COVID-19 pandemic clinical trials

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Conflict of interest declaration

- Received honorarium from:
  - Medscape
  - Roche
- International advisory board:
  - Gilead remdesivir (no honorarium)

COVID-19 and available treatment 2021

Stages of COVID19	Pre-exposure	Post-exposure	Early treatment of high risk COVID19	COVID19 pneumonia	Low flow and high flow oxygen	Mechanical ventilation
Therapeutic classes	Monoclonal antibodies, vaccines	Monoclonal antibodies	Monoclonal antibodies, remdesivir, molnupiravir, paxlovid	Remdesivir	Remdesivir, dexamethasone, tocilizumab, baricitinib, monoclonal antibodies	Remdesivir, dexamethasone, tocilizumab, baricitinib, monoclonal antibodies

In red, where Singapore has contributed

COVID-19 Clinical Trial – Approval Submission Timeline

National Centre for Infectious Diseases

	Study Name	Start/Received date	Executed/Approved Date	
DSRB	Gilead Remdesivir (5773 (severe) & 5774 (moderate)	28-Feb-20	07-Mar-20	9 days
	NIH ACTT1 (Remdesivir vs placebo)	28-Feb-20	09-Mar-20	11 days
	NIH ACTT2 (Baricitinib/Remdesivir vs Remdesivir)	08-May-20	12-May-20	5 days
	NIH ACCT3 (interferon-beta-1a/Remdesivir vs Remdesivir)	24-Jul-20	14-Aug-20	22 days
	NIH ACCT4 (Baricitinib/Remdesivir vs Dexamethasone/Remdesivir)	1-Dec-20	30-Dec-20	30 days
	INSIGHT ACTIV3 (Eli Lily LY3819253)	22-Aug-20	17-Sep-20	27 days
	INSIGHT ACTIV3 (BRII-196, BRII-198, VIR-7831)	11-Dec-20	14-Jan-21	35 days
	INSIGHT ACTIV3 (AZD8895, AZD1061)	15-Mar-21	19-Apr-21	36 days
	INSIGHT ACTIV3 (MP0420)	25-Apr-21	3-May-21	9 days
	DSO antibody AD01	24-Sep-20	24-Oct-20	
HSA	Gilead Remdesivir (5773 (severe) & 5774 (moderate)	28-Feb-20	07-Mar-20	9 days
	NIH ACCT1 (Remdesivir vs placebo)	28-Feb-20	02-Mar-20	4 days
	NIH ACCT2 (Baricitinib/Remdesivir vs Remdesivir)	08-May-20	11-May-20	4 days
	NIH ACCT3 (interferon-beta-1a/Remdesivir vs Remdesivir)	24-Jul-20	08-Aug-20	16 days
	NIH ACTT4 (Baricitinib/Remdesivir vs Dexamethasone/Remdesivir)	14-Dec-20	24-Dec-20	11 days
	INSIGHT ACTIV3 (Eli Lily LY3819253)	21-Aug-20	11-Sep-20	22 days
	INSIGHT ACTIV3 (BRII-196, BRII-198, VIR-7831)	18-Jan-21	22-Jan-21	5 days
	INSIGHT ACTIV3 (AZD8895, AZD1061)	15-Apr-21	21-Apr-21	7 days
	INSIGHT ACTIV3 (MP0420)	14-May-21	14-May-21	1 day
	DSO antibody AD01	24-Sep-20	25-Oct-20	

COVID-19 Clinical Trial – Approval Submission Timeline

National Centre for Infectious Diseases

	Study Name	Start/Received date	Executed/Approved Date	
Agreement	Gilead Remdesivir (5773 (severe) & 5774 (moderate)	27-Feb-20	10-Mar-20	12 days
	NIH ACTT	29-Feb-20	18-Mar-20	19 days
	INSIGHT ACTIV3	19-Aug-20	14-Sep-20	27 days
	DSO antibody AD01	24-Jul-20	14-Oct-20	

COVID-19 Clinical Trial – Recruitment Number

National Centre for Infectious Diseases

Trial Name	Participating Sites	Total Recruitment Number (Singapore)	Status
Gilead Remdesivir GS-US-540-5773 (severe)	NCID, SGH, NUH	60	Completed
Gilead Remdesivir GS-US-540-5774 (moderate)	NCID, SGH, NUH	32	Completed
NIH – ACTT1 (Remdesivir vs placebo)	NCID	16	Completed
NIH – ACTT2 (Baricitinib/Remdesivir vs Remdesivir)	NCID, CGH, NUH, NTFGH	44	Completed
NIH – ACTT3 (interferon-beta-1a/Remdesivir vs Remdesivir)	NCID, CGH, NUH, NTFGH	5	Completed
NIH – ACTT4 (Baricitinib/Remdesivir vs Dexamethasone/Remdesivir)	NCID, CGH, NUH, NTFGH, AH, SKH	4	Completed
INSIGHT ACTIV3 (Eli Lily LY3819253)	NCID	1	Completed
INSIGHT ACTIV3 (BRII-196, BRII-198, VIR-7831)	NCID	-	Completed
INSIGHT ACTIV3 (AZD8895, AZD1061)	NCID	21	Completed
INSIGHT ACTIV3 (MP0420)	NCID	21	Completed
DSO antibody AD01 (Part A- healthy volunteers)	PH Feng Centre	23	Completed

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JAMA | Original Investigation

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19

A Randomized Clinical Trial

JAMA. doi:10.1001/jama.2020.16349
Published online August 21, 2020.

