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Veklury® (remdesivir) Long COVID Symptoms

This document is in response to your request for information regarding long COVID symptoms following the use of Veklury® (remdesivir [RDV]). This response was developed according to principles of evidenced-based medicine and contains data from prospective studies (N≥100) and retrospective studies (N≥5000).

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Summary

Available Data on Long COVID Symptoms Following the Use of RDV

A prospective cohort study evaluated the prevalence of and risk factors for LCS in 449 participants hospitalized with COVID-19 who had ≥6 months of follow-up after discharge.[1]

- The prevalence of LCS was 71.7% at 1 month after discharge and 45.9% at 6 months after discharge. A multivariate analysis showed that treatment with RDV reduced the rate of LCS (OR, 0.641; 95% CI: 0.413–0.782; *P*<0.001) and reduced LCS severity (*P*<0.001) compared with treatment without RDV.[1]

A randomized, open-label, multicenter study evaluated the effects of RDV on participant recovery, LCS symptoms, and QoL outcomes 1 year after hospitalization in 181 adult participants who were hospitalized with COVID-19.[2]

- At 1 year posthospitalization, 85% of participants in the RDV group and 86% of participants in the SoC group reported that they were fully or largely recovered. The occurrence of LCS symptoms was not statistically different between the RDV and SoC groups (*P*>0.05), and the QoL outcome scores were similar between the two groups.[2]

A retrospective cohort study evaluated the effect of RDV on the incidence of LCS-related symptoms and diagnoses in 52,006 patients in the US who were hospitalized with COVID-19.[3,4]

- Results from an age-stratified analysis showed that treatment with RDV reduced the rate of LCS-related symptoms and diagnoses in patients aged <65 years (HR, 0.9; 95% CI: 0.86–0.93) as well as those aged ≥65 years (HR, 0.9; 95% CI: 0.86–0.95) compared with treatment without RDV.[3]
- In another analysis of overall patients hospitalized with COVID-19 and a subgroup of patients with immunocompromising conditions, RDV use was associated with a lower risk of any LCS-related symptom (weighted RR, 0.96; 95% CI: 0.94–0.97) in the overall population. RDV was also associated with a reduced risk of individual outcomes in

patients with immunocompromising conditions and in those who were moderately to severely compromised.[4]

In a retrospective cohort study that used data from a national COVID-19 registry in Singapore, there was no difference in the risk of new-onset, long-term sequelae as a composite outcome (aHR, 1.08; 95% CI: 0.97–1.2; *P*=0.147) or across individual, new-incident diagnoses with RDV vs no RDV up to 300 days post COVID-19 hospitalization.[5]

Available Data on Long COVID Symptoms Following the Use of RDV

Prospective Cohort Study[1]

Study design and demographics

A prospective cohort study evaluated the prevalence of and risk factors for LCS in participants hospitalized with COVID-19 from March 10, 2020, to January 15, 2021, at a hospital in Italy. Participants who required low-flow supplemental O_2 at admission/baseline and had ≥6 months of follow-up were included. The primary endpoint was the prevalence and severity of LCS at the 1-month (Visit 1) and 6-month (Visit 2) postdischarge follow-up visits. The PCFS scale (Grade 0–4) was used to assess the level of severity of LCS. Grades of 3 to 4 indicated significant functional limitations in daily life.

A total of 449 participants were included in the analysis, and of those, 163 received RDV for COVID-19 treatment. The median age of all participants was 65 years, 78% were male, 86.8% received corticosteroids, 15.8% had diabetes, and 14.2% had cardiovascular disease. The median (IQR) duration of hospitalization was 10.5 (7–14.5) days, 42% of participants required continuous positive airway pressure/noninvasive ventilation, 13.8% required ICU admission, 69.5% were discharged to home, 30.5% were discharged to a long-term care facility, 38% required supplemental O_2 at home, and 27.2% required rehabilitation after discharge and 0.9% required rehospitalization.

