GILEAD | Medical Information

Veklury® (remdesivir) Use With Hydroxychloroquine

This document is in response to your request for information regarding the use hydroxychloroquine (HCQ) with Veklury® (remdesivir [RDV]) for the treatment of COVID-19. This response was developed according to principles of evidence-based medicine and contains data from phase 3 clinical studies.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Summary

Product Labeling[1]

Coadministration of RDV and chloroquine phosphate or HCQ sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of RDV.

Due to potential antagonism based on data from cell culture experiments, concomitant use of RDV with chloroquine phosphate or HCQ sulfate is not recommended.

RDV EC_{50} values for SARS-CoV-2 in A549-hACE2 cells were not different when combined with chloroquine phosphate or HCQ sulfate at concentrations up to 2.5 mcM. In a separate study, the antiviral activity of RDV was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus. Higher RDV EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate or HCQ sulfate reduced formation of RDV triphosphate in A549-hACE2, HEp-2, and normal human bronchial epithelial cells.

Phase 3 Clinical Data on RDV Use With HCQ

In the SIMPLE study of RDV in participants with severe COVID-19, those in the RDV + HCQ group (n=160) were less likely to experience clinical improvement and recovery than those in the RDV alone (n=237) group.[2]

- Mortality rates were not increased in the RDV + HCQ group relative to those observed in the RDV alone group.
- A higher proportion of AEs was observed in participants in the RDV + HCQ group than the RDV alone group, and significantly more Grade ≥3 and RDV-related Grade ≥3 AEs were observed in the RDV + HCQ group than the RDV alone group.

In the SIMPLE study of RDV in participants with moderate COVID-19, the rate of recovery was not significantly different between participants in the RDV alone (n=274) and

RDV + HCQ (n=110) groups or between those in the SoC alone (n=107) and SoC + HCQ (n=93) groups.[3]

- Participants in the RDV alone group had significantly fewer treatment-emergent toxicities than those in the RDV + HCQ group, and similar rates of AEs and treatment-emergent toxicities were reported in the SoC alone and SoC + HCQ groups.

Phase 3 Clinical Data on RDV Use With HCQ

SIMPLE Study in Severe COVID-19

Study design, demographics, and participant disposition

A phase 3, randomized, two-part (Part A and Part B), open-label study evaluated RDV in participants with severe of COVID-19, defined as SARS-CoV-2 confirmed by reverse transcriptase-polymerase chain reaction, peripheral O_2 saturation ≤94% on room air, radiographic evidence of pulmonary infiltrates, and CrCl ≥50 mL/min.[4,5] An analysis of data from Part A of the study assessed the clinical outcomes and safety of concomitant use of RDV (5-day or 10-day RDV dosing regimens, in addition to SoC) and HCQ, which included treatment for ≥1 day with HCQ, HCQ sulfate, chloroquine, or aminoquinolines within 2 days before RDV initiation or anytime thereafter.[2]

Part A enrolled participants who were not mechanically ventilated between March 6 and March 26, 2020, and those who met all eligibility criteria were randomly assigned in a 1:1 ratio to receive RDV 200 mg IV loading dose on Day 1, followed by RDV 100 mg/day IV on Days 2 to 5 or Days 2 to 10 in addition to SoC therapy.[4]

Table 1. SIMPLE Severe: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Characteristics	All Participants (N=397)	RDV Alone (n=237)	RDV + HCQ (n=160)
Age, median (IQR), years	61 (20–98)	63 (20–98)	60 (21–88)
Male, n (%)	253 (64)	140 (59)	113 (71)[a]
Obesity (≥30 kg/m^2), n (%)	163 (41)	110 (46)	53 (33)[b]
Diabetes, n (%)	90 (23)	59 (25)	31 (19)
Cardiovascular disease, n (%)	114 (29)	78 (33)	36 (23)[c]
Clinical status on the 7-point ordinal scale, n (%)			
2- Required IMV or ECMO	13 (3)	5 (2)	8 (5)
3- Required NIPPV or high-flow O_2	109 (27)	44 (19)	65 (41)
4- Required low-flow supplemental O_2	220 (55)	144 (61)	76 (48)
5- Did not require supplemental O_2 but required medical care	55 (14)	44 (19)	11 (7)

Abbreviation: ECMO=extracorporeal membrane oxygenation; IMV=invasive mechanical ventilation; NIPPV=noninvasive positive pressure ventilation.
[a]*P*=0.02 vs RDV alone. [b]*P*=0.016 vs RDV alone. [c]*P*=0.033 vs RDV alone.