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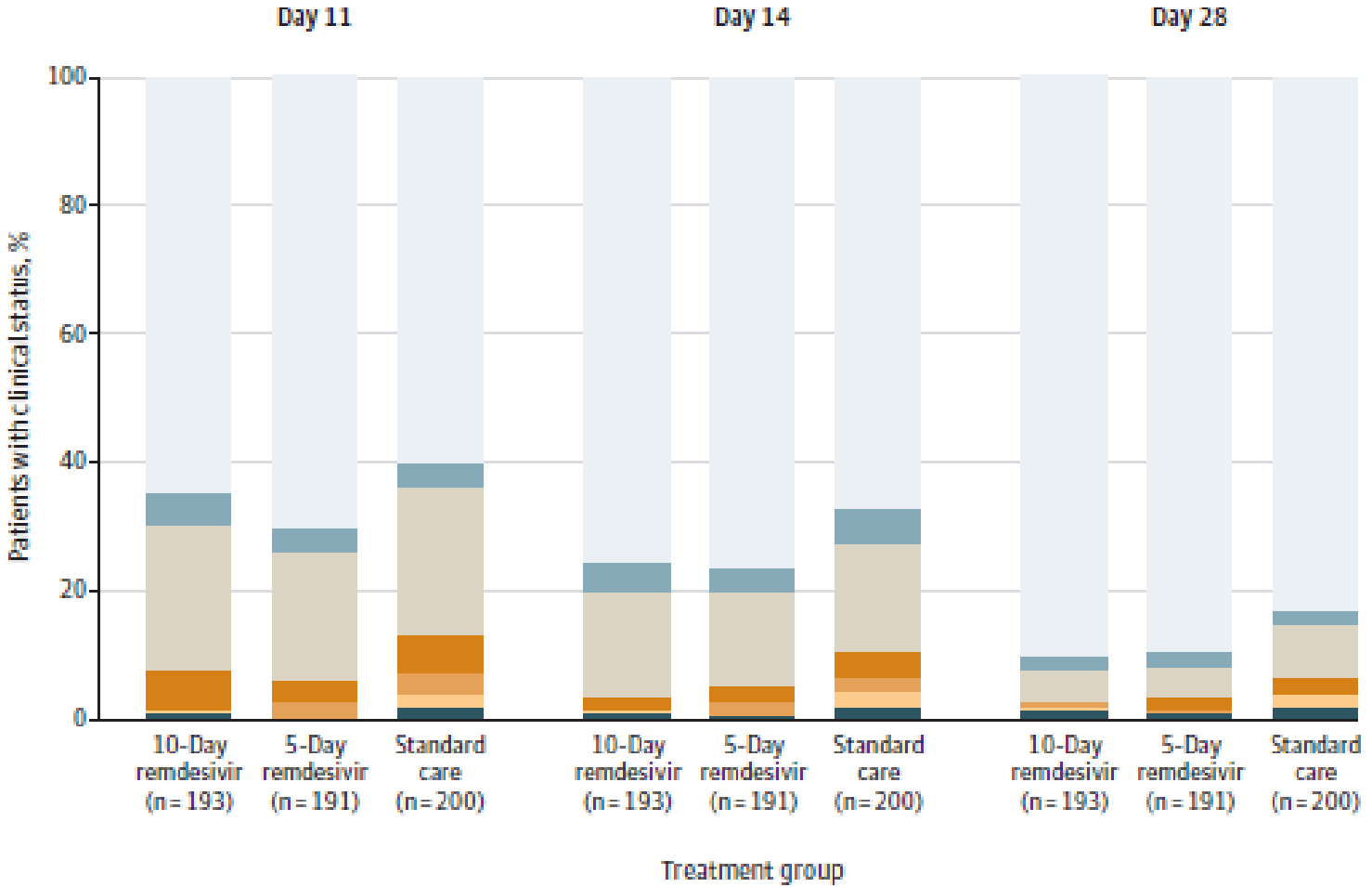
Figure 2. Clinical Status on a 7-Point Ordinal Scale on Study Days 11, 14, and 28 by Treatment Group



Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D., Ronald G. Nahass, M.D., Yao-Shen Chen, M.D., Devi SenGupta, M.D., Robert H. Hyland, D.Phil., Anu O. Osinusi, M.D., Huyen Cao, M.D., Christiana Blair, M.S., Xuelian Wei, Ph.D., Anuj Gaggar, M.D., Ph.D., Diana M. Brainard, M.D., William J. Towner, M.D., Jose Muñoz, M.D., Kathleen M. Mullane, D.O., Pharm.D., Francisco M. Marty, M.D., Karen T. Tashima, M.D., George Diaz, M.D., and Aruna Subramanian, M.D., for the GS-US-540-5773 Investigators*

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METHODS

We conducted a randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia. Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 days or 10 days. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale.

RESULTS

In total, 397 patients underwent randomization and began treatment (200 patients for 5 days and 197 for 10 days). The median duration of treatment was 5 days (interquartile range, 5 to 5) in the 5-day group and 9 days (interquartile range, 5 to 10) in the 10-day group. At baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group ($P=0.02$). By day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group ($P=0.14$). The most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

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Table 2. 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)	

Table 3. Additional Secondary Outcomes.

	Remdesivir (N=541)	Placebo (N=521)	Rate Ratio (95% CI)
Median time to clinical improvement (95% CI) — days			
Improvement of one category on ordinal scale	7.0 (6.0 to 8.0)	9.0 (8.0 to 11.0)	1.23 (1.08 to 1.41)
Improvement of two categories on ordinal scale	11.0 (10.0 to 13.0)	14.0 (13.0 to 15.0)	1.29 (1.12 to 1.48)
Discharge or National Early Warning Score ≤2 for 24 hr*	8.0 (7.0 to 9.0)	12.0 (10.0 to 15.0)	1.27 (1.10 to 1.46)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days†	12 (6 to 28)	17 (8 to 28)	−5.0 (−7.7 to −2.3)
Median duration of initial hospitalization among those who did not die (IQR) — days	10 (5 to 21)	14 (7 to 27)	−4.0 (−6.0 to −2.0)
Patients rehospitalized — % (95% CI)	5 (3 to 7)	3 (2 to 5)	2 percentage points (0 to 4)
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)	13 (5 to 28)	21 (8 to 28)	−8.0 (−11.8 to −4.2)
New use of oxygen			
No. of patients/total no.	27/75	28/63	
Percent of patients (95% CI)	36 (26 to 47)	44 (33 to 57)	−8 (−24 to 8)
Median days receiving oxygen (IQR)	4 (2 to 12)	5.5 (1 to 15)	−1.0 (−7.6 to 5.6)
Noninvasive ventilation or high-flow oxygen			
Median days of noninvasive ventilation or high-flow oxygen use during study if receiving these interventions at baseline (IQR)	6 (3 to 18)	6 (3 to 16)	0 (−2.6 to 2.6)
New use of new noninvasive ventilation or high-flow oxygen use during the study			
No. of patients/total no.	52/307	64/266	
Percent of patients (95% CI)	17 (13 to 22)	24 (19 to 30)	−7 (−14 to −1)
Median days of use during the study (IQR)	3 (1 to 10.5)	4 (2 to 23.5)	−1.0 (−4.0 to 2.0)
Mechanical ventilation or ECMO			
Median days of mechanical ventilation or ECMO during study if receiving these interventions at baseline (IQR)	17 (9 to 28)	20 (8 to 28)	−3.0 (−9.3 to 3.3)
New use of mechanical ventilation or ECMO during study			
No. of patients/total no.	52/402	82/364	
Percent of patients (95% CI)	13 (10 to 17)	23 (19 to 27)	−10 (−15 to −4)
Median days of use during the study (IQR)	21.5 (9 to 28)	23 (12 to 28)	1.0 (−6.0 to 8.0)

