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Impact of Concomitant Hydroxychloroquine Use on Safety and Efficacy of Remdesivir in Moderate COVID-19 Patients

Jose Ramon Arribas,[1] Arun J. Sanyal,[2] Alex Soriano Viladomiu,[3] Bum Sik Chin,[4] Shirin Kalimuddin,[5] Stefan Schreiber,[6] Emon Elboudwarej,[7] Yuan Tian,[7] Robert H. Hyland,[7] Devi SenGupta,[7] Anand Chokkalingam,[7] Anu O. Osinusi,[7] Diana M. Brainard,[7] Christoph Lübbert,[8] David Chien Boon Lye,[9] Judith A. Aberg,[10] Enrique Navas Elorza,[11] Karen T. Tashima,[12] Mark McPhail[13]

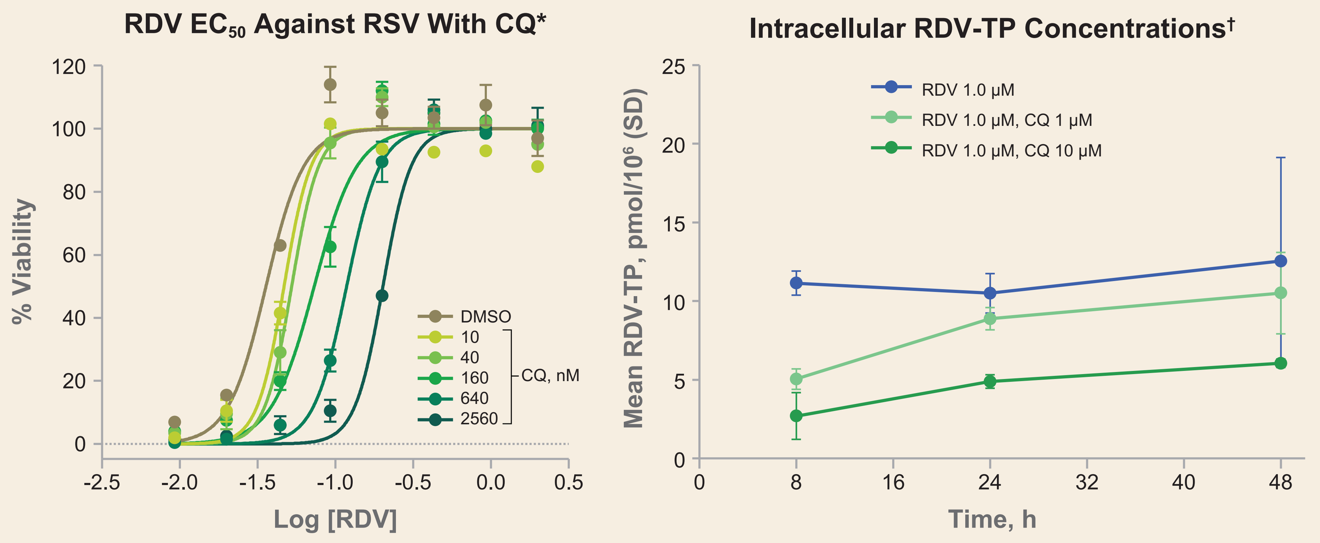
[1]Hospital Universitario La Paz, Madrid, Spain; [2]VCU Medical Center, Richmond, VA; [3]Hospital Clínic de Barcelona, Spain; [4]National Medical Center, Seoul, Republic of Korea; [5]Singapore General Hospital, Singapore; [6]Universitätsklinikum Schleswig-Holstein, Kiel, Germany; [7]Gilead Sciences, Inc., Foster City, CA; [8]Klinik für Infektiologie/Tropenmedizin, Nephrologie und Rheumatologie, Klinikum St. Georg, Leipzig, Germany; [9]National Centre for Infectious Diseases, Tan Tock Seng Hospital, Singapore; [10]Icahn School of Medicine at Mount Sinai, New York, NY; [11]Hospital Universitario Ramón y Cajal, Madrid; [12]The Miriam Hospital, Providence, RI; [13]King's College Hospital, London, UK

