EMA/691378/2020
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

CHMP assessment report

Procedure No. EMEA/H/C/005622/II/0012

Invented name: Veklury

International non-proprietary name: remdesivir

Marketing authorisation holder (MAH): Gilead Sciences Ireland UC

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 31 August 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	II

Submission of the final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1), listed as a Specific Obligation ('SOB 13') in the Annex II of the Product Information, in order to confirm the efficacy and safety of Remdesivir in patients on Invasive Mechanical Ventilation (IMV) and Extracorporeal Membrane Oxygenation (ECMO). In addition, the MAH discusses the potential imbalance in the use of corticosteroids and effect modification in the study.

The requested variation proposed amendments to the Annex II to the EC Decision on the granting of the conditional marketing authorisation in order to remove 'SOB 013'.

GLP/GCP inspections

N/A

2. Overall conclusion and impact on the benefit/risk balance

Clinical discussion (1st round)

Remdesivir was given a 'conditional marketing authorisation' in the EU on 3 July 2020 for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen (oxygen via nasal cannula, non-invasive ventilation or high flow oxygen devices, IMV or ECMO).

The pivotal NIAID-ACTT1 (CO-US-540-5776) study was a randomised, double-blinded and placebo controlled study conducted in hospitalised patients with COVID-19, with evidence of lower respiratory tract involvement. Treatment with Remdesivir or placebo, each on top of standard of care was for up to 10 days. The primary endpoint was time to recovery (defined as the first day of no longer being hospitalised or being hospitalised but no longer requiring medical care).

According to the inferential analysis, the median difference in time to recovery was 4 days favouring the Remdesivir group. In the primary endpoint Remdesivir was hence superior to placebo in the treatment of hospitalized participants with COVID-19 (HR: 1.32, 95% CI 1.12 to 1.55; p<0.001).

In the stratum of patients with "severe disease" (with pneumonia and need for supplemental oxygen), representing approximately 90% of patients in the study, the difference in median time to recovery was 12 versus 18 days, the RR was 1.37 (95% CI 1.15-1.163; p<0.001). No difference in time to recovery was seen in the stratum of "mild-moderate disease".

While the differentiation according to disease strata have been discussed and agreed by CHMP for the CMA, a higher degree of granularity with respect to subgroup analyses *within* the stratum of the severely ill patients was seen critical at the time of CMA in June 2020 and further data were requested, which are subject of this Specific Obligation ('SOB 013').

In the meantime, a number of studies, i.e. the Solidarity study [(1)] , the Recovery study [(2)], Tocilizumab trials[(3)(4)(5)] and Bamlanivimab[(6)] have become available to show that these subgroups would deserve to be carefully looked at separately, since the pathophysiology of the disease changes with severity and, hence, a uniform treatment response cannot be assumed since this is driven by the agent's mechanism of action, which, in turn, may be disease-stage dependent.

Moreover, no difference was seen in time to recovery in patients who started Remdesivir when they were already on IMV or ECMO (baseline ordinal score 7), the HR was 0.98 (95% CI 0.70-1.36). Therefore, CHMP requested the MAH to submit additional data including data on 28-day all-cause mortality as a SOB, in order to better characterise the efficacy and safety of Remdesivir in patients, particularly in this patient group.

The MAH has now submitted the final Day 28 mortality data by ordinal score category of the pivotal study (NIAID-ACTT1), listed as SOB 13 in the Annex II, in order to confirm the efficacy and safety of Remdesivir in patients on IMV or ECMO. In addition, data on the use of corticosteroids and potential effect modification in Study CO-US-540-5776 were provided.

With respect to Day-28 all-cause mortality, the data indicate a numerically lower risk of mortality for Remdesivir in the overall population (both strata). However, this effect is mainly driven by patients requiring supplemental oxygen (baseline ordinal score of 5). Between-group results vary considerably according to baseline disease severity. Neither for the subgroup with a baseline ordinal score of 6 (non-invasive ventilation or high flow oxygen devices), nor for the subgroup with a baseline ordinal score of 7 (IMV or ECMO) a beneficial effect was conclusively seen: not for time to recovery, and neither for mortality.

In contrast, the results may be indicative of a negative trend in patients on IMV or ECMO (21.9% vs. 19.3%, respectively, RR 1.13; CI 0.67, 1.89).

In addition, the interaction tests between treatment effect and baseline ordinal score indicate a reduced or even lack of efficacy in the higher baseline ordinal scores (of 6 and 7) with respect to time to recovery and mortality.

These results would substantiate the concept of a temporal window of opportunity for an antiviral substance, such as Remdesivir, in COVID-19. Based on the currently available data this window appears to be limited to patients in need of supplementary oxygen at high risk for disease progression but not yet suffering from more severe pulmonary affection. An effect of Remdesivir has not be observed in patients with more advanced disease, as their disease course is rather driven by the host inflammatory response than by the virus, and hence Remdesivir as antiviral drug may not have a benefit here.

These considerations are further supported by the recently published interim results of the WHO-SOLIDARITY trial that also indicate a negative trend in mortality in this patient population hospitalised for COVID-19. While in the analysis of the 28-day in-hospital mortality data in the overall population no definite effect of Remdesivir on mortality was seen (RR 0.95 [0.85-1.11, p=0.50), subgroup analyses stratified by ventilation status at randomisation did also show a negative trend in mortality in patients already ventilated at baseline (RR: 1.20, CI [0.89-1.64, p = 0.24] compared to patients not receiving ventilation at study entry (RR: 0.86 [0.72-1.04) although data did not reach statistical significance. Even when considering the uncertainties concerning subgroup analyses due to their limited sample sizes, the analyses indicate that Remdesivir may have no benefit in the population of critically ill COVID-patients.

However, comparisons of the D28 mortality data from different trials should be interpreted with some caution, due to questionable comparability of ventilation status between the different trials and also differences in the mortality endpoints (in-house mortality in Solidarity versus all-cause mortality in the NIAID trial).

Clinical discussion (2nd round):

During the assessment of this variation a major objection (MO) was raised at the first round, in which the MAH was explicitly asked to justify a favourable risk-benefit profile based on the overall available evidence in patients on IMV or ECMO when starting Remdesivir. However, in the response the MAH only addressed the potential risk/harmful effects of remdesivir in the subgroup of patients on IMV or ECMO at baseline but neither the observerd missing benefit on Time to recovery (TTR), the primary efficacy endpoint of this study, nor on mortality in patients with baseline ordinal score 7.

The analyses of efficacy in the subset of participants on invasive mechanical ventilation or ECMO at baseline do not indicate any benefit of RDV, neither for the time to recovery (HR: 0.98; CI 0.70, 1.36), nor for mortality (RR: 1.13; CI 0.67, 1.89; p = 0.652).

This is further supported by the requested additional mortality analyses for specific subgroups. The hazards of death in the subgroup of ventilated patient, i.e. those on non-invasive ventilation, invasive mechanical ventilation or ECMO at baseline (HR: 1.12; CI 0.7, 1.82) and for patients on non-invasive ventilation (HR: 1.11; CI 0.32, 3.83), were both similar to the results seen in patients on IMV/ECMO (HR: 1.13; CI 0.67, 1.89; p = 0.652), suggesting that being ventilated at the time of RDV treatment initiation may not be beneficial. Results for the primary endpoint 'Time to Recovery' for the subgroup of ventilated patients (non-invasive and invasive/ECMO) are not yet available. Hence, it remains unclear if RDV has a beneficial effect in this patient population.

In addition, the statistically significant effect of RDV treatment, when given during the first 10 days after symptom onset (RR: 1.37 CI. 1.14; 1.64) further supports that there is a temporal "window of opportunity" for RDV treatment at an earlier disease stage, while deterioration to IMV/ECMO has been reported to occur later in COVID-19.

It is also noted that based on these subgroup analyses and clinical experience, several national treatment guidelines and learned societies in the EU already do not recommend treatment with RDV in patients receiving IMV or ECMO at baseline and with onset of symptoms more than (5 to) 10 days ago.

Overall conclusion:

No difference was seen in time to recovery in patients who started Remdesivir when they were already on IMV or ECMO (baseline ordinal score 7), the HR was 0.98 (95% CI 0.70-1.36). Therefore, CHMP requested the MAH to submit additional data including data on 28-day all-cause mortality as 'SOB 013', in order to confirm the efficacy and safety of Remdesivir in patients on IMV or ECMO. The provided data failed to confirm the efficacy of RDV in patients on IMV or ECMO at baseline, in terms of mortality (RR: 1.13; CI 0.67, 1.89; p = 0.652).

Risk-benefit considerations triggered by the inconsistency of beneficial effect at primary and secondary endpoints analyses among the overall study population and subjects of patients on IMV or ECMO are regarded as credible because of the biological plausibility, and directional consistency. In addition, these results are corroborated by evidence coming from other independent trials [(1)(2)(3)(4)(5)(6)].

The CHMP concluded that taking the lack of evidence to support benefit in this subgroup into account, the B/R in this subgroup of patients has not been shown to be positive.

Therapy of patients on IMV/ECMO at baseline should no longer be indicated for RDV. Therefore, the wording of the therapeutic indication is revised accordingly by restricting the target population in section 4.1 of the

SmPC. Section 5.1 of the SmPC is also updated to reflect the study results, and the Annex II is updated to remove the completed specific obligation ('SOB 013'). The package leaflet is updated accordingly.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	I, II and IIIB

Update of section 4.1 of the SmPC to change the indication as a result of the assessment of the final D28 mortality data by ordinal scale categories of Study COUS-540-5776 (NIAID-ACTT1), listed as a Specific Obligation ('SOB 013') in the Annex II of the Product Information, in order to confirm the efficacy and safety of remdesivir in patients on Invasive Mechanical Ventilation and Extracorporeal Membrane Oxygenation (IMV/ECMO). Consequently section 5.1 of the SmPC is also updated to reflect the final study results. Furthermore, Annex II is updated to remove the completed specific obligation. The package leaflet is updated accordingly.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB are recommended as follows:

Taking the lack of evidence for a benefit in patients on IMV/ECMO into account, the B/R in this subgroup has not been shown to be positive. Therefore, the indication is restricted and patients on IMV/ECMO at baseline are excluded from the therapeutic indication of RDV. The wording of SmPC Section 4.1 is amended as follows:

- *Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen* ***(low- or high-flow oxygen or non-invasive ventilation at start of treatment)*** *(see section 5.1).*

In addition, section 5.1 of the SmPC is updated with the data from the post-hoc analysis of 28-day mortality by ordinal scale.

Annex II is updated to remove the completed specific obligation ('SOB 013').

The Package Leaflet is updated accordingly.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Veklury/H/C/005622/II/0012

Annex: CHMP assessment comments on the type II variation

5. Introduction

Veklury received a 'conditional marketing authorisation' in the EU on 3 July 2020 for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen, because the benefits to these severely ill patients outweigh the risks of making the medicine available despite having less complete data than normally expected.

At the time of authorisation, CHMP requested the MAH to submit additional data, either as specific obligations (SOB) or PAMs.

The current variation concerns the assessment of SOB No. 13, which was agreed on at the time of conditional marketing authorisation of Veklury. The MAH has now submitted the publication of the final results of Study CO-US-540-5776 (NIAID-ACTT1; Beigel *et al*., 2020 DOI: 10.1056/NEJMoa2007764) [(7)] that includes the final D28 mortality data by ordinal scale categories, listed as a Specific Obligation No. 13 in the Annex II of the EPAR - Product Information, in order to confirm the efficacy and safety of Remdesivir in patients on IMV or ECMO. In addition, data on the potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776 were provided.

6. Clinical Efficacy aspects

6.1. Final Day-28 mortality data by ordinal score of Study CO-US-540-5776 (NIAID-ACTT1)

Methods – analysis of data submitted

At the time of conditional marketing authorisation, data on the key secondary endpoint "Mortality at D28" were not available, as not all patients did have their 28-day visit. Now the publication of the final results of the NIAID-ACTT1 study, including the final D28 mortality data, have been submitted by the MAH {Beigel et al, 2020}. These are summarized below, supplemented with information from the study report, which was also submitted. However, the assessment of the complete CSR will be subject to the renewal procedure.

Statistical methods:

Mortality through Day 15 and Day 29 was analysed as a time-to-event endpoint and presented with median time-to-event along with 95% CIs for each treatment group along with the HR estimate and stratified log-rank p-values. Differences in time-to-event endpoints by treatment were summarized with KM curves. Analyses of mortality were performed on the ITT- and As Treated-Populations. Any participants who were lost to follow-up or terminated early prior to death were censored at the day of their last observed assessment or last captured event (e.g., the end date of an AE). If it was learned that a participant who terminated early had subsequently died prior to Day 29, then the participant was classified as dead. Participants who completed follow-up were censored at the earliest of their Day 29 visit and actual Day 29. Deaths that occurred after Day 29 were censored at Day 29.

CHMP's comment

Standard time to event methods were applied that are appropriate.

Results

Mortality (CSR):

Mortality status at day 29 was available for 508/541 patients in the RDV group and 499/521 patients in the Placebo group.

Table 1: Mortality data of patients with known mortality status at D29

	Overall		Mild-Moderate Disease		Severe Disease	
	RDV (N = 541)	Placebo (N = 521)	RDV (N = 55)	Placebo (N = 50)	RDV (N = 486)	Placebo (N = 471)
Mortality among all participants						
No. with known mortality status at Day 29 (% of total)	508 (93.9)	499 (95.8)	51 (92.7)	46 (92.0)	457 (94.0)	453 (96.2)
No. of deaths by Day 29 (% of no. with known mortality status at Day 29)	59 (11.6)	77 (15.4)	2 (3.9)	3 (6.5)	57 (12.5)	74 (16.3)

In the ITT Population, the mortality rate (95% CI) of participants by Day 15 was numerically lower in the RDV 10-day group (n = 541) than in the placebo group (n = 521) (7% [5%, 9%] versus 12% [9%, 15%], respectively).The mortality rate (95% CI) of participants by Day 29 was numerically lower in the RDV 10-day group than in the placebo group) (11% [9%, 15%] versus 15% [12%, 19%], respectively). Results were similar in the As Treated Population.

In the ITT Population, the risk of death by Day 15 was significantly lower in the RDV 10-day group compared with the placebo group (HR 0.55; 95% CI: 0.36, 0.83; p = 0.004) (Table 2). The risk of death by Day 29 was numerically lower in the RDV 10-day group compared with the placebo group (HR 0.73; 95% CI: 0.52, 1.02; p = 0.066). Results were similar in the As Treated Population.

In the ITT Population, the median time to death through Day 15 or Day 29 was not estimable for either treatment group.

Table 2: Deaths by Day 15 or Day 29 by treatment group ITT and as treated

		Remdesivir				Placebo			
Analysis Population	Study Day	N	n	Mortality Rate[a]	Rate 95% CI	N	n	Mortality Rate[a]	Rate 95% CI
ITT Population	Day 15	541	35	0.07	0.05, 0.09	521	61	0.12	0.09, 0.15
	Day 29	541	59	0.11	0.09, 0.15	521	77	0.15	0.12, 0.19
As Treated Population	Day 15	532	35	0.07	0.05, 0.09	516	61	0.12	0.09, 0.15
	Day 29	532	59	0.11	0.09, 0.14	516	77	0.15	0.12, 0.19

N = Number of subjects in the specified treatment group and analysis population.
n = Number of subjects in a given treatment group who died by the given timepoint
a Mortality rate is the Kaplan-Meier estimate.
Source: Section 15.1, Table 59

Ad Hoc Subgroup Analyses for Mortality (CSR)

Ad hoc subgroup analyses were performed for mortality by actual disease stratum or ordinal score. In the analyses according to actual disease stratum, the percentages of deaths among participants with known mortality status at Day 29 in the RDV 10-day group compared with those in the placebo group were as follows (Table 3):

Severe disease:

- 12.5% (57 of 457 participants) versus 16.3% (74 of 453 participants), respectively.

Mild-to-moderate disease:

- 3.9% (2 of 51 participants) versus 6.5% (3 of 46 participants), respectively.

Table 3: Mortality rates by treatment group and actual disease severity (ITT population)

	Overall		Mild-Moderate Disease		Severe Disease	
	RDV (N = 541)	Placebo (N = 521)	RDV (N = 55)	Placebo (N = 50)	RDV (N = 486)	Placebo (N = 471)
Mortality among all participants						
No. with known mortality status at Day 29 (% of total)	508 (93.9)	499 (95.8)	51 (92.7)	46 (92.0)	457 (94.0)	453 (96.2)
No. of deaths by Day 29 (% of no. with known mortality status at Day 29)	59 (11.6)	77 (15.4)	2 (3.9)	3 (6.5)	57 (12.5)	74 (16.3)
Mortality among participants crossing over from placebo to RDV						
No. unblinded (% of total)	16 (3.0)	35 (6.7)	0 (0.0)	1 (2.0)	16 (3.3)	34 (7.2)
No. crossovers from placebo to RDV arm (% of no. unblinded)	—	26 (74.3)	—	1 (100.0)	—	25 (73.5)
No. with known mortality status at Day 29[a] (% of no. crossovers)	—	26 (100.0)	—	1 (100.0)	—	25 (100.0)
No. of deaths by Day 29 (% of no. crossovers with known mortality status at Day 29)	—	3 (11.5)	—	0 (0.0)	—	3 (12.0)

Number with known mortality status at Day 29 is the number of participants who have data for a day on or after Day 26 or who are known to be deceased. Day 26 represents the beginning of the visit window for the Day 29 visit.
Source: Section 15.1, Addendum Table 16.2

In analyses according to baseline ordinal scores 4, 5, 6, and 7, the greatest difference in percentages of deaths among participants with known mortality status at Day 29 in the RDV 10-day group compared with that in the placebo group was observed in the subgroup with baseline ordinal score 5 (4.1% [9 of 222 participants] versus 12.8% [25 of 195 participants], respectively; HR [95% CI] = 0.30 [0.14, 0.64], p < 0.001) (Table 5). In none of the other subgroups (baseline ordinal scale 4, 6 and 7) a significant effect of Remdesivir on mortality was seen. In patients with baseline ordinal score 7, the percentage of death was larger at D29 in the Remdesivir group compared to the placebo group (22% [28 of 131 participants] vs. 19.6% [29 of 154 patients] respectively HR [95%] = 1.31 [0.67, 1.89].