Faster clinical recovery

Shorter hospital stay

Shorter time on oxygen

Lower progression high flow oxygen

Lower progression mechanical ventilation or ECMO

Remdesivir does not work?

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

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S0140-6736(20)31022-9

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

Florence Ader, Maude Bouscambert-Duchamp, Maya Hites, Nathan Peiffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Greil, Jérémie Guedj, Jose-Artur Paiva, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet, France Mentré*, and the DisCoVeRy Study Group*

Lancet Infect Dis 2021

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Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

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Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care

Susan A. Olender,[1] Katherine K. Perez,[2] Alan S. Go,[3] Bindu Balani,[4] Eboni G. Price-Haywood,[5] Nirav S. Shah,[6] Su Wang,[7] Theresa L. Walunas,[8] Shobha Swaminathan,[9] Jihad Slim,[10] BumSik Chin,[11] Stéphane De Wit,[12] Shamim M. Ali,[13] Alex Soriano Viladomiu,[14] Philip Robinson,[15] Robert L. Gottlieb,[16] Tak Yin Owen Tsang,[17] I-Heng Lee,[18] Hao Hu,[19] Richard H. Haubrich,[18] Anand P. Chokkalingam,[18] Lanjia Lin,[18] Lijie Zhong,[18] B. Nebiyou Bekele,[18] Robertino Mera-Giler,[18] Chloé Phulpin,[20] Holly Edgar,[20] Joel Gallant,[18] Helena Diaz-Cuervo,[21] Lindsey E. Smith,[18] Anu O. Osinusi,[18] Diana M. Brainard,[18] and Jose I Bernardino[22]; For the GS-US-540–5773 and GS-US-540–5807 Investigators

Clinical Infectious Diseases® 2020;XX(XX):1–9

Remdesivir Versus Standard-of-Care for Severe Coronavirus Disease 2019 Infection: An Analysis of 28-Day Mortality

Susan A. Olender,[1] Theresa L. Walunas,[2] Esteban Martinez,[3] Katherine K. Perez,[4] Antonella Castagna,[5] Su Wang,[6] Dax Kurbegov,[7] Parag Goyal,[8] Diego Ripamonti,[9] Bindu Balani,[10] Francesco G. De Rosa,[11,12,13] Stéphane De Wit,[14] Shin-Woo Kim,[15] George Diaz,[16] Raffaele Bruno,[17] Kathleen M. Mullane,[18] David Chien Lye,[19,20,21] Robert L. Gottlieb,[22,23] Richard H. Haubrich,[24] Anand P. Chokkalingam,[24] George Wu,[24] Helena Diaz-Cuervo,[25] Diana M. Brainard,[24] I-Heng Lee,[24] Hao Hu,[26] Lanjia Lin,[24] Anu O. Osinusi,[24] Jose I. Bernardino,[27] and Marta Boffito[28]

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› Clin Infect Dis. 2021 Aug 11;ciab695. doi: 10.1093/cid/ciab695. Online ahead of print.

Remdesivir for the prevention of invasive mechanical ventilation or death in COVID-19 - A post-hoc analysis of the Adaptive COVID-19 Treatment Trial-1 Cohort Data

Catharine I Paules [1], Shannon K Gallagher [1 2], Rekha R Rapaka [3], Richard T Davey [4], Sarah B Doernberg [5], Robert Grossberg [6], Noreen A Hynes [7], Philip Ponce [8], William R Short [9], Jocelyn Voell [4], Jing Wang [10], Otto O Yang [11], Cameron R Wolfe [12], David C Lye [13], Lori E Dodd [2], Constance A Benson [14]

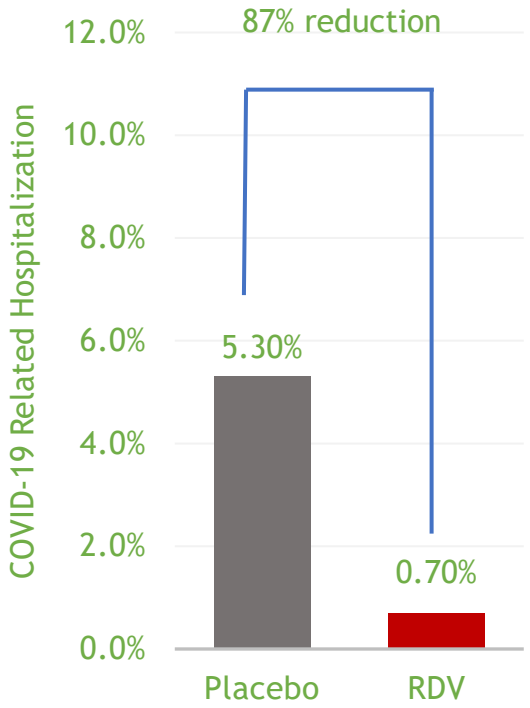
ACCEPTED MANUSCRIPT

Clinical improvement, outcomes, antiviral activity, and costs associated with early treatment with remdesivir for patients with COVID-19 FREE