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

- Remdesivir (RDV) has demonstrated potent in vitro and in vivo activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and favorable clinical efficacy and tolerability in patients with COVID-19[1]
- Results from the Phase 3 SIMPLE-Moderate study (GS-US-540-5774; NCT04292730) showed that hospitalized patients with COVID-19 not requiring O_2 support treated with RDV experienced better clinical status and good safety outcomes compared with standard of care (SOC)[2,3]
- Hydroxychloroquine (HCQ) is an experimental treatment for COVID-19 that may interfere with conversion of RDV to the active triphosphate (RDV-TP)

Preliminary In Vitro RDV and Chloroquine Data in RSV[4]



RDV EC50 Against RSV With CQ*
% Viability
Log [RDV]
DMSO
10
40
160
640
2560
CQ, nM
Intracellular RDV-TP Concentrations†
Mean RDV-TP, pmol/10^6 (SD)
Time, h
RDV 1.0 µM
RDV 1.0 µM, CQ 1 µM
RDV 1.0 µM, CQ 10 µM

*Respiratory syncytial virus (RSV) antiviral experiments were performed in human epithelial type 2 cells; †RDV metabolism studies were performed in normal human bronchial epithelial cells. CQ, chloroquine; DMSO, dimethyl sulfoxide; EC_{50}, half-maximal effective concentration; SD, standard deviation.

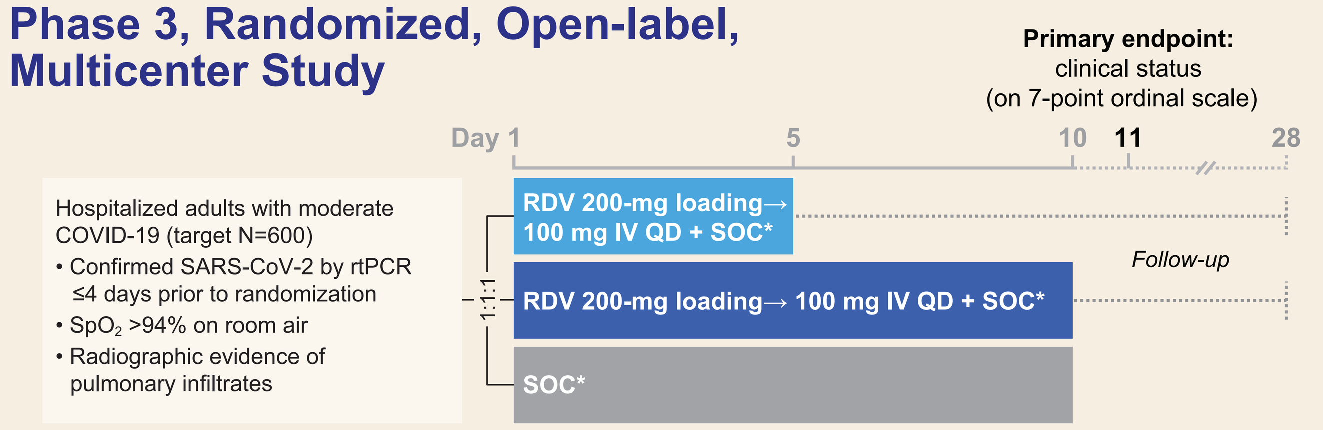
- CQ antagonizes RDV RSV antiviral activity in a dose-dependent manner in vitro
- Co-incubation of RDV and CQ shows dose-dependent inhibition of RDV-TP formation

Objectives

- To assess the impact of concomitant HCQ with RDV use on clinical outcomes and safety of RDV in the SIMPLE-Moderate Study

Methods

Phase 3, Randomized, Open-label, Multicenter Study



Primary endpoint:
clinical status
(on 7-point ordinal scale)
Day 1
5
10
11
28
Hospitalized adults with moderate COVID-19 (target N=600)
• Confirmed SARS-CoV-2 by rtPCR ≤4 days prior to randomization
• SpO2 >94% on room air
• Radiographic evidence of pulmonary infiltrates
1:1:1
RDV 200-mg loading→ 100 mg IV QD + SOC*
RDV 200-mg loading→ 100 mg IV QD + SOC*
SOC*
Follow-up

*SOC continued throughout study duration; agents with actual or possible direct-acting antiviral activity against SARS-CoV-2 were not allowed. rtPCR, reverse-transcriptase–polymerase chain reaction assay; SpO_2, peripheral oxygen saturation.

