17 September 2020
EMA/509632/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Dexamethasone in hospitalised patients with COVID-19

Procedure number: EMEA/H/A-5(3)/1500

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure

On 22 June 2020 the results of the RECOVERY study on the use of dexamethasone in adult patients hospitalised with SARS-CoV-2 (or COVID-19, as is also referred as) were made available in a pre-print.[1] Subsequently the results were published on 17 July 2020 in The New England Journal of Medicine[2].

This study is one arm of the 'Randomised Evaluation of COVID-19 therapy' (RECOVERY) trial (www.recoverytrial.net) which is a randomised, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual standard of care in adult patients hospitalised with COVID-19. In this publication the preliminary results for the comparison of dexamethasone 6 mg once daily for up to ten days versus usual standard of care alone are reported. The primary outcome was 28-day mortality.

The results of the primary outcome showed that the control arm fatality rate was consistent with the fatality rate in the UK hospitals, which is over 26% in all hospitalised patients and over 37% in patients requiring invasive mechanical ventilation. Significantly fewer patients allocated to dexamethasone met the primary outcome of 28-day mortality than in the usual standard of care group (454 of 2104 patients [21.6%] allocated dexamethasone versus 1065 of 4321 patients [24.6%] allocated usual standard of care; age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.74 to 0.92; P<0.001).

At randomisation, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only, and 24% were receiving neither.

In one of the pre-specified subgroup analysis by level of respiratory support received at randomisation, there was a noteworthy trend showing potential benefit among those patients receiving invasive mechanical ventilation at randomisation (test for trend p<0.001). Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio [RR] 0.64 [95% CI 0.51 to 0.81]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002). However, there was no evidence of benefit among those patients who were not receiving respiratory support (rate ratio 1.22 [95% CI 0.93 to 1.61]; p=0.14).

For the secondary outcome, allocation to dexamethasone was associated with a shorter duration of hospitalisation than usual standard of care ("no additional treatment" arm) (median 12 days versus 13 days) and a greater probability of discharge within 28 days (rate ratio 1.11 [95% CI 1.04 to 1.19]; p=0.002) with the greatest effect seen among patients receiving invasive mechanical ventilation at baseline (test for trend p=0.002).

Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower among those allocated to dexamethasone (risk ratio 0.91 [95% 0.82 to 1.00]; p=0.049), but with significantly greater effects among patients receiving oxygen at randomisation (test for trend p=0.008).

In subsidiary clinical outcomes the risk of progression to invasive mechanical ventilation was lower among patients allocated to dexamethasone group versus usual standard of care group (risk ratio 0.76 [95% CI 0.61 to 0.96]; p=0.021).

[1] Horby P. et al, 2020; https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1 (doi: https://doi.org/10.1101/2020.06.22.20137273)
[2] Horby P. et al, 2020; https://www.nejm.org/doi/pdf/10.1056/NEJMoa2021436?articleTools=true (doi: 10.1056/NEJMoa2021436)

Preliminary analyses indicated no excess risk of any particular cause.

In summary, these preliminary results indicated a potential benefit of dexamethasone in adult hospitalised patients with COVID-19 receiving invasive mechanical ventilation or oxygen supplementation and in hospitalised patients with more than 7 days after symptom onset.

On 17 July 2020, the Executive Director triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and asked the CHMP to assess the impact and give a scientific opinion on potential clinical use of dexamethasone in the treatment of hospitalised adult patients with COVID-19, for oral and intravenous medicinal products.

2. Scientific discussion

2.1. Introduction

Corticosteroids are commonly used for treatment of a variety of inflammatory conditions. They can be used in the form of daily regimen or as a pulse therapy to treat flares of autoimmune diseases. However, caution in the use of corticosteroids is needed due to various well described serious adverse drug reactions (hypertension, weight gain, diabetes, glaucoma, cataract, fluid retention, psychiatric and psychological effects, osteoporosis). Glucocorticoids generally suppress the immune system and increase risk of infections. Corticosteroids have potent anti-inflammatory and antifibrotic properties, which theoretically could have a role in suppressing lung inflammation, particularly in the advanced stages of the COVID-19 infection. Low doses of corticosteroids downregulate pro-inflammatory cytokine transcription by consequently preventing an extended cytokine response and accelerating the resolution of pulmonary and systemic inflammation in pneumonia. Additionally, corticosteroids may help improve the dysregulated immune response caused by sepsis, a possible complication of COVID-19, and can increase blood pressure in hypotensive patients. However, the use of corticosteroids can inhibit immune response, reduce pathogen clearance, and provoke viral replication (Rizk et al, 2020).

Corticosteroids have been used in conditions closely related to COVID-19, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), severe influenza, community acquired pneumonia, acute respiratory distress syndrome (ARDS) or cytokine release syndrome (cytokine storm), due to their potent anti-inflammatory effect. Earlier studies have shown that corticosteroid use in patients with SARS, MERS, and influenza was associated with no survival benefit and possible harm. Patients with SARS receiving corticosteroids reported adverse events such as avascular necrosis, psychosis, diabetes, and delayed viral clearance. Influenza patients manifest a higher risk of mortality and secondary infections with corticosteroids. In MERS patients, corticosteroids delayed lower respiratory tract clearance of MERS-CoV, although no effect on mortality was reported. Clinicians should balance the potential adverse effects of corticosteroids with the potential effects of prolonged coronavirus shedding. The evidence to support or discourage the use of corticosteroids in these conditions has been controversial due to various reasons, among others the lack of sufficiently powered randomised controlled trials, heterogeneity of studied populations and insufficient recording of data regarding corticosteroid doses, medical conditions, and disease severity. Based on mechanism of action and course of severe viral infections (viral replication phase followed by immune system inflammatory response phase) it is likely that the beneficial effect of corticosteroids in these diseases is dependent on timing of treatment, severity of the condition (stage) and dose administered and potentially also on not well understood individual patient characteristics (e.g. genetics, age, gender). Consequently, treatment with corticosteroids may be more harmful than helpful due to immunosuppressive effect when treatment is given at a time of viral replication.

The effects of dexamethasone in (non-COVID-19) ARDS have been assessed in several studies.

A recent multicentre randomised clinical trial (DEXA-ARDS; Villar et al, 2016; Villar et al, 2020) included 277 patients with non-COVID-19 related moderate to severe ARDS. Patients were randomised to receive routine care or intravenous dexamethasone 20 mg once daily from day 1 to 5, followed by 10 mg once daily from day 6 to 10. Patients in both groups were also on mechanical ventilator support. Results showed that patients in the dexamethasone group had more ventilator-free days compared to the control group (difference 4.8 days; 95% CI, 2.57 to 7.03; p<0.0001) and lower all-cause 60-day mortality (21% versus 36%; difference -15.3%; 95% CI, -25.9 to -4.9; p=0.0047). The incidence of adverse events did not differ significantly between treatment groups. However, as there was substantial heterogeneity in terms of ARDS aetiology (~ 50% caused by pneumonia), generalisability of these results to COVID-19 patients with ARDS may be limited. In addition, the trial had strict inclusion and exclusion criteria, 73% of otherwise eligible patients were excluded because of pre-existing comorbidities.

The term "cytokine release syndrome" (CRS) or "cytokine storm" has been used to describe the state of hyperinflammation characterised by elevated inflammatory biomarkers including e.g. CRP, IL-1, IL-6, ferritin, in patients who developed most severe respiratory failure in COVID-19 course. CRS has been described as complication of various autoimmune conditions, infections and malignancies. It is also part of inherited primary haemophagocytic lymphohistiocytosis. RoActemra (tocilizumab), IL-6 inhibitor, is indicated for treatment of CSR in the context of treatment of malignancies using CAR-T cells. Treatments supressing hyperinflammation including anti-cytokines and corticosteroids are therefore in development for patients with COVID-19.

In the absence of reliable evidence from large-scale randomised clinical trials, there was great uncertainty about the effectiveness of corticosteroids in COVID-19. Prior to RECOVERY, many COVID-19 treatment guidelines stated that corticosteroids were either contraindicated or not recommended. Guidelines issued by the WHO, National Institutes of Health (NIH, USA), European Society of Intensive Care Medicine, the Society of Critical Care Medicine (ESICM/SCCM) and the National Centre for Infectious Diseases (NCID, Singapore) did not recommend the routine use of systemic corticosteroids for COVID-19 unless patients were in refractory shock or were previously on chronic corticosteroid therapy prior to COVID-19 diagnosis. For mechanically ventilated patients with COVID-19 and ARDS, before RECOVERY trial publication NIH guidelines did not provide recommendation on the matter while ESICM/SCCM guidelines suggested that corticosteroids may be used.

However, China did recommend corticosteroids for severe cases, many clinical centres worldwide used corticosteroids in their standard protocols and number of clinical trials allowed or even demanded using corticosteroids as concomitant treatment. Practice has varied widely across the world: in some countries, as many as 50% or even more patients were treated with corticosteroids.

2.2. Clinical aspects

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY, www.recoverytrial.net) is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

The trial was conducted at 176 National Health Service (NHS) hospital organizations in the United Kingdom. Around 15% of all UK hospitalised patients with COVID-19 were enrolled in the trial.

Rationale

In early 2020, as the protocol was being developed, there were no approved treatments for COVID-19. The aim of the trial was to provide reliable evidence on the efficacy of candidate therapies (including

re-purposed and novel drugs) for suspected or confirmed COVID-19 infection on major outcomes in hospitalised adult patients receiving standard care.

Trial design

This is a multi-centre, multi-arm, adaptive, open-label, randomised controlled trial with three possible stages of randomisation. In the main randomisation (Part A) patients are allocated to no additional treatment or one of 4 anti-viral or host-directed treatments.

These included:

- Lopinavir 400mg-Ritonavir 100mg by mouth (or nasogastric tube) every 12 hours for 10 days.
- Corticosteroid in the form of dexamethasone, administered as an oral liquid or intravenous preparation 6 mg once daily for 10 days. In pregnancy, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead.
- Hydroxychloroquine by mouth for 10 days (4 doses in first 24 hours and 1 dose every 12 hours for 9 days).
- Azithromycin 500mg by mouth (or nasogastric tube) or intravenously once daily for a total of 10 days.

In addition, in a factorial design, eligible patients could also be randomly allocated simultaneously to no additional treatment or convalescent plasma (Part B).

Patients who deteriorate according to predefined criteria could be further randomised (second randomisation) to no additional treatment or an immunomodulatory treatment (tocilizumab).

The trial was designed with a streamlined process in order to facilitate rapid large-scale recruitment with minimal data collection.

i. Trial Objectives and outcomes

Primary objective

To provide reliable estimates of the effect of study treatments on all-cause mortality within 28 days of randomisation.

Secondary objectives

To investigate the effect of study treatments on the duration of hospital stay, the need for (and duration of) ventilation, and the need for renal replacement therapy.

Primary outcome

Mortality (all-cause)

Secondary clinical outcomes

- Time to discharge from hospital
- Use of mechanical ventilation/Extra Corporal Membrane Oxygenation (ECMO) or death (among patients not on ventilation or ECMO at baseline)

Subsidiary clinical outcomes

- Cause-specific mortality (COVID-19; cardiovascular; non-vascular; other)
- Use of renal dialysis or haemofiltration

- Serious cardiac arrhythmia (recorded in a subset)
- Use of ventilation (overall and by type)
- Duration of ventilation (overall and by type)

ii. Patient population

Inclusion criteria

Patients are eligible for the trial (Main randomisation) if all of the following are true:

- Hospitalised
- SARS-CoV-2 infection (clinically suspected or laboratory confirmed)
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.

Inclusion criteria for the second randomisation

Patients had to meet the following criteria:

- Randomised into the main RECOVERY trial no more than 21 days ago
- Clinical evidence of progressive COVID-19:

  - oxygen saturation <92% on room air or requiring oxygen (or in children, significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement); and

  - C-reactive protein (CRP) ≥75 mg/L
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in this aspect of the RECOVERY trial.

Exclusion criteria

If one or more of the active drug treatments was not available at the hospital or was believed by the attending clinician to be contraindicated (or definitely indicated) for the specific patient, then this fact was recorded via the web-based form prior to randomisation; random allocation was then between the remaining (or indicated) arms.

Blinding

This is an open-label study. However, while the study was in progress, access to tabular results of study outcomes by treatment allocation was not available to the research team, clinical investigators, trial statisticians, clinical teams, or members of the Steering Committee (SC) (unless the Data monitoring committee (DMC) advises otherwise). The DMC and DMC statisticians were unblinded.

Randomisation

Eligible patients were randomised using a 24/7 secure central web-based randomisation system, developed and hosted within Nuffield Department of Population Health (NDPH), University of Oxford. Users of the system had no insight into the next allocation, given that simple randomisation was used. In the event that a patient was randomised inadvertently more than once during the same hospital admission, the first allocation was used.

The implementation of the randomisation procedure was monitored by the Senior Trials Programmer, and the Steering Committee (SC) notified if an error in the randomisation process was identified.

The CHMP noted that while there was a centralised randomisation procedure and users did not have any insight to the next allocation, it is unclear whether any treating physicians changed the allocated treatment for any of their patients following randomisation, whether there was any procedure in place to identify this and how this was accounted for in the analysis.

Randomisation was not stratified by hospital site or any adjustment for imbalances per hospital site, including adjustment for clustering within sites, in the initial analysis.

Following additional information provided by the investigators, these issues do not appear that would alter the overall findings.

iii. Main randomisation (part A)

Simple randomisation was used with a 2:1:1:1:1 allocation ratio to one of the following treatment arms (in addition to usual care), which is subject to change:
No additional treatment; Lopinavir-Ritonavir; Corticosteroid; Hydroxychloroquine; Azithromycin

The randomisation programme allocated patients in a ratio of 2:1 between the 'no additional treatment' arm and each of the other arms that are not contra-indicated and available. Hence if all 4 active treatment arms were available, then the randomisation was in the ratio 2:1:1:1:1. If one or more of the active drug treatments was not available at the hospital or was believed by the attending clinician to be contraindicated for the specific patient, then this fact was recorded via the web-based form prior to randomisation; random allocation was then between the remaining arms (in a 2:1:1:1, 2:1:1 or 2:1 ratio).