Sixty-two percent of participants initiated HCQ within 2 days prior to starting RDV, and 16% initiated HCQ on the same day they started RDV. The remaining participants had initial exposure to HCQ up to Day 14 after they started RDV.

Results[2]

Participants in the RDV + HCQ group were less likely to experience clinical improvement (≥2-point improvement in ordinal score) than those in the RDV alone group (Table 2).

Participants in the RDV + HCQ group were less likely to experience recovery (improvement from a baseline ordinal score of 2 to 5 to a score of 6 or 7 or improvement from a baseline score of 6 to a score of 7) than those in the RDV alone group. The median times to clinical improvement and recovery were longer in the RDV + HCQ group than the RDV alone group. Mortality rates were not increased in the RDV + HCQ group relative to those observed in the RDV alone group.

Table 2. SIMPLE Severe: Clinical Outcomes[2]

Outcomes		RDV Alone (n=237)	RDV + HCQ (n=160)
Clinical improvement[a]	n (%)	163 (69)	93 (58)
	Adjusted hazard ratio (95% CI)	0.66 (0.49–0.9); *P*=0.007	
	Time to clinical improvement, median (IQR), days	9 (5–13)	11 (8–15)
Recovery[b]	n (%)	163 (69)	91 (57)
	Adjusted hazard ratio (95% CI)	0.61 (0.45–0.83); *P*=0.002	
	Time to recovery, median (IQR), days	9 (5–13)	11 (8–15)
Deaths	n (%)	23 (10)	21 (13)
	Adjusted hazard ratio (95% CI)	0.82 (0.38–1.81); *P*=0.63	
	Time to death, median (IQR), days	9 (6–13)	9 (6–12)

[a]Clinical improvement was defined as ≥2-point improvement in ordinal score and/or live discharge from hospital.
[b]Recovery was defined as an improvement from a baseline ordinal score of 2 to 5 to a score of 6 or 7 or an improvement from a baseline score of 6 to a score of 7.

Safety[2]

A higher proportion of AEs was observed in participants in the RDV + HCQ group than in the RDV alone group (*P*=0.34; Table 3). After adjustment for baseline covariates, significantly more Grade ≥3 and RDV-related Grade ≥3 AEs were observed in the RDV + HCQ group than the RDV alone group (*P*=0.045 and *P*=0.007, respectively).

Table 3. SIMPLE Severe: Additional Safety Outcomes[2]

Safety Outcomes, n (%)	All Participants (N=397)	RDV Alone (n=237)	RDV + HCQ (n=160)
AEs	286 (72)	163 (69)	123 (77)
RDV-related AEs	7 (2)	1 (<1)	6 (4)
Grade ≥3 AEs	145 (37)	71 (30)	74 (46)[a]
RDV-related Grade ≥3 AEs	18 (5)	4 (2)	14 (9)[b]
SAEs	110 (28)	55 (23)	55 (34)
AE that led to RDV discontinuation	29 (7)	13 (5)	16 (10)

[a]*P*=0.045. [b]*P*=0.007.

SIMPLE Study in Moderate COVID-19

Study design, demographics, and participant disposition

A phase 3, two-part (Parts A and B), open-label study evaluated the efficacy of two RDV regimens compared with SoC in participants with moderate COVID-19.[6] An analysis of data from Part A of the study assessed the clinical outcomes and safety of concomitant use of RDV and HCQ, which included treatment with HCQ, HCQ sulfate, chloroquine, or aminoquinolines.[3]

Part A was conducted between March 15 and April 18, 2020, and consisted of 584 participants who received SoC therapy according to local guidelines either alone or with

a 5- or 10-day course of RDV (loading dose of RDV 200 mg IV on Day 1, followed by RDV 100 mg/day IV on either Days 2–5 or Days 2–10).[6]

Table 4. SIMPLE Moderate: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics	RDV Alone (n=274)	RDV + HCQ (n=110)	*P*-Value	SoC Alone (n=107)	SoC + HCQ (n=93)	*P*-Value
Age, median (range), years	57 (12–94)	57 (20–86)	0.38	57 (24–89)	57 (23–95)	0.59
Male, n (%)	167 (61)	65 (59)	0.74	70 (65)	55 (59)	0.36
Cardiovascular disease, n (%)	177 (65)	45 (410)	<0.001	60 (56)	47 (51)	0.43
Diabetes, n (%)	129 (47)	27 (25)	<0.001	47 (44)	29 (31)	0.07
Baseline clinical status, n (%)						
3 – NIV or high-flow O_2	1 (<1)	2 (2)	<0.001	0	2 (2)	0.004
4 – Low-flow O_2	23 (8)	29 (26)		13 (12)	23 (25)	
5 – Room air and required ongoing medical care	245 (89)	78 (71)		92 (86)	68 (73)	
6 - Room air and did not require ongoing medical care	5 (2)	1 (1)		2 (2)	0	

Abbreviation: NIV=non-invasive ventilation.