- Study enrolled March 15–April 18, 2020; date of final follow-up: May 20
- 105 centers in 12 countries: Asia (Hong Kong, Republic of Korea, Singapore, and Taiwan), Europe (France, Germany, Italy, Netherlands, Spain, Switzerland, and UK), and North America (USA)
- Key exclusion criteria:
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal; creatinine clearance <50 mL/min
 - Use of any experimental treatment for COVID-19, including HCQ, ≤24 h prior to dosing
 - Any requirement for invasive mechanical ventilation (IMV) at screening
- HCQ includes WHODrug BMAR20 preferred name hydroxychloroquine, hydroxychloroquine sulfate, chloroquine, and aminoquinolines
 - Classification of each medication in the HCQ group and all other COVID-19 medications was determined by a Gilead medical monitor

Clinical Outcomes Were Measured on 7-Point Ordinal Scale[3]

	1	Death
Hospitalized +	2	IMV or ECMO
	3	Noninvasive ventilation or high-flow O_2
	4	Low-flow O_2
	5	Room air, ongoing medical care (COVID-19 related or otherwise)
	6	Room air, no ongoing medical care (other than per-protocol RDV administration)
	7	Discharged

ECMO, extracorporeal membrane oxygenation.

Statistical Methods

- Within each treatment group (RDV for 5 or 10 days vs SOC), patients who received concomitant HCQ (≥1 day of exposure) were compared with those who did not
 - Concomitant use excluded patients who stopped HCQ prior to study Day -21 or started after study Day 5
- Comparison of continuous covariates by HCQ status was tested using Wilcoxon rank-sum test; categorical variables were tested using Cochran Mantel-Haenszel test
- Clinical recovery, ≥2-point clinical improvement, and all-cause mortality were evaluated using Cox proportional hazards
 - Clinical recovery and ≥2-point clinical improvement were analyzed with death as a competing risk
- For adverse events (AEs) and death by Day 28, HCQ differences were evaluated using logistic regression
- Potential covariates for adjustment included:
 - Baseline (BL) demographics: age, sex, race, and region (Italy vs outside Italy)
 - Disease characteristics: symptom duration and ordinal scale score (clinical status)
 - Comorbidities: cardiovascular disease (CVD), diabetes, and obesity
- Results were considered significant at p <0.05

Results

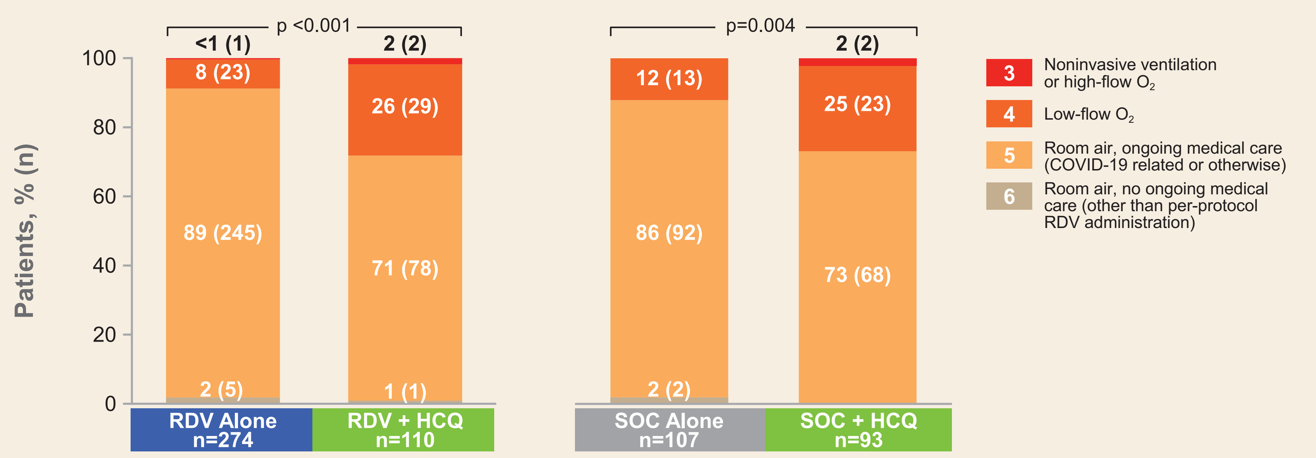
Baseline Demographics and Clinical Characteristics