Table 4: Mortality rates by treatment group and baseline ordinal score (ITT population)

Table 28. CO-US-540-5776: Mortality Rates by Treatment Group and Baseline Ordinal Score (ITT Population)

	Overall		Baseline Ordinal Score 4		Baseline Ordinal Score 5		Baseline Ordinal Score 6		Baseline Ordinal Score 7	
	RDV (N = 541)	Placebo (N = 521)	RDV (N = 75)	Placebo (N = 63)	RDV (N = 232)	Placebo (N = 203)	RDV (N = 95)	Placebo (N = 98)	RDV (N = 131)	Placebo (N = 154)
Mortality among all participants										
No. with known mortality status at Day 29 (% of total)	508 (93.9)	499 (95.8)	72 (96.0)	59 (93.7)	222 (95.7)	195 (96.1)	87 (91.6)	97 (99.0)	127 (96.9)	148 (96.1)
No. of deaths by Day 29 (% of no. with known mortality status at Day 29)	59 (11.6)	77 (15.4)	3 (4.2)	3 (5.1)	9 (4.1)	25 (12.8)	19 (21.8)	20 (20.6)	28 (22.0)	29 (19.6)
Hazard ratio (95% CI)	0.73 (0.52, 1.02)[a]		0.82 (0.17, 4.07)[b]		0.30 (0.14, 0.64)[b]		1.02 (0.54, 1.91)[b]		1.13 (0.67, 1.89)[b]	
P-value	0.066[c]		0.809[d]		<0.001[d]		0.949[d]		0.652[d]	
Mortality among participants crossing over from placebo to RDV										
No. unblinded (% of total)	16 (3.0)	35 (6.7)	0 (0.0)	2 (3.2)	1 (0.4)	6 (3.0)	9 (9.5)	8 (8.2)	6 (4.6)	19 (12.3)
No. crossovers from placebo to RDV arm (% of no. unblinded)	—	26 (74.3)	—	1 (50.0)	—	4 (66.7)	—	5 (62.5)	—	16 (84.2)
No. with known mortality status at Day 29 (% of no. crossovers)	—	26 (100.0)	—	1 (100.0)	—	4 (100.0)	—	5 (100.0)	—	16 (100.0)
No. of deaths by Day 29 (% of no. crossovers with	—	3 (11.5)	—	0 (0.0)	—	2 (50.0)	—	0 (0.0)	—	1 (6.3)

	Overall		Baseline Ordinal Score 4		Baseline Ordinal Score 5		Baseline Ordinal Score 6		Baseline Ordinal Score 7	
	RDV (N = 541)	Placebo (N = 521)	RDV (N = 75)	Placebo (N = 63)	RDV (N = 232)	Placebo (N = 203)	RDV (N = 95)	Placebo (N = 98)	RDV (N = 131)	Placebo (N = 154)
known mortality status at Day 29)										

Number with known mortality status at Day 29 is the number of participants who have data for a day on or after Day 26 or who are known to be deceased. Day 26 represents the beginning of the visit window for the Day 29 visit.

a HR is the ratio of the hazard of Death in each treatment group estimated from the stratified Cox model. The ratio is remdesivir to placebo.

b HR is the ratio of the hazard of Death in each treatment group estimated from the Cox model. The ratio is remdesivir to placebo

c P-value calculated using the stratified log-rank test

d P-value calculated using the log-rank test

Source: Section 15.1, Table 61, Addendum Table 16.1, and Addendum Table 22

The main outcomes overall and according to baseline ordinal score in the ITT-population, including outcomes on time to recovery and mortality described in the publication of Beigel et. al. 2020 are shown in Table 5 below:

Table 5 Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.

	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7)	7 (6–8)	9 (7–10)	15 (10–27)	20 (14–26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3–12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0	0	0	0
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.
† Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; the P value for this ratio was calculated with the stratified log-rank test (overall model stratified by actual disease severity). Recovery rate ratios greater than 1 indicate a benefit with remdesivir; hazard ratios less than 1 indicate a benefit with remdesivir.
‡ Mortality over the first 14 days includes data from all patients who were still alive through 14 days postenrollment, with data censored on day 15, as if 14 days was the maximum follow-up time. Mortality over the entire study period uses the totality of the study data and censors data from patients who completed follow-up alive at 28 days postenrollment.
§ The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. Four patients died 15 days after randomization and are recorded as having died for the ordinal score at the day 15 outcome but not for the mortality day 15 outcome. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Odds ratios and P values were calculated with the use of a proportional odds model (overall model adjusted for actual disease severity). Odds ratio values greater than 1 indicate a benefit with remdesivir.

Beigel et al, NEJM, October 2020.

The Kaplan Meier Estimates of survival by baseline ordinal score and the respective 95 % confidence intervals are shown in the figures below. In the overall population, the KM survival curves separated after approximately 5 days of study treatment, implying a lower mortality rate in the RDV-group versus the placebo group starting from Day 5 in the overall study population (Figure 1). The KM survival curves by baseline ordinal score demonstrate that the between-group differences in mortality vary considerably according to baseline disease severity, with the largest difference seen in patients with a baseline ordinal score of 5 (Figure 3), no effect in patients with baseline ordinal score 4 (Figure 2) and 6 (Figure 4) and an increased risk of mortality in patients with baseline ordinal scale 7 (Figure 5B).

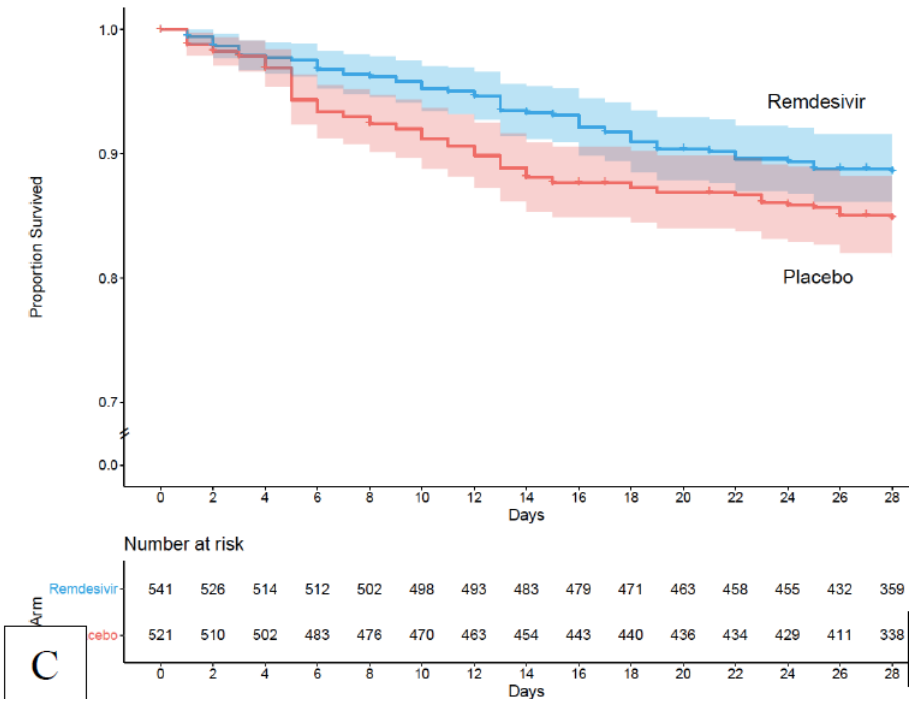

Figure 1: Kaplan-Meier Estimates of Survival Overall. The widths of confidence intervals have not been adjusted for multiplicity.

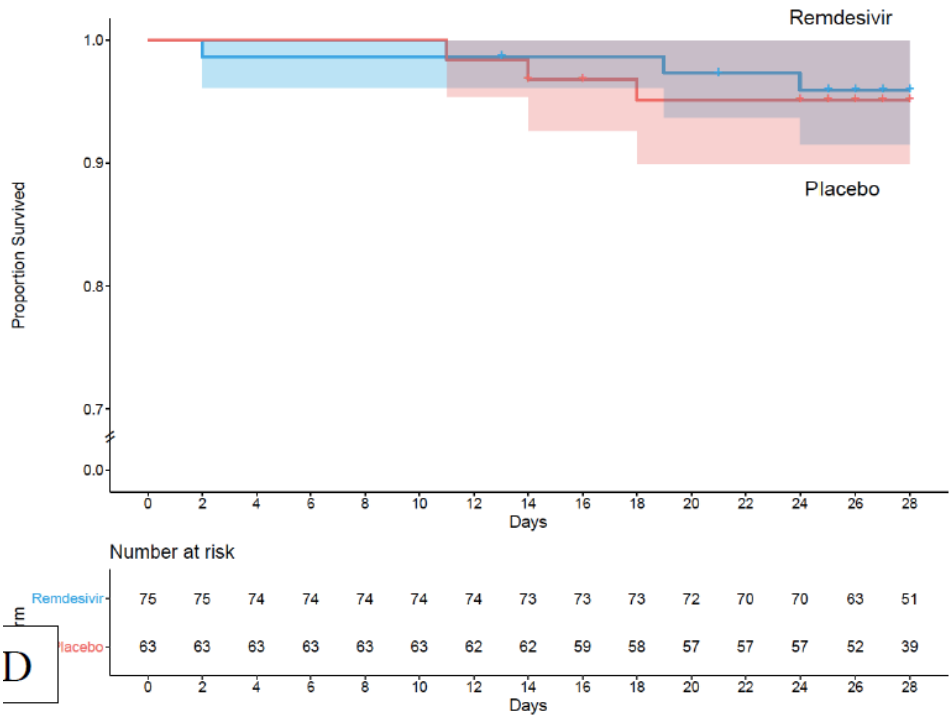

Figure 2: Kaplan-Meier Estimates of Survival by Baseline Ordinal Scale Category 4, The widths of confidence intervals have not been adjusted for multiplicity.

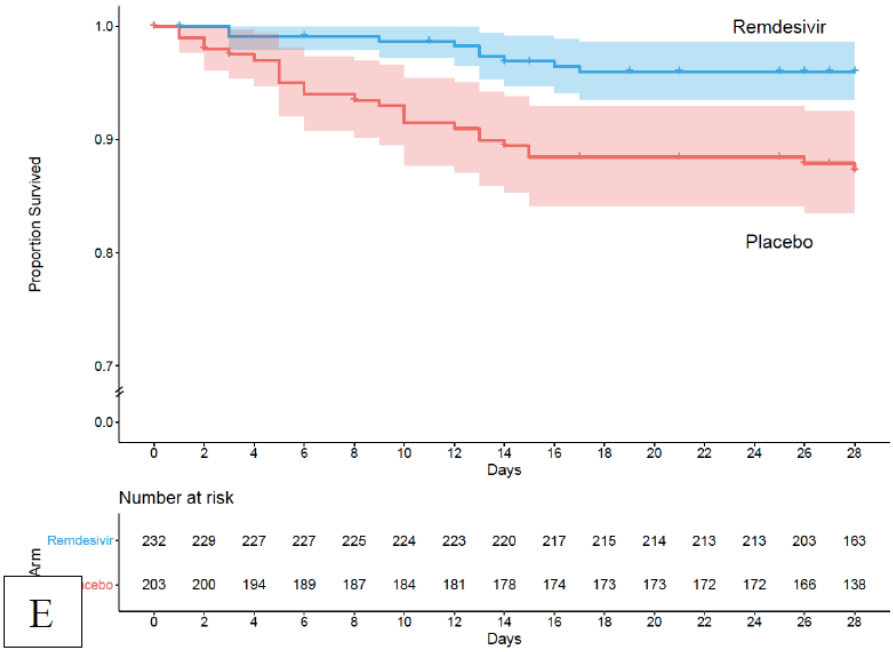

Figure 3: Kaplan-Meier Estimates of Survival by Baseline Ordinal Scale Category 5. The widths of confidence intervals have not been adjusted for multiplicity.

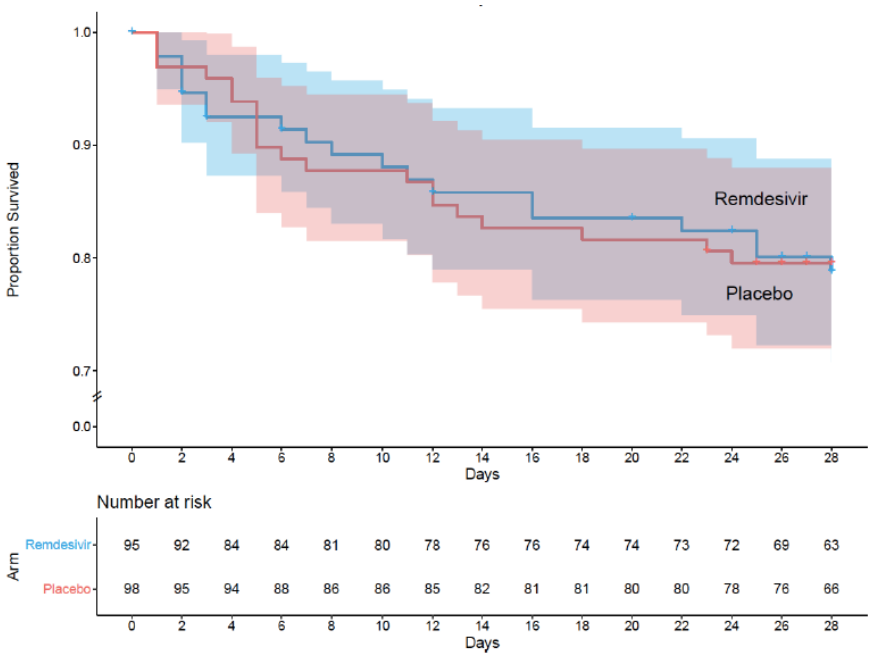

Figure 4: Kaplan-Meier Estimates of Survival by Ordinal Scale Category 6. The widths of confidence intervals have not been adjusted for multiplicity.

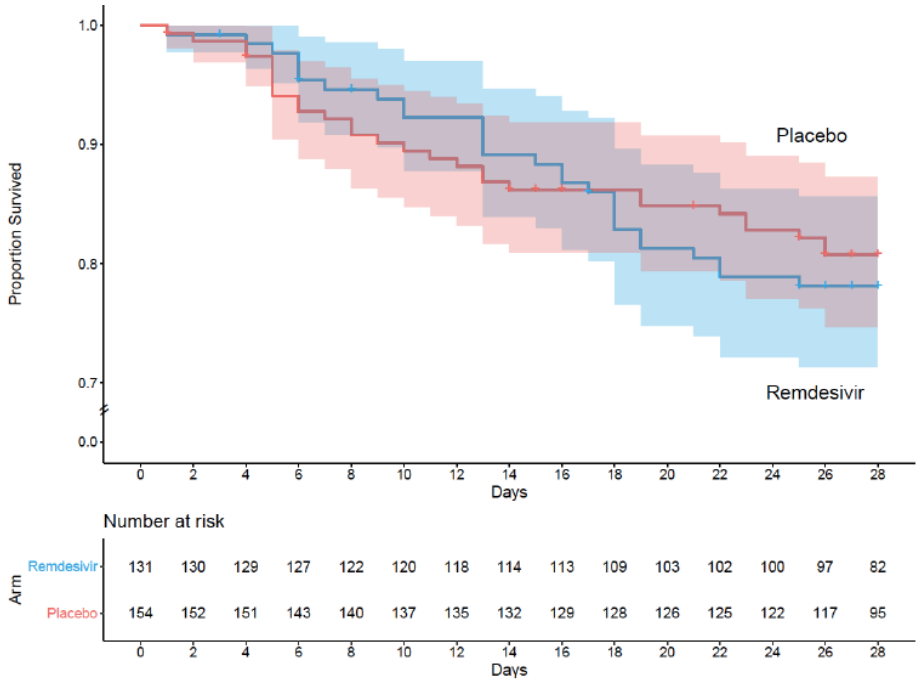

Figure 5B Kaplan-Meier Estimates of Survival by Ordinal Scale Category 7. The widths of confidence intervals have not been adjusted for multiplicity.

Figures taken from Beigel et al, NEJM, October 2020.

Information on interactions between treatment effect and baseline ordinal score with respect to mortality and time to recovery are shown in Table 6 below.