Results

In the overall study population, the prevalence of LCS was 71.7% (n=322) at Visit 1 and 45.9% (n=206) at Visit 2. At Visits 1 and 2, 147 and 133 participants, respectively, had a score of 2 to 3 on the PCFS, and 175 and 73 participants, respectively, had a score of >3.

In the multivariate analysis of risk factors for LCS, participants treated with RDV showed a 35.9% reduction in the rate of LCS (OR, 0.641; 95% CI: 0.413–0.782; *P*<0.001), whereas ICU admission (OR, 2.551; 95% CI: 1.998–6.819; *P*=0.019) and duration of hospitalization (OR, 2.255; 95% CI: 1.018–6.992; *P*=0.016) were positive predictors of LCS.

In a comparison of PCFS scale scores between patients treated with RDV and those without RDV treatment at Visit 1, 123 participants who were treated with RDV were not affected by LCS (Grade 0–1), compared with 81 who did not receive RDV. The group that received RDV treatment had a reduced rate of more severe PCFS scores (2–3 and >3) than the group that did not receive RDV treatment (*P*<0.001 for all comparisons; Table 1).

Table 1. PCFS Severity According to RDV Treatment (Boglione et al)[1]

PCFS Score	RDV		No RDV	
	Visit 1	Visit 2	Visit 1	Visit 2
0–1	123	132	81	97
2–3	27	23	120	110
4	13	3	85	70

A survival analysis found that participants treated with RDV were less likely to develop LCS than those who did not receive RDV (P<0.001; χ^2=14.614).

SOLIDARITY Finland Trial: Long-Term Effects on QoL[2]

Study design and demographics

A randomized, open-label, multicenter study conducted in Finland evaluated the effects of RDV on participant recovery (primary endpoint), LCS symptoms, and QoL outcomes 1 year after hospitalization in adult participants who were hospitalized with COVID-19 between July 23, 2020, and January 27, 2021. Participants were randomly assigned 1:1 to receive RDV plus local SoC treatment (RDV group, n=114) or local SoC treatment without RDV (SoC group, n=94). Study outcomes were evaluated based on results from questionnaires completed by the participants 1 year posthospitalization.

In the RDV and SoC groups, the mean age of participants was 57.2 and 59.7 years, respectively, most (64.9% and 63.8%) were male, 17.5% and 17% had diabetes, 74% and 79% required supplemental O_2 at the time of hospital admission, 69.3% and 76.6% received dexamethasone, and the median (IQR) duration of hospital stay was 8 (6–11) and 8.5 (6–15) days.

Results

Of the 208 participants enrolled in the study, 181 participants completed the 1-year survey. Five participants (2.4%) died due to COVID-19 during hospitalization, 5 participants (2.4%) died during the 1-year follow-up, 5 (2.4%) declined participation in the long-term evaluation, and 12 (5.8%) were unable to be reached. Of the 10 participants who died, 5 (4.4%) were in the RDV group, and 5 (5.3%) were in the SoC group (RR, 0.82; 95% CI: 0.25–2.76; absolute difference, -0.9%; 95% CI: -7.9 to 5.3%). For participants who received RDV, the median (IQR) duration of treatment was 5 (4–8) days.

At Year 1 posthospitalization, 85% of participants in the RDV group and 86% of participants in the SoC group reported they were fully or largely recovered (RR, 0.94; 95% CI, 0.47–1.9; absolute difference, -0.9%; 95% CI: -11 to 10%), and stratification by the need for supplemental O_2 at hospital admission did not change the recovery estimate. The occurrence of LCS symptoms (eg, anxiety, change in sense of smell/taste, chest pressure or discomfort) was not statistically different between the RDV and SoC groups (P>0.05), and the QoL outcome scores were similar between the two groups (Table 2). The median (IQR) EQ-visual analog scale score (self-report of overall health state ranging from 0 [worst imaginable health state] to 100 [best imaginable health state]) was 75.5 (67.8–85) and 80 (67.5–86.5) for the RDV and SoC groups, respectively (ordered logistic regression OR, 0.83; 95% CI: 0.49–1.4).