		All RDV: RDV Alone n=274	All RDV: RDV + HCQ n=110	All RDV: p-Value	SOC: SOC Alone n=107	SOC: SOC + HCQ n=93	SOC: p-Value
Median age, year (range)		57 (12–94)	57 (20–86)	0.38	57 (24–89)	57 (23–95)	0.59
≥65 years, n (%)		79 (29)	22 (20)	0.08	29 (27)	29 (31)	0.53
Men, n (%)		167 (61)	65 (59)	0.74	70 (65)	55 (59)	0.36
Median body mass index, kg/m² (range)		27.8 (16.1–63.2)	26.0 (17.3–76.9)	0.002	26.6 (16.6–53.9)	27.0 (15.9–52.7)	0.88
Obesity: ≥30 kg/m², n (%)		91 (35)	21 (20)	0.004	33 (32)	22 (25)	0.29
Region, n (%)	Italy	15 (5)	38 (35)	<0.001	2 (2)	24 (26)	<0.001
	Rest of world	259 (95)	72 (65)		105 (98)	69 (74)	
Race, n (%)	Black*	67 (24)	5 (5)	<0.001	18 (17)	9 (10)	<0.001
	White	124 (45)	92 (84)		46 (43)	66 (71)	
	Asian	63 (23)	2 (2)		32 (30)	5 (5)	
	Other	20 (7)	11 (10)		11 (10)	13 (14)	
Comorbidities, n (%)	CVD	177 (65)	45 (41)	<0.001	60 (56)	47 (51)	0.43
	Diabetes	129 (47)	27 (25)	<0.001	47 (44)	29 (31)	0.07
Median duration of symptoms before study Day 1, day (range)		7 (1–48)	9 (2–40)	<0.001	8 (2–26)	9 (1–34)	0.60
Clinical status, n (%)	High-flow O_2	1 (<1)	2 (2)	<0.001	0	2 (2)	0.005
	Low-flow O_2	23 (8)	29 (26)		13 (12)	23 (25)	
	Room air	250 (91)	79 (72)		94 (88)	68 (73)	

*33% (85/260) of all US patients.

- Patients treated with HCQ were commonly in Italy, had fewer comorbidities, and were more frequently receiving O_2 support