Table 6: Results of Cox proportional hazards models testing for interactions between treatment effect and baseline ordinal scale with respect to mortality

Cox Proportional Hazards Model	Group	HR (95% CI)
Mortality		
Model 4 – Mortality with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as continuous • Model terms: treatment, continuous baseline ordinal score, interaction between treatment and ordinal score	Baseline Score 4	0.34 (0.15,0.76)
	Baseline Score 5	0.50 (0.30,0.85)
	Baseline Score 6	0.75 (0.53,1.07)
	Baseline Score 7	1.13 (0.71,1.79)
Model 5 – Mortality with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal scores grouped as 4/5 versus 6/7 • Model terms: treatment, grouped baseline ordinal score, interaction between treatment and grouped ordinal score	Baseline Score 4/5	0.36 (0.18,0.70)
	Baseline Score 6/7	1.08 (0.73,1.62)
Model 6 – Mortality with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as categorical • Model terms: treatment, categorical baseline ordinal score, interaction between treatment and categorical ordinal score	Baseline Score 4	0.83 (0.17,4.13)
	Baseline Score 5	0.30 (0.14,0.64)
	Baseline Score 6	1.02 (0.55,1.92)
	Baseline Score 7	1.12 (0.67,1.89)

Cox Proportional Hazards Model	Group	HR (95% CI)
Recovery		
Model 1 – Time to recovery with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as continuous • Model terms: treatment, continuous baseline ordinal score, interaction between treatment and ordinal score	Baseline Score 4	1.59 (1.24,2.03)
	Baseline Score 5	1.37 (1.17,1.60)
	Baseline Score 6	1.18 (1.00,1.40)
	Baseline Score 7	1.02 (0.77,1.35)
Model 2 – Time to recovery with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal scores grouped as 4/5 versus 6/7 • Model terms: treatment, grouped baseline ordinal score, interaction between treatment and grouped ordinal score	Baseline Score 4/5	1.47 (1.23,1.76)
	Baseline Score 6/7	1.03 (0.81,1.32)
Model 3 – Time to recovery with interaction term for treatment effect by baseline ordinal score; • Baseline ordinal score treated as categorical • Model terms: treatment, categorical baseline ordinal score, interaction between treatment and categorical ordinal score	Baseline Score 4	1.36 (0.97,1.93)
	Baseline Score 5	1.51 (1.23,1.86)
	Baseline Score 6	1.10 (0.76,1.58)
	Baseline Score 7	0.97 (0.70,1.36)

CHMP's Comment:

Not for all enrolled patients in the NIAID trial the day-28 mortality status was available. It remains unclear why the mortality status of 19 patients in the RDV group and 13 patients in the placebo group is still missing, although the 29 days after randomization have long been completed and the patients with missing status have not discontinued the study. As the mortality status of patients is considered important, especially for the subgroups, in which even a single death more can make a difference on whether the point estimate for mortality is for or against RDV, the MAH is asked to clarify if these patients are loss to follow up or if they are missing due to other issues, i.e. problems with data transfer from the study centre.

The Day-28 all-cause mortality data indicated a numerically lower risk of mortality for RDV in the overall population (both strata, group [RR 0.73; 95% CI: 0.52, 1.02; p = 0.066]). However, this effect is mainly driven by patients requiring supplemental oxygen (baseline ordinal score of 5).

Between group differences vary considerably according to baseline disease severity. Neither for the subgroup with a baseline ordinal score of 6 (non-invasive ventilation or high flow oxygen devices), nor for the subgroup with a baseline ordinal score of 7 (IMV or ECMO) a beneficial effect was conclusively seen: not for time to recovery (HR: 1.09; CI: 0.76, 1.57 and HR: 0.98; CI 0.70, 1.36, respectively), and neither for mortality (RR: 1.02; CI: 0.54, 1.14; p=0.949 and RR: 1.13; CI 0.67, 1.89; p = 0.652, respectively).

The models including interaction between treatment effect and baseline ordinal scale indicate a reduced or even lack of efficacy in higher ordinal scale categories (ordinal scale 6 and 7) with respect to time to recovery and mortality, while a greater treatment benefit of Remdesivir was seen in lower ordinal scale categories, especially in category 5 (whereby model 4 and model 1 including baseline score as continuous covariate clearly provide a poor fit and should be disregarded, as the proportional hazards assumption for the treatment*baseline score interaction is obviously not fulfilled).

These results would substantiate the concept of a window of opportunity for an antiviral substance, such as Remdesivir, in COVID-19. Based on the currently available data this window appears to be limited to patients in need of supplementary oxygen at high risk for disease progression but not yet suffering from more severe pulmonary affection. An effect of Remdesivir has not be observed in patients with more advanced disease, as their disease course is rather driven by the host inflammatory response than by the virus, and hence Remdesivir as antiviral drug may not have a benefit here.

In order gain further understanding of the effect of Remdesivir on mortality in the subgroup of ventilated patients in the NIAID trial, the MAH is asked to provide:

a. An analysis of mortality in a subgroup of patients comprising those ventilated at the time of randomisation in the NIAID trial, including those on non-invasive ventilation, invasive ventilation and ECMO.

b. A separate analysis of all patients that were categorised in category 6 and received non-invasive ventilation at the time of randomisation.

c. Please provide symptom duration prior to randomisation (median +IQR) per ordinal scale stratum at baseline.

d. Please provide data on the duration of hospitalisation prior to baseline (median + IQR) per ordinal scale stratum at baseline.

e. Please provide key safety indices, including renal events, from the randomised NIAID-ACTT1 study for patients in baseline ordinal scale categories 6 and 7, per treatment arm.

No forest-plots on Day 28 mortality data by baseline ordinal status were provided.

6.2. Potential impact of Corticosteroids on treatment outcomes

Considering the reported outcomes of the Recovery study {The RECOVERY Collaborative Group, 2020}, an interest in combined use of Remdesivir and dexamethasone in the target population is anticipated. At time of the CMA, the extent of such co-administration in the NIAID-ACTT(1) study were unknown.

Now, the publication of the final results of the NIAID-ACTT1 study {Beigel et al, 2020} contains some information on the concomitant use of glucocorticoid. These are summarized below, supplemented with information from the study report, which was also submitted.

Methods – analysis of data submitted

In the severe strata, 105 patients in the Remdesivir group (22% of the 477 patients) and 116 patients in the Placebo group (25% of the 467 patients) received a glucocorticoid (Table 7).

Table 7: Concomitant Medication by Actual Disease Severity and Treatment Group (As Treated Population)

	Remdesivir (N = 532)		Placebo (N = 516)		All Subjects (N = 1048)	
	Mild-Moderate (N = 55)	Severe (N = 477)	Mild-Moderate (N = 49)	Severe (N = 467)	Mild-Moderate (N = 104)	Severe (N = 944)
Medication/Therapies	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Antivirals	—	10 (2)	2 (4)	6 (1)	2 (2)	16 (2)
Polymerase inhibitors	—	2 (< 1)	—	3 (1)	—	5 (1)
Protease inhibitors	—	8 (2)	2 (4)	3 (1)	2 (2)	11 (1)
Corticosteroids	10 (18)	105 (22)	10 (20)	116 (25)	20 (19)	221 (23)
Other anti-inflammatory drugs	5 (9)	37 (8)	7 (14)	30 (6)	12 (12)	67 (7)
Monoclonal antibodies targeting cytokines	1 (2)	22 (5)	3 (6)	23 (5)	4 (4)	45 (5)
Other biologic therapies	4 (7)	17 (4)	4 (8)	9 (2)	8 (8)	26 (3)
Potential treatments for COVID-19	15 (27)	175 (37)	20 (41)	181 (39)	35 (34)	356 (38)
Hydroxychloroquine/Chloroquine	15 (27)	169 (35)	19 (39)	170 (36)	34 (33)	339 (36)
Other	—	8 (2)	1 (2)	13 (3)	1 (1)	21 (2)

N = Number of subjects in the As Treated Population.
n = Number of subjects reporting taking at least one medication in the specified category.
Source: CSR dated 23 Aug 2020, Table 10

CHMP's comment:

Overall, in the severe strata there seems to be no important imbalances between the randomised groups with regard to concomitant use of corticosteroids. However, data regarding corticosteroid doses is not reported. In the Recovery study, patients were treated with a dexamethasone 6 mg once daily for up to ten days. Based on mechanism of action and course of severe viral infections it is likely that the beneficial effect of corticosteroids in these diseases is dependent on the dose administered. Singh AK *et al* (2020) reviewed five 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. Insofar, information regarding corticosteroid doses (e.g. low dose, high dose) is crucial but was insufficiently recorded.

In addition, there was not differentiation between corticosteroids that were initiated before and after enrolment:

	Remdesivir (N=541)	Placebo (N=521)
Number of Subjects with Concurrent CORT Use	115	126
Concurrent CORT First Use Relative to Randomization		
Prior to Enrollment	75 (65.2%)	79 (62.7%)
1	4 (3.5%)	4 (3.2%)
2	8 (7.0%)	8 (6.3%)
3	7 (6.1%)	5 (4.0%)
4	2 (1.7%)	6 (4.8%)
5	3 (2.6%)	6 (4.8%)
6	4 (3.5%)	5 (4.0%)
7	0	2 (1.6%)
8	3 (2.6%)	5 (4.0%)
9	2 (1.7%)	3 (2.4%)
10	3 (2.6%)	0
11	3 (2.6%)	2 (1.6%)
13	1 (0.9%)	1 (0.8%)

Source: Response to Questions SOB013, table req12647.15, p.114

Assessing the influence of post-baseline initiation of corticosteroid treatment is generally difficult as initiation of corticosteroids depends on clinical status of a patient that can be influenced by randomized treatment such that post-baseline differences between treatment groups may be explained by effects of study treatments.

Results

Results of an *ad-hoc* sensitivity analysis of the mortality outcomes to evaluate the effect of concomitant therapy that were intended as treatment for COVID-19 and were given to patients prior to and during the study are reported (Table 8).

Table 8: Time to Death through Day 15 and Day 29 by Treatment Group: Corticosteroid Sensitivity Analysis – ITT Population

				Median Time		HR	
Sensitivity Analysis	Study Day	Treatment Group	n	Estimate	95% CI	Estimate	95% CI
Corticosteroid Use	Day 15	Remdesivir (N=541)	25	NE	NE	0.74	0.44, 1.26
		Placebo (N=521)	32	NE	NE		
	Day 29	Remdesivir (N=541)	41	NE	NE	0.86	0.57, 1.32
		Placebo (N=521)	45	NE	NE		

Subjects that received corticosteroid are censored at time of first corticosteroid use.
NE = Not Estimated. Median was not reached so estimates were not calculated.
N= Number of subjects in the specified treatment group.
n = Number of subjects who died by the specified study day without any prior use of corticosteroids.
HR is the ratio of the hazard of Death in each treatment group estimated from the stratified Cox model. The ratio is Remdesivir to Placebo.
Source: CSR dated 23 Aug 2020, Table 10

CHMP's comment:

The statistical analysis that was provided by the applicant based on a Cox proportional-hazard model including treatment, corticosteroid use, interaction term of treatment and corticosteroid use and additional covariates is considered of limited value.

In the analysis, patients were assigned to the corticosteroid group irrespectively whether treatment was initiated before or after randomization. This is not appropriate: Firstly, this leads to immortal time bias because it is impossible that patients died before initiation of corticosteroid treatment. Secondly, the initiation of corticosteroid treatment after randomization depends on clinical status of a patient which may be influenced by treatment (Remdesivir or placebo). In addition, strata analyses (e.g. mild/moderate vs. severe) would have been required.

Overall, any conclusion from this model is questionable. In addition, concluding from a non-significant interaction effect on no relevant interaction is not valid (absence of evidence is not evidence of absence); the point estimates and confidence intervals should also be considered where some numerical differences are seen.

6.3. Interim WHO SOLIDARITY trial results – Remdesivir data

In early 2020, there were no approved anti-viral treatments for COVID, and WHO expert groups advised that four re-purposed drugs, Remdesivir, Lopinavir (given with Ritonavir, to slow hepatic degradation),

Interferon (β1a), and chloroquine or hydroxychloroquine should be evaluated in an international randomised trial. WHO SOLIDARITY trial is a large, simple, adaptive, multi-country, open label, randomised clinical trial in hospitalised adults. The protocol was designed to involve multiple potentially over-stressed hospitals in multiple countries. To facilitate collaborations even in those overloaded hospitals, patient enrolment and randomisation were done via online procedures and no paperwork was required.

On October 15, interim results of the WHO SOLIDARITY trial were published as a not-peer reviewed preprint on medrxiv. (https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1).[8] Only interim study results concerning Remdesivir are considered relevant for this variation, i.e. mortality data, are summarised and assessed below.

Methods – analysis of data submitted

The WHO SOLIDARITY trial is a large, simple, adaptive, multi-country, open label, randomised clinical trial in hospitalised adults diagnosed with COVID-19 to provide reliable estimates on any effects of these four alternative anti-viral treatments on in-hospital mortality in moderate and in severe COVID.

Study population

Main inclusion criteria

Consenting adults (age ≥18) hospitalised with definite COVID-19, not already receiving any of the study drugs, without known allergy or contra-indications to any of them (in the view of the physician responsible for their care), and without anticipated transfer within 72 hours to a non-study hospital. Patients invited to join the study will be those who are admitted to a collaborating hospital; no wider recruitment efforts were expected.

Exclusion Criteria

Significant contra-indication to any one of the study drugs (e.g., serious chronic liver or heart disease, some concurrent medication or pregnancy).

Data reported before randomisation

Information was entered electronically on

- Country, hospital (from a list of approved hospitals) and randomising doctor
- Confirmation that informed consent has been obtained Patient identifiers, age and sex
- Patient characteristics (yes/no): current smoking, diabetes, heart disease, chronic lung disease, chronic liver disease, asthma, HIV infection, active tuberculosis.
- COVID-19 severity at entry (yes/no): shortness of breath, being given oxygen, already on a ventilator, and, if lungs imaged, major bilateral abnormality (infiltrations/patchy shadowing)
- Whether any of the study drugs are currently NOT AVAILABLE at the hospital.

Treatments

Four potential anti-viral agents, Remdesivir, Chloroquine/Hydroxychloroquine, Lopinavir (given with Ritonavir, to slow hepatic degradation) and Interferon (β1a) were to be evaluated.

Objectives

The protocol-specified primary objective was to assess effects on in-hospital mortality (i.e., mortality during the original episode of hospitalization; follow-up ceased at discharge) not only in all patients but also

subdivided by severity of disease at the time of randomization (i.e. in those with moderate COVID and in those with severe COVID (subsequently defined as ventilated when randomized)).

Sample size

The protocol stated that: *"the appropriate sample sizes could not be estimated at the start of the trial and will depend on the evolution of the epidemic. The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops. If substantial numbers get hospitalised in the participating centres, it may be possible to enter several thousand hospitalised patients with relatively mild disease and a few thousand with severe disease."* The Executive Group, blinded to any findings, decided the timing of release of interim results.

Randomisation

Adults (age ≥18 years) recently hospitalised, or already in hospital, with definite COVID and, in the view of the responsible doctor, no contra-indication to any of the study drugs were randomised in equal proportions between control and whichever other study drug were locally available:

- Local standard of care alone,

OR local standard of care plus one of

- Remdesivir (daily infusion for 10 days)
- Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days)
- Lopinavir with Ritonavir (orally twice daily for 14 days)
- Lopinavir with Ritonavir (ditto) plus Interferon (daily injection for 6 days).

Follow-up:

When patients die or are discharged, follow-up ceases and it is reported:

- Which study drugs were given (and for how many days)
- Whether ventilation or intensive care was received (and, if so, when it began)
- Date of discharge, or date and cause of death while still in hospital.

If no report is received within 6 weeks of study entry, an electronic reminder is sent.

Drug safety:

Suspected unexpected serious adverse reactions that are life-threatening (e.g., Stevens- Johnson syndrome, anaphylaxis, aplastic anaemia, or anything comparably uncommon and serious) must be reported within 24 hours of being diagnosed, without waiting for death or discharge.

Data monitoring:

A global Data and Safety Monitoring Committee will keep the accumulating drug safety results and major outcome results under regular review.

CHMP's comment

Patients were classified with severe disease, if they were already ventilated at randomisation. However, the type of ventilation was not reported at study entry and remains unclear.

The primary endpoint of the Solidarity trial was in-house mortality, while the key secondary endpoint in NIAID study was all-cause mortality. This has to be kept in mind, when comparisons between studies are made.

Statistical methods

The protocol-specified primary objective was to assess effects on in-hospital mortality (i.e., mortality during the original episode of hospitalization; follow-up ceased at discharge) not only in all patients but also in those with moderate COVID and in those with severe COVID (subsequently defined as ventilated when randomized).

The four main sets of analyses involve the evenly randomized pairwise comparisons of each study drug vs its controls. The controls for those randomly allocated one particular drug were those patients who could by chance have been randomly allocated that drug (at that moment, in that hospital), but instead got allocated standard of care. If, for a particular study entrant, more than one study drug was available, allocation to standard of care would put that patient into the control group for each of them. Hence, there is partial overlap between the four control groups. Each comparison between a study drug and its controls, however, is evenly randomized (50/50) and unbiased, as both groups are affected equally by any differences between countries or hospitals and by any time trends in patient characteristics or standard of care.