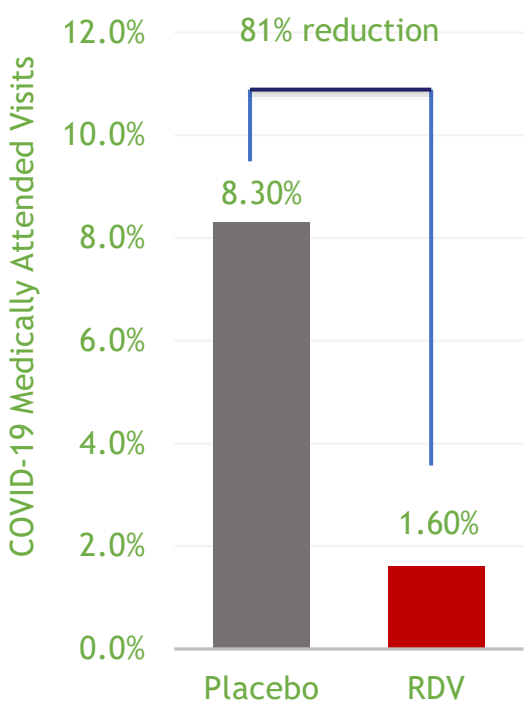
Carlos K H Wong, PhD ✉, Kristy T K Lau, MSc, Ivan C H Au, BSc, Xi Xiong, MSc, Eric H Y Lau, PhD, Benjamin J Cowling, PhD

Clinical Infectious Diseases, ciab631, https://doi.org/10.1093/cid/ciab631

Remdesivir early treatment high risk (PINETREE)



RDV treatment resulted in 87% reduction in risk of COVID-19 related hospitalisation or all-cause death by Day 28



RDV treatment resulted in 81% reduction in risk of COVID-19 related medically attended visits or all-cause death by Day 28

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, P. Goepfert, N. Ahuja, M. Frank, M. Oh, E.S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, and J.H. Beigel

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Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

Outcome	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Baricitinib (N=515)	Placebo (N=518)	Baricitinib (N=70)	Placebo (N=72)	Baricitinib (N=288)	Placebo (N=276)	Baricitinib (N=103)	Placebo (N=113)	Baricitinib (N=54)	Placebo (N=57)
Recovery										
No. of recoveries	433	406	67	69	262	243	82	73	22	21
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)	5 (4–6)	4 (4–6)	5 (5–6)	6 (5–6)	10 (9–12)	18 (13–21)	NE (25–NE)	NE (26–NE)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03]		0.88 (0.63–1.23)		1.17 (0.98–1.39)		1.51 (1.10–2.08)		1.08 (0.59–1.97)	
Mortality over first 14 days‡										
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)		NE		0.73 (0.16–3.26)		0.21 (0.02–1.80)		0.69 (0.19–2.44)	
No. of deaths by day 14	8	15	0	0	3	4	1	5	4	6
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)	0 (NE–NE)	0 (NE–NE)	1.1 (0.4–3.4)	1.5 (0.6–3.9)	1.0 (0.1–6.7)	4.6 (2.0–10.8)	7.6 (2.9–19.1)	11.3 (5.3–23.5)
Mortality over entire trial period‡										
Hazard ratio (95% CI)	0.65 (0.39–1.09)		NE		0.40 (0.14–1.14)		0.55 (0.22–1.38)		1.00 (0.45–2.22)	
No. of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)	0 (NE–NE)	0 (NE–NE)	1.9 (0.8–4.4)	4.7 (2.7–8.1)	7.5 (3.6–15.2)	12.9 (7.7–21.3)	23.1 (13.8–37.1)	22.6 (13.5–36.4)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	177 (34.4)	165 (31.9)	33 (47.1)	44 (61.1)	114 (39.6)	101 (36.6)	27 (26.2)	17 (15.0)	3 (5.6)	3 (5.3)
2	177 (34.4)	163 (31.5)	25 (35.7)	20 (27.8)	120 (41.7)	115 (41.7)	30 (29.1)	24 (21.2)	2 (3.7)	4 (7.0)
3	8 (1.6)	3 (0.6)	5 (7.1)	2 (2.8)	2 (0.7)	1 (0.4)	0	0	1 (1.9)	0
4	31 (6.0)	18 (3.5)	7 (10.0)	6 (8.3)	14 (4.9)	7 (2.5)	7 (6.8)	3 (2.7)	3 (5.6)	2 (3.5)
5	43 (8.3)	50 (9.7)	0	0	18 (6.2)	27 (9.8)	15 (14.6)	20 (17.7)	10 (18.5)	3 (5.3)
6	20 (3.9)	19 (3.7)	0	0	9 (3.1)	1 (0.4)	7 (6.8)	16 (14.2)	4 (7.4)	2 (3.5)
7	48 (9.3)	83 (16.0)	0	0	8 (2.8)	19 (6.9)	15 (14.6)	28 (24.8)	25 (46.3)	36 (63.2)
8	11 (2.1)	17 (3.3)	0	0	3 (1.0)	5 (1.8)	2 (1.9)	5 (4.4)	6 (11.1)	7 (12.3)
Odds ratio (95% CI)	1.3 (1.0–1.6)		0.6 (0.3–1.1)		1.2 (0.9–1.6)		2.2 (1.4–3.6)		1.7 (0.8–3.4)	

Table 3. Additional Secondary Outcomes.