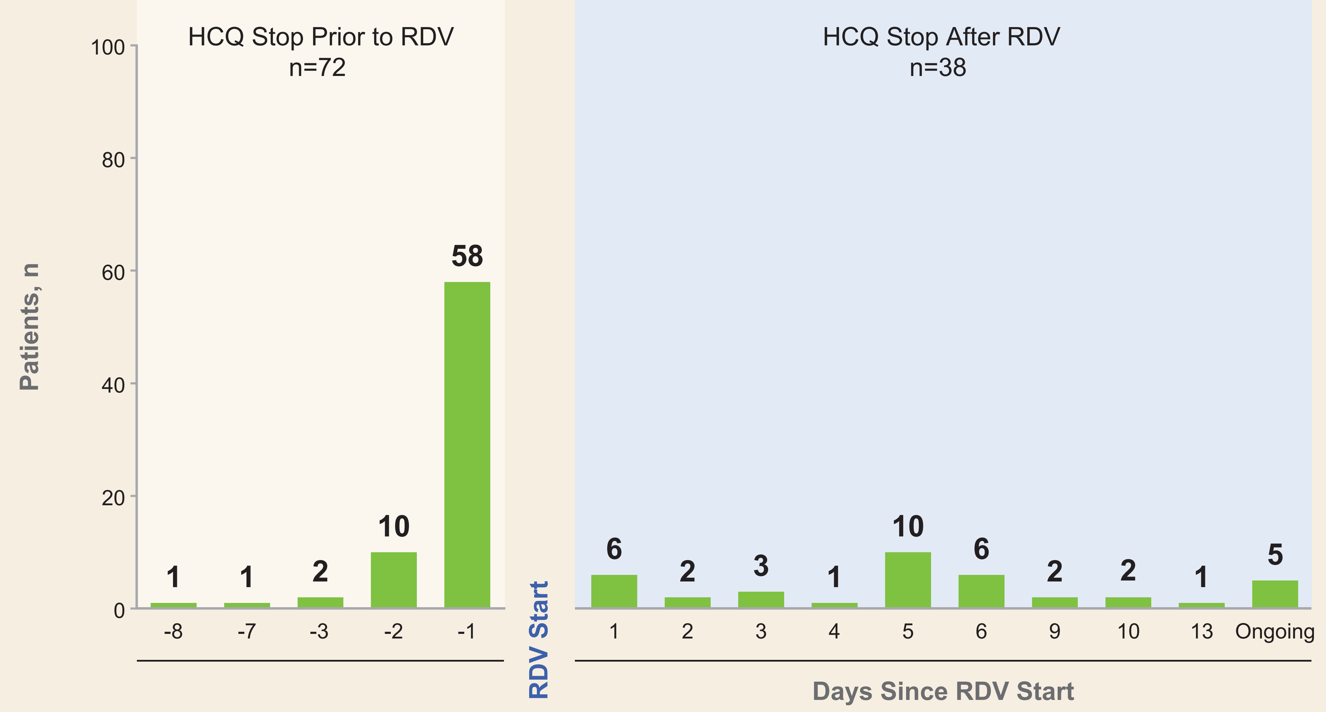
Baseline Clinical Status



Patients, % (n)
p <0.001
<1 (1)
8 (23)
89 (245)
2 (5)
2 (2)
26 (29)
71 (78)
1 (1)
p=0.004
12 (13)
86 (92)
2 (2)
2 (2)
25 (23)
73 (68)
RDV Alone n=274
RDV + HCQ n=110
SOC Alone n=107
SOC + HCQ n=93
3 Noninvasive ventilation or high-flow O2
4 Low-flow O2
5 Room air, ongoing medical care (COVID-19 related or otherwise)
6 Room air, no ongoing medical care (other than per-protocol RDV administration)

- Compared with patients not on HCQ, more patients on HCQ were receiving O_2 support at BL (3–4 on ordinal scale)

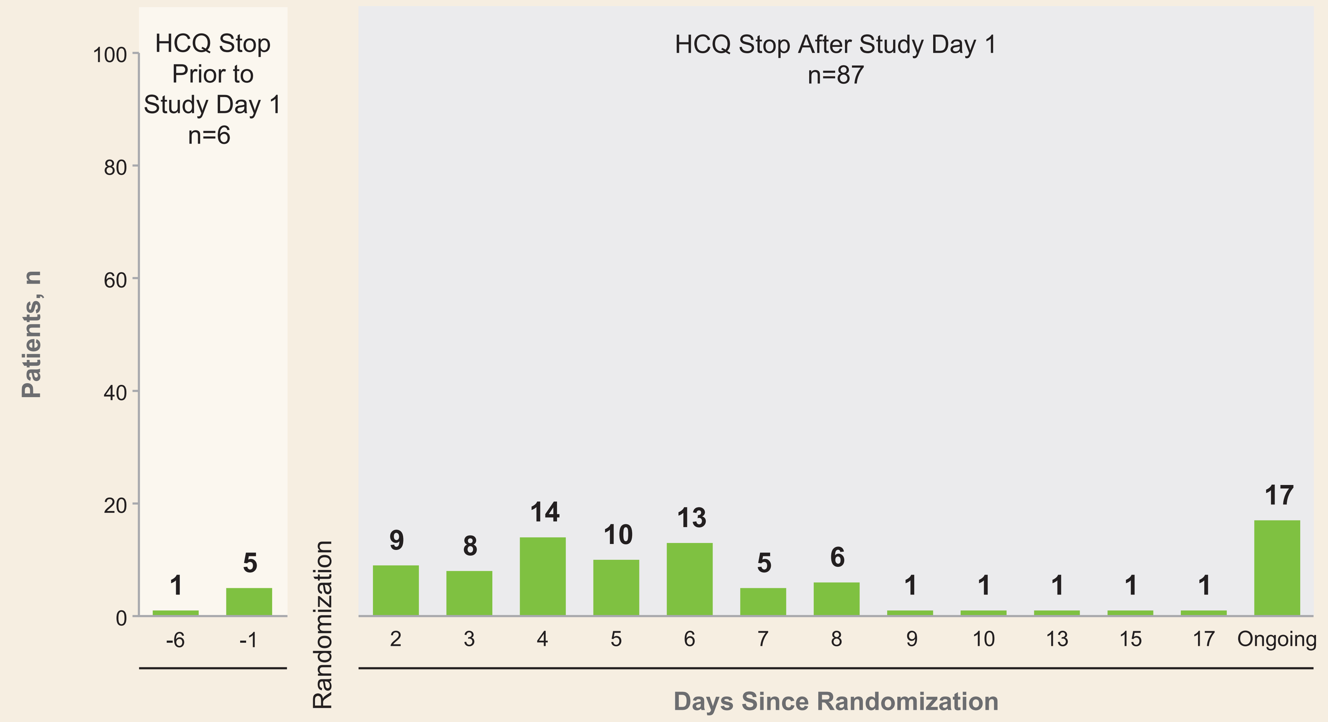
HCQ Exposure Relative to RDV Dosing (n=110)