All analyses relate mortality to allocated treatment (i.e., they are intent-to-treat analyses). The overall mortality analyses were of all randomised patients (drug vs its control), and the only protocol-specified subgroup analyses are those considering separately patients with moderate and with severe COVID (i.e., already ventilated; the type of ventilation was not recorded at study entry.)

Unstratified Kaplan-Meier methods plot 28-day risk. Death rate ratios (RRs) and p-values are from log-rank analyses, stratified for 3x2=6 strata of age and ventilation at entry. If the stratified log-rank Observed minus Expected number of deaths is O-E with variance V, $\log_e$RR is calculated as (O-E)/V with variance 1/V and a Normal distribution. The few currently uncertain death times were taken as day 7. Analyses censored patients with outcome not yet reported at day 0, and censored the few inter-hospital transfers at transfer. They did not censor patients discharged alive, as analyses were of mortality during the initial hospitalisation. Forest plots (with 95% CIs only for overall results, otherwise 99% CIs) and chi-squared statistics (sum of [O-E]2/V, with no p-value given) help interpret any apparent heterogeneity of treatment RRs between subgroups.

The Discussion includes meta-analyses of the major trial results, based on the inverse-variance-weighted average of b=$\log_e$RR from each stratum of each trial, using odds ratios where hazard or death rate ratios were unavailable. (This weighted average is derived from the sums of [O-E] and of V over strata) In general, the more deaths in a stratum the larger V is and, correspondingly, the smaller is the variance of $\log_e$RR, so the more weight that stratum gets. Homogeneity of different RRs is not needed for this weighted average to be informative.

CHMP's comment

Only a high-level description of statistical methods was provided in this preliminary report. In the core protocol that was referred to in the report, no specific statistical methods were described. As far as it can be concluded from the information provided, statistical analyses appear overall appropriate. However, it is unclear whether any of the analyses was pre-specified. It is even unclear how the time point for analysis was determined as a sample size for primary analysis appears not to have been defined.

The study includes several comparisons: In-hospital mortality for each of the four study drug vs its controls was analyzed in the overall population but also in those with moderate and severe COVID. In addition,

there were several secondary endpoints and additional subgroup analyses. It is not clear which comparisons were pre-specified and there seems to have been no strategy for type 1 error control.

The analysis set for each study drug includes the evenly randomized pairwise comparisons of each study drug vs its controls, i.e. those patients who were allocated to the specific study drug vs those who could have been allocated to it (because it was available at the hospital when patient was randomised). This is a pragmatic approach and acceptable in so far as it ensures an unbiased comparison. However, it is not fully clear whether these analysis sets being defined in dependency of current drug availability of specific experimental drugs at their hospitals are fully representative for the target populations.

The primary endpoint was in-hospital mortality. The preliminary report includes results for 28-day in-hospital mortality but it is unclear whether the time horizon 28 days was pre-specified. Follow-up ceased at discharge. Patients discharged alive were not censored (resp. they were censored at maximal follow-up), which is appropriate for analysis of in-hospital mortality because discharged patients can be considered to have survived hospital stay indefinitely (because it is known that they survived hospitalization, independently what happened afterwards). Patients were censored at inter-hospital transfer, implying the assumption that these were at the same risk of death as those patients not transferred. This is not plausible as there must be a reason for the transfer that could be related to patient's prognosis; however, this is unlikely to have a relevant influence on outcomes as there were only a 'few' transfers (exact number not given).

Outcomes not yet reported are censored at day 0 such that these are de facto excluded from analysis, assuming these patients are missing completely at random (i.e. missing independently from their outcome and prognostic factors).

The statistical methods for meta-analysis are standard methods and are in principle appropriate. However, while a systematic summary of the available evidence for RDV is clearly useful, particularly regarding effects in subpopulations, the added value of common effect estimates from a meta-analysis seems to be limited in this case, among other issues, there are e.g. differences in the definitions of subpopulations between studies.

Results

CHMP's comment

Only the published interim study results from the Solidarity trial concerning Remdesivir are considered relevant for this variation, i.e. mortality data, are presented and assessed below.

Participant flow

From March 22 to October 4, 2020, 11,330 patients were entered from 405 hospitals in 30 countries in all 6 WHO regions. Of these, 64 (0.6%) had no, or uncertain, consent to follow-up, leaving 11,266 for intent-to-treat analyses of these 2750 were allocated to remdesivir (Figure 5).

After asking which treatments were locally available, random allocation (with equal probability) was between local standard of care (SoC) and the available treatments. After excluding 64/11,330 (0.6%) with no/uncertain consent to follow-up, 11,266 remain in the ITT analyses. Each pairwise ITT analysis is between a particular treatment and its controls, i.e., those who could have been allocated it but were concurrently allocated the same management without it. There is partial overlap between the four control groups.

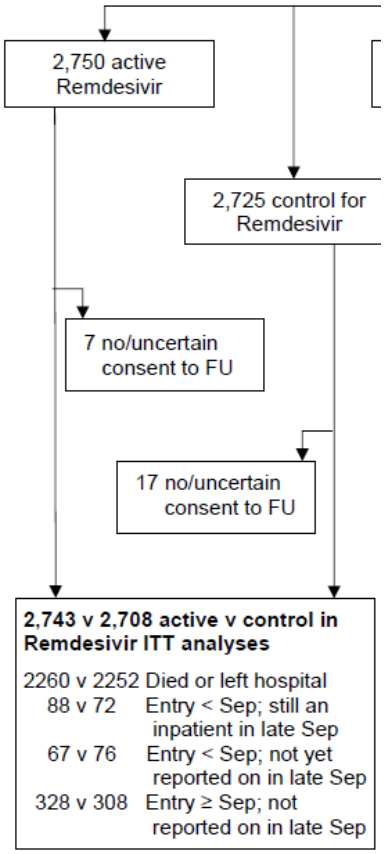

Figure 5: WHO Solidarity Trial – information to October 4, 2020 on entry, follow-up (FU) and intent-to-treat (ITT) analyses

WHO Solidarity Trial Consortium, NEJM ,Dec 2020.

Baseline data

Table 9 shows patient characteristics: 9120 (81%) age <70 years, 6985 (62%) male, 2768 (25%) with diabetes, 916 (8%) already ventilated, and 7002 (62%) randomized on days 0-1. For each drug, patient characteristics were well balanced by the unstratified 50/50 randomization between it and its controls. Deaths were at median day 8 (IQR 4-14) and discharges at median day 8 (IQR 5-13). With 1253 deaths, the Kaplan-Meier estimate of 28-day mortality was 11.8%. This risk depended on several factors, particularly age (20% if ≥70 years, 6% if <50 years) and ventilation (39% if ventilated, otherwise 10%).

Table 9 also describes compliance. For Remdesivir the scheduled treatment period was 10 days (or to prior death or discharge). Of those allocated Remdesivir, 98.5% began treatment. Midway through this period, 96% were still taking it (as against only 2% of the Remdesivir controls).

Table 9: Entry characteristics by random allocation, and compliance with that allocation Excludes 64 without clear consent to follow-up. Comparisons are of Remdesivir vs concurrent allocation to the same treatment without it, as the control group.

	All in any intent-to-treat analysis				Remdesivir vs its control	
	Entered No.	%	No. died	28-d KM%	Active	Control
All participants	11266	100	1253	11.8	2743	2708
Entry characteristics						
Age (years)						
<50	3995	35	237	6.2	961	952
50-69	5125	45	618	12.8	1282	1287
70+	2146	19	398	20.4	500	469
Respiratory support						
No oxygen at entry	3204	28	78	2.5	661	664
On oxygen at entry	7146	63	844	12.8	1828	1811
Already ventilated	916	8	331	39.0	254	233
Bilateral lung lesions						
No	1266	11	49	3.7	287	259
Yes	8832	78	1043	12.7	2175	2153
Not imaged at entry	1168	10	161	14.9	281	296
Prior days in hospital						
0	3289	29	319	9.8	724	712
1	3713	33	384	10.8	917	938
2+	4264	38	550	14.6	1102	1058
Geographic location						
Europe** or Canada	2488	22	188	7.8	715	698
Latin America§	1941	17	400	22.7	470	514
Asia and Africa†	6837	61	665	10.3	1558	1496
Other characteristics						
Male	6985	62	852	13.0	1706	1725
Current smoking	830	7	93	11.8	178	161
History of – Diabetes	2768	25	379	14.7	707	666
- Heart disease	2337	21	319	14.7	571	567
- Chronic lung disease	635	6	102	17.2	151	145
- Asthma	529	5	56	11.5	139	139
- Chronic liver disease	135	1	21	17.2	36	41
Compliance with allocated treatment						
% who were taking the study drug midway through its scheduled duration‡					95.8	1.6
% of those reported as discharged who were still in hospital on:	Day 7				69	59
	Day 14				22	19
	Day 21				9	8

Notes: The few with a particular characteristic unknown are merged with the largest category of that characteristic.

"28-d KM %" is the Kaplan-Meier 28-day % risk of in-hospital death. "No. died" includes any in-hospital deaths after day 28.

* Interferon randomisation was interferon + Lopinavir vs Lopinavir until 4 July, then it was interferon vs standard of care.

** Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, Macedonia, Norway, Spain, Switzerland.

§ Argentina, Brazil, Colombia, Honduras, Peru.

† Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, Philippines, Saudi Arabia, South Africa.

‡ Compliance is calculated only among those who died or were discharged alive, and is defined as the % taking the study drug midway through its scheduled duration (or midway through the time from entry to death or discharge, if this is shorter).

WHO Solidarity Trial Consortium, NEJM, Dec 2020.

CHMP's comment:

With 1253 deaths, the Kaplan-Meier estimate of 28-day mortality was 11.8%. This risk depended on several factors, particularly age (20% if ≥70 years, 6% if <50 years) and ventilation (39% if ventilated, otherwise

10%). For patients already ventilated at randomisation (8%) the Kaplan-Meier estimate of 28-day mortality was 39%, compared to 10% in patients not ventilated at randomisation.

Interestingly, of those allocated Remdesivir (98.5% began treatment), midway through this period, 96% were still taking it (as against only 2% of the Remdesivir controls). Hence, compliance to the allocated treatment duration was higher in the SOLIDARITY trial than in the NIAID trial, where less than 62% completed the full study course.

Outcomes and estimation

For the pairwise comparison of Remdesivr to placebo, Figure 6 shows the unstratified Kaplan-Meier analyses of the 28-day in house-mortality. No effect of Remdesivr on the 28-day in-house mortality was seen (12.5% for RDV compared to 12.7% for control). The death rate-ratio (RR) for Remdesivir was 0.95 (0.81-1.11) with a p value of 0.50.

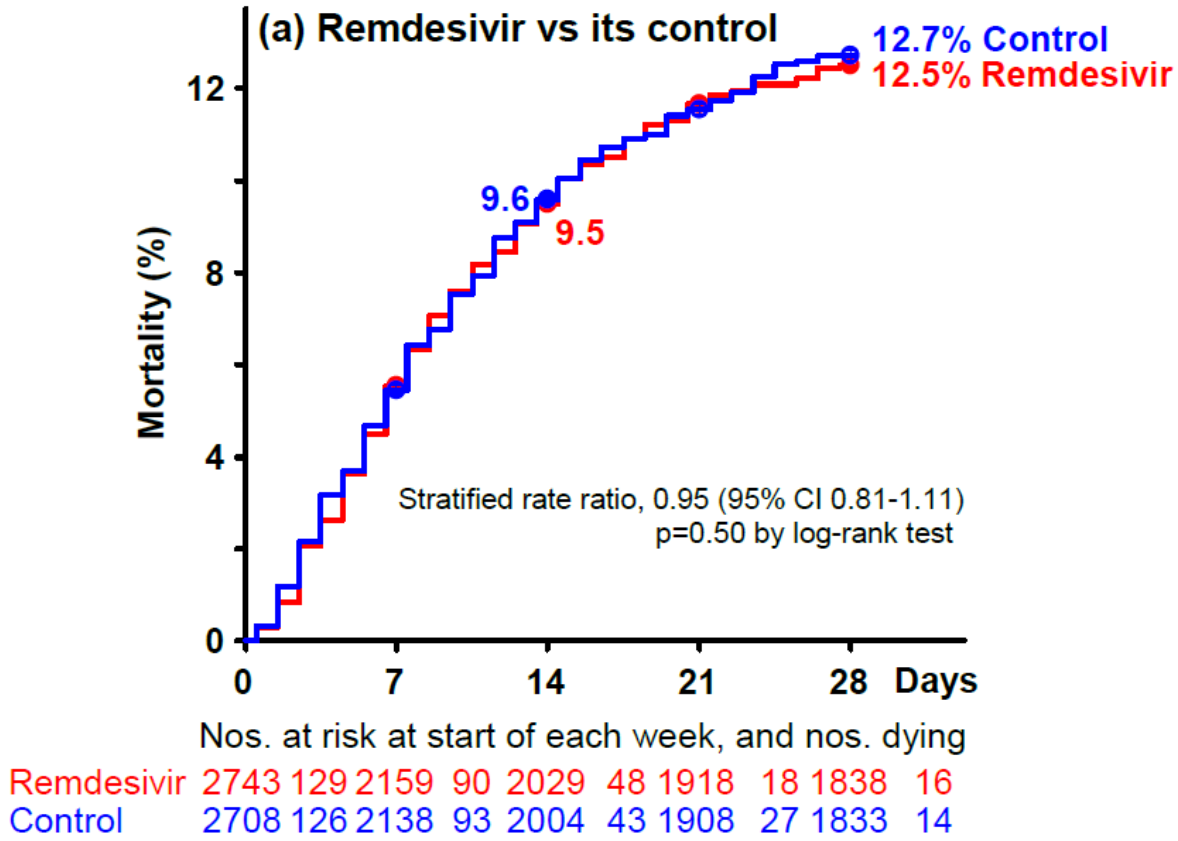

Figure 6: Kaplan-Meier graphs on in-house mortality.

WHO Solidarity Trial Consortium, NEJM ,Dec 2020.

In Figure 7 below death rate ratios (RRs) stratified by age and respiratory support at entry and overall RRs stratified by both are shown. Overall, when stratified by both age and respiratory support at entry no effect of Remdesivir on mortality was seen (RR: 0.95 [0.81 – 1.11] p-value = 0.50). In the subgroup of patients who were ventilated at the time of randomisation, the risk of death was increased (RR: 1.20 [0.80-1.80]), compared to those not ventilated at study entry (RR: 0.86 [0.67-1.11]).

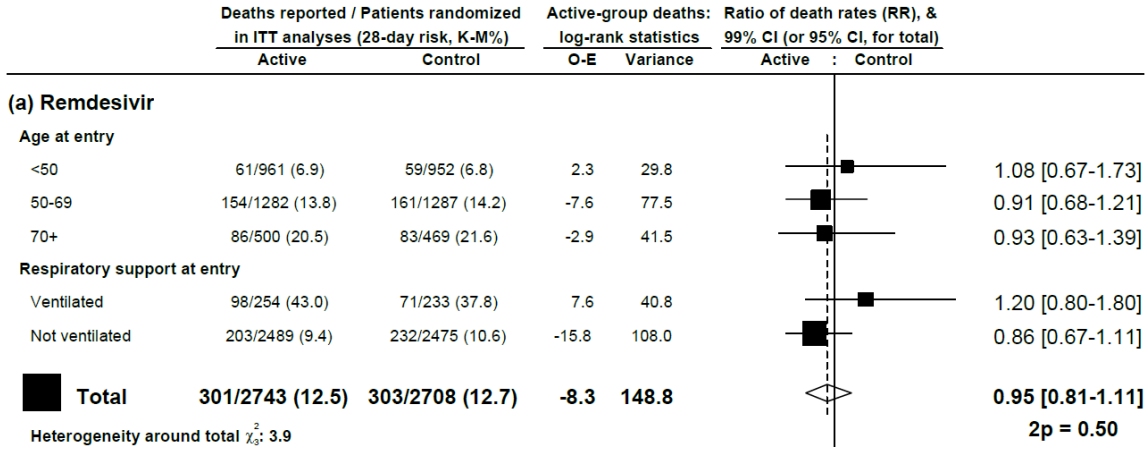

Figure 7: Rate Ratio of any death stratified by age and respiratory support at entry

WHO Solidarity Trial Consortium, NEJM ,Dec 2020.

Subgroup analyses by ventilation status at randomisation on the effect of Remdesivr on the 28-day probability of death is shown in Figure 8 below. The Kaplan-Meier estimate of death for Remdesivir in the subgroup of ventilated patients is 43% compared to 37.8 % in the control arm. The age stratified RR of death in the subgroup of patients ventilated at baseline is 1.20 [0.89-1.64, p = 0.24], compared to 0.86 [0.73-1.04; p = 0-13] in those not ventilated at study entry.