The CHMP noted that data on route of administration (oral or intravenous) and formulation (tablet or liquid) were not recorded. However, it is likely that the majority of patients on mechanical ventilation received intravenous (IV) dexamethasone compared to those patients who were receiving oxygen only.

It is also not entirely clear how the dose of 6 mg was decided as a sufficient dose as well as the treatment duration of 10 days.

In the study, the physicians were free to choose the use of the drug both *per os* (PO) or IV. The route of administration was not recorded in the study documentation. While in patients with mechanical ventilation the expected route of administration was intravenous, on the contrary it was probably the oral route in patients who did not require oxygen or were not subject to mechanical ventilation. Given the bioavailability of oral dexamethasone has been reported to be between 70% and 78%, it appears that those taking dexamethasone in tablets could be sub-optimally treated. Moreover, it was shown by Spoorenberg and colleagues (2013) that the AUC of 6 mg oral dexamethasone did not differ significantly from the AUC of 4 mg intravenous dexamethasone in patients hospitalized with pneumonia. Therefore, it cannot be excluded that a higher dose of dexamethasone should be administered orally, however a beneficial effect was demonstrated in patients receiving oxygen only (i.e. not mechanically ventilated) with dexamethasone, where it is likely a majority would have received oral therapy.

<u>Second randomisation for patients with progressive COVID-19</u>

Eligible participants could be randomised using simple randomisation with an allocation ratio 1:1 between the following arms, of either no additional treatment or tocilizumab.

<u>Data collection schedule</u>

Baseline and outcome information will be collected on trial-specific electronic case report forms (eCRFs) and entered into a web-based IT system by a member of the hospital or research staff. Follow-up information was collected on all study participants, irrespective of whether or not they

complete the scheduled course of allocated study treatment. Follow-up information through was sought by various means, including routine healthcare systems and registries.

All randomised participants were followed up until death or 6 months post-randomisation to the main trial (whichever is sooner). NHS Digital and equivalent organisations in the devolved nations had supply data fields relevant to trial baseline and outcome measures to NDPH, University of Oxford on a regular basis, for participants enrolled into the trial. This was combined with the trial-specific data collected via the web-based IT system and adjudicated internally.

Longer term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

Data monitoring

During the study all study data were supplied in strict confidence to the independent DMC for independent assessment and evaluation. The DMC requested such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC was requested to determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (the mortality effect was greater than 3.5 Standard deviations between the randomised groups to affect national and global treatment strategies. Hence, multiple reviews by the Data Monitoring Committee have no material impact on the final analysis. There is a slight increase in the type I error from multiple looks at the data. This was quantified as spending 0.06% of the alpha. In such a circumstance, the DMC will inform the SC who will make the results available to the public and amend the trial arms accordingly.

Trial reporting

The trial was reported according to the principles of the CONSORT statements. The exact composition of the trial publication(s) depends on the size of the epidemic, the availability of drugs, and the findings from the various pairwise comparative analyses (with the 'no additional treatment' arm) in the main trial.

Baseline comparability of randomised groups

The protocol stated that baseline characteristics would be described separately for patients randomised to each main comparison (for each separate pairwise comparison of active treatment with the 'no additional treatment' arm), and separately for the first and second randomisation.

iv. Main randomisation (part A and B)

Age at randomisation; Sex; Ethnicity; Time since COVID-19 symptoms onset; Time since hospitalisation; Current respiratory support requirement; Currently requiring renal dialysis or haemofiltration; Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment); If female, known to be pregnant

Second randomisation

In addition to the above:

Type of ventilation support currently required (none, CPAP alone, non-invasive ventilation, high-flow nasal oxygen, mechanical ventilation, ECMO); Latest oxygen saturation measurement (%); Latest CRP measurement (mg/L); Latest ferritin measurement (ng/mL); Latest creatinine measurement (µmol/L); Allocation in first randomisation; Interval between first and second randomisation;

The number and percentage were presented for binary and categorical variables. The mean and standard deviation or the median and the interquartile range were presented for continuous variables, or the range if appropriate.

Completeness of follow-up

All reasonable efforts were taken to minimise loss to follow-up, which was expected to be minimal as data collection for primary and secondary outcomes using trial-specific eCRFs is combined with linkage to routine clinical data on study outcomes from NHS Digital, ICNARC, and similar organisations in the devolved nations.

The number and percentage of participants with follow-up information at day 28 and at 6 months after the main randomisation were reported. Data was shown for each of the following: all-cause mortality, hospital discharge status, ventilation status, and was shown for each randomised group for the main and second randomisation separately.

v. Statistical Methodology

Sample size

The larger the number randomised, the more accurate the results are, but the numbers that can be randomised depends critically on the epidemic dynamic. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with moderate disease and a few thousand with severe disease. Some indicative sample sizes and projected recruitment were estimated using emerging data for several different scenarios. Sample size and recruitment were monitored by the Steering Committee (SC) throughout the trial.

Population definitions

The intention to treat (ITT) population was all participants randomised, irrespective of treatment received. This ITT population was used for analysis of efficacy and safety data.

For interim analyses, baseline data was reported for all participants with data available and outcome data was reported for all participants who have died, been discharged from hospital, or reached day 28 after the first randomisation.

Adherence to treatment

The number and proportion of patients who did not receive the treatment they were allocated to were reported. If any other trial treatment options were known to be received, instead of or in addition to, the allocated treatment during the 28-day follow-up period after the first randomisation, these were collected and reported. Details on the number of days (or doses) of treatment received were reported for all trial treatments received where available.

Comparative analyses

For all outcomes, the primary analysis was performed on the intention to treat (ITT) population at 28 days after the main randomisation. An ITT analysis of all outcomes at 6 months post-randomisation was also conducted.

Pairwise comparisons was made between each treatment arm and the 'no additional treatment' arm (reference group) in that particular randomisation (main randomisation part A, main randomisation part B and second randomisation). Since not all treatments may be available or suitable for all patients, those in the 'no additional treatment' arm would only be included in a given comparison if, at the point of their randomisation, they could alternatively have been randomised to the active treatment of interest (i.e. the active treatment was available at the time and it was not contra-

indicated). The same applied to treatment arms added at a later stage; they would only be compared to those patients recruited concurrently.

Main randomisation (part A)

Primary outcome

Mortality (all-cause) was summarised with counts and percentages by randomised comparison group. A time-to-event analysis was conducted using the log-rank test, with the p-value reported. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) was used to estimate the average event rate ratio and confidence interval for each treatment group versus the no additional treatment group. For the primary outcome, discharge alive before the relevant time period (28 days) was assumed as absence of the event (unless there is additional data confirming otherwise).

Secondary outcomes

Time to discharge from hospital

A time-to-event analysis was used to compare each treatment group with the no additional treatment group using Kaplan-Meier and the log-rank test, as described. Patients who die in hospital will be censored after 28 days. This would give an unbiased estimate of the recovery rate and comparable estimates to the competing risks approach in the absence of other censoring (which is expected to be very minimal).

Use of mechanical ventilation/ECMO or death (among those not on ventilation or ECMO at randomisation)

Counts and percentages were presented by randomised group and the risk ratio was calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference was also presented with confidence intervals. Each component of this composite outcome was also summarised. Patients who were already on ventilation or ECMO at randomisation would be excluded from the denominator.

Subsidiary clinical outcomes

Cause-specific mortality

Cause-specific mortality was analysed in a similar manner to the primary outcome. Deaths from other causes were censored at the date of death and a separate survival curve was presented for each cause of death (COVID-19, other infection, cardiovascular, and other).

Use of renal dialysis or haemofiltration

Counts and percentages were presented by randomised group and the risk ratio would be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference was presented with confidence intervals. Patients who were already on renal dialysis or haemofiltration at randomisation were excluded from the denominator.

Major cardiac arrhythmia

Counts and percentages were presented by randomised group and the risk ratio for any major cardiac arrhythmia was calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference was also presented with confidence intervals. Types of arrhythmia were also described: (i) atrial flutter or fibrillation; (ii)

supraventricular tachycardia; (iii) ventricular tachycardia; (iv) ventricular fibrillation; (v) atrioventricular block requiring intervention, with subtotals for (i)-(ii) and (iii)-(iv).

Use of ventilation (overall and by type)

Counts and percentages were presented by randomised group for patients who received any assisted ventilation. Patients who were already on assisted ventilation or required oxygen (as this includes people on continuous positive airway pressure (CPAP), other non-invasive ventilation and high-flow nasal oxygen) at randomisation will be excluded from the denominator. The number of patients receiving the different types of ventilation will also be reported: non-invasive ventilation (i.e. CPAP, other non-invasive ventilation or high-flow nasal oxygen), and invasive mechanical ventilation (i.e. invasive mechanical ventilation or ECMO).

Duration of ventilation (overall and by type)

The mean (SD) duration of ventilation will be calculated in days from the main randomisation for each randomised group in those who received ventilation, separately for survivors and non-survivors. This was reported overall for any assisted ventilation and separately for mechanical ventilation or ECMO. The mean difference and confidence intervals will be presented for each pairwise comparison with the no additional treatment arm.

Second randomisation

Evaluation of treatment effects in the main randomisation and the second randomisation was conducted independently. In addition to the overall comparison for Tocilizumab versus no additional treatment, results were stratified according to allocation in the main randomisation (part A and part B), however no interaction tests were performed between the allocations in the two stages.

Pre-specified subgroup analyses

Pre-specified subgroup analyses were conducted for the main randomisation (part A and part B) and the second randomisation, for the following outcomes:

(i) Mortality (all-cause); (ii) Time to discharge from hospital; (iii) Use of mechanical ventilation/ECMO or death.

The analyses were conducted using a test for heterogeneity (or test for trend for 3 or more ordered groups). Results were presented on forest plots as event rate ratios, or risk ratios with confidence intervals. The following subgroups were examined:

- Risk group (three risk groups with approximately equal number of deaths based on factors recorded at randomisation)
- Requirement for respiratory support at randomisation (None; Oxygen only; Ventilation or ECMO)
- Time since illness onset (≤7 days; >7 days)
- Age (<70; 70-79; 80+ years)
- Sex (Male; Female)
- Ethnicity (White; Black, Asian or Minority Ethnic)

Additional analyses would set the results for children (<18 years) and pregnant women in the context of the overall results.

Adjustment for baseline characteristics

The main analyses described above were unadjusted for baseline characteristics. However, in the event that there were any important imbalances between the randomised groups in key baseline subgroups, emphasis was placed on analyses that were adjusted for the relevant baseline characteristic(s). This was done through the use of Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios.

Significance levels and adjustment of p-values for multiplicity

Evaluation of the primary trial (main randomisation) and secondary randomisation was conducted independently, and no adjustment was made for these. Formal adjustment was not made for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses. 95% confidence intervals (CI) were presented for the main comparisons.

Statistical software employed

The statistical software SAS version 9.4, R Studio 3.6.2 and Stata/SE version 15 (or later) for Windows was used for the interim and final analyses.

Data standards and coding terminology

Datasets for analysis was prepared using Clinical Data Interchange Standards Consortium (CDISC) standards for Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM). Wherever possible, clinical outcomes (which may be obtained in a variety of standards, including ICD10 and OPCS-4) will be coded using MedDRA version 20.1.

Differences from Protocol V6.0

Use and duration of ventilation were described as secondary objectives in the protocol, and listed as subsidiary outcomes in the statistical analysis plan. The testing of multiple treatment arms was not formally adjusted for, but given the number of comparisons, due allowance was made in their interpretation. Formal methods of adjustment for multiplicity were not adopted because of treatment arms being added over time (including the factorial convalescent plasma comparison), unequal recruitment into each arm, and the ultimate number of treatments under evaluation not known in advance. While methods for these situations exist, it was felt that the resulting change in level of significance was not appropriate.

The CHMP noted the changes to the protocol. There were also changes made to the statistical analysis plan after the dexamethasone part of the study finished (date of last SAP 21st June 2020). This would not be standard best practice; however, these were unusual circumstances in the rapid establishment of the trial during a pandemic. The CHMP is of the view that results from the trial can still be relied upon.

According to the CHMP the lack of adjustment for multiplicity was a limitation of the trial, however, this was taken into account in any interpretation of results from the multiple comparisons made.

2.3. Data on efficacy

Data on efficacy was provided in the publication from the Recovery collaborative group (Horby et al, 2020).

Of the 11303 patients who underwent randomisation from 19 March to 8 June 2020, a total of 9355 patients (83%) were eligible to receive dexamethasone (i.e. the drug was available in the hospital at the time and the patient had no known indication for or contraindication to dexamethasone). Of these patients, 6425 underwent randomization to receive either dexamethasone (2104 patients) or usual care alone (4321 patients).

Baseline demographics

The mean (+/-SD) age of the patients in this comparison was 66.1+/- 15.7 years, and 36% of the patients were female. A history of diabetes was present in 24% of the patients, heart disease in 27%, and chronic lung disease in 21%, with 56% having at least one major coexisting illness recorded. In this analysis, 89% of the patients had laboratory-confirmed SARS-CoV-2 infection, and 0.4% were currently awaiting the result. Overall, there were 15% of patients without polymerase chain reaction (PCR) confirmation.

At randomisation, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.