Outcome	Baricitinib+RDV	Placebo+RDV	Rate Ratio (95% CI)
Median time to event (95% CI) — days			
Improvement by one category on ordinal scale	6.0 (5.0 to 7.0)	8.0 (7.0 to 9.0)	1.21 (1.06 to 1.39)
Improvement by two categories on ordinal scale	12.0 (12.0 to 13.0)	13.0 (NE)	1.20 (1.05 to 1.38)
Discharge or National Early Warning Score ≤2 for 24 hr*	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.24 (1.07 to 1.44)
Death or progression to noninvasive or invasive mechanical ventilation	NE	NE	0.77 (0.60 to 0.98)
Death or progression to invasive mechanical ventilation	NE	NE	0.69 (0.50 to 0.95)
New use of oxygen	NE	NE (3.0 to NE)	0.53 (0.29 to 0.98)
New use of invasive mechanical ventilation or ECMO	NE	NE	0.64 (0.44 to 0.93)
Use of noninvasive ventilation or high-flow oxygen	NE	NE	0.82 (0.60 to 1.13)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days			
With imputation of data for those who died†	8 (5 to 15)	8 (5 to 20)	0.0 (−1.1 to 1.1)
Among those who did not die	8 (5 to 13)	8 (5 to 15)	0.0 (−1.0 to 1.0)
Patients rehospitalized — % (95% CI)	3 (2 to 5)	2 (1 to 4)	1.0 (−1.1 to 3.1)‡
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)			
With imputation of data for those who died†	10 (4 to 27)	12 (4 to 28)	−2.0 (−5.2 to 1.2)
Among those who did not die	9 (4 to 23)	10 (4 to 28)	−1.0 (−3.5 to 1.5)
New use of oxygen during trial			
No. of patients/total no.	16/70	29/72	
Percent of patients (95% CI)	23 (15 to 34)	40 (30 to 52)	−17.4 (−31.6 to −2.1)‡
Median days receiving oxygen (IQR)	3 (2 to 4)	3 (2 to 6)	0.0 (−2.2 to 2.2)
Noninvasive ventilation or high-flow oxygen			
Median days of noninvasive ventilation or high-flow oxygen use during trial if receiving these interventions at baseline (IQR)			
With imputation of data for those who died†	4 (3 to 9)	5 (2 to 12)	−1.0 (−2.9 to 0.9)
Among those who did not die	4 (3 to 6)	4 (2 to 9)	0.0 (−1.7 to 1.7)
New use of noninvasive ventilation or high-flow oxygen during trial			
No. of patients/total no.	70/358	82/348	
Percent of patients (95% CI)	20 (16 to 24)	24 (19 to 28)	−4.0 (−10.1 to 2.1)‡
Median days of use during trial (IQR)	6 (3 to 13)	4 (2 to 11)	2.0 (−0.4 to 4.4)
Mechanical ventilation or ECMO			
Median days of mechanical ventilation or ECMO during trial if receiving these interventions at baseline (IQR)			
With imputation of data for those who died†	20 (9 to 28)	25 (11 to 28)	−5.0 (−12.9 to 2.9)
Among those who did not die	13 (7 to 24)	16 (6 to 28)	−2.0 (−11.4 to 7.4)
New use of mechanical ventilation or ECMO during trial			
No. of patients/total no.	46/461	70/461	
Percent of patients (95% CI)	10 (8 to 13)	15 (12 to 19)	−5.2 (−9.5 to −0.9)‡
Median days of use during trial§	16 (7 to 28)	27 (12 to 28)	−11.0 (−18.3 to −3.7)

Significant
(1) Shorter time to 1 or 2 point Improvement ordinal scale
(2) Shorter time to discharge
(3) Fewer new oxygen use (23% vs. 40%)
(4) Fewer need IMV (10% vs. 15%)
(5) Shorter time on IMV (16 vs. 27 days)

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

*Vincent C Marconi, Athimalaipet V Ramanan, Stephanie de Bono, Cynthia E Kartman, Venkatesh Krishnan, Ran Liao, Maria Lucia B Piruzeli, Jason D Goldman, Jorge Alatorre-Alexander, Rita de Cassia Pellegrini, Vicente Estrada, Mousumi Som, Anabela Cardoso, Sujatro Chakladar, Brenda Crowe, Paulo Reis, Xin Zhang, David H Adams, E Wesley Ely, on behalf of the COV-BARRIER Study Group**

Lancet Respir Med 2021

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https://doi.org/10.1016/
S2213-2600(21)00331-3

ACTT-4 under review
Baricitinib vs dexamethasone on backbone of remdesivir in low and high flow oxygen COVID-19

Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomised, Placebo-Controlled Trial.

*E. Wesley Ely, Athimalaipet V. Ramanan, Cynthia E. Kartman, Stephanie de Bono, Ran Liao, Maria Lucia B. Piruzeli, Jason D. Goldman, José Francisco Kerr Saraiva, Sujatro Chakladar, and Vincent C. Marconi on behalf of the COV-BARRIER Study Group**

Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial

*Andre C Kalil, Aneesh K Mehta, Thomas F Patterson, Nathaniel Erdmann, Carlos A Gomez, Mamta K Jain, Cameron R Wolfe, Guillermo M Ruiz-Palacios, Susan Kline, Justino Regalado Pineda, Anne F Luetkemeyer, Michelle S Harkins, Patrick E H Jackson, Nicole M Iovine, Victor F Tapson, Myoung-don Oh, Jennifer A Whitaker, Richard A Mularski, Catharine I Paules, Dilek Ince, Jin Takasaki, Daniel A Sweeney, Uriel Sandkovsky, David L Wyles, Elizabeth Hohmann, Kevin A Grimes, Robert Grossberg, Maryrose Laguio-Vila, Allison A Lambert, Diego Lopez de Castilla, EuSuk Kim, LuAnn Larson, Claire R Wan, Jessica J Traenkner, Philip O Ponce, Jan E Patterson, Paul A Goepfert, Theresa A Sofarelli, Satish Mocherla, Emily R Ko, Alfredo Ponce de Leon, Sarah B Doernberg, Robert L Atmar, Ryan C Maves, Fernando Dangond, Jennifer Ferreira, Michelle Green, Mat Makowski, Tyler Bonnett, Tatiana Beresnev, Varduhi Ghazaryan, Walla Dempsey, Seema U Nayak, Lori Dodd, Kay M Tomashek, John H Beigel, on behalf of the ACTT-3 study group members**