Within the RDV + HCQ group, 72 participants discontinued HCQ before RDV treatment started, 33 participants discontinued HCQ after RDV treatment started (range, 1–13 days), and 5 participants were receiving ongoing HCQ at the time of analysis. Within the SoC + HCQ group, 87 participants continued HCQ after randomization, of whom 70 had discontinued HCQ (range, 2–17 days) and 17 continued to receive HCQ at the time of analysis.[3]

Results[3]

After adjustment for baseline covariates, the rate of recovery was not significantly different between participants in the RDV alone and RDV + HCQ groups (recovery rate ratio, 0.88; 95% CI: 0.68–1.14) or between participants in the SoC alone and SoC + HCQ groups (recovery rate ratio, 1.13; 95% CI: 0.82–1.56; Table 5). Similar observations were noted for both comparisons regarding the rate of ≥2-point improvements in ordinal scores.

Table 5. SIMPLE Moderate: Recovery Outcomes[3]

Recovery Results	RDV Alone (n=274)	RDV + HCQ (n=110)	SoC Alone (n=107)	SoC + HCQ (n=93)
Recovery, n (%)	255 (93)	104 (95)	91 (85)	82 (88)
Time to recovery, median (Q1, Q3), days	6 (4, 12)	8 (6, 12)	7 (4, 16)	7 (5, 14)
Recovery rate ratio (95% CI)	0.88 (0.68–1.14)		1.13 (0.82–1.56)	

Safety[3]

Participants in the RDV alone group had significantly fewer treatment-emergent toxicities than those in the RDV + HCQ group, and similar rates of AEs and treatment-emergent toxicities were reported in the SoC alone and SoC + HCQ groups (Table 6).

Table 6. SIMPLE Moderate: Safety Outcomes[3]

Safety Outcomes, n (%) or n/N (%)	RDV Alone (n=274)	RDV + HCQ (n=110)	*P*-Value[a]	SoC Alone (n=107)	SoC + HCQ (n=93)	*P*-Value[a]
AEs	145 (53)	66 (60)	0.38	46 (43)	47 (51)	0.45
Grade ≥3 AEs	34 (12)	10 (9)	0.24	11 (10)	13 (14)	0.78
SAEs	13 (5)	6 (5)	0.4	7 (7)	11 (12)	0.27
RDV-related SAEs	1 (<1)	0	NE	-	-	-
AEs that led to RDV discontinuation	7 (3)	5 (5)	NE	-	-	-
Deaths	4 (1)	1 (1)	NE	1 (1)	3 (3)	NE
Any treatment-emergent toxicity	173/253 (68)	86/106 (81)	0.03	69/96 (72)	67/90 (74)	0.95
ALT level increase	70/250 (28)	48/106 (45)	0.07	37/92 (40)	34/90 (38)	0.41
AST level increase	74/248 (30)	38/104 (37)	0.74	28/92 (30)	32/90 (36)	0.78
CrCl decrease	45/248 (18)	26/106 (25)	0.26	25/94 (27)	30/89 (34)	0.35

Abbreviation: NE=not evaluable due to low numbers of AEs.
[a]*P*-values were calculated in a logistic regression model that adjusted for clinical status (high- or low-flow O_2 vs room air), age (<65 vs ≥65 years), sex, race, and ethnicity.

References

1. VEKLURY®, Gilead Sciences Inc. Veklury® (remdesivir) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Diaz G, Cattelan AM, Balani B, et al. Association Between Concomitant Hydroxychloroquine Use and Safety and Efficacy of Remdesivir in Severe COVID-19 Patients [Poster 11781]. Paper presented at: Virtual COVID-19 Conference; 10-11 July, 2020.
3. Arribas JR, Sanyal AJ, Viladomiu AS, et al. Impact of Concomitant Hydroxychloroquine Use on Safety and Efficacy of Remdesivir in Moderate COVID-19 Patients [Poster 557]. Paper presented at: IDWeek Virtual; 21-25 October, 2020.
4. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Eng J Med.* 2020:1-11.
5. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [Protocol]. *N Eng J Med.* 2020.
6. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(11):1048-1057.

Abbreviations

AE=adverse event
EC_{50}=half-maximal effective concentration
hACE2=human angiotensin-converting enzyme 2
HCQ=hydroxychloroquine
HEp-2=human larynx epidermal carcinoma cell line
HR=hazard ratio
O_2=oxygen
RDV=remdesivir
SAE=serious adverse event
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

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.