Follow-up information for the primary outcome was complete for 6418 patients (99.9%) who had undergone randomization. In the dexamethasone group, 95% of the patients received at least one dose of the medicinal product (Table 1). The median duration of treatment was 7 days (interquartile range, 3 to 10). In the usual care group, 8% of the patients received dexamethasone as part of their clinical care. The use of azithromycin during the follow-up period was similar in the dexamethasone group and the usual care group (24% versus 25%), and 0 to 3% of patients received hydroxychloroquine, lopinavir/ritonavir, or interleukin-6 (IL-6) antagonists during follow-up.

Table 1. Treatments given, by randomized allocation

(Source: Horby et al, 2020)

	Treatment allocation	
	Dexamethasone (n=2104)	**Usual care (n=4321)**
Follow-up forms received	2079	4278
Treatments given		
Dexamethasone	1975 (95%)	336 (8%)
Lopinavir/ritonavir	2 (<0.5%)	4 (<0.5%)
Hydroxychloroquine	17 (1%)	22 (1%)
Azithromycin	499 (24%)	1082 (25%)
Tocilizumab or sarilumab	43 (2%)	128 (3%)
Not recorded	7 (<0.5%)	12 (<0.5%)

Percentages are of those with a completed follow-up form. Among patients allocated dexamethasone, it was taken for a median of 7 days [IQR 3-10 days].

After remdesivir became available in the United Kingdom on May 26, 2020, remdesivir was administered to 3 patients in the dexamethasone group and 2 patients in the usual care group.

The investigators were asked to clarify the number of patients receiving concomitant therapy and were included in the ITT analysis and provide the outcomes. They clarified that the subgroup of patients who underwent a second randomization to tocilizumab versus usual care included 95 of 2104 patients (4.5%) in the dexamethasone group and 276 of 4321 patients (6.4%) in the usual care group. In addition, 13 patients were randomly assigned to receive either convalescent plasma or usual care alone. Because these other drugs were given post-randomisation, analyses of the effects of allocation to dexamethasone in the three respiratory support groups adjusted for (or matched by) use of these other drugs is not recommended.

Table 2. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support. (Source: Horby et al, 2020)

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female†	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

Table 3. Baseline characteristics by randomized allocation, separately among those not receiving oxygen at randomization, those receiving oxygen only, and those on invasive mechanical ventilation. (Source: Horby et al, 2020)

	No oxygen received		Oxygen only		Invasive mechanical ventilation	
	Dexamethasone (n=501)	Usual care (n=1034)	Dexamethasone (n=1279)	Usual care (n=2604)	Dexamethasone (n=324)	Usual care (n=683)
Age, years	71.1 (16.3)	68.5 (18.0)	67.2 (15.2)	66.4 (15.3)	58.8 (11.3)	59.2 (11.5)
<70	197 (39%)	462 (45%)	675 (53%)	1473 (57%)	269 (83%)	569 (83%)
≥70 to <80	114 (23%)	224 (22%)	306 (24%)	531 (20%)	49 (15%)	104 (15%)
≥80	190 (38%)	348 (34%)	298 (23%)	600 (23%)	6 (2%)	10 (1%)
Sex						
Male	286 (57%)	605 (59%)	819 (64%)	1643 (63%)	233 (72%)	501 (73%)
Female*	215 (43%)	429 (41%)	460 (36%)	961 (37%)	91 (28%)	182 (27%)
Number of days since symptom onset	6 (3-10)	7 (3-10)	8 (5-13)	9 (5-12)	13 (9-18)	13 (8-18)
Number of days since hospitalization	2 (1-6)	2 (1-5)	2 (1-4)	2 (1-4)	5 (3-10)	5 (3-9)
Previous diseases						
Diabetes	119 (24%)	223 (22%)	320 (25%)	630 (24%)	82 (25%)	172 (25%)
Heart disease	180 (36%)	339 (33%)	357 (28%)	717 (28%)	49 (15%)	115 (17%)
Chronic lung disease	121 (24%)	230 (22%)	259 (20%)	624 (24%)	35 (11%)	77 (11%)
Tuberculosis	2 (<0.5%)	6 (1%)	1 (<0.5%)	10 (<0.5%)	3 (1%)	3 (<0.5%)
HIV	2 (<0.5%)	3 (<0.5%)	9 (1%)	12 (<0.5%)	1 (<0.5%)	5 (1%)
Severe liver disease	13 (3%)	19 (2%)	20 (2%)	52 (2%)	4 (1%)	11 (2%)
Severe kidney impairment	28 (6%)	91 (9%)	85 (7%)	168 (6%)	53 (16%)	99 (14%)
Any of the above	313 (62%)	598 (58%)	702 (55%)	1473 (57%)	159 (49%)	346 (51%)
SARS-Cov-2 test result						
Positive	425 (85%)	908 (88%)	1123 (88%)	2293 (88%)	302 (93%)	647 (95%)
Negative	74 (15%)	119 (12%)	152 (12%)	300 (12%)	21 (6%)	34 (5%)
Test result not yet known	2 (<0.5%)	7 (1%)	4 (<0.5%)	11 (<0.5%)	1 (<0.5%)	2 (<0.5%)

The CHMP noted that there was no stratification of randomisation in this study. However, overall the treatment assignment between dexamethasone and usual care was relatively balanced between both cohorts (i.e. dexamethasone and standard of care).

The baseline patient characteristics for respiratory support received at randomisation showed a lower mean age of 59.1+/- 11.4 years compared to those who did not receive oxygen or oxygen only at baseline (69.4 +/- 17.5 years and 66.7 +/-15.3 years respectively). This results in a much higher percentage of patients <70 years (83%) in the mechanically ventilated group compared to the other 2 cohorts (no oxygen 43% and oxygen only 55%).

Reviewing the baseline in previous coexisting disease, patients receiving invasive mechanical ventilation had lower heart disease (16%) and chronic lung disease (11%), compared to the other two cohorts, of no oxygen and oxygen alone, and standard of care group, which had 27% heart disease and 22% chronic lung disease. There does not appear to be any standardised criteria across the hospital sites regarding the allocation to mechanical ventilation as hospital practices may vary and may have had a small impact on the findings. Nevertheless, the above shows that 16 patients received invasive mechanical ventilation (6 dexamethasone and 10 usual care) and were aged over 80 years.

In a supplemental analyses provided by investigators regarding baseline characteristics comparing each cohort on level of respiratory support at baseline, the groups appeared to be well balanced in terms of age, gender, days since symptoms commenced or days in hospital. Furthermore, baseline previous disease status also appears to be balanced between the cohorts.

There is no information on the severity of illness/disease and how this is comparable across the groups. This variable is probably confounded by whether the patients had oxygen or mechanical ventilation. It was further clarified by the investigators that data on oxygen saturation at time of randomisation was not collected. The investigators provided information from practice guidelines on the optimal use of Oxygen therapy during the coronavirus pandemic in UK[3] on the prescription of oxygen to patients hospitalised with COVID-19 which states *"Oxygen prescribing targets for all adults treated in NHS hospitals should be adjusted from the current range (of oxygen saturation 94% - 98%) to oxygen saturation 92% - 96% in the first instance."* Assuming these guidelines were followed, oxygen would have been prescribed to patients with oxygen saturation <92% on air.

Patients analysed

Follow-up information for the primary outcome was complete for 6418 patients (99.9%) who had undergone randomization. In the dexamethasone group, 95% of the patients received at least one dose of the drug (Figure 1, below). The median duration of treatment was 7 days (interquartile range, 3 to 10). In the usual care group, 8% of the patients received dexamethasone as part of their clinical care. The use of azithromycin during the follow-up period was similar in the dexamethasone group and the usual care group (24% versus 25%), and 0 to 3% of patients received hydroxychloroquine, lopinavir ritonavir, or interleukin-6 antagonists during follow-up.

Figure 1. Enrolment, randomisation, and inclusion in the Primary analysis
(Source: Horby et al, 2020)

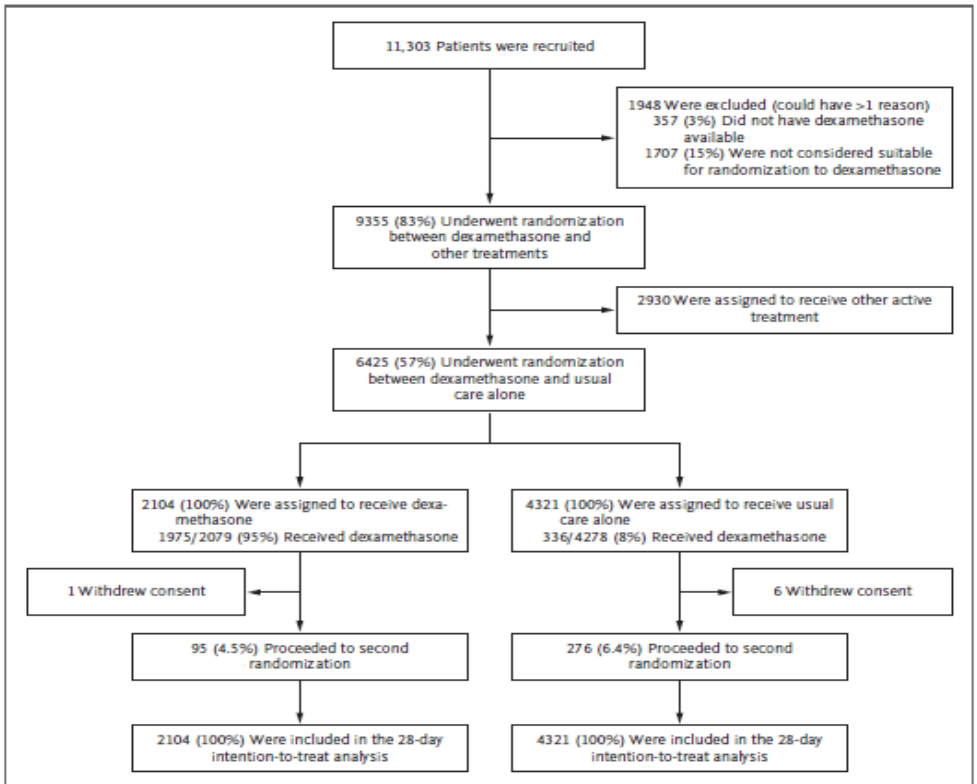


Figure 1. Enrollment, Randomization, and Inclusion in the Primary Analysis.
At the time of this analysis, completed follow-up forms were available for 2079 of 2104 patients (98.8%) in the dexamethasone group and 4278 of 4321 patients (99.0%) in the usual care group. The subgroup of patients who later underwent a second randomization to tocilizumab versus usual care in the RECOVERY trial included 95 of 2104 patients (4.5%) in the dexamethasone group and 276 of 4321 patients (6.4%) in the usual care group. In addition, 13 patients were randomly assigned to receive either convalescent plasma or usual care alone.

[3] https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0256-specialty-guide-oxygen-therapy-and-coronavirus-9-april-2020.pdf

Regarding the statistical assessment the CHMP noted that the trial has many strengths, primary amongst those is the randomisation and the hard endpoint of mortality. Such an endpoint could likely ameliorate the lack of blinding. The trial randomised a large number of patients, which crucially provides a substantial number of both subjects and cases in important subgroups that allow further assessment of the data.

It is also remarkable how the study data combined the limited clinical data collected at each site with data from national healthcare databases.

Methodological concerns

Trial conduct

The Statistical Analysis Plan (SAP) was finalised on 21 June 2020. Results from the study were reported online on 23 June 2020. It is unclear when the trial statisticians were unblinded to the results, but the SAP states the following were changed after unblinding:

- Additional clarification of ventilation denominators.
- Adjustment for any imbalances of subgroup characteristics between treatment arms at randomisation.
- Clarification of analysis of composite outcome. Removal of 'Unknown' ethnicity subgroup.
- Addition of section on Adjustment for baseline characteristics.

The CHMP noted that there was no concern with the randomisation - no imbalance was observed between treatment arms. It is noted that the data presented for the number of days since onset (as a continuous number) is different from that specified in the SAP (<7, >=7). It seems clear the SAP was finalised after the study was unblinded to the trial statisticians. Under usual circumstances this would be a serious breach of regulatory expectations and render the results from the study untrustworthy. But this issue has to be interpreted in the light of the unusual circumstances and the CHMP considered that the results can still be relied upon.

Pre-Specified Analysis

According to the protocol, the primary objective was to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after first randomisation

The secondary objectives were to assess the effects of study treatments on duration of hospital stay; the need for (and duration of) ventilation; and, among patients not on ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO.

According to the SAP, the secondary objectives are to investigate the effect of study treatments on the duration of hospital stay, the need for (and duration of) ventilation, and the need for renal replacement therapy.

For the CHMP it is unclear how and when the secondary endpoints changed, and whether the definitions given in the SAP changed after the blind had been broken. There appears to be no pre-specified approach to control for type I error in testing of the secondary outcomes, no account for the change in outcomes, and no findings reported on the effect of dexamethasone on renal replacement therapy included in the documentation provided. Therefore, the results of the secondary analyses need to be treated with caution and may not meet the usual standard of robustness.

The results of the primary analysis are statistically significant at the 5% level.

It was clarified that the data monitoring committee (DMC) in the trial had determined that in order to consider stopping a treatment early for benefit would require at least a 3 to 3.5 standard error reduction in mortality. The DMC concluded that examinations of the data at every 10% (or even 5%) of the total data would lead to only a marginal increase in the overall type I error rate.

The CHMP noted that the interim analyses spent 0.06% of the alpha for testing which leaves an alpha of 0.0494 (or 4.94%) preserved for testing. However, alpha=0.05 was used in the final results, so no adjustment was made for the multiple interim analyses.

In addition, the investigators did not adjust for multiplicity in the study, between treatment arms or for the endpoints. While this is unlikely to have any effect on the overall primary endpoint for mortality, it may be a more significant issue for comparisons between dexamethasone and usual care for the secondary endpoints.