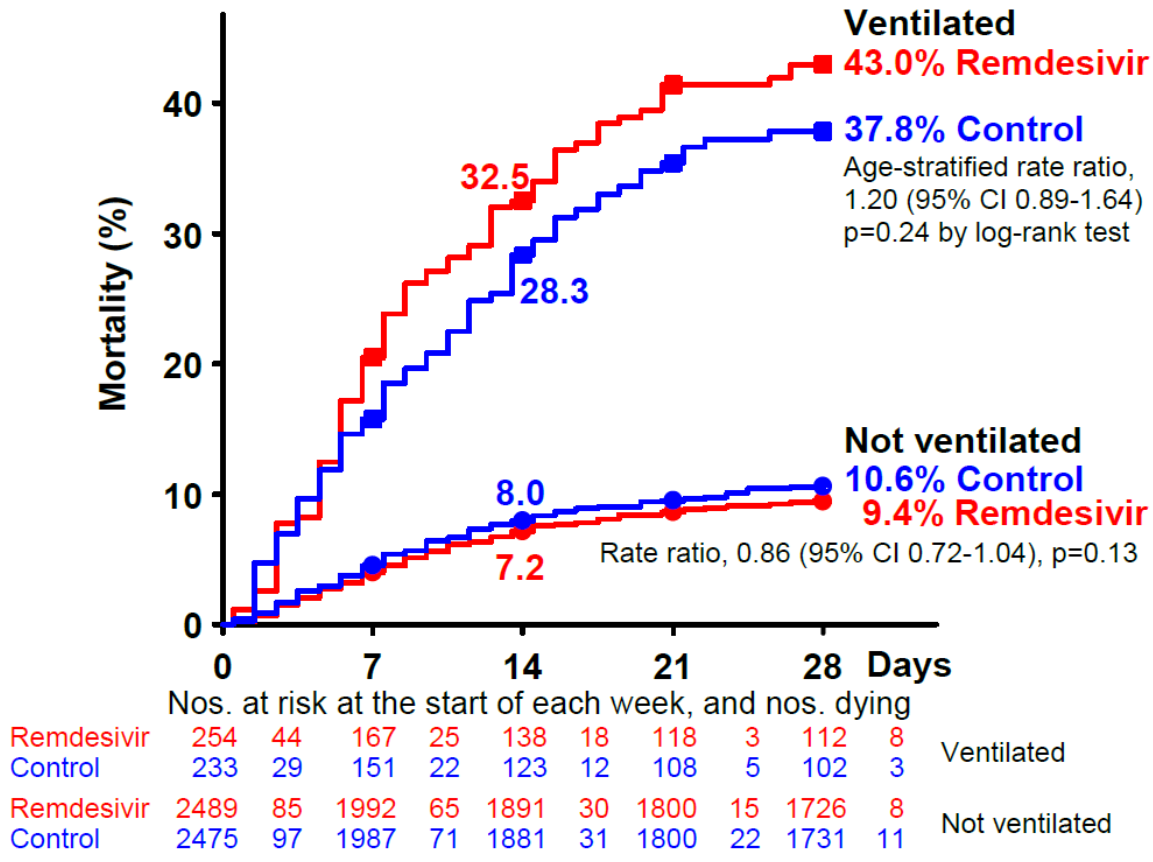

Figure 8: Kaplan-Meier graphs on in-house mortality stratified by ventilation status at baseline.

WHO Solidarity Trial Consortium, NEJM ,Dec 2020.

CHMP's comment:

In the overall analyses of the day 28 mortality data no definite effect of Remdesivir on mortality was seen, with overall p-values > 0.10 and a calculated death rate ratio of 0.95 [0.85-1.11, p=0.50). Subgroup analysis stratified by both age and ventilation status at randomisation did show similar results with RR of 0.95 [0.85-1.11, p=0.50).

However, subgroup analyses stratified by ventilation status at randomisation did show an increased 28-day mortality by 20% in patients already ventilated at baseline (RR: 1.20, CI [0.89-1.64, p = 0.24] compared to patients not receiving ventilation at study entry (RR: 0.86 [0.72-1.04). Even when considering the uncertainties concerning subgroup analyses due to their limited sample sizes, the analyses indicate that Remdesivir may not be effective in the population of critically ill COVID-patients.

Rate ratios of any death stratified by age and respitatory support at entry were also analysed by entry charateristics and steroid use at any time (Figure 9).

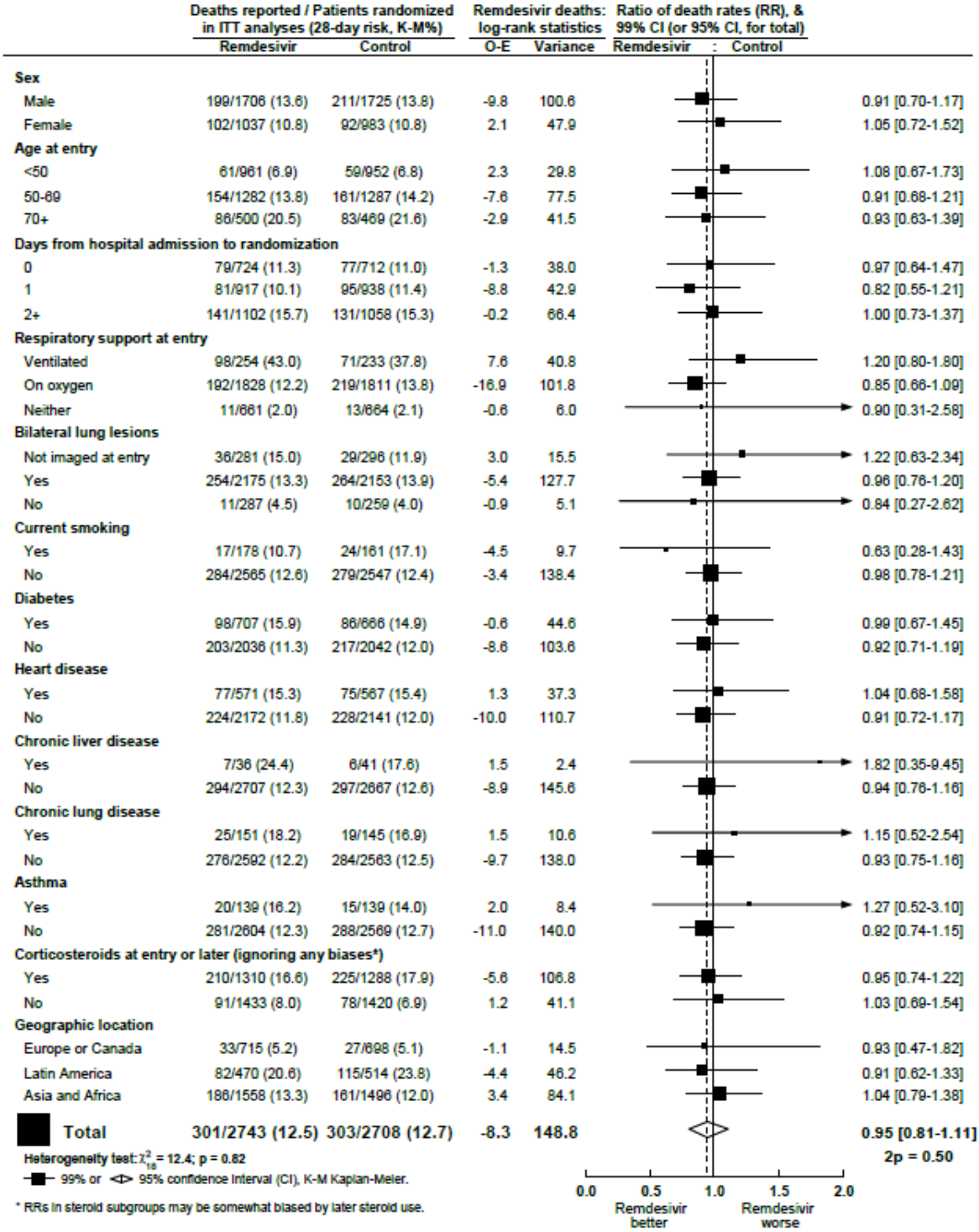

Figure 9: Rate ratios of any death, stratified by age and respiratory support at entry, Remdesivir versus Control, by entry characteristics and steroid use at any time.

WHO Solidarity Trial Consortium, NEJM ,Dec 2020.

CHMP's comment:

No significant effect of Remdesivir use on mortality rates by geographic regions were identified. However, it is notably that the probability of death is higher in Latin America (23%), Asia and Africa (12%) than in Europe and Canada (5%), which could be related to the dynamics of the pandemic leading to over-stressed hospitals or to the quality of the health care systems in this regions. However, there is no clear evidence for differences in the treatment effect between regions (broad and overlapping confidence intervals).

Different viral variants with reduced susceptibility to RDV circulating in different geographic regions could also account for the slight differences in RR seen in the different geographic regions. However, no virology data are available that could support this assumption for the Solidarity trial. However, according to the authors of the publication, additional data, including virology data were collected in the Add-on clinical trials Discovery (EU) and CATCO (Canada), which will be published separately. In general, the numbers of deaths in Europe and Canada are too small, to draw any conclusion between geographic regions.

In addition, in the subgroup of patients with chronic liver disease, mortality was 7% larger in the RDV group (RDV: 7/36, control: 6/41) (24.4% RDV vs. 17.6 % control). This finding is also supported by the higher risk of death in patients receiving RDV with chonic liver disease (24.4%) compared to those without chronic liver disease (12.3%). In contrast, in the control group the risk of death was not increased in patients with chornic liver disease (12.3%) compared to those without chronic liver disease (12.7%). However, the confidence intervals are wide (RR 1.82 [0.35-9.45]) and the numbers of death are too small to draw any conclusions. Hepatoxicity was identified as important potential risk and is listed as Category 2 imposed additional pharmacovigilance activities in the RMP. Data addressing this issue are awaited / will be assessed within the next Renewal procedure.

The Meta-analysis of the mortality data from four different trials with random allocation of Remdesivir vs. SoC in hospitalised COVID-19 patients is shown in Figure 10. These meta-analyses included mortality data from the Solidarity trial (604 deaths in 5000 randomised), the ACTT-1 trial (136 deaths in about 1000) and two smaller trials (China trial, Simple moderate trial). Mortality results from each trial, subdivided by the initial respiratory support are shown. The like-vs-like comparison shown below allow for the proportion already on high-flow and non-invasive ventilation or invasive ventilation at entry into ACTT-1. The number of patients already mechanically ventilated was lower in the ACTT-1 trial than those in the Solidarity trial. The combined data from all four studies resulted in an overall death ratio of Remdesvir vs control of 0.91 [0.79-1.05, p = 0.20].

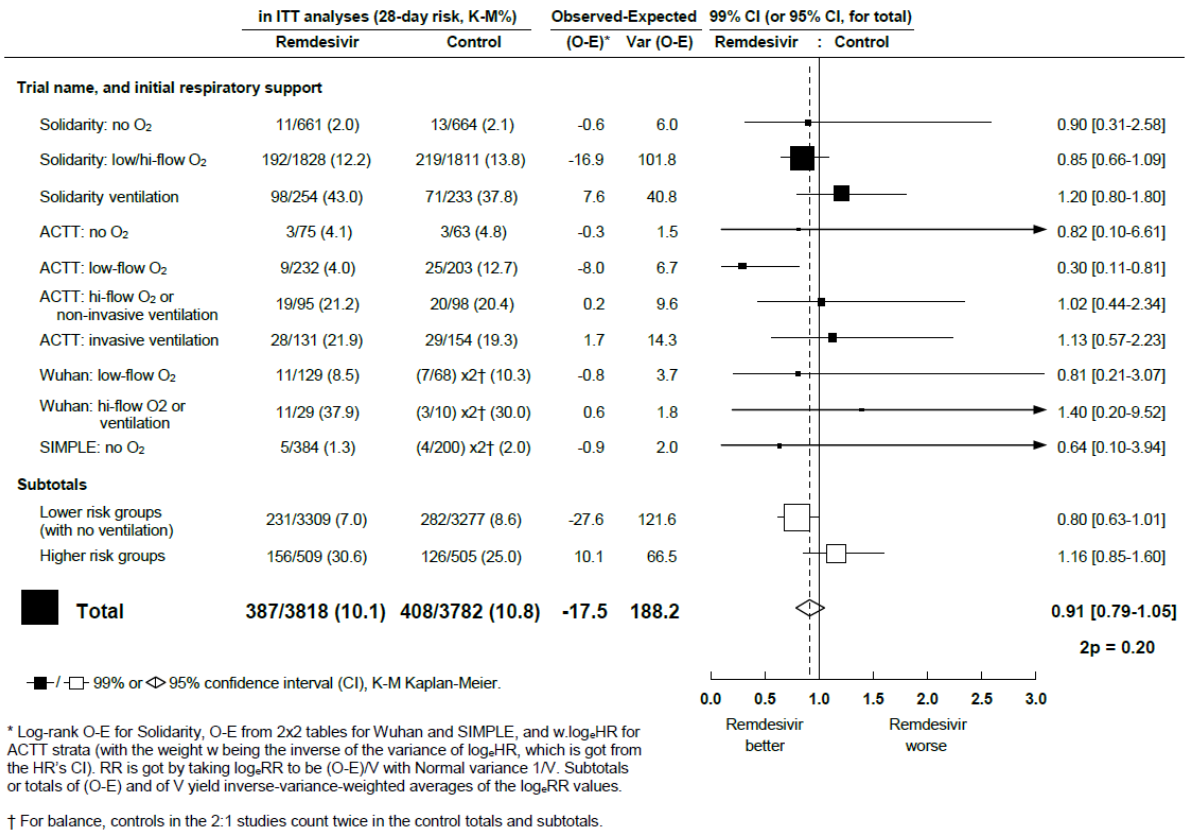

Figure 10: Remdesivir vs control – Meta-analysis of mortality in trials of random allocation of hospitalised COVID-19 patients to Remdesivir or the same treatment without it

WHO Solidarity Trial Consortium, NEJM ,Dec 2020.

CHMP's comment:

Overall, 28-day mortality data are now available from four different trials with random allocation of Remdesivir vs. SoC in hospitalised COVID-19 patients. The systematic summary of results in subgroups across trials is very valuable for assessment of consistency across studies. However, due to the differences between studies (different endpoint definition, different definition of subgroups), the pooled estimates that were calculated across trials should be interpreted with some caution.

The meta-analysis of the day 28 mortality data from the four different trials with random allocation of remdesivir vs. SoC in hospitalised COVID-19 patients, included mortality data from the Solidarity trial (604 deaths in 5000 randomised), the ACTT-1 trial (136 deaths in about 1000) and two smaller trials (China trial, Simple moderate trial: 41 deaths). The combined data from all four studies resulted in an overall death ratio of Remdesvir vs control of 0.91 [0.79-1.05, p = 0.20].

However, in all trials including "severely ill" and "critically ill", a consistent trend of a different effect of Remdesivir on mortality was observed for "severely ill" and "critically ill" patients. In hospitalised patients receiving supplemental oxygen but not on ventilation, a trend for some benefit of Remdesivir on mortality was seen. On the other side, for more critically ill patients, in particular for those receiving ventilation, a consistent trend for an increased mortality was observed for Remdesivir in all studies (13% increase for NIAID ACTT-1, RR: 1.13 [0.57-2.23]; 20% increase for Solidarity, RR: 1.20 [0.80 – 1.80]; 40% increase for China trial, RR: 1.40 [0.20 – 9.52]).

However, between trial comparisons of the D28 mortality data from the four different trials should be interpreted with some caution, due to:

1. Differences in the mortality endpoints that were used, i.e. in-hospital mortality in the Solidarity trial versus. all-cause mortality in the NIAID study.
2. The type of ventilation in the solidarity trial was not reported at the time of randomisation, hence the proportion of ventilated patients that received non-invasive ventilation, IVM or ECMO remains unclear.
3. In the NIAID trial category 6 included patients receiving high-flow oxygen and non-invasive mechanical ventilation. Hence, an analysis of all patients receiving ventilation at randomisation is not available for the NIAID.
4. In line with this, it remains unclear how many of the patients in category 6 received high-flow oxygen. In particular, the subgroup of patients receiving supplemental oxygen (low or high flow) was not separately analysed in the NIAID trial.
5. The post-hoc nature of the subgroup analyses according to low-risk/high-risk which increases the overall uncertainties should be taken into account both for the NIAID and the Solidarity studies.

6.3.1. Potential impact of Corticosteroids on treatment outcomes

As already highlighted above, considering the reported outcomes of the Recovery study {The RECOVERY Collaborative Group, 2020}, an interest in combined use of Remdesivir and dexamethasone in the target population is anticipated.

The publication from the Solidarity study contains some information on the concomitant use of glucocorticoid.

Methods – analysis of data submitted

During the study, 1310 patients in the Remdesivir group (47.8% of the 2743 patients) and 1288 patients in the Control group (47.6% of the 2708 patients) received a glucocorticoid (Table 10).

Table 10: Use of corticosteroids and other non-study drugs

	Remdesivir vs its control		Hydroxychloroquine vs its control		Lopinavir vs its control		Interferon vs its control*	
Corticosteroids	1310	1288	140	140	316	328	981	1053
Number & percentage	47.8	47.6	14.8	15.5	22.6	23.9	47.9	51.4
Convalescent plasma	52	58	7	3	24	15	43	33
	1.9	2.1	0.7	0.3	1.7	1.1	2.1	1.6
Anti-IL-6 drug	133	143	21	18	42	42	52	68
	4.9	5.3	2.2	2.0	3.0	3.1	2.5	3.3
Non-trial interferon	3	25	2	1	4	0	1	26
	0.1	0.9	0.2	0.1	0.3	0.0	0.1	1.3
Non-trial antiviral	65	152	62	54	86	90	102	144
	2.4	5.6	6.6	6.0	6.2	6.6	5.0	7.0
Number entered	2743	2708	947	906	1399	1372	2050	2050
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Source: {Hongchao P et al, 2020}, Supplementary online material, Table S2

CHMP's comment:

Overall, there seems to be no important imbalances between the randomised groups with regard to concomitant use of corticosteroids. However, data regarding corticosteroid doses is not reported. In the Recovery study, patients were treated with a dexamethasone 6 mg once daily for up to ten days. Also, there was not differentiation between corticosteroids that were initiated before and after enrolment.

