Justification of substantial amendment for RECOVERY protocol V16.0

This document is a detailed justification for the changes to the RECOVERY protocol in version 16.0. The change number refers to the Amendment Tool change number included with this amendment.

Change 1: Addition of [SGLT-2i]

SGLT-2 (sodium-glucose co-transporter-2) inhibitors (SGLT-2i) have recognised benefits in treating chronic diseases such as type 2 diabetes mellitus, atherosclerotic cardiovascular disease in people with type 2 diabetes,[1-3] heart failure with reduced ejection fraction (in people with and without diabetes)[4,5] and chronic kidney disease.[6] They have been licensed since 2013 and are now widely recommended for these indications; there were over 200,000 prescriptions in England in March 2021 alone. In the large-scale trials of these agents, the benefits emerge very soon after randomisation. SGLT-2i also have rapid effects on metabolic, inflammatory and other pathways which may be of benefit in patients hospitalised with COVID-19, as described below.

SGLT-2i decrease glucose and insulin levels, and shift energy metabolism to an increased reliance on lipid oxidation, with a reduced reliance on glucose, and inhibition of glycolysis.[7] This mechanism may be particularly important in COVID-19, as SARS-CoV-2 may depend on the glycolytic pathway for its replication, stimulating lipogenesis, which appears to be one of the key drivers of cellular damage.[8,9] SGLT-2i rapidly improve endothelial function, possibly because of reduced oxidative stress.[10] SGLT-2i have significant anti-inflammatory effects, reducing levels of C-reactive protein and interleukin-6.[11] Experimental studies have also shown reduced activation of the NLRP3 inflammasome.[12] SGLT-2i increase erythropoiesis resulting in increased haematocrit,[13,14] and together with improved endothelial function[10] may improve oxygen delivery to tissues. Moreover, SGLT-2i result in reduced extracellular volume in patients with fluid overload,[15,16] and appear to reduce pulmonary artery pressure in patients with heart failure rapidly,[17] leading to haemodynamic decongestion. Thus, SGLT-2i may favourably affect multiple processes, including but not limited to energy metabolism, endothelial function, oxidative stress, inflammation and autophagy, which are dysregulated during a major acute illness such as COVID-19.

The DARE-19 trial compared dapagliflozin 10 mg with placebo for 30 days among 1250 patients admitted to hospital with COVID-19 who had mild hypoxia (SpO_2 ≥94% on ≤5 L/min oxygen) and at least one risk factor (hypertension, type 2 diabetes mellitus, atherosclerotic cardiovascular disease, heart failure or chronic kidney disease).[18] The treatment was well tolerated (11% discontinued prematurely with similar proportion in treatment and placebo group). The hazard ratio for the co-primary outcome of organ failure (non-invasive or invasive ventilation, requirement for cardiovascular support or new/worsened heart failure, doubling of creatinine or dialysis) or death was 0.80 (95% CI 0.58-1.10; 70 *vs* 86 events). The “win ratio” for recovery was non-significantly increased (1.09; 95% CI 0.97-1.22). Although this trial lacked statistical sensitivity, it supports the rationale for a larger trial.

Dose selection

The selected dose is 10 mg once daily for 28 days after randomisation (or stopped earlier if discharged before 28 days). This is the standard licensed dose of [SGLT-2i].

Participant population

It is possible that SGLT-2i will have benefits across the disease spectrum. Therefore, adult hospitalised patients will be eligible as long as their responsible clinician does not consider treatment with SGLT-2i to be absolutely indicated or absolutely contraindicated.

SGLT-2i are not considered to be safe in pregnancy so pregnant women will be excluded from this comparison. We do not plan to recruit children to this assessment.

Based on the mode of action there are no theoretical grounds to modify the dose in elderly patients, or those with hepatic impairment beyond those described below. SGLT-2i have been tested across a broad range of kidney function in the CREDENCE (canagliflozin), DAPA-CKD (dapagliflozin) and EMPA-KIDNEY (empagliflozin) trials. Eligibility criteria in these trials extend down to an eGFR of 20 ml/min/1.73m^2 and treatment is continued up to after the initiation of renal replacement therapy with no specific safety concerns identified.

Contraindications and cautions

Ketoacidosis

The main risk of SGLT-2i is ketoacidosis, with the largest excess risk observed in people with type 1 diabetes mellitus. Ketoacidosis does occur rarely in people with type 2 diabetes mellitus, usually when a superimposed illness occurs. In order to mitigate this risk we will:

- Exclude participants with type 1 diabetes from this comparison
- Recommend that participants with type 2 diabetes who cannot maintain oral calorific intake (e.g. those ventilated with supplemental enteral nutrition) discontinue SGLT-2i until oral intake is restored (when SGLT-2i can be restarted)
- Train study staff to be aware of "euglycaemic" ketoacidosis which may occur with SGLT-2i, so they have a low threshold for considering this diagnosis in participants taking SGLT-2i

Hypoglycaemia

SGLT-2i do not cause hypoglycaemia in isolation, but may do so in patients taking insulin or insulin secretogogues like sulphonylureas. Training materials for study staff will include advice to monitor sugar levels and temporarily reduce the dose or withdraw other medications accordingly. This risk exists for patients not taking SGLT-2i as well.