It is noted that the secondary outcomes presented are also statistically significant at the 5% level. It is of note that not all of the pre-specified analyses in both the SAP and the Protocol (which as noted, differ) have been presented.

Subgroup Analysis

The protocol stated that pre-specified subgroup analysis (e.g. disease severity; time since onset of symptoms; sex; age group) were conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate). Further details were fully described in the Statistical Analysis Plan (SAP) published (www.recoverytrial.net).

2.4. Results on efficacy

Primary Outcome

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001)

Table 4. Primary and Secondary Outcomes

(Source: Horby et al, 2020)

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

In a pre-specified analysis according to the level of respiratory support that the patients were receiving at randomisation, there was a trend showing the greatest absolute and proportional benefit among

patients who were receiving invasive mechanical ventilation (see Figure 2 below; 11.5 by chi square test for trend).

Figure 2. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory support at Randomisation. (Source: Horby et al, 2020)

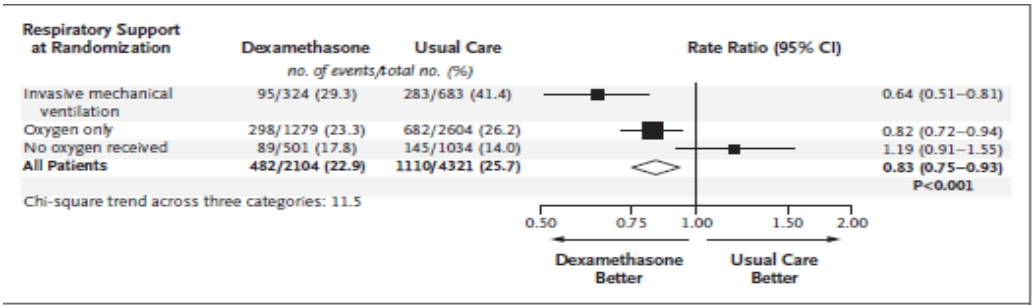


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.
Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% versus 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving oxygen without invasive mechanical ventilation (23.3% versus 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94).

There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% versus 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

The results were similar in a post-hoc exploratory analysis restricted to the 5698 patients (89%) with a positive SARS-CoV-2 test result. Likewise, sensitivity analyses without adjustment for age resulted in similar findings.

Figure 3. Mortality at 28 Days in All patients and According to Respiratory support at Randomisation. (Source: Horby et al, 2020)

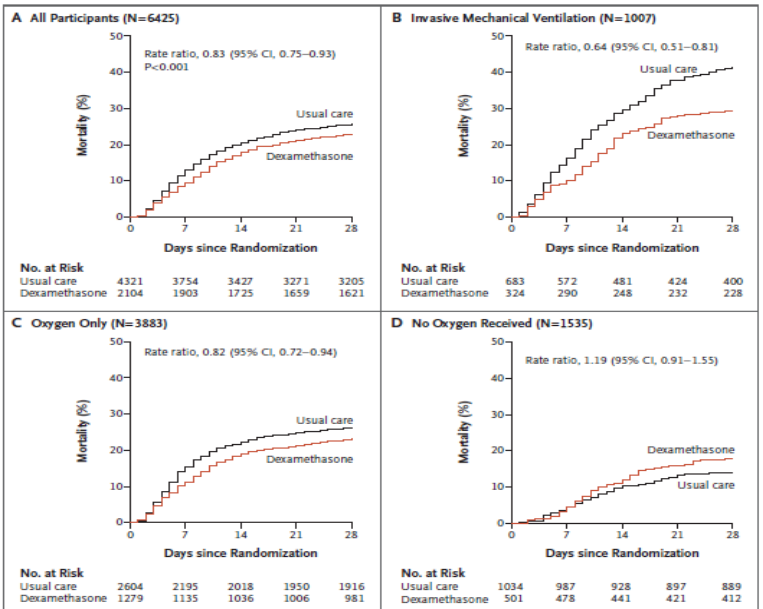


Figure 2. **Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.**
Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

The CHMP noted that there is a clear benefit on the primary endpoint – 28-day mortality - after administration of dexamethasone in patients receiving mechanical ventilation and patients receiving supplemental oxygen. In those, where no oxygen is received dexamethasone does not appear to be beneficial. Therefore, the efficacy for the overall group (Dexamethasone versus standard of care) is mainly accounted for by the beneficial effects seen in the mechanically ventilated and supplemental oxygen patients.

It is noteworthy that the patients selected for mechanical ventilation were younger and were less likely to have co-existing disease, compared to those not mechanically ventilated (i.e. supplemental oxygen and no oxygen groups), although adjustment for hospital sites did not appear to alter the overall findings.

Through the play of chance in the un-stratified randomization, the mean age was 1.1 years older among patients in the dexamethasone group than among those in the usual care group. To account for this imbalance in an important prognostic factor, estimates of rate ratios were adjusted for the baseline age in three categories (<70 years, 70 to 79 years, and ≥80 years).

This adjustment was not specified in the first version of the statistical analysis plan but was added once the imbalance in age became apparent.

Table 5. Impact of adjusting for the 1.1-year age imbalance between randomised arms on the estimated effect of allocation to dexamethasone on 28-day mortality, both in all randomized patients and in subgroups defined by respiratory support received at randomization (Source: Horby et al, 2020)

	Treatment allocation		Age-adjusted Cox regression*		One-step estimate†	
Subgroup	Dexamethasone (n=2104)	Usual care (n=4321)	RR (95% CI)	p	RR (95% CI)	p
No oxygen received	89/501 (17.8%)	145/1034 (14.0%)	1.19 (0.91-1.55)	0.20	1.30 (0.99-1.71)	0.06
Oxygen only	298/1279 (23.3%)	682/2604 (26.2%)	0.82 (0.72-0.94)	0.0042	0.86 (0.75-0.99)	0.0305
Invasive mechanical ventilation	95/324 (29.3%)	283/683 (41.4%)	0.64 (0.51-0.81)	0.0002	0.67 (0.54-0.84)	0.0003
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75-0.93)**	**0.0009**	**0.87 (0.78-0.97)**	**0.0089**

RR=rate ratio, CI=confidence interval. P-values shown to 2 dp if >0.05 and 4 dp if between 0.0001 and 0.05.

* Main analysis shown in Figures 2 and 3, in which the 28-day age-adjusted (ie, conditional) mortality rate ratio is estimated by the hazard ratio from a Cox regression analysis adjusted for age in three categories (<70 years, 70-79 years, and 80 years or older). With this analysis, a test for linear trend in the log RRs across the three respiratory support subgroups gives a chi-squared trend statistic of 11.5 (corresponding to a p-value for trend of 0.0007, or a 1 in ~1400 chance of observing effect modification this extreme by chance alone).

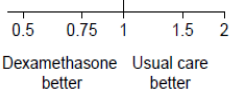
† Original pre-specified analysis without adjustment for the 1.1-year age-imbalance between the randomized groups. With this method the 'one-step' method is used to estimate the average unadjusted (ie, marginal) mortality rate ratio from the log-rank 'observed minus expected' statistic (O –E) and its variance (V), through the formula exp([O – E] ÷ V). Its 95% CI is then given by exp([O – E] ÷ V ± 1.96 ÷ √V). With this analysis, a test for linear trend in the log RRs across the three respiratory support subgroups gives a chi-squared trend statistic of 13.1 (corresponding to a p-value for trend of 0.0003, or a 1 in ~3300 chance of observing effect modification this extreme by chance alone).

Additional analyses

Pre-specified analyses of the primary outcome were performed in five subgroups, as defined by characteristics at randomization: age, sex, level of respiratory support, days since symptom onset, and predicted 28-day mortality risk. (One further prespecified subgroup analysis regarding race will be conducted once the data collection has been completed.)

Table 6. Effect of allocation to dexamethasone on 28−day mortality by other pre−specified baseline characteristics. (Source: Horby et al, 2020)

Characteristic	Dexamethasone	Usual care	RR (95% CI)
Age, years (χ^2_1=4.9; p=0.03)			
<70	129/1141 (11.3%)	428/2504 (17.1%)	0.64 (0.53−0.78)
≥70 <80	155/469 (33.0%)	271/859 (31.5%)	1.03 (0.84−1.25)
≥80	198/494 (40.1%)	411/958 (42.9%)	0.89 (0.75−1.05)
Sex (χ^2_1=0.9; p=0.33)			
Men	331/1338 (24.7%)	782/2749 (28.4%)	0.80 (0.71−0.91)
Women	151/766 (19.7%)	328/1572 (20.9%)	0.90 (0.74−1.09)
Days since symptom onset (χ^2_1=12.3; p<0.001)			
≤7	269/916 (29.4%)	500/1801 (27.8%)	1.01 (0.87−1.17)
>7	212/1184 (17.9%)	604/2507 (24.1%)	0.69 (0.59−0.80)
Baseline risk (χ^2_1=0.4; p=0.51)			
<30%	150/1268 (11.8%)	377/2682 (14.1%)	0.83 (0.69−1.00)
≥30% <45%	146/464 (31.5%)	334/878 (38.0%)	0.77 (0.63−0.94)
≥45%	186/372 (50.0%)	399/761 (52.4%)	0.90 (0.76−1.07)
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75−0.93) p<0.001**



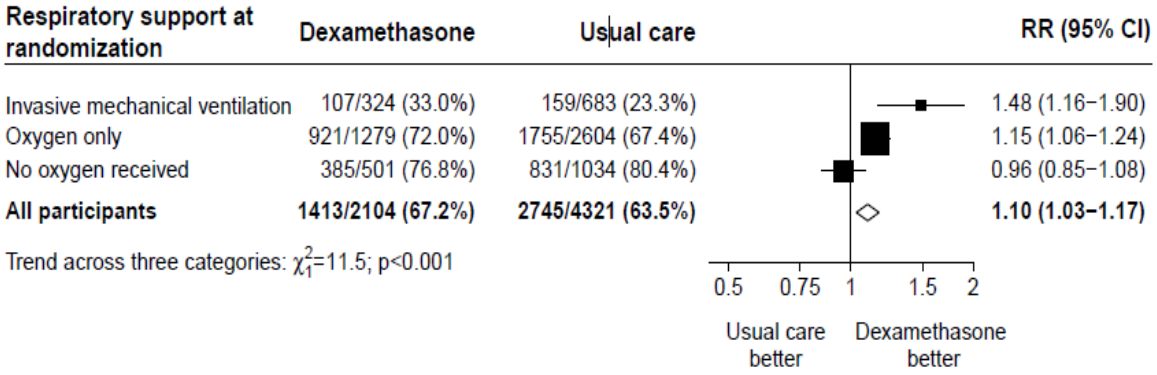
Secondary Outcomes

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days versus 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

The greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio, 1.48; 95% CI, 1.16 to 1.90)

Figure 4. Discharge from hospital alive within 28 days

(Source: Horby et al, 2020)

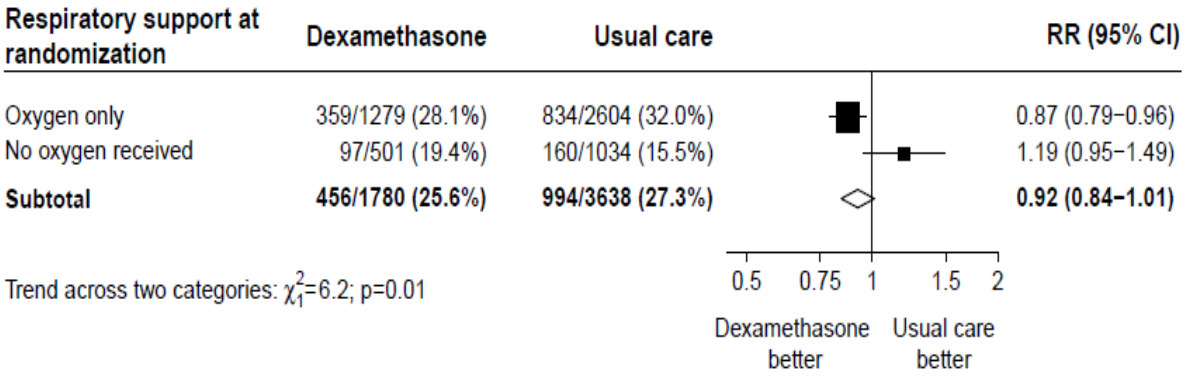


Among the patients who were not receiving invasive mechanical ventilation at randomisation, the number of patients who progressed to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower in the dexamethasone group than in the usual care group (risk ratio, 0.92; 95% CI, 0.84 to 1.01).

This effect of dexamethasone was greater among the patients who were receiving oxygen at randomization (rate ratio, 0.87; 95% CI, 0.79 to 0.96).

Figure 5. Effects of dexamethasone versus usual care

(Source: Horby et al, 2020)



Other Pre-specified Clinical Outcomes

The risk of progression to invasive mechanical ventilation was lower in the dexamethasone group than in the usual care group (risk ratio, 0.77; 95% CI, 0.62 to 0.95)

Analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation.

Figure 6. Primary and Secondary Outcomes.
(Source: Horby et al, 2020)

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
		no./total no. of patients (%)	
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

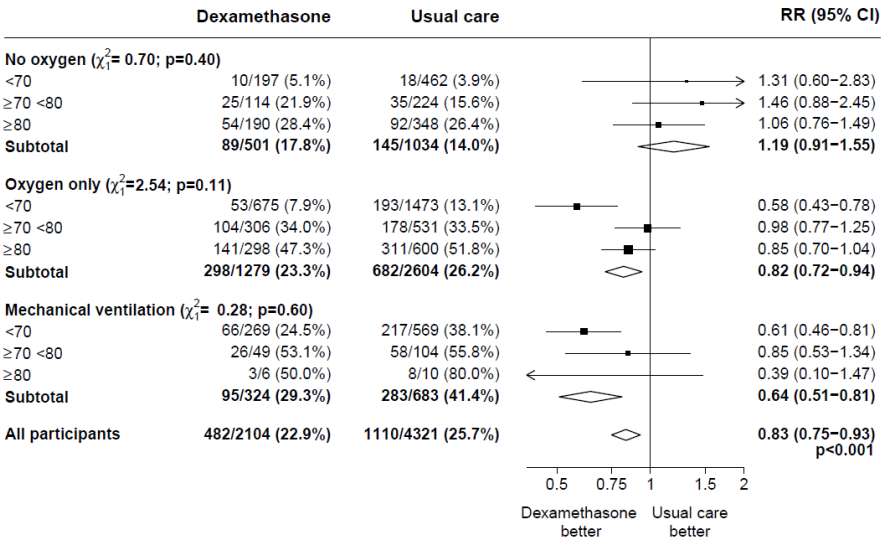
* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

Additional data was requested by CHMP on some specific issues.