Table 2. SOLIDARITY Finland: 1-Year QoL Outcomes[2]

Outcome (Option Categories in Questionnaire)	RDV (n=98)	SoC (n=83)	RR (95% CI)
How do you feel you have recovered from the COVID-19 infection you had a year ago? n (%)			
Fully or largely (1–2)	83 (84.7)	71 (85.5)	0.94 (0.47–1.9)
About halfway recovered to not recovered at all (3–5)	15 (15.3)	12 (14.5)	
Exertional dyspnea,[a] mMRC dyspnea scale, n (%)			
No to slight dyspnea (mMRC 0–1)	92 (93.9)	76 (91.6)	0.61 (0.2–1.85)
At least a need to walk slower than usually (mMRC 2–4)	5 (5.1)	7 (8.4)	
Excluded (paralyzed before COVID-19)	1	0	–
Fatigue, n (%)			
No or slight fatigue (1–2)	74 (75.5)	60 (72.2)	0.88 (0.54–1.44)
Moderate or severe fatigue (3–4)	24 (24.5)	23 (27.7)	
Mobility, walking (EQ-5D-5L), n (%)			
No or slight problems (1–2)	81 (82.7)	69 (83.1)	1.03 (0.54–1.96)
From moderate problems to unable to walk (3–5)	17 (17.3)	14 (16.9)	
Self-care, washing, or dressing oneself (EQ-5D-5L), n (%)			
No or slight problems (1–2)	95 (96.9)	78 (94)	0.51 (0.13–2.08)
From moderate problems to inability to wash or dress (3–5)	3 (3.1)	5 (6)	
Usual activities (eg, work, study, housework, family, or leisure activities; EQ-5D-5L), n (%)			
No or slight problems (1–2)	88 (89.8)	71 (85.5)	0.71 (0.32–1.55)
From moderate problems to inability to do usual activities (3–5)	10 (10.2)	12 (14.5)	
Pain or discomfort (EQ-5D-5L), n (%)			
No or slight pain (1–2)	83 (84.7)	68 (81.9)	0.85 (0.44–1.63)
From moderate to extreme pain (3–5)	15 (15.3)	15 (18.1)	
Anxiety or depression (EQ-5D-5L), n (%)			
No or slight problems (1–2)	89 (90.8)	77 (92.8)	1.27 (0.47–3.42)
From moderate to extreme problems (3–5)	9 (9.2)	6 (7.2)	

Abbreviation: mMRC=modified Medical Research Council.
[a]Absolute difference: -3.3% (95% CI: -12 to 4.4%).

Fatigue (26%), joint pain (22%), persistent respiratory mucus (21%), and problems with memory (19%) or attention/concentration (18%) were the LCS symptoms most often reported as moderately or severely bothersome.

Retrospective Cohort Study in the US

Study design

A retrospective cohort study evaluated the effect of RDV use during the first 2 days of hospitalization on the incidence of symptoms and diagnoses associated with LCS in patients in the US who were hospitalized with COVID-19 between May 1, 2020, and September 30, 2021. Patients aged ≥12 years who were hospitalized with COVID-19 for ≥2 days were identified from the HealthVerity database, and the maximum duration of follow-up was 270 days. A total of 52,006 patients were included in the analyses below.[3,4]

Subgroup analysis by age <65 vs ≥65 years[3]

In one analysis, results were stratified according to age (<65 vs ≥65 years) at the time of hospitalization and included 33,578 patients aged <65 years (12,145 of whom received RDV) and 18,428 aged ≥65 years (5019 of whom received RDV). The RDV and no RDV groups in both age cohorts were generally similar, with approximately 50% of patients

requiring ICU admission and 44% to 52% of patients who were male. Fewer patients in the RDV group than in the no RDV group required no supplemental O_2 support on Days 1 and 2 of hospitalization (<65 years, 63% vs 74%; ≥65 years, 63% vs 72%). More patients in the RDV group than in the no RDV group received treatment with corticosteroids (<65 years, 95% vs 52%; ≥65 years, 94% vs 48%), immunomodulators (<65 years, 9% vs 2%; ≥65 years, 6% vs 1%), convalescent plasma (<65 years, 11% vs 2%; ≥65 years, 14% vs 2%), and/or anticoagulants (<65 years, 16% vs 26%; ≥65 years, 26% vs 38%).