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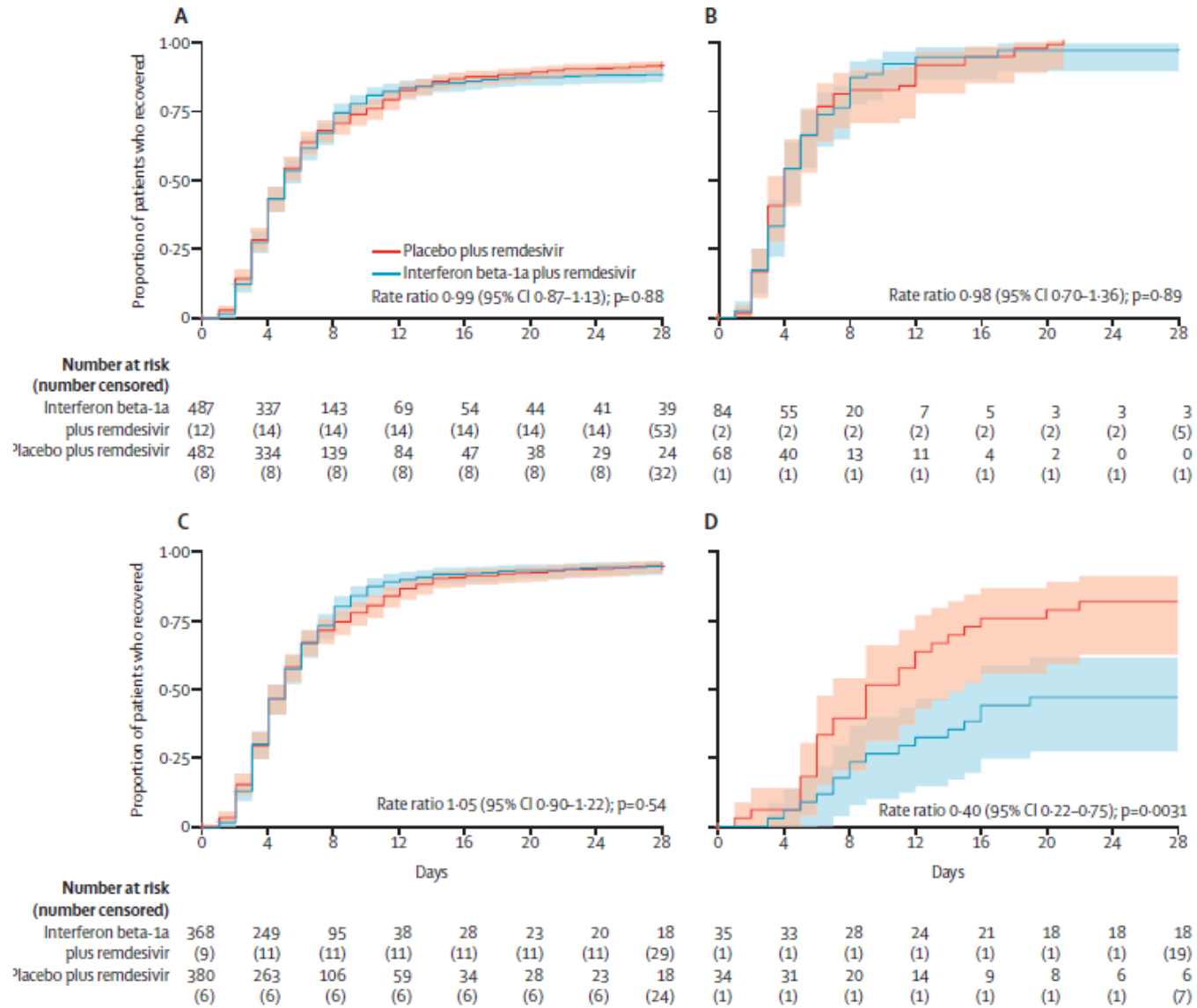

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial

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Published Online
May 8, 2020
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S0140-6736(20)31042-4

Ivan Fan-Ngai Hung, Kwok-Cheung Lung, Eugene Yuk-Keung Tso, Raymond Liu, Tom Wai-Hin Chung, Man-Yee Chu, Yuk-Yung Ng, Jenny Lo, Jacky Chan, Anthony Raymond Tam, Hoi-Ping Shum, Veronica Chan, Alan Ka-Lun Wu, Kit-Man Sin, Wai-Shing Leung, Wai-Lam Law, David Christopher Lung, Simon Sin, Pauline Yeung, Cyril Chik-Yan Yip, Ricky Ruiqi Zhang, Agnes Yim-Fong Fung, Erica Yuen-Wing Yan, Kit-Hang Leung, Jonathan Daniel Ip, Allen Wing-Ho Chu, Wan-Mui Chan, Anthony Chin-Ki Ng, Rodney Lee, Kitty Fung, Alwin Yeung, Tak-Chiu Wu, Johnny Wai-Man Chan, Wing-Wah Yan, Wai-Ming Chan, Jasper Fuk-Woo Chan, Albert Kwok-Wai Lie, Owen Tak-Yin Tsang, Vincent Chi-Chung Cheng, Tak-Lun Que, Chak-Sing Lau , Kwok-Hung Chan, Kelvin Kai-Wang To, Kwok-Yung Yuen

Methods This was a multicentre, prospective, open-label, randomised, phase 2 trial in adults with COVID-19 who were admitted to six hospitals in Hong Kong. Patients were randomly assigned (2:1) to a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group). The primary endpoint was the time to providing a nasopharyngeal swab negative for severe acute respiratory syndrome coronavirus 2 RT-PCR, and was done in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT04276688.

Findings Between Feb 10 and March 20, 2020, 127 patients were recruited; 86 were randomly assigned to the combination group and 41 were assigned to the control group. The median number of days from symptom onset to start of study treatment was 5 days (IQR 3–7). The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4·37 [95% CI 1·86–10·24], p=0·0010). Adverse events included self-limited nausea and diarrhoea with no difference between the two groups. One patient in the control group discontinued lopinavir–ritonavir because of biochemical hepatitis. No patients died during the study.

