Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Final results of the DisCoVeRy trial of remdesivir for patients admitted to hospital with COVID-19

We reported the preliminary results of the DisCoVeRy trial regarding the efficacy and safety of remdesivir in hospitalised patients with COVID-19 in February, 2022.[1] Remdesivir did not have a clinical or virological benefit in the studied population. Notably, the number of patients included was lower than initially expected, because inclusions in this trial group were prematurely stopped by the data and safety monitoring board. Here, after completion of data monitoring, we report the final analysis, including two secondary endpoints that were not previously reported.

Briefly, the DisCoVeRy trial is a phase 3, open-label, randomised controlled trial evaluating the efficacy and safety of repurposed drugs in adults hospitalised for COVID-19, sponsored by Inserm (NCT04315948). Eligible participants were adults (aged ≥18 years) who were admitted to hospital with a positive PCR test for SARS-CoV-2 (<72 h before randomisation) and also had pulmonary rales or crackles with a peripheral oxygen saturation of 94% or less or required supplemental oxygen. The primary endpoint was the clinical status at day 15 as measured on a 7-point ordinal scale, which was analysed with a proportional odds model. Full details of the trial design are available in the preliminary report.[1]

In the final dataset, 857 participants were randomly assigned to a treatment group and 843 participants (remdesivir, n=420; control, n=423) were evaluable for analysis. The final odds ratio (OR) for clinical improvement based on the primary endpoint and adjusted for disease severity at randomisation was not in favour of remdesivir (adjusted OR 1·02 [95% CI 0·62–1·70], p=0·93; figure). This finding was consistent across all prespecified subgroup analyses.[2]

Full results regarding secondary outcomes are available elsewhere.[2] Two secondary endpoints were not previously reported: in-hospital mortality and mortality at 3 months after randomisation. Remdesivir did not have a significant effect on in-hospital mortality (33 of 420 participants in the remdesivir group *vs* 38 of 423 participants in the control group; adjusted OR 0·84 [95% CI 0·51–1·37]; p=0·48), nor on mortality at 3 months (43 of 420 *vs* 49 of 423; 0·87 [0·56–1·36]; p=0·55). Similar to findings from preliminary analyses, participants from the remdesivir group who were not on mechanical ventilation or ECMO when they were randomly assigned to a treatment group (n=692) had a significantly longer time to the composite endpoint of new mechanical ventilation, ECMO, or death in the 29 days following randomisation than did the control group (cumulative incidence in the remdesivir group was 58 [17%] of 343 participants *vs* 88 [25%] of 349 in the control group; adjusted hazard ratio [HR] 0·63 [95% CI 0·45–0·88]; p=0·010). In non-prespecified analyses, this effect was significant in participants with severe disease when they were randomly assigned to a treatment group (cumulative incidence in the remdesivir group 25 [29%] of 87 *vs* 47 [50%] of 94 in the control group; unadjusted HR 0·49 [95% CI 0·30–0·80]; p=0·0040) but not in those with moderate disease (33 (13%) of 256 *vs* 41 (16%) of 255; 0·79 [0·50–1·25]; p=0·31). No significant effect of remdesivir on the viral kinetics was observed (effect of remdesivir on the slope of decrease of the nasopharyngeal viral load was –0·006 $\log_{10}$ copies per 10 000 cells per day [95% CI –0·02 to 0·03]; p=0·66).

Among the 833 participants included in the safety analysis (remdesivir, n=410; control, n=423), no significant difference was evidenced in the occurrence of grade 3–4 adverse events (143 of 410 participants in the remdesivir group *vs* 150 of 423 participants in the control group; unadjusted OR 0·98 [95% CI 0·73–1·32]; p=0·91) nor of serious adverse events (147 of 410 *vs* 138 of 423; 1·17 [0·87–1·57]; p=0·29).

Overall, the final results of the DisCoVeRy trial for the efficacy and safety of remdesivir reinforce the observations in the preliminary report, supporting recommendations against its use in hospitalised patients with COVID-19.