HCQ Stop Prior to RDV
n=72
HCQ Stop After RDV
n=38
Patients, n
1
1
2
10
58
-8
-7
-3
-2
-1
RDV Start
6
2
3
1
10
6
2
2
1
5
1
2
3
4
5
6
9
10
13
Ongoing
Days Since RDV Start

- Most patients treated with RDV + HCQ (65%) were discontinued from HCQ prior to start of RDV

HCQ Exposure Relative to Randomization in SOC Arm (n=93)



HCQ Stop Prior to Study Day 1
n=6
HCQ Stop After Study Day 1
n=87
Patients, n
1
5
-6
-1
Randomization
9
8
14
10
13
5
6
1
1
1
1
1
17
2
3
4
5
6
7
8
9
10
13
15
17
Ongoing
Days Since Randomization

- Most patients treated with SOC + HCQ (94%) were continued on HCQ therapy after randomization (94%)

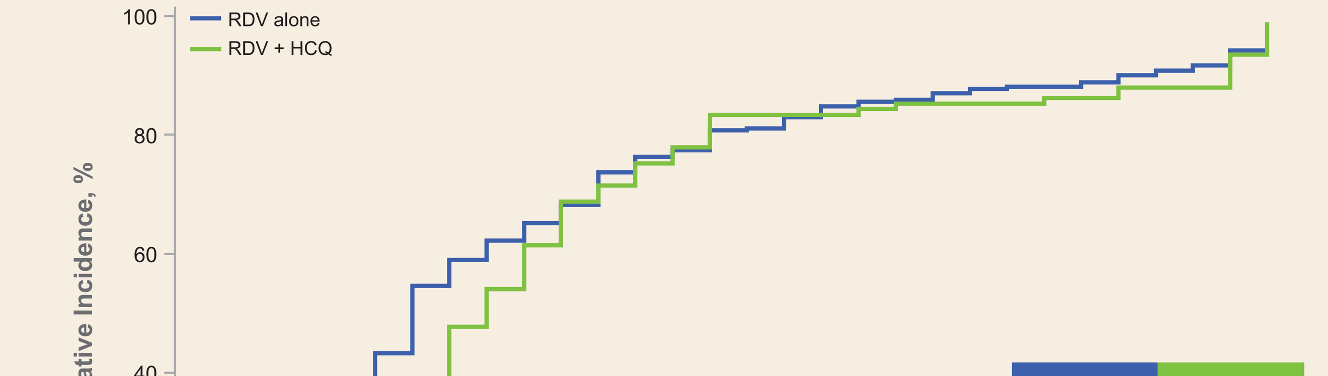
Safety

n (%)	All RDV: RDV Alone n=274	All RDV: RDV + HCQ n=110	All RDV: p-Value*	SOC: SOC Alone n=107	SOC: SOC + HCQ n=93	SOC: p-Value*
AE	145 (53)	66 (60)	0.38	46 (43)	47 (51)	0.45
Grade ≥3	34 (12)	10 (9)	0.24	11 (10)	13 (14)	0.78
Serious AE	13 (5)	6 (5)	0.4	7 (7)	11 (12)	0.27
RDV related	1 (0)	0	NE	—	—	—
AE leading to discontinuation	7 (3)	5 (5)	NE	—	—	—
Death	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
White blood cell decrease	12/251 (5)	10/106 (9)	0.09	2/95 (2)	6/89 (7)	0.12
ALT increase	70/250 (28)	48/106 (45)	0.07	37/92 (40)	34/90 (38)	0.41
AST increase	74/248 (30)	38/104 (37)	0.74	28/92 (30)	32/90 (36)	0.78
Creatinine clearance decrease	45/248 (18)	26/106 (25)	0.26	25/94 (27)	30/89 (34)	0.35

*From logistic-regression model adjusting for BL clinical status (high- or low-flow O_2 vs room air), age (< vs ≥65 years), sex, race, and ethnicity. NE, not evaluable due to few AEs.