US NIH ACTIV-3 trial

Singapore participated in:
Eli Lilly monoclonal antibody
Astrazeneca long acting monoclonal antibody
Molecular Partner designed ankyrin repeat proteins

Futility:
Eli Lilly
Vir-7831
Brii-196 and Brii-198
Ensovibep

Completed and phase readout early 2022:
AZD7442

Agent	Trial Phase	Description	More Information
LY-CoV555 *This study has closed.*	Phase 3	An investigational antibody developed by Eli Lilly and Co. in partnership with AbCellera Biologics. AbCellera collaborated with NIAID's Vaccine Research Center to identify and isolate the antibody from a blood sample from a person who recovered from COVID-19. This sub-study closed because the Data and Safety Monitoring Board determined low likelihood that the intervention would be of clinical value in this hospitalized patient population.	• Clinical Trial Record • News Release • Statement on Closure
VIR-7831 *This study has closed.*	Phase 3	A monoclonal antibody developed through a partnership between Glaxo-SmithKline plc and Vir Biotechnology, Inc. The Data and Safety Monitoring Board recommended that recruitment in the sub-study should cease, due to futility.	• Clinical Trial Record • News Release • Statement on Closure
BRII-196 and BRII-198 *This study has closed.*	Phase 3	Two monoclonal antibodies developed by Brii Biosciences. The Data and Safety Monitoring Board determined that the therapeutics did not meet the inclusion for criteria for further enrollment in the trial, due to futility.	• Clinical Trial Record • News Release • Statement on Closure
AZD7442	Phase 3	An investigational long-acting antibody combination developed by AstraZeneca.	• Clinical Trial Record • News Release
Ensovibep (MP0420)	Phase 3	A small-molecule therapeutic designed by Molecular Partners in partnership with Novartis. It consists of a single kind of small molecule, from a novel class of antimicrobials known as DARPins (designed ankyrin repeat proteins). Ensovibep has been designed to bind to three different locations on the spike protein on the surface of SARS-CoV-2. This may prevent the virus from infecting human cells.	• Clinical Trial Record
PF-07304814	Phase 3	A selective inhibitor of the SARS-CoV-2 3CLpro (a viral protease) developed by Pfizer to be administered as an IV infusion treatment for patients hospitalized with COVID-19	• Clinical Trial Record

A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19

ACTIV-3/TICO LY-CoV555 Study Group*

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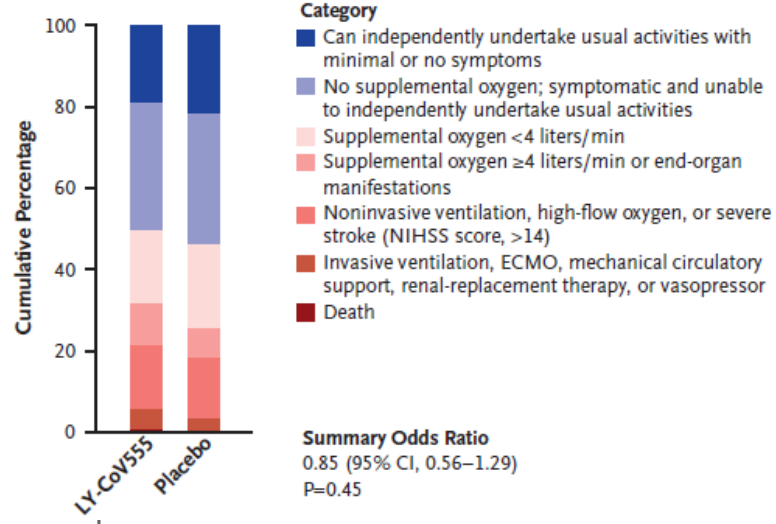
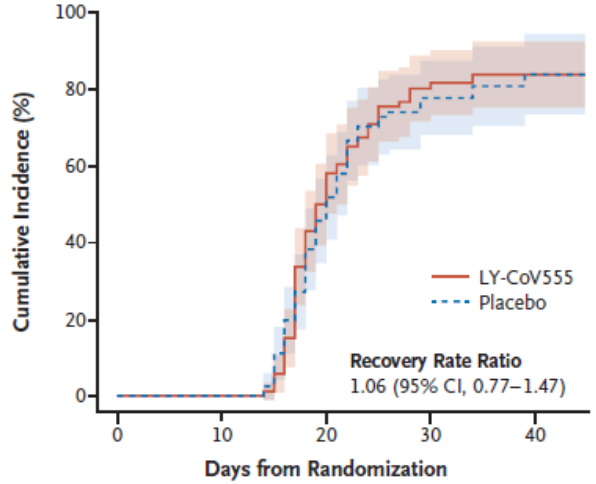
DOI: 10.1056/NEJMoa2033130

A Pulmonary Ordinal Outcome on Day 5

Category		LY-CoV555 (*no. of patients (%)*)	Placebo (*no. of patients (%)*)
Better	1	31 (19.3)	33 (22.0)
	2	50 (31.1)	48 (32.0)
	3	29 (18.0)	31 (20.7)
	4	17 (10.6)	11 (7.3)
	5	25 (15.5)	22 (14.7)
	6	8 (5.0)	5 (3.3)
Worse	7	1 (0.6)	0 (0.0)

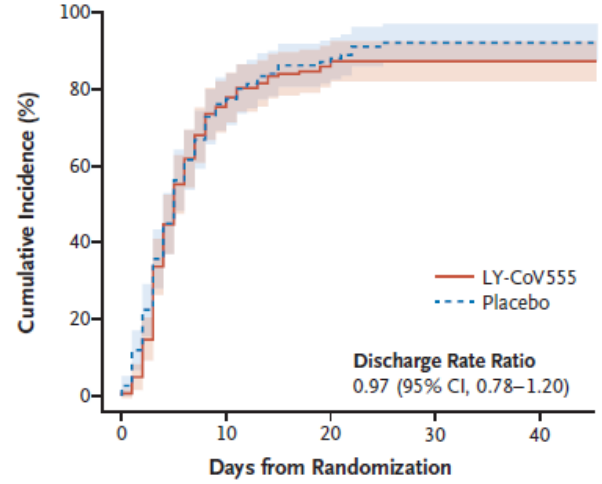


B Time to Sustained Recovery



No. at Risk					
LY-CoV555	87	86	41	9	3
Placebo	81	81	41	10	4

C Time to Hospital Discharge



No. at Risk					
LY-CoV555	163	38	17	6	3
Placebo	151	36	13	6	4

The Singapore Regeneron collaboration

- Scheduled call with Regeneron, 5 February 2020
- Second call with Regeneron, 21 February 2020
- Material transfer agreement
- First collection of 3 patients, 12 March 2020
- Second collection of 2 patients, 23 March 2020

Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail

Cite as: J. Hansen *et al.*, *Science* 10.1126/science.abd0827 (2020).