The Investigators were asked by CHMP to further investigate possible interactions between subgroups on mortality at day 28, and whether they could provide some additional analyses for the main endpoint of mortality, point estimate and confidence intervals. The treatment effect in the 9 subgroups defined by the interaction of respiratory support at randomisation and age (e.g. the effect in under 70s with no oxygen received, the effect in 70-80 years old with no oxygen received, the effect in more than 80 years old with no oxygen received, the effect in under 70s receiving oxygen only, etc.

This post−hoc exploratory subgroup analysis is provided in Figure 7, below. Although there is insufficient statistical power to estimate any of the 9 subgroup-specific estimates reliably, there is no evidence that the proportional effects of allocation to dexamethasone on mortality vary with age once level of respiratory support is taken into account (all three tests for trend p>0.1).

Figure 7: Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation. (Source: Horby et al, 2020)

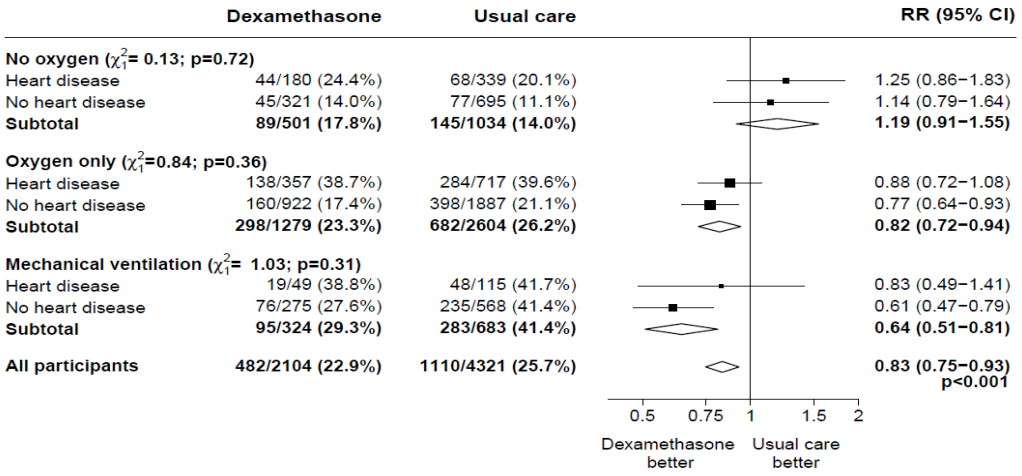


In the above table patients under 70 years had better outcomes compared to those between 70-80 years in both oxygen only and in mechanically ventilated patients and compared to those over 80 years in the oxygen only group. However, the point estimates are in favour of treatment and the trial is underpowered for these analyses.

Also, the investigators were asked to clarify mortality in the 6 subgroups defined by the interaction of respiratory support at randomisation and heart disease (e.g. the effect in those with heart disease with no oxygen received, the effect in those without heart disease, no oxygen received, the effect in those with heart disease receiving oxygen only etc.)

This analysis is provided in Figure 8 below, in which it can be seen that, at each level of respiratory support, there was no evidence that the proportional effect of allocation to dexamethasone differed between those with versus those without heart disease.

Figure 8: Effects of allocation to DEXAMETHASONE on 28−day mortality, by respiratory support received at randomisation and history of heart disease. (Rate ratio [RR])
(Source: Horby et al, 2020)



For completeness, the investigators provided equivalent analyses by history of diabetes, chronic lung disease, kidney disease and any chronic disease (which includes the above or tuberculosis, HIV, or severe liver disease). Overall, the investigators stated that there was no good evidence that the proportional effects of allocation to dexamethasone varied depending on the presence or absence of disease.

The CHMP took into account the above additional analyses provided by the investigators which gave additional insight on the effect of dexamethasone on 28-day mortality in different subgroups. The study was not designed to address these additional post-hoc analyses so those analyses should be interpreted with caution.

Patients without a history of heart disease compared to those with a history of heart disease at baseline and on oxygen alone had a significantly reduced risk of death (risk ratio, 0.77 (0.64-0.93) and 0.88 (0.72-1.08) respectively) on dexamethasone. A similar beneficial effect of dexamethasone on reduced mortality was found for those without compared to with a history of heart disease at baseline and receiving mechanical ventilation (0.61 (0.47-0.79) and 0.83 (0.49-1.41) respectively).

Patients with or without a history of underlying diabetes at baseline showed a consistent beneficial effect with dexamethasone compared to usual care in patients receiving oxygen only (although not statistically significant in those with a history of diabetes; (risk ratio, 0.80; 95% CI, 0.62-1.03). In patients on mechanically ventilation a significant beneficial effect was demonstrated in those without a history of diabetes (0.63 (0.48-0.82)) and in those with diabetes (0.71 (0.44-1.13)) but not statistically significant. This is perhaps expected as patients with a history of diabetes would tend to have higher underlying cardiovascular disease and are more likely to be prone to infection.

Similarly, in patients who received mechanical ventilation and did not have an underlying lung disease, a significant beneficial effect of dexamethasone was found (risk ratio 0.63 (0.49-0.81)). Although, a beneficial effect was also found in those with underlying lung disease, it did not reach statistical significance (risk ratio 0.76 (0.40-1.43)). There is some uncertainty in the true effect in patients with underlying lung disease. In those who received oxygen only, a beneficial effect of dexamethasone on 28 day mortality was demonstrated in those with underlying lung disease and those without (0.86 (0.73-1.01) and 0.75 (0.58-0.97) respectively), although only reaching significance in those with lung disease with a 25% reduced risk of death in the dexamethasone group.

This may indicate that patients receiving oxygen only and who had underlying lung disease may have been treated more aggressively, maybe due to patient numbers or other risk factors.

For the data on differential effects based on underlying kidney disease in both, oxygen only and mechanically ventilated patient, cohorts receiving dexamethasone had lower mortality compared to those receiving usual care in the group without underlying kidney disease only. The risk of death was increased in those on oxygen and having underlying kidney disease (risk ratio, 1.44; 95% 1.00-2.09). However, the numbers are low and confidence intervals wide for these comparisons.

In summary, 28-day mortality outcome in patients without prior history of any chronic disease shows a clear significant beneficial effect of dexamethasone treatment in patients receiving oxygen or mechanical ventilation. While the point estimates for patients with prior chronic disease favours dexamethasone treatment for those on oxygen alone or mechanical ventilation, the effect does not reach statistical significance.

Overall, the additional data shows a beneficial effect (improved survival) with dexamethasone treatment in patients who received oxygen or were mechanically ventilated.

The results for patients who were 70 years or older or with prior underlying disease show a survival beneficial effect for dexamethasone treatment, the confidence limits cross 1 it is likely due to lack of power and other factors such as the severity of their underlying chronic disease.

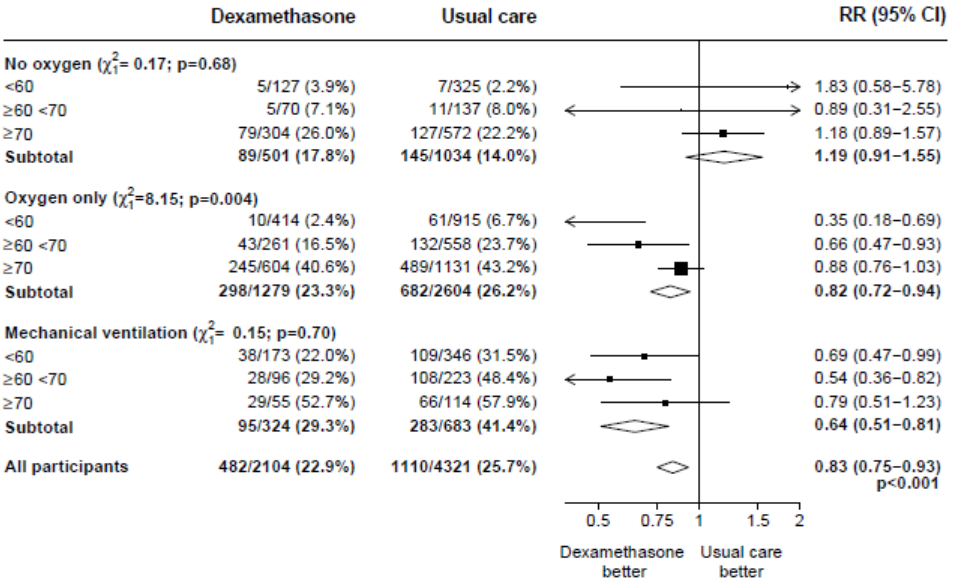
Initially, recruitment was limited to patients who were at least 18 years of age, but the age limit was removed starting on 9 May 2020. The investigators were also asked for a further analysis on the primary endpoint be conducted based on age - below 70 and above 70 years of age as it is important to obtain additional data regarding other age groups - below 18 years of age, 18-39, 40-49, 50-59, 60-69 years of age respectively.

Of the 557 deaths within 28 days among those aged <70 years, there were zero deaths among those aged <18 years, 18 deaths among those aged 18-39 years, 44 deaths among those aged 40-49 years, 168 deaths among those aged 50-59 years, and 327 deaths among those aged 60-69 years. In total, therefore, there were just 62 deaths among those aged <50 at randomisation, and meaningful analyses of these are not possible (particularly because these deaths would also need to be subdivided by level of respiratory support).

However, in Figure 9 below exploratory analyses of age at years <60, 60-69, and ≥70 was done. These indicate that effects of allocation to dexamethasone on mortality are at least as large in younger

as in older patients (although these analyses should be considered very exploratory due to the small number of deaths among younger people).

Figure 9: Effects of allocation to DEXAMETHASONE on 28−day mortality, by alternative age groups and level respiratory support received at randomisation. (Source: Horby et al, 2020)



RR=age−specific rate ratio. CI=confidence interval. Subgroup−specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% confidence intervals. The 9 subgroup estimates by age and level of respiratory support are estimated from a single regression model that includes an interaction term between age (in 3 groups) and respiratory support (in 3 groups). The three subtotal diamonds are age−adjusted, as is the overall summary diamond.

It is noted that there were few patient deaths in patients under 50 years of age.

There was no information in the publication on whether any regional differences were seen between hospital regions.

The investigators clarified that among the 164 hospitals that randomised at least one patient to the dexamethasone comparison, the median number randomised was 30 patients (inter−quartile range 15 to 54). In a post-hoc sensitivity analysis in which each hospital was included as a random effect in the regression model, the age-adjusted rate ratios were 1.21 (95% CI 0.93-1.58) for those not receiving additional oxygen, 0.81 (0.71-0.93) for those on oxygen only, and 0.65 (0.51-0.82) for those on invasive mechanical ventilation. That is, the results were virtually identical to the main pre-specified analyses published in the NEJM report.

The CHMP noted that there appears to be limited effect on the overall findings when adjusting for differences in regions and hospitals which was considered reassuring by the CHMP.

The investigators were also asked to clarify the causes of death recorded in the study.

The investigators clarified that cause of death information was ascertained by follow-up form and through linkage to national death certificate data which are provided monthly. The main cause-specific 28-day mortality available data (cut off 2 August 2020; unpublished data) was COVID-19 (436 on the dexamethasone arm versus 1025 usual care; RR 0.82 (95% CI, 0.73 – 0.91) compared to total mortality (482 dexamethasone arm versus 1110 usual care; RR 0.83 (95% CI, 0.75 – 0.93), followed by cases of other infections, cardiovascular events and causes from known health issues.

Clinical efficacy conclusions

Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001).

The day 28 mortality outcomes based on respiratory support showed that patients receiving mechanical ventilation (n=1007) and dexamethasone had a beneficial effect with a rate ratio of 0.64 (95% CI 0.51-0.81).

Patients receiving oxygen only (n=3883) and received dexamethasone had a beneficial effect with a rate ratio of 0.82 (95% CI, 0.72-0.94), whereas those not receiving oxygen did not show any benefit with an increased mortality with rate ratio 1.19 (95% CI, 0.91-1.55) compared to usual care.

This demonstrates that patients with COVID-19 and in need of oxygen could benefit from dexamethasone treatment.

Further pre-specified analyses of the primary outcome were performed in five subgroups, as defined by characteristics at randomization: age, sex, level of respiratory support (already discussed above), days since symptom onset and predicted 28-day mortality risk.

The results demonstrated that patients < 70 years of age had the best outcome (rate ratio 0.64 (95% CI 0.53-0.78)) where as for those aged 70-80 years and those > 80 years a beneficial effect is not seen (rate ratio 1.03 (0.84-1.25) and rate ratio 0.89 (0.75-1.05) respectively).

Men had a better response (rate ratio 0.80 (0.71-0.91)) compared to females (rate ratio 0.90 (0.74-1.09), however, this may be due to sample size as more men were included in this analysis compared to women and a differential outcome would not be expected.