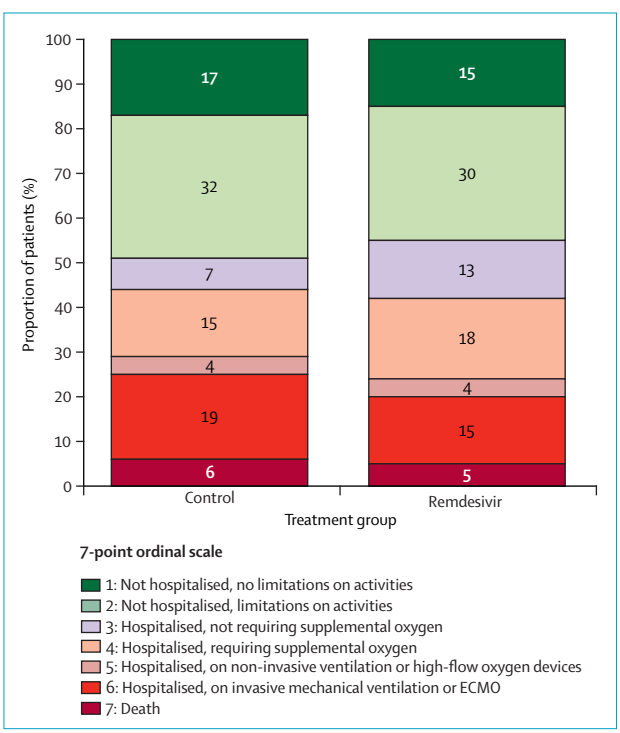

Figure: **Clinical status at day 15 of patients included in the intention-to-treat population**
As measured by the 7-point ordinal scale. Reported numbers refer to the proportion of patients with the corresponding level in each group. The intention-to-treat population included all participants with a positive SARS-CoV-2 PCR test obtained in the past 9 days who were randomly assigned to a treatment group, for whom a valid consent form was obtained and who did not receive any investigational treatment in the past 29 days. ECMO=extracorporeal membrane oxygenation.

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Government), and the European Commission, during the conduct of the study, and grants from Sanofi and Roche, unrelated to this Correspondence. MH reports grants from The Belgian Center for Knowledge and Fonds Erasme-COVID-ULB, during the conduct of the study, and personal fees from Gilead, unrelated to this Correspondence. CB reports personal fees from Da Volterra and Mylan Pharmaceuticals, unrelated to this Correspondence. All other authors declare no competing interests. This study received funding from the EU's Horizon 2020 Research and Innovation Programme, Austrian Group Medical Tumor, Belgian Health Care Knowledge Centre, Fonds Erasme-COVID-Université Libre de Bruxelles, Inserm REACTing network, the French Ministry of Health, Paris Ile-de-France Region, European Regional Development Fund, Portugal Ministry of Health, Portugal Agency for Clinical Research and Biomedical Innovation, European Union Commission, and Domaine d'intérêt majeur One Health Île-de-France. Remdesivir was provided by Gilead free of charge. FM and CB are joint last authors. Members of the DisCoVeRy Study Group are listed in the appendix.

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Is triple artemisinin-based combination therapy necessary for uncomplicated malaria?

We thank Chengchao Xu and colleagues[1] and Charlotte Rasmussen and Pascal Ringwald[2] for their interest in our studies[3,4] on triple antimalarial combination therapies (TACTs). TACTs are developed to counter the increasing problem of *Plasmodium falciparum* resistance to artemisinins and their partner drugs in artemisinin combination therapies (ACTs).

Xu and colleagues suggest that rotating ACTs with different partner drugs, adjusting the time course of artemisinin treatments, or exploring improved artemisinin derivatives would be better strategies to counter these resistance problems. Drug rotation is what has been happening already, albeit reactively, but it is operationally challenging. Experience from several countries in southeast Asia suggests that changing first-line antimalarial therapy often takes several years to implement, even when treatment failure rates have risen. Meanwhile, artemisinin resistance facilitates the emergence and selection of partner-drug resistance, jeopardising the small number of available ACT partner drugs. Combining the potent, but short-acting, artemisinin component with two slower, but longer-acting, matching partner drugs in TACTs provides mutual protection against resistance.[5] The alternative of prolonging the standard 3-day ACT course might improve treatment efficacy but for several ACTs this would require a shift to a second ACT halfway through the treatment course to avoid partner-drug accumulation and toxicity. This more complex treatment regimen would likely compromise treatment adherence. Unfortunately, improved artemisinin derivatives and other new antimalarial compounds are not expected within the next 5 years.

We agree that reducing adverse effects and increasing cost-effectiveness are essential in the development of TACTs. The expected longer therapeutic lifespan of TACTs compared with ACTs will also be a crucial element of this cost–benefit analysis.

Rasmussen and Ringwald state that well matched (triple) combinations might be the future of malaria treatment. Delaying antimalarial drug resistance with TACTs has become an increasingly relevant consideration with the emergence of artemisinin resistance in Africa.[6] Ideally, a triple combination would include only drugs that are individually curative, and without existing resistance. However, the current reality is a choice between a small number of available antimalarials. Artemether–lumefantrine–amodiaquine was studied because of the well matched pharmacokinetic profiles of the partner drugs and the in-vitro counteracting resistance mechanisms.[7] In addition, the combination has shown excellent safety and efficacy in areas of highly resistant falciparum malaria in the Greater Mekong subregion, in which the number of cases is falling but elimination has not yet been achieved.[4,5] Artemether–lumefantrine–amodiaquine is now being further evaluated in a large randomised trial in Africa and a fixed-dose combination is in development.

The Mahidol–Oxford Research Unit (MORU) has received funding for other studies of antimalarial treatment from Fosun Pharmaceuticals, which manufactures artemisinin combination therapies. We declare no other competing interests.

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See **Online** for appendix