Results

Rate ratios of any death, stratified steroid use at any time are reported in Table 10 above. This subgroup analysis did not identify any effect of Remdesivir and the concomitant use of corticosteroids on mortality (16.6% vs. 17.9%) or the rate ration of death compared to the control arm (RR: 0.95 [0.74-1.22]).

CHMP's comment:

Notable, in the analysis patients were assigned to the corticosteroid group irrespectively whether treatment was initiated before or after randomization. In addition, subgroup analyses (e.g. based on respiratory status at entry) would have been required.

Subgroup analysis by steroid use at any time did not identify any effect of Remdesivir and the concomitant use of corticosteroids on mortality (16.6% vs. 17.9%) or the rate ration of death compared to the control arm (RR: 0.95 [0.74-1.22]). In patients not using corticosteroids a slight increase in death rates were noted in the Remdesivir group, i.e. 8.0% vs. 6.9% in the control arm (RR 1.03 [0.69 – 1.54], assuming that concomitant corticosteroid use may be beneficial for patients. However, it has to be noted that the use of corticosteroids was not stratified between use at entry or use during treatment, hence the RR in the steroid subgroups may be somewhat biased by later steroid use.

Interestingly, the use of corticosteroids was associated with higher risk of death in both groups, Remdesivir and control (16.6% vs. 8.0% and 17.9% vs. 6.9%), which may be explained by corticosteroid treatment being preferably initiated in patients with a worse clinical status (although no definite conclusion is possible). Slight imbalance in corticosteroid use seen within the groups were noted in the Solidarity trial (47.8% used corticosteroids vs. 52.2% no corticosteroids use in the RDV group, and 47.6% Corticosteroid use vs. 52.4% not using corticosteroids in the control group).

6.4. Discussion

The Day-28 all-cause mortality data from the NIAID study indicated a numerically lower risk of mortality for Remdesivir in the overall population (both strata; RR 0.73; 95% CI: 0.52, 1.02; p = 0.066). However, this effect is mainly driven by patients requiring supplemental oxygen (baseline ordinal score of 5).

Between-group results vary considerably according to baseline disease severity:

- For the subgroup with a baseline ordinal score of 5 (supplemental oxygen), a beneficial effect was seen: for time to recovery (HR: 1.45; CI: 1.18, 1.79), and also for mortality (RR: 0.33; CI: 0.14, 0.64; p<0.001).
- For the subgroup with a baseline ordinal score of 6 (non-invasive ventilation or high flow oxygen devices), no beneficial effect was conclusively seen: not for time to recovery (HR: 1.09; CI: 0.76, 1.57), and neither for mortality (RR: 1.02; CI: 0.54, 1.14; p=0.949).
- Also for the subgroup with a baseline ordinal score of 7 (IMV or ECMO), no beneficial effect was seen: not for time to recovery (HR: 0.98; CI 0.70, 1.36), and neither for mortality (RR: 1.13; CI

0.67, 1.89; p = 0.652). In contrast, the results may be indicative of a negative trend in this patient population.

In addition, the interaction tests between treatment effect and baseline ordinal score indicates a reduced or even lack of efficacy in higher baseline ordinal scores (of 6 and 7) with respect to time to recovery and mortality.

Further subgroup analysis by baseline characteristics and steroid use at any time, did not identify any effect of Remdesivir and the concomitant use of corticosteroids on mortality (16.6% vs. 17.9%) or the rate ratio of death compared to the control arm (RR: 0.95 [0.74-1.22]). In patients not using corticosteroids a slight increase in death rates were noted in the Remdesivir group, i.e. 8.0% vs. 6.9% in the control arm (RR 1.03 [0.69 – 1.54], assuming that concomitant corticosteroid use may be beneficial for patients. However, it has to be noted that the use of corticosteroids was not stratified between use at entry or use during treatment, hence the RR in the steroid subgroups may be biased by later steroid use.

Recently pre-published interim results of the SOLIDARITY trial were published. While in the analyses of the 28-day in-hospital mortality data in the overall population no definite effect of Remdesivir on mortality was seen (RR 0.95 [0.85-1.11, p=0.50), subgroup analyses stratified by ventilation status at randomisation may also be indicate a negative trend in patients already ventilated at baseline (RR: 1.20, CI [0.89-1.64, p = 0.24] compared to patients not receiving ventilation at study entry (RR: 0.86 [0.72-1.04).

In the SOLIDARITY trial, no significant effect of Remdesivir use on mortality rates by geographic regions were identified. However, it is notably that the probability of death is higher in Latin America (23%), Asia and Africa (12%) than in Europe and Canada (5%), which could be related to the dynamics of the pandemic leading to over-stressed hospitals or to the quality of the health care systems in this regions. However, there is no clear evidence for differences in the treatment effect between regions (broad and overlapping confidence intervals).

Different viral variants with reduced susceptibility to RDV circulating in different geographic regions could also account for the slight differences in RR seen in the different geographic regions. However, no virology data are available that could support this assumption for the Solidarity trial. In general, the numbers of deaths in Europe and Canada are too small, to draw any conclusion between geographic regions.

In addition, in the subgroup of patients with chronic liver disease, mortality was 7% larger in the RDV group (RDV: 7/36, control: 6/41) (24.4% RDV vs. 17.6 % control). However, the confidence intervals are wide (RR 1.82 [0.35-9.45]) and the numbers of death are too small to draw any conclusions. However, as hepatotoxicity was identified as important potential risk and is listed as Category 2 imposed additional pharmacovigilance activities in the RMP, further data addressing this issue are awaited / will be assessed within the next Renewal procedure.

Overall conclusion:

Overall, in the context of a CMA, the final D28 mortality data from the pivotal NIAID study, listed as a SOB 013, were requested in order to confirm the efficacy and safety of Remdesivir in patients on IMV or ECMO. The final D28 mortality data did not confirm the efficacy of Remdesivir in these patients (RR: 1.13; 95% CI 0.67, 1.89; p = 0.652). In contrast, the results may be indicative of a negative trend in this patient population. Thus, the applicant is requested to justify a favourable risk-benefit profile based on overall available evidence in patients on IMV or ECMO when starting Remdesivir. In addition, further clarification is sought on the provided data.

7. PRAC advice

N/A

8. Changes to the Product Information

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above. However, as SOB 013 is currently not considered fulfilled, the acceptability of changes will dependent on the responses to the request for supplementary information (RSI).

9. Request for supplementary information

9.1. Major objections

Clinical aspects

1.-In the context of a CMA, the final D28 mortality data from the pivotal NIAID study, listed as a SOB No. 13, were requested in order to confirm the efficacy and safety of Remdesivir in patients on IMV or ECMO. The final D28 mortality data did not confirm the efficacy of Remdesivir in these patients (RR: 1.13; CI 0.67, 1.89; p = 0.652). In contrast, the results may be indicative of a negative trend in this patient population. Thus, the applicant is requested to justify a favourable risk-benefit profile based on overall available evidence in patients on IMV or ECMO when starting Remdesivir.

9.2. Other concerns

Clinical aspects

1) Day-28 mortality status was not available for all enrolled patients in the NIAID trial. It remains unclear why the mortality status of 19 patients in the RDV group and 13 patients in the placebo group is still missing, although the 29 days after randomization have long been completed and the patients with missing status have not discontinued the study. The MAH is asked to clarify the status of these patients.
2) The MAH is asked to include the final Day-28 mortality data in section 5.1 of the SmPC (including mortality data by WHO score).
3) In order gain further understanding of the effect of Remdesivir on mortality in the subgroup of ventilated patients in the NIAID trial, the MAH is asked to provide:
    a. An analysis of mortality in a subgroup of patients comprising those ventilated at the time of randomisation in the NIAID trial, including those on non-invasive ventilation, invasive ventilation and ECMO.
    b. A separate analysis of all patients that were categorised in category 6 and received non-invasive ventilation at the time of randomisation.
    c. Please provide symptom duration prior to randomisation (median +IQR) per ordinal scale stratum at baseline.
    d. Please provide data on the duration of hospitalisation prior to baseline (median + IQR) per ordinal scale stratum at baseline.
    e. Please provide key safety indices, including renal events, from the randomised NIAID-ACTT1 study for patients in baseline ordinal scale categories 6 and 7, per treatment arm.

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

Clinical aspects

Major Objection 1

In the context of a CMA, the final D28 mortality data from the pivotal NIAID study, listed as a SOB No. 13, were requested in order to confirm the efficacy and safety of Remdesivir in patients on IMV or ECMO. The final D28 mortality data did not confirm the efficacy of Remdesivir in these patients (RR: 1.13; CI 0.67, 1.89; p = 0.652). In contrast, the results may be indicative of a negative trend in this patient population. Thus, the applicant is requested to justify a favourable risk-benefit profile based on overall available evidence in patients on IMV or ECMO when starting Remdesivir.

Summary of the MAH's response

The MAH presented the following data and considerations to support a favorable benefit-risk profile for RDV for the treatment of patients with coronavirus disease 2019 (COVID-19) requiring invasive mechanical ventilation or ECMO (baseline ordinal score of 7):

- In reference to patient benefit, the MAH clarified that Study CO-US-540-5776 was designed and powered to evaluate time to recovery for the entire study population, not within specific subpopulations. The study met its primary endpoint. Given this context, the MAH maintains that statistical findings within subpopulations of the study should be interpreted with caution.
- A detailed assessment of potential risk in participants with COVID-19 requiring invasive mechanical ventilation or ECMO was performed to address the safety concerns outlined in this objection. Multiple safety analyses reaffirmed the favorable safety profile of RDV when compared with placebo across the range of COVID-19 severities. Importantly, a negative trend associated with RDV therapy could not be identified in participants on invasive mechanical ventilation or ECMO.

Given the current state of knowledge regarding the management of COVID-19, the MAH considers it premature to restrict treatment with a well-tolerated antiviral such as RDV in patients requiring invasive mechanical ventilation or ECMO. The potential benefits of combining well-tolerated, direct-acting antiviral therapy with corticosteroids, immunomodulatory agents, and other therapeutics are currently being evaluated in critically ill patients, those with the greatest unmet medical need, in several global studies. Results are expected in the coming months, and these data will further elucidate the role of RDV and other therapies in this population.

Further details and considerations of the MAH are described below.

Study CO-US-540-5776 was designed to evaluate time to recovery as the primary endpoint. The study met its primary endpoint, with a statistically significantly shorter median time to recovery in the RDV group (10 days [95% CI: 9, 11]) than in the placebo group (15 days [95% CI: 13, 18]; recovery rate ratio 1.29; 95% CI: 1.12, 1.49; p < 0.001).

Mortality was analyzed as a secondary endpoint of Study CO-US-540-5776, and the overall risk of death by Day 29 was numerically lower in the RDV group than in the placebo group (hazard ratio 0.73; 95% CI: 0.52, 1.02; p = 0.066). To identify whether any subpopulations might benefit more from RDV treatment,

ad hoc analyses of time to recovery and mortality by baseline ordinal score were conducted by NIAID (Table 11). Among participants with a baseline ordinal score of 7 (hospitalized, on invasive mechanical ventilation or ECMO), the hazard ratio for mortality by Day 29 was 1.13, with a 95% confidence interval of 0.67 to 1.89. Thus, it can be stated with 95% confidence that the hazard ratio lies somewhere between 0.67 and 1.89. Given this confidence interval containing 1, it is difficult to interpret the significance of an apparent negative trend in this population and, for that reason, an in-depth assessment of safety/risk is included in this response.

Table 11: CO-US-540-5776: Time to Mortality by Day 29 by Treatment Group

	Overall		Baseline Ordinal Score 4		Baseline Ordinal Score 5		Baseline Ordinal Score 6		Baseline Ordinal Score 7	
	RDV (N = 541)	Placebo (N = 521)	RDV (N = 75)	Placebo (N = 63)	RDV (N = 232)	Placebo (N = 203)	RDV (N = 95)	Placebo (N = 98)	RDV (N = 131)	Placebo (N = 154)
No. with known mortality status at Day 29 (% of total)	508 (93.9)	499 (95.8)	72 (96.0)	59 (93.7)	222 (95.7)	195 (96.1)	87 (91.6)	97 (99.0)	127 (96.9)	148 (96.1)
No. of deaths by Day 29 (% of no. with known mortality status at Day 29)	59 (11.6)	77 (15.4)	3 (4.2)	3 (5.1)	9 (4.1)	25 (12.8)	19 (21.8)	20 (20.6)	28 (22.0)	29 (19.6)
Hazard ratio (95% CI)	0.73 (0.52, 1.02)[a]		0.82 (0.17, 4.07)[b]		0.30 (0.14, 0.64)[b]		1.02 (0.54, 1.91)[b]		1.13 (0.67, 1.89)[b]	
P-value	0.066[c]		0.809[d]		< 0.001[d]		0.949[d]		0.652[d]	

CI = confidence interval
Number with known mortality status at Day 29 is the number of participants who have data for a day on or after Day 26 or who are known to be deceased. Day 26 represents the beginning of the visit window for the Day 29 visit.
a Hazard ratio is the ratio of the hazard of death in each treatment group estimated from the stratified Cox model. The ratio is remdesivir to placebo.
b Hazard ratio is the ratio of the hazard of death in each treatment group estimated from the Cox model. The ratio is remdesivir to placebo.
c P-value calculated using the stratified log-rank test.
d P-value calculated using the log-rank test.
Source: CO-US-540-5776 Final CSR, Table 28

A review of safety outcome measures by baseline ordinal score was conducted by the MAH to identify any additional risks associated with RDV therapy for participants across the spectrum of COVID-19 severity, including among those on invasive mechanical ventilation or ECMO at baseline (see also the response to Question 3e, below). The results of these analyses demonstrate that the safety profile of RDV is generally comparable to placebo in participants with COVID-19 across all baseline ordinal scores, including those with a baseline ordinal score of 7 (hospitalized, on invasive mechanical ventilation or ECMO). In general, the incidence of AEs, study drug-related AEs, SAEs, and AEs leading to study drug discontinuation was comparable between the RDV and placebo groups within each baseline ordinal score subgroup (Table 18), and the incidence of the individual AEs (by preferred term [Table 19]) and study drug-related AEs (by preferred term [data not shown]) was generally similar between the RDV and placebo groups within each baseline ordinal score subgroup. Furthermore, the overall incidence of renal AEs (Table 20) and hepatic AEs (Table 22) was generally comparable between the RDV and placebo groups within each baseline ordinal score subgroup, and the incidence of the individual renal AEs (by preferred term [Table 21]) and hepatic AEs (by preferred term [Table 13]) was generally similar between the RDV and placebo groups within each baseline ordinal score subgroup. Thus, the MAH concluded that the detailed review of safety parameters does not reveal any negative safety trends associated with RDV therapy in participants with COVID-19, including among those receiving invasive mechanical ventilation or ECMO at baseline.

As noted in the Assessment Report, severe COVID-19 is associated with a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. In many cases, corticosteroids and immunomodulators are administered to manage an excessive inflammatory response that is a consequence of severe infection. Corticosteroid use has been associated with delayed clearance of coronaviruses {Arabi 2018, Stockman 2006}. Corticosteroids have also been associated with worse clinical outcomes in cases of

severe pneumonia caused by influenza {Rodrigo 2016}. Therefore, it is reasonable to posit that the coadministration of a direct-acting antiviral during corticosteroid or immunomodulatory treatment of COVID-19 has the potential to provide clinical benefit, as observed in the treatment of other viral infections.

The potential benefits of combining a well-tolerated, direct-acting antiviral therapy, such as RDV, with corticosteroids, immunomodulatory agents, and other therapeutics are currently being evaluated in critically ill patients, those with the greatest unmet medical need, in several global studies (ACTIV-1 [NCT04593940], ACTIV-3 [NCT04501978], ACTIV-5 [NCT04583969], ACTT-2 [NCT04401579], ACTT-3 [NCT04492475], and I-SPY [NCT04488081]). On 19 November 2020, the United States (US) Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for baricitinib, in combination with RDV, for the treatment of COVID-19 in hospitalized patients, including those receiving invasive mechanical ventilation or ECMO. This EUA was based on favorable results from a clinical study conducted by NIAID (ACTT-2 [NCT04401579]), where the combination of RDV and baricitinib reduced time to recovery relative to treatment with RDV and placebo. Baricitinib remains an investigational therapy for use in the treatment of COVID-19, and is not authorized or approved as a stand-alone treatment for COVID-19. Additional results from this and other studies are expected in the coming months. These data will further elucidate the role of RDV, as well as other therapies, in the treatment of COVID-19 in this patient population.