- Patients treated with RDV alone had fewer AEs and treatment-emergent toxicities than those treated with RDV + HCQ
- Patients treated with SOC alone and SOC + HCQ had similar rates of AEs and treatment-emergent toxicities

Time to Recovery
Patients on RDV With and Without HCQ



RDV alone
RDV + HCQ
Cumulative Incidence, %
Study Day

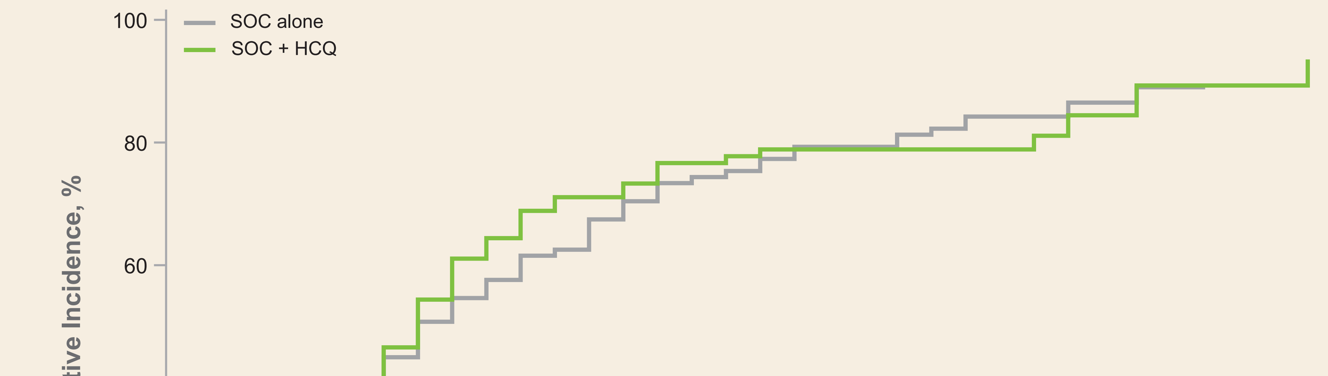
	RDV Alone n=274	RDV + HCQ n=110
Recovery, n (%)	255 (93)	104 (95)
Recovery rate ratio (95% CI)	0.88 (0.68, 1.14)	
Median time to recovery, day (Q1, Q3)	6 (4, 12)	8 (6, 12)

n at risk	BL	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
RDV alone	274	272	217	154	110	93	70	60	50	40	37	32	30	24	18	0
RDV + HCQ	110	108	103	85	57	41	30	23	17	17	15	15	14	12	12	0

CI, confidence interval; Q, quartile.

- After adjusting for BL covariates, there was no statistically significant difference in the rate of recovery between RDV patients on HCQ and RDV alone
- Similar results were observed in direction and magnitude for the rate of ≥2-point improvement

Time to Recovery
Patients on SOC With and Without HCQ



SOC alone
SOC + HCQ
Cumulative Incidence, %
Study Day

	SOC Alone n=107	SOC + HCQ n=93
Recovery, n (%)	91 (85)	82 (88)
Recovery rate ratio (95% CI)	1.13 (0.82, 1.56)	
Median time to recovery, day (Q1, Q3)	7 (4, 16)	7 (5, 14)

n at risk	BL	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
SOC alone	107	103	82	63	51	42	37	29	25	22	20	18	14	13	10	2	
SOC + HCQ	93	93	81	58	39	30	24	22	19	17	17	17	17	15	11	2	2

- After adjusting for BL covariates, there was no statistically significant difference in the rate of recovery between SOC patients on HCQ and SOC alone
- Similar results were observed in direction and magnitude for the rate of ≥2-point improvement

Conclusions

- In patients with moderate COVID-19, concomitant HCQ may delay recovery on RDV and showed no impact on recovery with SOC alone
- Patients treated with HCQ had more safety events than those not receiving HCQ irrespective of RDV treatment

References: 1. Gordon CJ, et al. J Biol Chem 2020;295:6785-97; 2. Goldman JD, et al. N Engl J Med 2020 May 27;NEJMoa2015301; 3. Spinner CD, et al. JAMA 2020;324:1048-57; 4. US Food and Drug Administration. Fact Sheet for Patients and Parent/Caregivers Emergency Use Authorization (EUA) of Hydroxychloroquine Sulfate for Treatment of COVID-19 in Certain Hospitalized Patients; 3/28/20; revoked 6/15/20.

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