Patients with onset of symptoms for more than 7 days showed a better response (rate ratio 0.69 (0.59-0.80)) compared to those ≤7 days (rate ratio 1.01 (0.87-1.17)). This is understandable as it takes some days before patients progress into an inflammatory stage. It would be more helpful if the intervention could be more precisely guided such as clinical signs and inflammatory markers rather than days, however further investigation would be needed.

Baseline risk of mortality showed the highest response in patents with ≥30% to < 45% risk.

It is unclear how this risk was calculated.

Overall, the subgroups contributing most to the primary outcome are level of respiratory support at randomisation, age < 70 years, > 7 days since symptom onset and baseline risk of death 30-45%.

In order to better understand the interaction across key subgroups to help elucidate the true effect e.g. the effect in under 70s without oxygen, in those 70-80 without oxygen etc. Additional post-hoc analyses were requested.

These analyses demonstrated that patients receiving dexamethasone who were less than 70 years of age in both oxygen only and mechanical ventilation groups had clear beneficial effects, rate ratio 0.58 (0.43-0.78) and rate ratio 0.61 (0.46-0.81) respectively compared to older patients, 70-80 years and > 80 years of age.

Taking into consideration the effects in patients with underlying disease, patients without heart disease had a lower mortality rate compared to those with heart disease in both oxygen and mechanical ventilation cohorts.

No differences were seen in patients with underlying diabetes. Patients who received mechanical ventilation and who had underlying chronic lung disease had a higher incidence of mortality compared

to those who did not. Conversely patients on oxygen only had a better outcome in patients with chronic lung disease compared to those without.

Overall, when prior disease was considered patients without any chronic disease had better outcomes compared to those without based on level of oxygen support.

However, conclusions drawn from sub-groups should be interpreted cautiously due to the lower power associated with these and increased likelihood of type I errors.

Secondary efficacy endpoints

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days versus 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

In line with the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only rate ratio =1.15 (95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen rate ratio =0.96 (0.85-1.08).

Among the patients who were not receiving invasive mechanical ventilation at randomisation, the number of patients who progressed to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower in the dexamethasone group than in the usual care group (risk ratio rate ratio =0.92; 95% CI, 0.84 to 1.01). However, as the upper limit crosses 1 this can only be considered as a trend. Examining for each separately shows a lower percentage of patients progressing to invasive mechanical ventilation rate ratio =0.77 (0.62-0.95) however this did not translate into an improvement in 28-day mortality, therefore the timing of mechanical ventilation is also important.

2.5. Data on safety

Dexamethasone is a well-known medicinal product with an established safety profile and is in widespread use across the EU for a number of indications however, its use in patients with COVID-19 is still under investigation.

In the RECOVERY trial it was stated that suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation, however no safety data was provided or published in the NEJM.

It was important to know whether any of these adverse events caused or significantly contributed to any patient mortality by level of respiratory support received at randomization.

The investigators provided relevant information and stated that there were four serious adverse events (SAEs) reported as being related to study treatment (all were expected with dexamethasone). Two were hyperglycaemia (which required a longer admission for stabilisation); there was one case of steroid-induced psychosis and one participant had an upper gastrointestinal bleed. All events resolved; none of the participants died.

Further information was requested on the actual causes of death recorded in the study. The investigators stated that information on causes of death was ascertained by a follow-up form and through linkage to national death certificate data which are provided monthly.

In previous observational studies conducted in patients with SARS-CoV-2 (Yuan et al, 2020; Xu K et al, 2020; Giacobbe et al, 2020) treatment with corticosteroids such as methylprednisolone was associated with a prolongation of viral shedding and an association with ICU-acquired blood stream infections. The RECOVERY trial did not collect information on viral shedding or specifically record for ICU-acquired blood stream infections. This would be of interest for any future marketing authorisation or other applications, especially in other populations such as elderly or patients who may have been taking immunosuppression or with diabetes. Further immediate and longer-term safety data could be collected in specific populations such as older and frail patients, immunosuppression, or underlying comorbidity as part of any subsequent marketing application.

Missing safety data should also be part of any subsequent risk management plans of medicinal products.

2.6. Literature review

Late breaking studies and WHO metanalysis

During the current assessment data on additional studies on steroids and a metanalysis were made available.

Three (3) multicenter RCTs that assessed corticosteroid therapy in critically ill patients with COVID-19, as well as the WHO-sponsored prospective metaanalysis. All 3 trials halted enrollment in June 2020 after the RECOVERY result information was made publicly available.

In the REMAP-CAP trial (Angus et al, 2020), 403 patients with severe COVID-19 (in the intensive care unit [ICU] and receiving respiratory or cardiovascular organ support) were randomised to 1 of 3 open-label groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone.

The primary study outcome was the number of days patients remained alive and free of organ support to day 21.

The bayesian model found that fixed-dose hydrocortisone (93% probability), as well as shock-dependent hydrocortisone (80%probability) were both likely superior to no hydrocortisone, but data were insufficient to confirm a single optimal regimen.

The CoDEX trial (Tomazini et al, 2020) randomised 299 patients in 41 ICUs in Brazil with moderate or severe ARDS and COVID-19 to open label high-dose dexamethasone (20 mg/d for 5 days, then10 mg/d for 5 days) versus usual care alone.

The primary outcome was ventilator-free days through day 28, which were greater in patients randomized to dexamethasone (6.6 versus 4.0, P = 0.04)

28-day mortality was not significantly different between patients randomized to corticosteroids versus usual care (56.3% versus 61.5%, P = 0.83), stopping the study early when RECOVERY results announced underpowered study.

CAPE COVID (Dequin et al, 2020) randomised 149 patients in 9 ICUs in France with severe respiratory disease from COVID-19 to low-dose hydrocortisone (200mg/d infusion, tapered per protocol) versus placebo.

The primary outcome of 21-day treatment failure, defined as death or ongoing respiratory support with mechanical ventilation or high-flow oxygen, occurred in 42.1% of patients randomised to hydrocortisone versus 50.7% of those randomised to placebo (P = 0.29).

A prospective meta-analysis was done by WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group pooled data (Sterne et al, 2020) from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials) totalling 1703 patients (678 had been randomized to corticosteroids and 1025 to usual care or placebo), of which 59% of patients were from the RECOVERY trial.

The 28-day mortality was lower in patients randomised to corticosteroids: 222 deaths among 678 patients randomized to corticosteroids compared with 425 deaths among 1025 patients randomised to usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53,-0.82]; P < 0.001).

Reduced mortality was similar for dexamethasone and hydrocortisone, suggesting the benefit is a general class effect of glucocorticoids and not specific to any particular corticosteroid; was similar with lower- versus higher-dose corticosteroid regimens, although these estimates were imprecise, leaving the question of dose less definitively answered; and was similar among patients with fewer versus greater than 7 days of symptoms at randomisation, although all patients were hospitalized with COVID-19 critical illness.

Literature search

Two databases of references and abstracts were used, namely Medline/PubMed and EMBASE in several searches until 12 August 2020. To reduce the number of duplicates, the results of the PubMed query were excluded from the search criteria for EMBASE.

The search was performed periodically (latest cut-off date was 12 Aug 2020), focussing on comparative and non-comparative studies, systematic review and meta-analysis excluding publications on case series and single case reports. In this chapter only most relevant with the use of corticosteroids publications are being summarised.

Overall, 24 reviews were retrieved in the literature search addressing treatment of COVID-19 disease and effect on various outcomes in general and including corticosteroids among the treatment options or referring to special populations with background immunosuppressive treatment involving corticosteroids. Until cut-off date (12 Aug 2020), the RECOVERY trial was the main interventional clinical trial reviews are referring to with further observational studies that have been published on the role of corticosteroids that are however of limited quality of evidence, often low in size with a lot of them poorly addressing confounding issues and reporting crude unadjusted results. Meta-analyses of these observational studies suffer the same limitations with some of them pooling unadjusted effect estimates into overall effect estimates. The number of reviews specifically addressing the role of steroids in COVID-19 is increasing, while some of them and early publications were also based on review of literature including other coronaviruses e.g. SARS and MERS.

Siemieniuk and colleagues (2020) conducted a systematic review and network meta-analysis to compare the effects of treatments for coronavirus disease 2019 (COVID-19) and conclude that glucocorticoids probably reduce mortality and mechanical ventilation in patients with COVID-19 compared with standard care. Overall, the study is small and can not provide any additional information or conclusions than the RECOVERY trial itself. Lee and colleagues (2020) conducted a systematic review and meta-analysis on the use of corticosteroids in critical coronavirus infections, including SARS, MERS or COVID-19 and conclude that if not contraindicated, and in the absence of side effects, the use of steroids should be considered in coronavirus infection including COVID-19. Hasan and colleagues (2020) conducted a systematic review on ARDS secondary to viral pneumonitis in COVID-19 patients and concluded that the high mortality in COVID-19 associated ARDS necessitates a prompt and aggressive treatment strategy including corticosteroids. Improvement in clinical outcomes (e.g. oxygenation indices, a marker of inflammation, resolution of signs, and symptoms) in COVID-19 patients was also noted though without certainty due to methodological flaws. Figliozzi and colleagues

(2020) conducted a review and a metanalysis identifying outcome predictors for severe outcomes and in-hospital death in COVID-19 and noted that steroid therapy in the acute phase was associated with adverse outcomes. As the association is likely to be related to confounding by indication, no conclusions on causal effects of steroids on treatment outcomes can be drawn based on the results of this analysis.

Russel and colleagues (2020b) concluded that corticosteroids may be beneficial if utilised in the early acute phase of infection. Lu and colleagues (2020) performed a review addressing use in COVID-19 with and without ARDS and concluded that corticosteroids may reduce mortality for patients with COVID-19 and ARDS, but for patients with severe COVID-19 without ARDS, evidence is inconsistent. Veronese and colleagues (2020) concluded that literature available does not fully encourage routine use of corticosteroids in COVID-19, but some findings suggest that methylprednisolone could lower mortality rate in more severe forms such as ARDS. Singh and colleagues (2020) reviewed 5 studies on the role of steroids for COVID-19 reporting variable outcomes and highlight possible dose effects of steroids indicating use of lower doses might be associated with more favourable outcomes. However, the studies reviewed are of limited quality and limitations were not discussed including the possibility of confounding by indication (and dose) making conclusions on the clinical relevance of these findings difficult. Yang and colleagues (2020) reviewed effects of corticosteroids in pandemic viral pneumonia and concluded that corticosteroid therapy was reported to improve viral pneumonia in some cases, but that confirmed evidence on reduction of mortality in COVID-19 patients is lacking and advice for cautious use. Ortiz-Prado and colleagues (2020) reviewed clinical and epidemiological data on COVID-19 and based on clinical reasoning advise that use of corticoids should depend on stage of COVID-19 disease recommending usage for patients with COVID-19 and refractory shock and just ICU patients.

Many 'early' reviews and guidelines base their recommendations on indirect evidence from steroid treatment within the setting of other coronaviruses, e.g. SARS and MERS. They conclude that there is some evidence for efficacy of steroids in SARS, but that there is no sound evidence on efficacy in COVID-19 (Russell et al, 2020a; Russell et al, 2020b; Lu et al, 2020; Ye et al, 2020b; Li H et al, 2020; Veronese et al, 2020).

Lu and colleagues (2020) concluded that long-term use of high dose was reported to increase risk of adverse reactions such as coinfections advising against routine use of systemic glucocorticoids for patients with COVID-19. Some cohort studies of low quality included in a review conducted by Ye and colleagues (2020b) suggested that corticosteroid use was associated with prolonged viral shedding.

Among the observational studies identified for inclusion, the majority consisted of retrospective cohort studies that were of limited size and mainly descriptive in nature. Only a small number of studies applied epidemiological and statistical methods to address potential confounding between treatment groups and for a lot of studies reporting use of corticosteroid use, the timing of use is unknown, and it is difficult to ascertain whether treatment was associated with disease severity.

Wang and colleagues (2020) concluded that early, low-dose and short-term application of methylprednisolone was associated with better outcomes in severe patients with COVID-19 pneumonia based on a descriptive study without any adjustment for confounding. Zhang and colleagues (2020) evaluated factors influencing hospital stay and survival and divided patients, based on statistically significant risk factors associated with mortality, into those who present at baseline a high risk versus those who present a low risk for mortality using a scoring system. They observed no effect of corticosteroid use on mortality in the high-risk group, but found that in the low risk group, patients not receiving corticosteroids had shorter hospital stays and duration of disease. It can therefore not be concluded that the worse outcomes associated with corticosteroid treatment in patients in the low-risk group are causally associated with corticosteroid treatment as confounding cannot be excluded. Nelson and colleagues (2020) reported an earlier time to recovery associated with methylprednisolone use in

patients with COVID-19 related pneumonia receiving ventilation. The study did only observe a trend towards lower mortality in patients receiving methylprednisolone but was probably too small to detect meaningful effects on mortality. Liu and colleagues (2020) conducted a retrospective, single-centre cohort study including 1190 adult inpatients with laboratory-confirmed COVID-19 from Wuhan and conclude that glucocorticoids had no beneficial effects in patients hospitalised for COVID-19. However, glucocorticoids seem to have been used more predominantly in more severe patients and it is unclear whether confounding by indication was sufficiently addressed in the regression model. Langer-Gould and colleagues (2020) concluded that prompt identification and treatment of COVID-19 prior to intubation may be more important than the specific type of anti-inflammatory treatment based on a retrospective cohort study evaluating treatment with anakinra or tocilizumab together with corticosteroids. Huang and colleagues (2020) did not observe significant differences in the duration of severe illness or the number of days on high-level respiratory support between a low-dose methylprednisolone group and a high-dose methylprednisolone group.