The MAH concludes that RDV has demonstrated statistically significant and clinically meaningful benefit for patients with COVID-19. Analyses of efficacy in the subset of participants on invasive mechanical ventilation or ECMO at baseline are inconclusive; however, an extensive analysis of safety has shown that there are no additional risks associated with the use of RDV in this patient population. Given the current state of knowledge regarding the management of COVID-19, the MAH considers it premature to restrict treatment with a well-tolerated antiviral, such as RDV, in patients requiring invasive mechanical ventilation or ECMO. The potential benefits of combining a well-tolerated, direct-acting antiviral therapy with corticosteroids, immunomodulatory agents, and other therapeutics are currently being evaluated in critically ill patients, those with the greatest unmet medical need, in several global studies. Results are expected in the coming months, and these data will further elucidate the role of RDV and other therapies in this population.

Assessment of the MAH's response

Remdesivir received in July 2020 a conditional marketing approval (CMA). This CMA was conditional to certain specific obligations. As part of the CMA SOB 013 was agreed, to explicitly demonstrate the benefit/risk of Remdesivir in patients on on Invasive Mechanical Ventilation (IMV) and Extracorporeal Membrane Oxygenation (ECMO).

As part of the RSI of this variation procedure a MO was raised, in which the MAH was explicitly asked to justify a favourable risk-benefit profile based on overall available evidence in patients on IMV or ECMO when starting Remdesivir. However, the response of the MAH only addressed the potential risk/harmful effects of remdesivir in the subgroup of patients on IMV or ECMO at baseline but neither the observerd missing benefit on Time to recovery (TTR), the primary efficacy endpoint of this study, nor on mortality in patients with baseline ordinal score 7.

In view of the Rapporteur, the analyses of efficacy in the subset of participants on invasive mechanical ventilation or ECMO at baseline (ordinal score 7) do neither indicate a benefit of RDV in terms of the primary endpoint Time to recovery (HR: 0.98; CI 0.70, 1.36), nor for mortality (RR: 1.13; CI 0.67, 1.89; p = 0.652). There is also inconsistency of a beneficial effect at primary and secondary endpoints analyses among the overall study population and subjects of "subgroup 7". HRs obtained by Cox proportional hazard models testing for interaction between treatment*baseline ordinal scale with respect to TTR abd mortality show a clear trend towards worse outcomes with increasing baseline ordinal scale, though not statistically significant.

This is further supported by the requested additional mortality analyses for specific subgroups. The hazards

of death for ventilated patients, i.e. on non-invasive ventilation, invasive mechanical ventilation or ECMO at baseline (HR: 1.12; CI 0.7, 1.82) and for those patients on non-invasive ventilation (HR: 1.11; CI 0.32, 3.83), were both similar to those reported in patients on IMV/ECMO (HR: 1.13; CI 0.67, 1.89; p = 0.652), suggesting that remdesivir may not be beneficial in patients ventilated at the time of RDV treatment initiation (please refer to Question 3a and b below).

The modest variation across study subgroups in median time to randomization from symptom onset and hospitalization are in agreement with the hypothesis that participants receiving ventilation or IVM/ECMO at baseline differ from non-ventilated subjects by disease characteristics (i.e. inflammatory state associated with rapid disease progression) rather than disease history. This further supports the temporal "window of opportunity" for Remdesivir use.

Although study ACTT-1 showed overall a statistically significant effect of RDV on time to recovery and a numerically positive trend for mortality, the findings from the subgroup analysis with baseline ordinal score 7 are of concern. No beneficial effect was seen in terms of TTR and mortality in this subgroup, which was observed across different studies. Taking the lack of evidence for a benefit in this subgroup into account, the B/R in these subgroup of patients is negative. It is also noted that based on these subgroup analyses and clinical experience, several national treatment guidelines and learned societies in the EU do not recommend treatment with RDV in patients receiving IMV or ECMO at baseline and with onset of symptoms more than (5 to) 10 days ago.

The ACTT-2 trial with baricitinib was cited by the MAH, but it does not provide relevant additional evidence based on the data presented here.

Overall conclusion:

SOB 013 was explicity requested by CHMP as part of the conditional marketing authorisation in order to confirm the efficacy and safety of Remdesivir in patients on Invasive Mechanical Ventilation (IMV) or Extracorporeal Membrane Oxygenation (ECMO). The provided data failed to confirm a benefical effect of Remdesivir in this subset of patients.

Hence, the data submitted in the context of SOB 13, considered as key for substantiation of the therapeutic indication at the time of CMA, did not provide proof of a positive benefit/risk ratio of RDV in patients on IMV/ECMO at baseline. Therefore, in view of the CHMP, therapy of patients on IMV/ECMO at the start of therapy should no longer be indicated for RDV.

Conclusion

Issue <u>not</u> resolved.

10.2. Other concerns

Clinical aspects

Question 1

Day-28 mortality status was not available for all enrolled patients in the NIAID trial. It remains unclear why the mortality status of 19 patients in the RDV group and 13 patients in the placebo group is still missing, although the 29 days after randomization have long been completed and the patients with missing status have not discontinued the study. The MAH is asked to clarify the status of these patients.

Summary of the MAH's response

The MAH clarified that Day 29 mortality status is known for 508 participants (93.9%) in the RDV group and 499 participants (95.8%) in the placebo group (Table 12 and CO-US-540-5776 Final CSR, Table 27). Excluding those who died or recovered, 14 participants (2.6%) in the RDV group and 9 participants (1.7%) in the placebo group prematurely discontinued from the study (Table 12 and CO-US-540-5776 Final CSR, Figure 2). The remaining 19 participants (3.5%) in the RDV group and 13 participants (2.5%) in the placebo group either did not receive study drug (RDV 10 participants [1.8%]; placebo 4 participants [0.8%]; Table 12 and CO-US-540-5776 Final CSR, Figure 2) or were recovered at the time of premature discontinuation from the study (RDV 9 participants [1.7%]; placebo 9 participants [1.7%]; Table 12).

Table 12: CO-US-540-5776: Summary of Known/Unknown Mortality Status at Day 29 (ITT Population)

	Remdesivir (N = 541)	Placebo (N = 521)	Total (N = 1062)
Known mortality status at Day 29	508 (93.9%)	499 (95.8%)	1007 (94.8%)
Unknown mortality status at Day 29	33 (6.1%)	22 (4.2%)	55 (5.2%)
Randomized, but treatment not administered	10 (1.8%)	4 (0.8%)	14 (1.3%)
Early termination, but recovered	9 (1.7%)	9 (1.7%)	18 (1.7%)
Lost to follow-up	4 (0.7%)	7 (1.3%)	11 (1.0%)
Voluntary withdrawal by participant	2 (0.4%)	2 (0.4%)	4 (0.4%)
Voluntary withdrawal by participant, transition to comfort care	1 (0.2%)	0	1 (< 0.1%)
Withdrawal by investigator	2 (0.4%)	0	2 (0.2%)
Early termination, excludes death and recovery	14 (2.6%)	9 (1.7%)	23 (2.2%)
Voluntary withdrawal by participant	6 (1.1%)	5 (1.0%)	11 (1.0%)
Voluntary withdrawal by participant, transition to comfort care	3 (0.6%)	2 (0.4%)	5 (0.5%)
Adverse Event	4 (0.7%)	0	4 (0.4%)
Transferred to another hospital	1 (0.2%)	1 (0.2%)	2 (0.2%)
Withdrawal by investigator	0	1 (0.2%)	1 (< 0.1%)

Participants with known mortality status at Day 29 are those who have data for a day on or after Day 26 or who are known to be deceased. Day 26 represents the beginning of the visit window for the Day 29 visit.
Source: Table req12690.14; CO-US-540-5776 Final CSR, Figure 2 and Table 27

Assessment of the MAH's response

The question was raised because there was a discrepancy between the numbers of patients who terminated the study according to the presented patients' flow and the number of patients with available mortality status at day 29. The MAH clarified that there were three categories of patients with unknown mortality status at day 29:

1) Patients who were randomized but not treated (it is not clear why these patients were not followed for outcomes, which would have been required for a true ITT analysis);

2) Patients who terminated the study early but were considered recovered at time of study termination;

3) Patients who terminated the study early without recovery at termination.

Only patients in category 3) were listed as "early termination" in the patient flow, explaining the discrepancy. Although some aspects in study design with regard to missing data appear not to have been ideal (not following patients that were not treated, termination of 4 patients with AEs), the number of patients with missing data was low such that no relevant concerns result from missing data.

Conclusion

Issue resolved.

Question 2

The MAH is asked to include the final Day-28 mortality data in section 5.1 of the SmPC (including mortality data by WHO score).

Summary of the MAH's response

The MAH added the final Day 29 mortality data (presented by NIAID's baseline ordinal score and where participants with unknown mortality status at Day 29 were censored at their last study visit) to Section 5.1 of the summary of product characteristics (SmPC; Table 13). Proposed updates to the remainder of the NIAID text in SmPC Section 5.1 are planned to be included in the conditional marketing authorisation (CMA) renewal submission.

Table 13: 29-Day Mortality Outcomes by Ordinal Scalea at Baseline—NIAID

	Ordinal Score at Baseline							
	4		5		6		7	
	Not on oxygen		Requiring low-flow oxygen		Requiring high-flow oxygen or non-invasive mechanical ventilation		Requiring invasive mechanical ventilation or ECMO	
	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
29-day mortality	4.1	4.8	4.0	12.7	21.2	20.4	21.9	19.3
Hazard ratio[b] (95% CI)	0.82 (0.17, 4.07)		0.30 (0.14, 0.64)		1.02 (0.54, 1.91)		1.13 (0.67, 1.89)	

ECMO = Extracorporeal membrane oxygenation
a Not a pre-specified analysis.
b Hazard ratios for baseline ordinal score subgroups are from unstratified Cox proportional hazards models.
Source: {Beigel 2020}

Assessment of the MAH's response

The MAH included the final Day-28 mortality data in section 5.1 of the SmPC (including mortality data by WHO score) as requested. However, the proposed table is not endorsed, as only the final Day-28 mortality data relevant for the approved indication should be included in section 5.1. As RDV use is not approved for treatment of patients who do not require supplemental oxygen, information concerning ordinal scale category 4 and also category 7 should be deleted.

In addition, the proposed updates to the SmPC should be included at this procedural stage. This also applies to the restriction of the indication to patients not on IMV/ECMO.

Conclusion

Issue <u>not</u> resolved.

Question 3a

In order gain further understanding of the effect of Remdesivir on mortality in the subgroup of ventilated patients in the NIAID trial, the MAH is asked to provide:

a. An analysis of mortality in a subgroup of patients comprising those ventilated at the time of randomisation in the NIAID trial, including those on non-invasive ventilation, invasive ventilation and ECMO.

Summary of the MAH's response 3a

The MAH provided an analysis of time to Mortality by Day 29 by Treatment Group with non-invasive ventilation, invasive mechanical ventilation, or ECMO at the time of randomization and known mortality status (Table 14).

Table 14: CO-US-540-5776: Time to Mortality by Day 29 by Treatment Group (ITT Population – Participants with Noninvasive Ventilation, Invasive Ventilation, or ECMO at Baseline and Known Mortality Status at Day 29)

	RDV (N = 147)	Placebo (N = 172)
Death by Day 29, n (%)	33 (22%)	34 (20%)
Kaplan-Meier Estimate (95% CI)	22% (15.7%, 29.1%)	20% (13.8%, 25.8%)
Hazard Ratio (95% CI)	1.12 (0.70, 1.82)	
P-value	0.631	

CI = confidence interval; KM = Kaplan-Meier
Participants with known mortality status at Day 29 are those who have data for a day on or after Day 26 or who are known to be deceased. Day 26 represents the beginning of the visit window for the Day 29 visit.
Number of participants at risk is calculated at the beginning of interval; cumulative events and KM percent (95% CI) is calculated at the end of interval.
Hazard ratio is the ratio of the hazard of death in each treatment group estimated from the Cox model. The ratio is remdesivir to placebo.
P-value calculated using the log-rank test.
Source: Table req12690.15.1

Assessment of the MAH's response

The MAH did provided the requested analyses of time to Mortality by Day 29 by Treatment Group with Noninvasive Ventilation, Invasive Ventilation, or ECMO at Baseline and Known Mortality Status at Day 29). Based on the provided data only 21 patients in the RDV group and 24 patients in the placebo group with known mortality status were on non-invasive ventilation at baseline. The Kaplan-Meier estimate was higher in the RDV group compared to the control group (22% vs. 20%, respectively). The hazard of death in the group of patients on non-invasive ventilation, invasive ventilation or ECMO at baseline and with known mortality status at Day 29 (HR: 1.12; CI 0.7, 1.82) was similar to that seen in patients on IMV/ECMO (HR: 1.13; CI 0.67, 1.89; p = 0.652), suggesting that being ventilated at the time of RDV treatment initiation may not be beneficial. However, results for the primary endpoint Time to Recovery for the subgroup of ventilated patients (non-invasive and invasive/ECMO) are not yet available. Therefore, it remains unclear if RDV has a beneficial effect in this patient population.

The initial thought behind this question was to allow for a better comparability of the mortality results of the NIAID study and the Solidarity study. However, data published in the BMJ journal (A living WHO guideline on drugs for Covid-19; *doi: https://doi.org/10.1136/bmj.m3379*) indicate that of 5451 patients enroled in the Solidarity trial, 8.9% were on invasive mechanical ventilation at baseline. Hence, this means that all patients who were ventilated at baseline according to the published interim WHO Solidarity results were on IMV (487/5451 = 8.9%). Hence, data of the subgroup on IMV/ECMO at baseline are comparable between the NIAID and Solidarity trial in this regard.

Conclusion

Issue resolved.

Question 3 b

A separate analysis of all patients that were categorised in category 6 and received non-invasive ventilation at the time of randomisation.

Summary of the MAH's response 3 b

The MAH provided an analysis of mortality in participants who were on non-invasive ventilation at the time of randomization (Table 15).

Table 15: CO-US-540-5776: Time to Mortality by Day 29 by Treatment Group (ITT Population – Participants with Noninvasive Ventilation at Baseline and Known Mortality Status at Day 29)

	RDV (N = 21)	Placebo (N = 24)
Death by Day 29, n (%)	5 (24%)	5 (21%)
Kaplan-Meier Estimate (95% CI)	24% (5.6%, 42.0%)	21% (4.6%, 37.0%)
Hazard Ratio (CI)	1.11 (0.32, 3.83)	
P-value	0.871	

CI = confidence interval; KM = Kaplan-Meier
Participants with known mortality status at Day 29 are those who have data for a day on or after Day 26 or who are known to be deceased. Day 26 represents the beginning of the visit window for the Day 29 visit.
Number of participants at risk is calculated at the beginning of interval; cumulative events and KM percent (95% CI) is calculated at the end of interval.
Hazard ratio is the ratio of the hazard of death in each treatment group estimated from the Cox model. The ratio is remdesivir to placebo.
P-value calculated using the log-rank test.
Source: Table req12690.15.2

Assessment of the MAH's response

The MAH did provided the requested analysis of time to Mortality by Day 29 in participants who were on non-invasive ventilation at the time of randomization. The Kaplan-Meier estimate was higher in the RDV group compared to the control group (24% vs. 21%, respectively). The hazard of death in the group of patients on non-invasive ventilation and with known mortality status at Day 29 (HR: 1.11; CI 0.32, 3.83) was similar to that seen in patients on IMV/ECMO (HR: 1.13; CI 0.67, 1.89; p = 0.652), suggesting that being on non-invasive ventilation at the time of RDV treatment initiation may not be beneficial. However, results for the primary endpoint Time to Recovery for the subgroup of non-invasive ventilated patients are not yet available. Thus, it remains unclear if RDV has a beneficial effect in this patient population.

Conclusion

Issue resolved.

Question 3 c

Please provide symptom duration prior to randomisation (median +IQR) per ordinal scale stratum at baseline.

Summary of the MAH's response 3c

The MAH provided the median (Q1, Q3) duration of symptoms prior to randomization (Table 16).

Table 16: CO-US-540-5776: Median (Q1, Q3) Duration of Symptoms (in Days) Prior to Randomization by Baseline Ordinal Score and Treatment Group (ITT Population)

Baseline Ordinal Score	Treatment	n	Median	Q1, Q3
4	Remdesivir (N = 75)	75	7.0	5, 10
	Placebo (N = 63)	63	9.0	7, 11
5	Remdesivir (N = 232)	232	9.0	6, 12
	Placebo (N = 203)	201	9.0	6, 12
6	Remdesivir (N = 95)	95	8.0	6, 13
	Placebo (N = 98)	98	10.0	7, 13
7	Remdesivir (N = 131)	130	9.0	7, 13
	Placebo (N = 154)	154	10.0	7, 14

Q1 = 25th percentile; Q3 = 75th percentile
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the ITT Population.
Eleven participants with missing ordinal score at baseline were excluded from this analysis.
Three participants had missing values in duration of symptom prior to randomization.
Duration was relative to randomization date, which was calculated as randomization date − start date of symptoms.
Source: Table req12690.13

Assessment of the MAH's response

The MAH provided the median (Q1, Q3) duration of symptoms prior to randomization. In general, symptom duration increases with disease severity. This data in combination with the observed statistically significant effect of RDV treatment in study ACTT-1, when given during the first 10 days after symptom onset (RR: 1.37 CI. 1.14; 1.64) support the assumption that there is a temporal window of opportunity for RDV treatment early during the disease, which is not the case for patients on IMV/ECMO as those are more likely to have longer duration of symptom onset.

