazid, pyrazinamide and ethambutol between days 8 and 14.

Results In the 40 mg·kg^{-1} cohort (n=15), 13 patients experienced a total of 36 adverse events during monotherapy, resulting in one treatment discontinuation. In the 50 mg·kg^{-1} cohort (n=17), all patients experienced adverse events during monotherapy, 93 in total; 11 patients withdrew or stopped study medication. Adverse events were mostly mild/moderate and tolerability rather than safety related, *i.e.* gastrointestinal disorders, pruritis, hyperbilirubinaemia and jaundice. There was a more than proportional increase in the rifampicin geometric mean area under the plasma concentration–time curve from time 0 to 12 h ($AUC_{0-24\,h}$) for 50 mg·kg^{-1} compared with 40 mg·kg^{-1}; 571 (range 320–995) *versus* 387 (range 201–847) mg·L^{-1}·h, while peak exposures saw proportional increases. Protein-unbound exposure after 50 mg·kg^{-1} (11% (range 8–17%)) was comparable with lower rifampicin doses. Rifampicin exposures and bilirubin concentrations were correlated (Spearman's ρ=0.670 on day 3, p<0.001). EBA increased considerably with dose, with the highest seen after 50 mg·kg^{-1}: 14-day EBA −0.427 (95% CI −0.500–−0.355) $\log_{10}$CFU·mL^{-1}·day^{-1}.

Conclusion Although associated with an increased bactericidal effect, the 50 mg·kg^{-1} dose was not well tolerated. Rifampicin at 40 mg·kg^{-1} was well tolerated and therefore selected for evaluation in a phase IIc treatment-shortening trial.