Yuan and colleagues (2020) explored the effects on various clinical outcomes in patients with COVID-19 in 35 matched patient pairs noting that in the corticosteroid group more patients progressed to severe cases and had longer duration of viral shedding while fever time was shortened and further noted a possible negative effect on lung injury in recovery. Xu and colleagues (2020) noted that corticosteroid usage was related to prolonged viral RNA shedding time in a cohort of 113 symptomatic patients. Li TZ and colleagues (2020) found an increased risk of long duration of viral shedding in patients treated with corticosteroids. Qi and colleagues (2020) observed increased odds of prolonged duration of viral shedding associated with steroids that did not reach statistical significance. Chen and colleagues (2020) observed that corticosteroids were associated with prolonged viral shedding alongside other factors. Shi and colleagues(2020) did not observe that corticosteroid treatment was an independent factor for duration of viral shedding, but note that high percentage of patients in their cohort received corticosteroids and that dosages were relatively low.

Following the literature review direct evidence from studies in patients with COVID-19 was limited and based on small observational studies. Taking into account all the above published information there is very limited evidence to suggest that corticosteroid treatment in COVID-19 disease may be beneficial in patients with COVID-19 and ARDS and in patient with more severe disease and COVID-19 associated pneumonia, in the management of COVID-19 related cytokine storm response (CSR), in combination with other substances (tocilizumab or anakinra), a condition which however requires also prompt identification and intervention.

Furthermore corticosteroids may be associated with prolonged viral shedding increased risk of ICU-acquired blood stream infections with liver enzyme elevation or associated with hyperglycaemia that is managed with insulin.

2.7. Discussion

Recovery study

The CHMP noted that there was no concern with the randomisation - no imbalance was observed between treatment arms.

The results of the primary analysis of the RECOVERY study are statistically significant at the 5% level.

The investigators concluded that the interim analyses spent 0.06% of the alpha for testing which leaves an alpha of 0.0494 preserved for testing. However, they still use alpha=0.05 in the final results, so no adjustment was made for the interim analyses.

The investigators did not adjust for multiplicity in the study, between treatment arms or for any of the pre-specified endpoints. While it is unlikely to have any effect on the overall primary endpoint for mortality, it may be more of an issue for some of the secondary endpoints.

The SAP was finalised after the blind had been broken. It is unclear whether these amendments relate to the estimation of effect in the subgroups identified by the investigators and what impact, if any, this has on the overall findings and conclusions.

Usual care may not have been standardised across hospital sites although subsequent adjustment for hospital appears not to alter the findings for the primary outcome.

There was a significant (P = 0.01) difference in the mean age between patients in the dexamethasone group and those in the usual care group. The estimates of rate ratios were adjusted for the baseline age in three categories (<70 years, 70 to 79 years, and >80 years).

The age adjustment did appear to have an effect on the estimates of rate ratios, particularly as those on mechanical ventilation were 10 years younger on average than those without respiratory support.

Also, the SAP suggested that adjustment *'will be done through the use of Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios'*. It is unclear if the rate ratios present adjusted risk ratios based on Cox or log-binomial regression as the supplementary information received only provided results based on the Cox regression model (referred to as RR).

In 10-12% of the randomized cases COVID-19 did not have a positive SARS-CoV-2 test result and the results were unknown for <1%.

The investigators suggested that the results were similar in a post-hoc exploratory analysis restricted to the 5698 patients (89%) with a positive SARS-CoV-2 test result.

For the secondary outcome, use of mechanical ventilation/ECMO or death (among those not on ventilation or ECMO at randomisation, the SAP suggests that the absolute risk difference will also be presented with confidence intervals. The absolute risk difference was not presented, but only as risk ratio.

Conclusions drawn from sub-groups should be interpreted cautiously due to the lower power associated with these and increased likelihood of type I errors.

Data regarding other age groups (<70 years of age) were limited and meaningful analyses of these are not possible. However, it is expected that younger age groups would respond to dexamethasone treatment favourably. Taking into account the posology for administration for patients of more than 12 years of age similarly as adults, as well as the fact that the excretion of dexamethasone is approximately equal in children and adults if dosage is adjusted to their body area, adolescents of more than 40 kg weight could be given the same dose as for adults if needed. In view of the unprecedented need due to the pandemic, the known safety profile of dexamethasone when used in adolescents, and the fact that the proposed treatment dose for COVID-19 treatment is not very high compared to other indications, the posology for adolescents can be acceptable. It needs to be emphasised that the collection of more data will be necessary in the younger patient populations as part of future research.

Pregnant or breastfeeding women were also eligible but results are not available in these two populations, and no definite conclusions can be drawn for dexamethasone use in COVID-19 infection to this population.

The data on route of administration (oral or intravenous) and formulation (tablet or liquid) were not recorded. However, it is likely that the majority of patients on mechanical ventilation received intravenous (IV) dexamethasone compared to those patients who were receiving oxygen only. It is also not entirely clear how the dose of 6 mg was decided as a sufficient dose as well as the treatment duration of 10 days. Given the bioavailability of oral dexamethasone has been reported to be between 70% and 78%, it appears that those taking dexamethasone in tablets could be sub-optimally treated. Moreover, it was that the AUC of 6 mg oral dexamethasone did not differ significantly from the AUC of 4 mg intravenous dexamethasone in patients hospitalised with pneumonia. Therefore, it cannot be excluded that a higher dose of dexamethasone should be administered orally. Generally, there are some uncertainties; nevertheless the CHMP concluded that overall benefit is overwhelming and overcomes uncertainties at present.

Nevertheless, the dose of 6 mg once daily was chosen (also based on published literature) and the CHMP recommended that this dose be used for the treatment of COVID-19 hospitalised patients. Further refining of the dose may need to be done in future investigations, as well the comparison between intravenous and oral administration and bioavailability.

The treatment duration of 10 days was not clear and as in the study patients were treated in average between 7 and 10 days, the CHMP recommended that the treatment duration is up to 10 days taking into account the study results and RECOVERY protocol. It is recommended that the duration of treatment should be guided by clinical response and individual patient requirements.

Overall a beneficial effect on day 28 mortality has been demonstrated in RECOVERY study.

Safety

The investigators provided relevant information and stated that there were four serious adverse events (SAEs) reported as being related to study treatment (all were expected with dexamethasone). Two were hyperglycaemia (which required a longer admission for stabilisation); there was one case of steroid-induced psychosis and one participant had an upper gastrointestinal bleed. All events resolved; none of the participants died. The trial did not collect information on viral shedding or specifically record for ICU-acquired blood stream infections. This would be of interest for any potential marketing authorisation or other applications, especially in other populations such as elderly or patients who may have been taking immunosuppression or with diabetes.

WHO meta-analysis

Additional trial data and meta-analysis also supports use of dexamethasone in hospitalised patients with COVID-19.

WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials) totalling 1703 patients (678 had been randomized to corticosteroids and 1025 to usual care or placebo), of which 59% were from the RECOVERY trial.

The 28-day mortality was lower in patients randomized to corticosteroids: 222 deaths among 678 patients randomized to corticosteroids compared with 425 deaths among 1025 patients randomized to usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53,-0.82]; $P < .001$).

Reduced mortality was similar for dexamethasone and hydrocortisone, suggesting the benefit is a general class effect of glucocorticoids and not specific to any particular corticosteroid; was similar with lower- versus higher-dose corticosteroid regimens, although these estimates were imprecise, leaving the question of dose less definitively answered; and was similar among patients with fewer versus

greater than 7 days of symptoms at randomization, although all patients were hospitalized with COVID-19 critical illness.

Considering the current available evidence, the CHMP is of the opinion that given the high unmet medical need for therapies in the current pandemic, that the results of the trial together with any supplemental data are of importance in the treatment of in-hospital COVID-19 patients requiring oxygen support either as supplementary oxygen or invasive mechanical ventilation.

3. Overall conclusions and benefit-risk balance

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY)[4] is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

The trial was conducted at 176 hospital organizations in the United Kingdom.

There were 6425 Patients randomised to receive either dexamethasone (2104 patients) or usual care alone (4321 patients). 89% of the patients had laboratory-confirmed SARS-CoV-2 infection.

At randomization, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.

The mean age of patients was 66.1+/-15.7 years. 36% of the patients were female. 24% of patients had a history of diabetes, 27% of heart disease and 21% of chronic lung disease.

For the primary endpoint, mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001).

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% versus 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving supplementary oxygen without invasive mechanical ventilation (23.3% versus 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94).

There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomisation (17.8% versus 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

For the secondary efficacy endpoints, patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days versus 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

In line with the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only (rate ratio 1.15; 95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen (rate ratio 0.96; 95% CI 0.85-1.08).

There is no information on the reasons why 6 mg once daily was selected and while the recovery protocol randomisation part A stated corticosteroids and included posology for children, only data on dexamethasone at a dose of 6 mg was reported in adults. Further refining of the dosing regimen may

[4] www.recoverytrial.net

be useful. For the treatment of COVID-19 the CHMP recommended a posology of 6 mg IV/PO, once a day for up to 10 days.

No dose adjustment is needed for the elderly, renal and, hepatic impaired patients.

It is recognised that there may be patients who despite being > 70 years, or having co existing chronic disease may be relatively healthy in terms of cardiovascular and respiratory status and therefore may benefit from dexamethasone treatment. Therefore the CHMP support the use of dexamethasone in COVID-19 patients above 70 years. The timing of treatment should be initiated during the inflammatory stage of the disease; this may be evident clinically when supportive oxygen or ventilation is needed additionally patients may have elevated inflammatory markers such as ESR, C-reactive protein, D-dimers, lactate dehydrogenase, ferritin, and increased levels of pro-inflammatory cytokines including as IL-1 and IL-6. It is unclear how long treatment should be given for but this will be guided by clinical assessment of the patient response. The RECOVERY trial reported a median duration of treatment was 7 days (interquartile range, 3 to 10 days). The CHMP considered the duration of treatment is up to 10 days as the range of treatment during the study was between 7 and 10 days, and that the duration of treatment should be guided by clinical response and individual patient requirements.

Dexamethasone is a well-known medicinal product with an established safety profile and is in widespread use across the EU for a number of therapeutic indications. No significant safety concerns were noted to occur in the RECOVERY study.

In published literature, treatment with corticosteroids such as methylprednisolone can be associated with a prolongation of viral shedding and an association with ICU-acquired blood stream infections. The RECOVERY trial did not collect information on viral shedding or specifically record for ICU-acquired blood stream infections. This would be of interest for any potential marketing authorisation or other applications, especially in other populations such as elderly or patients who may have been taking immunosuppression or with diabetes. Further immediate and longer-term safety data could be collected in specific populations such as older and frail patients, immunosuppression, or underlying comorbidity as part of any subsequent investigation or in the framework of a marketing authorisation. Missing safety data should also be part of any subsequent risk management plans of medicinal products.

Detail on severity of underlying chronic disease at baseline was not provided. While the action of dexamethasone would not be different between patients with underlying chronic disease and those without, the significance of underlying disease may affect the mortality outcome. Further analyses would be needed on this in the future.

Of special interest is the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group which pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials) totaling 1703 patients (678 had been randomized to corticosteroids and 1025 to usual care or placebo), of which 59% were from the RECOVERY trial. The 28-day mortality was lower in patients randomised to corticosteroids: 222 deaths among 678 patients randomized to corticosteroids compared with 425 deaths among 1025 patients randomized to usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53,-0.82]; P < .001). Reduced mortality was similar for dexamethasone and hydrocortisone, suggesting the benefit is a general class effect of glucocorticoids and not specific to any particular corticosteroid, which is in line with the conclusions from the RECOVERY study.

Overall, the CHMP concluded that on the benefit-risk balance of the use of dexamethasone in COVID-19 patients is positive and a beneficial effect on day 28 mortality has been demonstrated. Given the high unmet medical need for therapies in the current COVID-19 pandemic, it is the CHMP's opinion that the results of the trial are of importance in the treatment of in-hospital patients requiring respiratory

support either as supplementary oxygen or invasive mechanical ventilation. Safety data has not highlighted any additional safety concerns which therefore support a positive benefit-risk balance.

4. CHMP Proposal for amendments to product information

The CHMP considered all data and agreed that the available evidence support the use of dexamethasone in certain COVID-19 patients and proposed wording for sections 4.1, 4.2, 4.4, and 5.1 of the summary of product characteristics (SmPC).

For section 4.1 Therapeutic indications, the following wording is proposed:

> *<Invented name> is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.*

Dexamethasone-containing products should be used in adult patients as 6 mg IV/PO treatment, once a day for up to 10 days. No dose adjustment is needed in the elderly and patients with renal or hepatic impairment.

Further warnings and precautions of use relating to the risks associated with the use of dexamethasone oral or intravenous medicinal products were also included especially in the prior use of corticosteroids in patients before starting the treatment for COVID-19.

The results of the RECOVERY study should be included in the section 5.1 of SmPC to inform the treating physicians accordingly.

Consequential wording for the Package Leaflet was also proposed.

The exact test wording for changes to the product information is presented in the Annex to this report.

5. Grounds for Opinion

Whereas,

The Committee assessed the issue under the Article 5(3) of Regulation (EC) No 726/2004.

The Committee, as a consequence, considers that the benefit-risk balance of dexamethasone in use for treatment of certain COVID-19 patients is favourable when taking into account the proposed wording amendments to the product information.