June 2020

Johanna Hansen[1*], Alina Baum[1*], Kristen E. Pascal[1], Vincenzo Russo[1], Stephanie Giordano[1], Elzbieta Wloga[1], Benjamin O. Fulton[1], Ying Yan[1], Katrina Koon[1], Krunal Patel[1], Kyung Min Chung[1], Aynur Hermann[1], Erica Ullman[1], Jonathan Cruz[1], Ashique Rafique[1], Tammy Huang[1], Jeanette Fairhurst[1], Christen Libertiny[1], Marine Malbec[1], Wen-yi Lee[1], Richard Welsh[1], Glen Farr[1], Seth Pennington[1], Dipali Deshpande[1], Jemmie Cheng[1], Anke Watty[1], Pascal Bouffard[1], Robert Babb[1], Natasha Levenkova[1], Calvin Chen[1], Bojie Zhang[1], Annabel Romero Hernandez[1], Kei Saotome[1], Yi Zhou[1], Matthew Franklin[1], Sumathi Sivapalasingam[1], David Chien Lye[2], Stuart Weston[3], James Logue[3], Robert Haupt[3], Matthew Frieman[3], Gang Chen[1], William Olson[1], Andrew J. Murphy[1], Neil Stahl[1], George D. Yancopoulos[1], Christos A. Kyratsous[1]†

Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies

Science **369**, 1014–1018 (2020)

June 2020

Alina Baum, Benjamin O. Fulton, Elzbieta Wloga, Richard Copin, Kristen E. Pascal, Vincenzo Russo, Stephanie Giordano, Kathryn Lanza, Nicole Negron, Min Ni, Yi Wei, Gurinder S. Atwal, Andrew J. Murphy, Neil Stahl, George D. Yancopoulos, Christos A. Kyratsous*

REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters

Cite as: A. Baum *et al.*, *Science* 10.1126/science.abe2402 (2020).

October 2020

Alina Baum[1], Dharani Ajithdoss[1], Richard Copin[1], Anbo Zhou[1], Kathryn Lanza[1], Nicole Negron[1], Min Ni[1], Yi Wei[1], Kusha Mohammadi[1], Bret Musser[1], Gurinder S. Atwal[1], Adelekan Oyejide[1], Yenny Goez-Gazi[2], John Dutton[2], Elizabeth Clemmons[2], Hilary M. Staples[2], Carmen Bartley[2], Benjamin Klaffke[2], Kendra Alfson[2], Michal Gazi[2], Olga Gonzalez[2], Edward Dick Jr.[2], Ricardo Carrion Jr.[2], Laurent Pessaint[3], Maciel Porto[3], Anthony Cook[3], Renita Brown[3], Vaneesha Ali[3], Jack Greenhouse[3], Tammy Taylor[3], Hanne Andersen[3], Mark G. Lewis[3], Neil Stahl[1], Andrew J. Murphy[1], George D. Yancopoulos[1], Christos A. Kyratsous[1*]

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, B.J. Musser, Y. Soo, D. Rofail, J. Im, C. Perry, C. Pan, R. Hosain, A. Mahmood, J.D. Davis, K.C. Turner, A.T. Hooper, J.D. Hamilton, A. Baum, C.A. Kyratsous, Y. Kim, A. Cook, W. Kampman, A. Kohli, Y. Sachdeva, X. Graber, B. Kowal, T. DiCioccio, N. Stahl, L. Lipsich, N. Braunstein, G. Herman, and G.D. Yancopoulos, for the Trial Investigators*

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Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19

M.P. O'Brien, E. Forleo-Neto, B.J. Musser, F. Isa, K.-C. Chan, N. Sarkar, K.J. Bar, R.V. Barnabas, D.H. Barouch, M.S. Cohen, C.B. Hurt, D.R. Burwen, M.A. Marovich, P. Hou, I. Heirman, J.D. Davis, K.C. Turner, D. Ramesh, A. Mahmood, A.T. Hooper, J.D. Hamilton, Y. Kim, L.A. Purcell, A. Baum, C.A. Kyratsous, J. Krainson, R. Perez-Perez, R. Mohseni, B. Kowal, A.T. DiCioccio, N. Stahl, L. Lipsich, N. Braunstein, G. Herman, G.D. Yancopoulos, and D.M. Weinreich, for the Covid-19 Phase 3 Prevention Trial Team*

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REGEN-COV® for Treatment of Hospitalized Patients with Covid-19

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REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients

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Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Running title: REGEN-COV for COVID-19

RECOVERY Collaborative Group*

Ildong Pharmaceutical has started a Phase 2/3 clinical trial of S-217622, an investigational oral medication developed by its Japanese partner Shionogi Pharmaceutical to treat Covid-19 symptoms, at home, the South Korean company announced on Thursday.

The Ministry of Food and Drug Safety cleared the company's IND application for a clinical study for the Covid-19 cure to evaluate its safety and pharmacological properties of the drug last week.

Under the protocol, Ildong Pharmaceutical plans to recruit more than 200 patients with asymptomatic and mild-to-moderate cases at Inha University Hospital in Korea, while Shionogi Pharmaceutical will conduct global clinical trials in Singapore and Japan among others.

Ildong Pharmaceutical aims to receive emergency use authorization for the drug in the first half of next year in Korea. Ildong Pharmaceutical expects it can sign on an agreement with its Japanese partner for technology transfer and local production of the drug for stable supply if granted marketing authorization.

S-217622 taken once daily for five days has demonstrated excellent safety and tolerability. It is known to inhibit 3CL-protease, present only in the Covid-19 virus, to prevent viral proliferation. In non-clinical studies, the treatment also showed a comparable level of viral inhibition across major Covid-19 variants, including Alpha, Beta, Gamma, and Delta.

NCID/TTSH, SGH and CGH
Coordinated by SCRI

Summary

- Rapid coordinated national efforts
  - COVID19 research workgroup, NMRC
  - NHG DSRB, HSA
  - SCRN comprising all public hospitals in Singapore

- Singapore participated in international COVID19 trial networks
  - Participated in industry (Gilead) as well as NIH ACTT 1-4 and ACTIV3 trials
  - Missed out on WHO Solidarity and UK Recovery trials
  - Insights into top candidates for therapeutics

- Singapore contributed to definitive clinical trials on remdesivir, baricitinib and monoclonal antibodies
  - Missed out on dexamethasone and tocilizumab
  - National COVID19 treatment stockpile and guideline