Volume depletion and acute kidney injury

SGLT-2i cause an osmotic diuresis which may cause volume depletion. All patients with COVID-19 require careful fluid balance assessment (not just to avoid dehydration but also because overhydration may contribute to worsening respiratory status), so this will be highlighted in the training materials.

Although acute kidney injury was initially thought to be an adverse effect of SGLT-2i, all of the large trials have demonstrated that SGLT-2i actually *reduce* the risk of acute kidney injury.

Urinary tract and genital infections

Urinary tract infections have been reported with SGLT-2i, but the large randomized trials have found similar rates in people allocated SGLT-2i as placebo. SGLT-2i do cause a clear excess of genital candidiasis, but this is unlikely to occur during the short-term therapy proposed in RECOVERY. If it does, such infections are easily treated with topical antifungals and may not require interruption of treatment. Fournier's gangrene is a very rare genital

infection and it is unclear whether SGLT-2i increase the risk or not, but this will be included in training materials so that investigators are alerted to the potential association.

Lower limb amputations

An increase in lower limb amputations (usually of the toe) was reported by one trial of canagliflozin, but this has not been replicated in other trials. This risk would be very low in RECOVERY due to the short duration of therapy.

Additional data to be collected

In order to assess these risks so they can be balanced with any benefits observed, the following additional data will be collected on the follow-up case report form.

- Ketoacidosis (if occurring in a participant allocated SGLT-2i this would also usually be reported as a suspected serious adverse reaction)
- Severe hypoglycaemia ie, hypoglycaemia associated with reduced conscious level requiring another person to recover
- Peak creatinine during admission: creatinine at baseline and information on the use of renal replacement therapy is already collected. In addition, the peak creatinine during the admission will be collected to assess in detail any effect on acute kidney injury.

Change 2: Removing REGN-COV2 from the protocol

The Trial Steering Committee reviewed the blinded data on the comparison of REGN-COV2 and decided to end recruitment on 22 May 2021. A sufficient number of participants have been recruited to provide good power to detect plausible risk reductions in both the seronegative subgroup and all trial participants. The updated Statistical Analysis Plan that will be used for these analyses was published on the trial website (https://www.recoverytrial.net/results) on 21 May 2021. The results were published online on 16 June 2021 (https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1).

Change 3: Removal of infliximab from the protocol

Since adding infliximab to the protocol in the last amendment, we now wish to remove it. No participants were recruited to this comparison. The reasons for removal are:

i. The costs of purchasing infliximab and supplying it to the international trial sites would have been prohibitive.
ii. Infliximab is very expensive outside the UK and therefore the results would be difficult to implement internationally.
iii. Some clinicians were concerned about the potential of infliximab to reactivate latent tuberculosis, so would have been reluctant to recruit participants to this comparison.
iv. Infliximab is now included in the international WHO SOLIDARITY trial protocol, so including in RECOVERY would have been unnecessary duplication.

This also means that the “Endemic infections” section of the protocol is no longer required as only infliximab required extra screening and monitoring.

Change 4: Addition of South Africa, India, Sri Lanka and Pakistan

We are establishing a collaboration with some sites in South Africa which will be coordinated by the University of Witwaterstrand, Johannesburg. We are also setting up sites in India (which will be coordinated by the Indian Council of Medical Research), and Sri Lanka and Pakistan

in collaboration with the Critical Care Asia network based at the National Intensive Care Surveillance centre, Colombo, Sri Lanka. The details of the South African coordinating centre were added to the protocol in V15.1 (which was approved by the sponsor but not submitted) to arrange insurance.

References

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015;373:2117-28.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644-57.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019;380:347-57.
4. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;383:1413-24.
5. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.
6. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020;383:1436-46.
7. Daniele G, Xiong J, Solis-Herrera C, et al. Dapagliflozin Enhances Fat Oxidation and Ketone Production in Patients With Type 2 Diabetes. Diabetes Care 2016;39:2036-41.
8. Codo AC, Davanzo GG, Monteiro LB, et al. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis. Cell Metab 2020;32:437-46.e5.
9. Icard P, Lincet H, Wu Z, et al. The key role of Warburg effect in SARS-CoV-2 replication and associated inflammatory response. Biochimie 2021;180:169-77.
10. Solini A, Giannini L, Seghieri M, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol 2017;16:138.
11. Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease. Diabetes & metabolism 2018;44:457-64.
12. Kim SR, Lee SG, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. Nat Commun 2020;11:2127.
13. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes, obesity & metabolism 2013;15:853-62.
14. Ghanim H, Abuaysheh S, Hejna J, et al. Dapagliflozin Suppresses Hepcidin And Increases Erythropoiesis. The Journal of clinical endocrinology and metabolism 2020;105.
15. Ohara K, Masuda T, Morinari M, et al. The extracellular volume status predicts body fluid response to SGLT2 inhibitor dapagliflozin in diabetic kidney disease. Diabetol Metab Syndr 2020;12:37.
16. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects. Circulation 2020;142:1028-39.
17. Mullens W, Martens P, Forouzan O, et al. Effects of dapagliflozin on congestion assessed by remote pulmonary artery pressure monitoring. ESC Heart Fail 2020;7:2071-3.
18. Kosiborod M, Berwanger O, Koch GG, et al. Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: Design and rationale for the DARE-19 study. Diabetes, obesity & metabolism 2021;23:886-96.