6. References

Angus et al. The Writing Committee for the REMAP-CAP Investigators, Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial JAMA 2020, JAMA. doi:10.1001/jama.2020.17022

Chen X, Zhu B, Hong W, et al. Associations of Clinical Characteristics and Treatment Regimens with Viral RNA Shedding Duration in Patients with COVID-19 [published online ahead of print, 2020 Jun 30]. Int J Infect Dis. 2020;S1201-9712(20)30526-9. doi:10.1016/j.ijid.2020.06.091

Dequin et al., the CAPE COVID Trial Group and the CRICS-TriGGERSep Network, Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19, A Randomized Clinical Trial JAMA, 2020, doi:10.1001/jama.2020.16761

Figliozzi S, Masci PG, Ahmadi N, et al. Predictors of Adverse Prognosis in Covid-19: A Systematic Review and Meta-analysis [published online ahead of print, 2020 Jul 29]. Eur J Clin Invest. 2020;e13362. doi:10.1111/eci.13362

Giacobbe DR, Battaglini D, Ball L, et al. Bloodstream infections in critically ill patients with COVID-19 [published online ahead of print, 2020 Jun 14]. Eur J Clin Invest. 2020;e13319. Doi:10.1111/eci.13319

Hasan SS, Capstick T, Ahmed R, et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis [published online ahead of print, 2020 Jul 31]. Expert Rev Respir Med. 2020;10.1080/17476348.2020.1804365 doi:10.1080/17476348.2020.1804365

Horby et al., The RECOVERY Collaborative Group, Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report (2020), N Engl J Med, doi: 10.1056/NEJMoa2021436

Huang H, Song B, Xu Z, et al. Predictors of coronavirus disease 2019 severity: A retrospective study of 64 cases [published online ahead of print, 2020 Aug 1]. Jpn J Infect Dis. 2020;10.7883/yoken.JJID.2020.298. doi:10.7883/yoken.JJID.2020.298

Langer-Gould A, Smith JB, Gonzales EG, et al. Early Identification of COVID-19 Cytokine Storm and Treatment with Anakinra or Tocilizumab [published online ahead of print, 2020 Aug 5]. Int J Infect Dis. 2020;S1201-9712(20)30609-3. doi:10.1016/j.ijid.2020.07.081

Lee KH, Yoon S, Jeong GH, et al. Efficacy of Corticosteroids in Patients with SARS, MERS and COVID-19: A Systematic Review and Meta-Analysis. J Clin Med. 2020;9(8):E2392. Published 2020; Jul 27. doi:10.3390/jcm9082392

Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukemia. 2020;34(6):1503-1511. Doi:10.1038/s41375-020-0848-3

Li TZ, Cao ZH, Chen Y, et al. Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19 [published online ahead of print, 2020 Jul 9]. J Med Virol. 2020;10.1002/jmv.26280. doi:10.1002/jmv.26280

Liu J, Zhang S, Wu Z, et al. Clinical outcomes of COVID-19 in Wuhan, China: a large cohort study. Ann Intensive Care. 2020;10(1):99. Published 2020 Jul 31. doi:10.1186/s13613-020-00706-3

Lu S, Zhou Q, Huang L, et al. Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis. Ann Transl Med. 2020;8(10):627. doi:10.21037/atm-20-3307

Nelson BC, Laracy J, Shoucri S, et al. Clinical Outcomes Associated with Methylprednisolone in Mechanically Ventilated Patients with COVID-19 [published online ahead of print, 2020 Aug 9]. Clin Infect Dis. 2020;ciaa1163. doi:10.1093/cid/ciaa1163

Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L, et al. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review [published online ahead of print, 2020 May 30]. Diagn Microbiol Infect Dis. 2020;98(1):115094. doi:10.1016/j.diagmicrobio.2020.115094

Qi L, Yang Y, Jiang D, et al. Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study. Int J Infect Dis. 2020;96:531-537. doi:10.1016/j.ijid.2020.05.045

Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-Immunomodulatory Therapy in COVID-19 [published online ahead of print, 2020 Jul 21]. Drugs. 2020;1-26. doi:10.1007/s40265-020-01367-z

Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience. 2020;14:1022. Published 2020(a) Mar 27. Doi:10.3332/ecancer.2020.1022

Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting?. Ecancermedicalscience. 2020;14:1023. Published 2020(b) Mar 30. Doi:10.3332/ecancer.2020.1023

Shi D, Wu W, Wang Q, et al. Clinical characteristics and factors associated with long-term viral excretion in patients with SARS-CoV-2 infection: a single center 28-day study [published online ahead of print, 2020 Jul 2]. J Infect Dis. 2020;jiaa388. doi:10.1093/infdis/jiaa388

Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980. Published 2020 Jul 30. doi:10.1136/bmj.m2980

Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective [published online ahead of print, 2020 Jun 27]. Diabetes Metab Syndr. 2020;14(5):971-978. doi:10.1016/j.dsx.2020.06.054

Spoorenberg, S. Deneer,V, Grutters, J, Pulles, A, Voorn, G.P, Rijkers, G Bos W, and van de Garde, E. (2013). Pharmacokinetics of oral versus intravenous dexamethasone in patients hospitalized with community-acquired pneumonia. Br J Clin Pharmacol, 78:1, 78–83. doi.org/10.1111/bcp.12295

Sterne et al., the REACT working group, Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19, A Meta-analysis, The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, JAMA 2020, doi:10.1001/jama.2020.17023

Tomazini et al., the COALITION COVID-19 Brazil III Investigators. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19, The CoDEX Randomized Clinical Trial, JAMA 2020,doi 10.1001/jama.2020.1702

Veronese N, Demurtas J, Yang L, et al. Use of Corticosteroids in Coronavirus Disease 2019 Pneumonia: A Systematic Review of the Literature. Front Med (Lausanne). 2020;7:170. Published 2020 Apr 24. doi:10.3389/fmed.2020.00170

Villar et al, Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. Trials; 2016; 17, 342 (2016). doi.org/10.1186/s13063-016-1456-4

Villlar et al, Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. The Lancet, 2020;8, 3, 267-276, doi.org/10.1016/S2213-2600(19)30417-5

Wang, Y., Jiang, W., He, Q. et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Sig Transduct Target Ther, 2020; 5, 57.

Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19 [published online ahead of print, 2020 Apr 9]. Clin Infect Dis. 2020;ciaa351. Doi:10.1093/cid/ciaa351

Yang JW, Yang L, Luo RG, Xu JF. Corticosteroid administration for viral pneumonia: COVID-19 and beyond [published online ahead of print, 2020 Jun 27]. Clin Microbiol Infect. 2020;S1198-743X(20)30364-5. doi:10.1016/j.cmi.2020.06.020

Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis [published online ahead of print, 2020 May 14]. CMAJ. 2020;cmaj.200645. doi:10.1503/cmaj.200645

Yuan M, Xu X, Xia D, et al. Effects of Corticosteroid Treatment for Non-Severe COVID-19 Pneumonia: A Propensity Score-Based Analysis [published online ahead of print, 2020 Jun 2]. *Shock*. 2020;10.1097/SHK.0000000000001574. doi:10.1097/SHK.0000000000001574

Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk Factors of Severe Disease and Efficacy of Treatment in Patients Infected with COVID-19: A Systematic Review, Meta-Analysis and Meta-Regression Analysis [published online ahead of print, 2020 May 14]. Clin Infect Dis. 2020;ciaa576. Doi:10.1093/cid/ciaa576.

7. Annex

Product Information

(for dexamethasone only-containing oral or IV medicinal products)

[The product information may be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

A. Summary of Product Characteristics

[…]

Section 4.1 – Therapeutic indications

[…]

<Invented name> is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

[…]

Section 4.2 – Posology and methods of administration

[…]

For the treatment of Covid-19

Adult patients 6 mg IV or PO, once a day for up to 10 days.

Paediatric population

Paediatric patients (adolescents aged 12 years and older) are recommended to take 6mg/dose IV or PO once a day for up to 10 days.

Duration of treatment should be guided by clinical response and individual patient requirements.

Elderly, renal impairment, hepatic impairment

No dose adjustment is needed.

[…]

Section 4.4 – Special warnings and precautions for use

[…]

Systemic corticosteroids should not be stopped for patients who are already treated with systemic (oral) corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease) but not requiring supplemental oxygen.

[…]

Section 5.1 - Pharmacodynamic properties

[…]

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY,)[5] is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

The trial was conducted at 176 hospital organizations in the United Kingdom.

There were 6425 Patients randomised to receive either dexamethasone (2104 patients) or usual care alone (4321 patients). 89% of the patients had laboratory-confirmed SARS-CoV-2 infection.

At randomization, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non invasive ventilation), and 24% were receiving neither.

The mean age of patients was 66.1+/-15.7 years. 36% of the patients were female. 24% of patients had a history of diabetes, 27% of heart disease and 21% of chronic lung disease.

Primary endpoint

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001).

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% versus 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving supplementary oxygen without invasive mechanical ventilation (23.3% versus 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94).

There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% versus 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

Secondary endpoints

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days versus 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

In line with the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only (rate ratio, 1.15 ;95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen (rate ratio, 0.96 ; 95% CI 0.85-1.08).

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

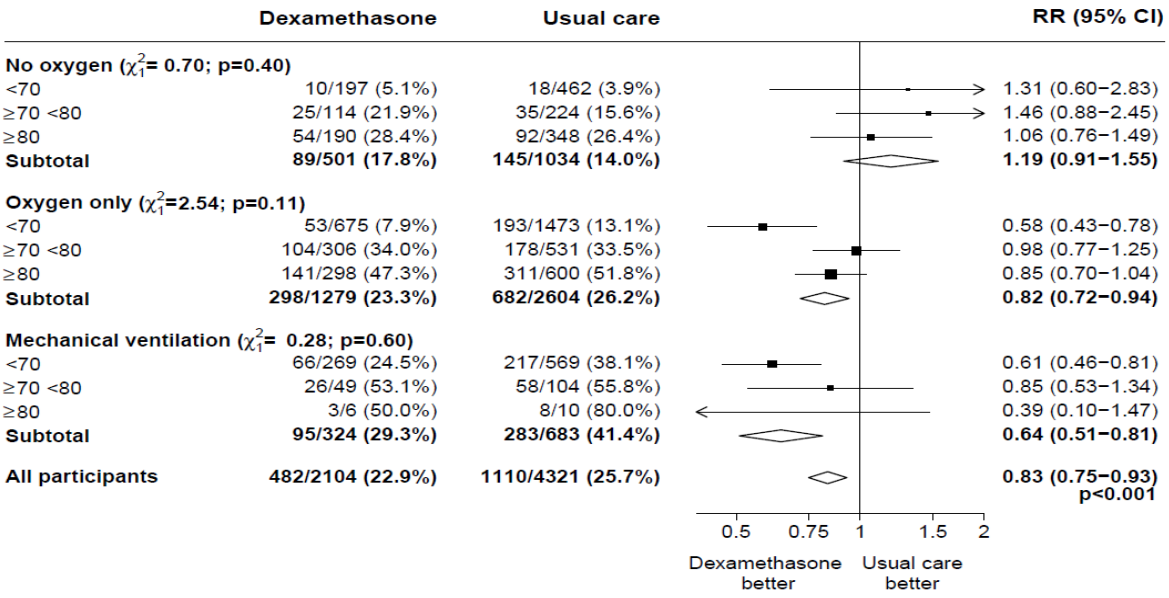
[5] www.recoverytrial.net

Safety

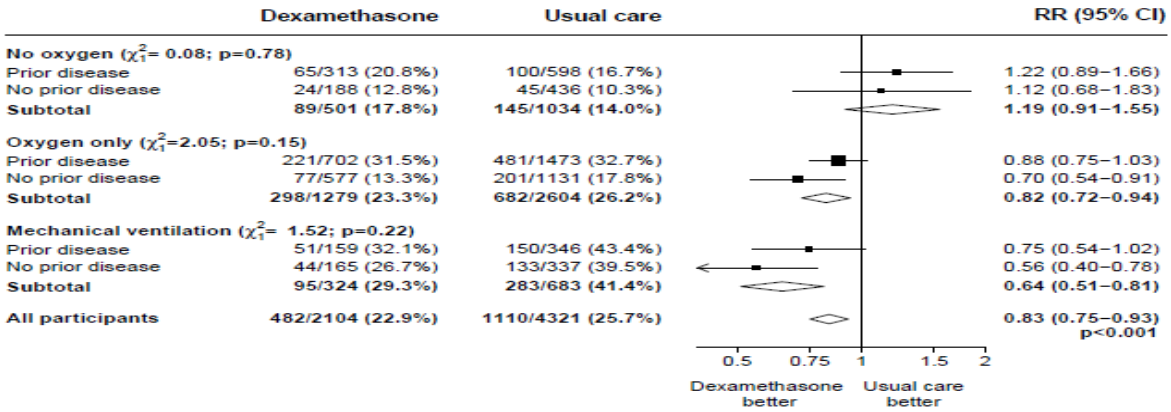
There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

Effects of allocation to DEXAMETHASONE on 28−day mortality, by age and respiratory support received at randomisation[6]



Effects of allocation to DEXAMETHASONE on 28−day mortality, by respiratory support received at randomisation and history of any chronic disease.[7]



[6, 3] (source: Horby P. et al., 2020; https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1 ; doi: https://doi.org/10.1101/2020.06.22.20137273)

Package Leaflet

1. What <invented name> is and what it is used for

Dexamethasone is a synthetic glucocorticoid (adrenocortical hormone)

[…]

<invented name> is used as a treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) with difficulty breathing and need of oxygen therapy.

[…]

2. What you need to know before you <take> <use> <invented name>

[…]

You should not stop taking any other steroid medications unless your doctor has instructed you to do.

Talk to your doctor, pharmacist or nurse before you take <invented name>.

General precautions regarding steroid use in specific diseases, masking infection, concomitant medicines etc. in line with current recommendations.

[…]

3. How to <take> <use> <invented name>

[…]

Take <invented name> as only as prescribed by your doctor. Your doctor will decide how long you should take dexamethasone for. Check with your doctor or pharmacist if you are not sure.

For the treatment of Covid-19

Adult patients are recommended to <take> <be given> *[PO or IV; amend to specific formulation, as appropriate]* 6 mg once a day for up to 10 days.

Use in adolescents

Paediatric patients (adolescents of 12 years of age or older) are recommended to <take> <be given> *[PO or IV amend to specific formulation, as appropriate]* 6 mg once a day for up to 10 days.

[…]