Treatment with RDV was associated with reduced risk of experiencing any LCS-related symptom or diagnosis in both patients aged <65 years (HR, 0.9; 95% CI: 0.86–0.93) and those aged ≥65 years (HR, 0.9; 95% CI: 0.86–0.95). Of the 16 individual LCS-related symptoms and diagnoses included in the analysis, RDV treatment was associated with reduced risk of eight symptoms in patients aged <65 years and six symptoms in patients aged ≥65 years (Table 3).

Table 3. Effect of RDV on Risk of LCS-Related Symptoms and Diagnoses (Berry et al)[3]

LCS Symptom/Diagnosis	HR (95% CI)	
	Age <65 Years (n=33,578)	Age ≥65 Years (n=18,428)
Cognitive dysfunction	0.71 (0.64–0.8)	0.76 (0.7–0.83)
Cerebrovascular disease	0.73 (0.65–0.83)	0.83 (0.75–0.93)
Neuropsychiatric features	0.83 (0.79–0.87)	0.89 (0.83–0.96)
Diarrhea	0.7 (0.6–0.82)	0.76 (0.61–0.95)
Thromboembolic disease	0.83 (0.74–0.94)	0.92 (0.79–1.07)
Chest pain	0.88 (0.81–0.94)	0.87 (0.78–0.98)
Ischemic heart disease	0.86 (0.73–1)	0.97 (0.82–1.13)
Headache	0.82 (0.7–0.95)	0.82 (0.62–1.09)
Dysautonomia	0.38 (0.15–0.98)	0.08 (0.01–0.62)
Fatigue	0.94 (0.88–1.02)	0.98 (0.89–1.07)
Smell disturbance/anosmia	1.9 (0.86–4.21)	1.11 (0.31–4)
Muscle pain/myalgia	1.04 (0.9–1.22)	1.1 (0.8–1.51)
Taste disturbance/dysgeusia/ageusia	0.52 (0.18–1.47)	1.28 (0.43–3.87)
Dyspnea/breathlessness	1.01 (0.95–1.08)	1.05 (0.96–1.16)
Joint pain/arthralgia	1.03 (0.96–1.1)	0.99 (0.9–1.1)
Cough	0.97 (0.87–1.09)	1.08 (0.94–1.26)

Note: Shaded cells indicate outcomes with lower relative hazards (upper bound of 95% CI was <1).

Subgroup analysis by immunocompromised status[4]

In another analysis, the association of RDV use during acute COVID-19 with later development of LCS-related conditions was assessed in the overall population of patients hospitalized with COVID-19 (N=52,006) and in a subgroup of patients with immunocompromising conditions (n=20,246). An immunocompromising condition was reported in 5980 of the 17,164 patients (29.5%) who received RDV and in 14,266 of the 34,842 patients (70.5%) who did not receive RDV. In total, 5673/52,006 patients (10.9%) were considered moderately to severely immunocompromised (RDV, n=1686 [29.7%]; no RDV, n=3987 [70.3%]). Baseline demographics were similar between patients in the RDV and no RDV groups: overall, the mean age was 59 years, and 51% were female. More patients in the RDV group than in the no RDV group received corticosteroid treatment (94.9% vs 50.4%, respectively), immunomodulators (8.1% vs 1.3%), or convalescent plasma (12.1% vs 1.9%), whereas fewer patients in the RDV group than the no RDV group received anticoagulants (18.4% vs 31%).