Interestingly, the median time from symptoms onset was shorter in the Remdesivir group as compared to the placebo group in patients with baseline ordinal score 6 and 7. Having in mind the above mentioned statistically significant effect of RDV treatment when given during the first 10 days after symptom onset (RR: 1.37 CI. 1.14; 1.64) longer duration of symptom onset in patients of the placebo group in baseline ordinal scale categories 6 and 7 might have prevented a more pronounced negative trend of RDV treatment in these patients.

Conclusion

Issue resolved.

Question 3 d

Please provide data on the duration of hospitalisation prior to baseline (median + IQR) per ordinal scale stratum at baseline.

Summary of the MAH's response 3d

The MAH provided the median (Q1, Q3) duration of hospitalization prior to randomization was similar across the baseline ordinal score subgroups (Table 17).

Table 17: CO-US-540-5776: Median (Q1, Q3) Duration of Hospitalization (in Days) Prior to Randomization by Baseline Ordinal Score and Treatment Group (ITT Population)

Baseline Ordinal Score	Treatment	n	Median	Q1, Q3
4	Remdesivir (N = 75)	75	2.0	1, 2
	Placebo (N = 63)	63	2.0	1, 2
5	Remdesivir (N = 232)	232	2.0	1, 3
	Placebo (N = 203)	203	2.0	1, 3
6	Remdesivir (N = 95)	95	2.0	1, 4
	Placebo (N = 98)	98	2.0	1, 4
7	Remdesivir (N = 131)	131	2.0	1, 4
	Placebo (N = 154)	154	2.0	1, 5

Q1 = 25th percentile; Q3 = 75th percentile
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the ITT Population.
Eleven participants with missing ordinal score at baseline were excluded from this analysis.
Duration was relative to randomization date, which was calculated as randomization date − start date of hospitalization.
Source: Table req12690.13

Assessment of the MAH's response

The median (Q1, Q3) duration of hospitalization prior to randomization was generally similar across the baseline ordinal score subgroups.

Conclusion

Issue resolved.

Question 3 e

Please provide key safety indices, including renal events, from the randomised NIAID-ACTT1 study for patients in baseline ordinal scale categories 6 and 7, per treatment arm.

Summary of the MAH's response 3e

The MAH provided an overall summary of AEs by baseline ordinal score and treatment group (Table 18). The incidence of AEs increased with increasing baseline disease severity; however, within each baseline ordinal score subgroup, AE incidence was generally similar between the RDV and placebo groups.

Table 18: CO-US-540-5776: Overall Summary of Treatment-Emergent Adverse Events by Baseline Ordinal Score and Treatment Group (As Treated Population)

	Baseline Ordinal Score							
	4		5		6		7	
Participants with	RDV (N = 75)	Placebo (N = 63)	RDV (N = 231)	Placebo (N = 202)	RDV (N = 94)	Placebo (N = 98)	RDV (N = 132)	Placebo (N = 153)
Any TEAE	26 (34.7%)	18 (28.6%)	100 (43.3%)	104 (51.5%)	65 (69.1%)	65 (66.3%)	114 (86.4%)	136 (88.9%)
Any study drug-related TEAE	4 (5.3%)	2 (3.2%)	12 (5.2%)	12 (5.9%)	5 (5.3%)	10 (10.2%)	20 (15.2%)	23 (15.0%)
Any TESAE	9 (12.0%)	10 (15.9%)	41 (17.7%)	53 (26.2%)	32 (34.0%)	43 (43.9%)	49 (37.1%)	57 (37.3%)
Any TEAE leading to discontinuation of study drug	3 (4.0%)	2 (3.2%)	12 (5.2%)	24 (11.9%)	16 (17.0%)	23 (23.5%)	26 (19.7%)	28 (18.3%)

Adverse events were coded using MedDRA 23.0.
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the As Treated Population.
Source: Table req12690.12.1

The AEs reported in at least 5% of total participants by preferred term, baseline ordinal score, and treatment group are provided in Table 19. The incidence of AEs generally increased with increasing baseline disease severity; however, within each baseline ordinal score subgroup, AE incidence was generally similar between the RDV and placebo groups. A similar trend was observed in an analysis of study drug-related AEs by preferred term, baseline ordinal score, and treatment group (data not shown).

Table 19: CO-US-540-5776: Treatment-Emergent Adverse Events Occurring in at Least 5% of Total Participants by Preferred Term, Baseline Ordinal Score, and Treatment Group (As Treated Population)

	Baseline Ordinal Score							
	4		5		6		7	
Preferred Term	RDV (N = 75)	Placebo (N = 63)	RDV (N = 231)	Placebo (N = 202)	RDV (N = 94)	Placebo (N = 98)	RDV (N = 132)	Placebo (N = 153)
Glomerular filtration rate decreased	3 (4.0%)	2 (3.2%)	22 (9.5%)	20 (9.9%)	14 (14.9%)	16 (16.3%)	21 (15.9%)	38 (24.8%)
Haemoglobin decreased	5 (6.7%)	3 (4.8%)	8 (3.5%)	8 (4.0%)	14 (14.9%)	12 (12.2%)	22 (16.7%)	39 (25.5%)
Lymphocyte count decreased	1 (1.3%)	2 (3.2%)	8 (3.5%)	15 (7.4%)	15 (16.0%)	13 (13.3%)	21 (15.9%)	24 (15.7%)
Respiratory failure	1 (1.3%)	0	14 (6.1%)	25 (12.4%)	12 (12.8%)	24 (24.5%)	10 (7.6%)	11 (7.2%)
Anaemia	2 (2.7%)	1 (1.6%)	9 (3.9%)	9 (4.5%)	1 (1.1%)	7 (7.1%)	30 (22.7%)	36 (23.5%)
Pyrexia	1 (1.3%)	2 (3.2%)	10 (4.3%)	11 (5.4%)	6 (6.4%)	2 (2.0%)	21 (15.9%)	19 (12.4%)
Blood creatinine increased	1 (1.3%)	0	10 (4.3%)	6 (3.0%)	6 (6.4%)	10 (10.2%)	15 (11.4%)	20 (13.1%)
Hyperglycaemia	2 (2.7%)	0	9 (3.9%)	8 (4.0%)	7 (7.4%)	5 (5.1%)	16 (12.1%)	21 (13.7%)
Blood glucose increased	2 (2.7%)	1 (1.6%)	14 (6.1%)	9 (4.5%)	10 (10.6%)	5 (5.1%)	13 (9.8%)	12 (7.8%)
Acute kidney injury	0	1 (1.6%)	6 (2.6%)	9 (4.5%)	8 (8.5%)	7 (7.1%)	14 (10.6%)	16 (10.5%)
Aspartate aminotransferase increased	1 (1.3%)	1 (1.6%)	1 (0.4%)	11 (5.4%)	5 (5.3%)	8 (8.2%)	11 (8.3%)	13 (8.5%)

Adverse events were coded using MedDRA 23.0.
Multiple AEs were counted only once per participant per preferred term.
Preferred terms are presented by descending order of the total frequencies.
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the As Treated Population.
Source: Table req12690.12.5

An overall summary of renal AEs by baseline ordinal score is provided in Table 20. Renal impairment is associated with the underlying disease process, which is evident in the increase in renal AE incidence with increasing baseline disease severity. However, renal AE incidence was generally similar between treatment groups within the baseline ordinal score subgroup.

Table 20: CO-US-540-5776: Overall Summary of Treatment-Emergent Renal Adverse Events by Baseline Ordinal Score and Treatment Group (As Treated Population)

	Baseline Ordinal Score							
	4		5		6		7	
Participants with	RDV (N = 75)	Placebo (N = 63)	RDV (N = 231)	Placebo (N = 202)	RDV (N = 94)	Placebo (N = 98)	RDV (N = 132)	Placebo (N = 153)
Any renal TEAE	3 (4.0%)	3 (4.8%)	31 (13.4%)	30 (14.9%)	22 (23.4%)	24 (24.5%)	38 (28.8%)	61 (39.9%)
Any study drug-related renal TEAE	0	1 (1.6%)	4 (1.7%)	1 (0.5%)	0	2 (2.0%)	4 (3.0%)	6 (3.9%)
Any renal TESAE	0	0	0	9 (4.5%)	5 (5.3%)	4 (4.1%)	10 (7.6%)	7 (4.6%)
Any renal TEAE leading to discontinuation of study drug	0	1 (1.6%)	5 (2.2%)	8 (4.0%)	6 (6.4%)	14 (14.3%)	18 (13.6%)	14 (9.2%)

Adverse events were coded using MedDRA 23.0.
Renal AEs include preferred terms from MedDRA 23.0 SMQ "Acute Renal Failure".
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the As Treated Population.
Source: Table req12690.12.2

Renal AEs by preferred term, baseline ordinal score, and treatment group are summarized in Table 21. Most of the renal AEs observed occurred in similar percentages of participants between the RDV and placebo groups. It is notable that there is higher incidence of glomerular filtration rate decreased among placebo participants versus RDV participants in the Category 7 subgroup.

Table 21: CO-US-540-5776: Treatment-Emergent Renal Adverse Events by Preferred Term, Baseline Ordinal Score, and Treatment Group (As Treated Population)

	Baseline Ordinal Score							
	4		5		6		7	
Preferred Term	RDV (N = 75)	Placebo (N = 63)	RDV (N = 231)	Placebo (N = 202)	RDV (N = 94)	Placebo (N = 98)	RDV (N = 132)	Placebo (N = 153)
Glomerular filtration rate decreased	3 (4.0%)	2 (3.2%)	22 (9.5%)	20 (9.9%)	14 (14.9%)	16 (16.3%)	21 (15.9%)	38 (24.8%)
Blood creatinine increased	1 (1.3%)	0	10 (4.3%)	6 (3.0%)	6 (6.4%)	10 (10.2%)	15 (11.4%)	20 (13.1%)
Acute kidney injury	0	1 (1.6%)	6 (2.6%)	9 (4.5%)	8 (8.5%)	7 (7.1%)	14 (10.6%)	16 (10.5%)
Creatinine renal clearance decreased	0	0	0	2 (1.0%)	0	0	4 (3.0%)	4 (2.6%)
Renal failure	0	0	1 (0.4%)	3 (1.5%)	2 (2.1%)	0	0	3 (2.0%)
Renal impairment	0	0	1 (0.4%)	2 (1.0%)	1 (1.1%)	2 (2.0%)	0	0
Proteinuria	0	0	0	0	1 (1.1%)	0	0	1 (0.7%)
Renal tubular necrosis	0	0	0	0	0	0	0	2 (1.3%)
Blood creatinine abnormal	0	0	0	0	0	0	0	1 (0.7%)
Continuous haemodiafiltration	0	0	0	0	0	1 (1.0%)	0	0
Glomerular filtration rate abnormal	0	0	0	0	0	0	0	1 (0.7%)

Adverse events were coded using MedDRA 23.0.
Renal AEs include preferred terms from MedDRA 23.0 SMQ "Acute Renal Failure".
Multiple AEs were counted only once per participant per preferred term.
Preferred terms are presented by descending order of the total frequencies.
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the As Treated Population.
Source: Table req12690.12.6

An overall summary of hepatic AEs by baseline ordinal score is provided in Table 22. The trend in hepatic AEs was similar to that observed for overall AEs. Incidence of hepatic AEs increased with increasing baseline disease severity, but was generally similar between treatment groups within the baseline ordinal score subgroup.

Table 22: CO-US-540-5776: Overall Summary of Treatment-Emergent Hepatic Adverse Events by Baseline Ordinal Score and Treatment Group (As Treated Population)

	Baseline Ordinal Score							
	4		5		6		7	
Participants with	RDV (N = 75)	Placebo (N = 63)	RDV (N = 231)	Placebo (N = 202)	RDV (N = 94)	Placebo (N = 98)	RDV (N = 132)	Placebo (N = 153)
Any hepatic TEAE	7 (9.3%)	5 (7.9%)	14 (6.1%)	26 (12.9%)	16 (17.0%)	17 (17.3%)	34 (25.8%)	32 (20.9%)
Any study drug-related hepatic TEAE	4 (5.3%)	1 (1.6%)	7 (3.0%)	9 (4.5%)	4 (4.3%)	7 (7.1%)	14 (10.6%)	15 (9.8%)
Any hepatic TESAE	0	0	0	1 (0.5%)	0	0	0	0
Any hepatic TEAE leading to discontinuation of study drug	2 (2.7%)	1 (1.6%)	3 (1.3%)	4 (2.0%)	1 (1.1%)	2 (2.0%)	4 (3.0%)	5 (3.3%)

Adverse events were coded using MedDRA 23.0.
Hepatic AEs include preferred terms from MedDRA 23.0 SMQ "Acute and Non-infectious Liver Events."
Ordinal score 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care; 5 = Hospitalized, requiring supplemental oxygen; 6 = Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 7 = Hospitalized, on invasive mechanical ventilation or ECMO.
N = Number of participants in the As Treated Population.
Source: Table req12690.12.3

Assessment of the MAH's response

The MAH provided the requested key safety indices, including renal events, from the randomised NIAID-ACTT1 study for patients in baseline ordinal scale categories 6 and 7, per treatment arm. Based on the provided safety analyses, the safety in the subgroup of patients on IMV or ECMO was in general similar between the two groups.

However, it has to be noted, that the numbers of study drug related AEs was generally low in the ACTT-1 study, which is not surprising as the unknown disease, the variety of comedications and the pandemic situation could seriously hamper the discern of the relationship to study drug. While the MAH concluded that there were no additional risks identified with the use of RDV in this patient population, it has to be noted that there were more patients in category 7 with treatment emrérgent serious renal AEs and with treatment emergent renal AEs who discontinued the study drug in the RDV group compated to the control group. The results may be indicative of a negative trend in patients receiving IMV or ECMO at treatment initiation, which might be explained by an increased risk due to longer therapy duration, i. e. higher cumulative exposure. In this context it is worth noting that PRAC has started a review of a safety signal to assess reports of acute kidney injury in some patients with COVID-19 taking Remdesivir. Nevertheless, presented numbers of the ACTT-1 trial are too small to draw any conclusions on this finding. Finally, it is important to highlight that the assessement of the safety aspect of remdesivir is being very closely followed by the PRAC including also the safety signal on renal toxicity. Once the assessment is concluded, in case of any concern or finding the correspondant regulatory action will be taken.

Conclusion

Issue resolved.

11. Comments from member states

Following circulation of the preliminary AR, the following comments were received from 8 MS.

MS1, MS2, MS3 and MS 4 fully support the Rapporteurs proposed restricted indication.

MS5 and MS6 consider a restriction of the indication to specifically exclude patients on IMV/ECMO is not necessary. A warning in section 4.4, stating the current lack of benefit in patients on IMV/ECMO, is considered to be sufficient.

MS7 and MS8 do not support the proposed changes of the SmPC (neither for 4.1 nor for 4.4).

12. Request for supplementary information

12.1. Major objections

Clinical aspects

SOB 13, considered as key for substantiation of the therapeutic indication at the time of CMA, did not provide proof of a positive benefit/risk ratio of RDV in patients on IMV/ECMO at baseline. Therefore, therapy of patients on IMV/ECMO at the start of therapy should no longer be indicated for RDV. Consequentely, the indication should be restricted as follow (add underline to text): "*Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or non-invasive ventilation at start of treatment) (see section 5.1)*.".

12.2. Other concerns

Clinical aspects

2. The proposed table of the final Day-28 mortality data in section 5.1 of the SmPC (including mortality data by WHO score) is not endorsed, as only the final Day-28 mortality data relevant for the approved indication should be included in section 5.1. Information concerning ordinal scale 4 and 7 should be deleted. In addition, the propossed updates to the SmPC should be included now and not withing the renewal procedure.

MAH responses:

The MAH provided a new table with the correct data in SmPC Section 5.1 and an updated PI with the indication agreed by the CHMP:

"*Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or non-invasive ventilation at start of treatment) (see section 5.1)*.".

Therefore, all the issues are considered solved.

Conclusion:

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly (see above).

13. References:

(1) Repurposed Antiviral Drugs for Covid-19 —Interim WHO Solidarity Trial Results, WHO clinical trial consortium, NEJM, December 2020, https://doi.org/10.1056/nejmoa2023184)

(2) Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report, The RECOVERY Collaborative Group NEJM, July 2020 https://doi.org/10.1056/nejmoa2021436

(3) Efficacy of Tocilizumab in Patients Hospitalized with Covid-19, Stone et al., NEJM Oct. 2020 https://doi.org/10.1056/nejmoa2028836,

(4) Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia A Randomized Clinical Trial, Salvarani et al., JAMA, Oct 2020, https://doi.org/10.1001/jamainternmed.2020.6615

(5) Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19, Gupta et al., Oct. 2020, JAMA https://doi.org/10.1001/jamainternmed.2020.6252

(6) FDA Fact sheet for healthcare provider Bamlanivimab. https://c212.net/c/link/?t=0&l=en&o=29755111&h=1388363115&u=http%3A%2F%2Fpi.lilly.com%2Feua%2Fbamlanivimab-eua-factsheet-hcp.pdf&a=Fact+Sheet+for+Healthcare+Providers

(7) Remdesivir for the Treatment of Covid-19 — Final Report. John H. Beigel et al., N Engl J Med. 2020 Oct 8 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262788/?report=classic

(8) WHO SOLIDARITY trial were published as a not-peer reviewed preprint on medrxiv. (https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1).