RDV use was associated with a lower risk of any LCS-related symptoms (*P*<0.001) and of individual outcomes in the overall population. In subgroup analyses of patients with immunocompromising conditions and patients who were moderately to severely compromised, RDV was associated with a reduced risk of individual outcomes (Table 4).

Table 4. Effect of RDV on LCS-Related Symptoms in the Overall Population and in Subgroups of Patients With Immunocompromising Conditions or Who Were Moderately to Severely Compromised (Berry et al)[4]

Population and Events, n		RDV	No RDV	Weighted RR (95% CI)
Overall population	Any long COVID outcome	8643	20,202	0.96 (0.94–0.97)
	Neuropsychiatric features	4416	12,461	0.91 (0.89–0.94)
	Cognitive dysfunction	1404	5826	0.8 (0.76–0.84)
	Chest pain	1817	4905	0.89 (0.85–0.94)
	Cerebrovascular disease	1039	3908	0.81 (0.77–0.87)
	Thromboembolic disease	888	2415	0.84 (0.78–0.9)
	Ischemic heart disease	638	2115	0.89 (0.82–0.97)
	Diarrhea	433	1588	0.73 (0.65–0.81)
	Headache	356	1040	0.82 (0.72–0.93)
	Dysautonomia	7	43	0.18 (0.04–0.51)
Patients with an immunocompromising condition	Cognitive dysfunction	653	2807	0.8 (0.74–0.86)
	Chest pain	835	2553	0.88 (0.81–0.94)
	Cerebrovascular disease	489	1946	0.83 (0.75–0.9)
	Diarrhea	224	948	0.71 (0.61–0.82)
Patients who were moderately to severely immunocompromised	Diarrhea	79	343	0.57 (0.44–0.73)

Note: Results for all other outcomes were nonsignificant, and RDV was not associated with an increased risk of any outcome.

Retrospective Cohort Study in Singapore[5]

Study design and demographics

A retrospective, population-based cohort study was conducted using data from a national COVID-19 registry in Singapore to assess the impact of RDV use on risks of new-onset, long-term diagnoses or symptoms up to 300 days post hospitalization for COVID-19 (N=30,175). Patients were excluded if they had received other antivirals, received RDV >7 days after admission, died ≤30 days after admission, or were reinfected with COVID-19 within 300 days of hospitalization. The composite outcome included the occurrence of any new-incident cardiovascular, neurological, respiratory, or autoimmune diagnosis, and the risks of new diagnoses or symptoms were estimated in patients in the RDV group (n=11,353) and compared with those of patients in the no RDV group (n=18,822). Post weighting, baseline characteristics were balanced between the RDV group and the no RDV group; overall, 88.9% were fully vaccinated, 60.5% had received a booster dose, and 77.4% had COVID-19 during the Omicron period.

Results

With a mean follow-up duration of 241 days in the RDV group and 256.9 days in the no RDV group, there was no difference in the risk of new-onset, long-term sequelae as a composite outcome (aHR, 1.08; 95% CI: 0.97–1.2; *P*=0.147) or across individual, new-incident

diagnoses with RDV vs no RDV. In the subgroup of patients with mild comorbidity burden, the RDV group had a lower risk of sensory disorders (anosmia/dysgeusia) than the no RDV group (aHR, 0.49; 95% CI: 0.29–0.8; *P*=0.002). There were no significant differences between groups in the risk reduction in all other subgroup analyses, including in patients ≥60 years of age and in patients with severe disease (ie, concurrent steroid use, supplemental O_2 use, or ICU/high-dependency status upon admission).

References

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Abbreviations

aHR=adjusted hazard ratio
HR=hazard ratio
ICU=intensive care unit
LCS=long COVID syndrome
O_2=oxygen
OR=odds ratio
PCFS=Post-COVID-19 Functional Status Scale
QoL=quality of life
RDV=remdesivir
RR=risk ratio
SoC=standard of care

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Veklury US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Follow-Up

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