Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among patients with COVID-19, should regdanvimab be used for treatment?

Evidence Reviewers: Furqaan I. Lim, MD, April P. Padua-Zamora, MD, Marissa M. Alejandria, MD, MSc

RECOMMENDATION

We suggest against the use of regdanvimab for the treatment of mild to moderate COVID-19. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues
Very limited evidence (2 small randomized controlled trials, one of which is still a pre-print) support the use of regdanvimab in treatment of mild to moderate COVID-19. Although regdanvimab showed potential benefit in terms of clinical recovery at Day 14 and Day 28, the evidence was inconclusive for other critical outcomes such as all-cause mortality, need for hospitalization, or clinical deterioration. Clinical recovery among patients with moderate to severe symptoms at baseline was defined as improvement of symptoms and not necessarily complete resolution of symptoms. Concern regarding the effect of possible publication bias on subjective outcomes such as clinical recovery was raised, since currently available studies were both funded by regdanvimab's manufacturing company. Hence, the panel suggested against use of regdanvimab considering its limited evidence, potentially large cost, and availability of treatment alternatives with more robust evidence that has shown benefit on more objective outcomes (e.g., all-cause mortality and need for hospitalization) among patients with mild to moderate COVID-19.

Key Findings

Two (2) randomized controlled trials (RCTs) evaluated the efficacy of regdanvimab as treatment for patients with COVID-19. The overall certainty of evidence was very low because of serious risk of bias, imprecision, and high probability of publication bias. Among patients with mild to moderate COVID-19 infection, regdanvimab showed minimal potential benefit in terms of clinical recovery at Day 14 and Day 28. There was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, need for hospitalization, and oxygen therapy requirement. There was no significant difference in adverse events between patients treated with regdanvimab compared to placebo.

Introduction

Regdanvimab or CT-P59 is a recombinant human monoclonal immunoglobulin G1 antibody, which has shown potent neutralizing activity against SARS-CoV-2 isolates. It binds to the receptor binding domain (RBD) of the virus' spike protein, thereby preventing viral entry into human cell via the angiotensin-converting enzyme 2 (ACE2) receptor and subsequent viral replication.[1]

Review Methods

We conducted a literature search for studies published from 2019 to December 5, 2021. Databases searched were Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), Epistemonikos, and Google Scholar with a combined MeSH and free text search using the terms Regdanvimab OR CT-P59 AND COVID-19 OR coronavirus. Registries for ongoing or completed clinical trials were also searched (*clinicaltrials.gov*, ISRCTN registry, and World Health Organization International Clinical Trials Registry Platform). We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. References of all studies were reviewed to identify other studies. Only randomized controlled trials that compared regdanvimab against placebo or standard of care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, hospitalization status, and dosing strategy of regdanvimab. Subgrouping by severity was planned.

Results

Of the 137 records identified from the search, 2 RCTs with total of 345 participants were included in this review. The first RCT is a Phase 1 trial involving healthy subjects and COVID-19 patients with mild infection. Only patients with mild COVID-19 infection were included in this review.[2] The second RCT is a pre-print Phase 2/3 trial of the earlier study, which enrolled COVID-19 patients with mild to moderate infection.[3] Both trials were funded by the manufacturing company of regdanvimab. Comparing with placebo, the Phase 1 trial [2] used three doses of regdanvimab (20 mg/kg, 40 mg/kg, and 80 mg/kg), while the Phase 2/3 trial [3] used two doses (40 mg/kg and 80 mg/kg), all given as one dose of IV infusion. The characteristics of studies are reported in Appendix 3.

The overall certainty of evidence was assessed to be very low due to serious risk of bias, imprecision in some critical outcomes, and probability of publication bias. Publication bias was considered for all outcomes because the only trials available were sponsored by the manufacturing company of regdanvimab. The risk of bias summary is shown in Appendix 4. The GRADE evidence profile is in Appendix 5.

Based from 2 RCTs, which enrolled patients with mild-moderate COVID-19 infection, regdanvimab showed a trend towards benefit in terms of clinical recovery at Day 14 for both 40mg/kg (RR 1.23, 95% CI 1.02-1.47; $I^2 = 0$) and 80mg/kg (RR 1.25, 95% CI 1.04-1.49; $I^2 = 0$). Clinical recovery was defined as all symptoms being absent or mild for $\geq$ 24 hours. A patient has clinical recovery if symptoms scored as moderate or severe at baseline became mild or absent at recovery. A patient has clinical recovery if symptoms scored as mild or absent at baseline became absent at recovery. At Day 7, 40mg/kg dose showed trend towards benefit (RR 1.46, 95% CI 1.08-1.97; $I^2 = 0$), whereas the result was inconclusive for 80mg/kg (RR 1.34, 95% CI 0.98-1.81; $I^2 = 0$). There was no benefit at Day 7 and 14 for 20mg/kg dose. There was no significant difference in terms of time to recovery among those with mild COVID-19 infection given regdanvimab, for both 40 mg/kg (MD -1.9 days, 95% -4.96 to 1.15; $I^2 = 0$) and 80 mg/kg (MD -1.58 days, 95% -4.29 to 1.14; $I^2 = 0$) compared to placebo.[2,3]

Based from 1 RCT, regdanvimab showed a trend towards benefit in terms of clinical recovery at Day 28 for both 40 mg/kg (RR 1.22, 95% CI 1.06-1.42) and 80mg/kg (RR 1.2, 95% CI 1.03-1.4).[3]

The median time to recovery was shorter among patients with moderate COVID-19 infection who were given regdanvimab 40mg/kg (5.73 days, 95% CI 4.13-7.33) and 80mg/kg (7.3 days, 95% CI 5.58-10.72) compared to placebo (10.81 days, 95% CI 6.81-not calculable). There is insufficient data to conclude whether these differences were statistically significant. Subgroup analysis showed that for moderate infection and patients aged ≥ 50 years old, the median time to recovery was 6.64 days (95% CI 4.13-11.94) for 40 mg/kg dose, 7.29 days (95% CI 5.54-12.33) for 80 mg/kg dose, and 12.97 days(95% CI 6.81-not calculable) for placebo.[3]

None of the patients with mild COVID-19 infection were hospitalized or required oxygen therapy. Regdanvimab did not significantly reduce the need for hospitalization among patients with mild to moderate COVID-19 infection compared to placebo, for both 40mg/kg (RR 0.45, 95% CI 0.14-1.42) and 80mg/kg (RR 0.56, 95% CI 0.19-1.6). Likewise, there was no significant difference in terms of oxygen therapy requirement among those given regdanvimab 40mg/kg (RR 0.45, 95% CI 0.14-1.42) and 80mg/kg (RR 0.44, 95% CI 0.14-1.4) compared to placebo. Subgroup analyses considering only patients aged ≥ 50 years old with moderate infection still showed inconclusive results on need for hospitalization or oxygen therapy for both 40mg/kg dose (RR 0.32, 95% CI 0.09-1.08) and 80mg/kg dose (RR 0.42, 95% CI 0.14-1.26).[3]
Mean change in viral titers (log_{10} copies/ml) measured from baseline up to 7 days following treatment showed trend towards benefit among patients given regdanvimab 20mg/kg (MD -2.11, 95% CI -3.97 to -0.25), but not among those given 40mg/kg (MD -0.76, 95% CI -2.57 to 1.05) or 80mg/kg (MD -1.29, 95% CI -2.78 to 0.19).[2]

Safety
There was no significant difference in adverse events between patients treated with regdanvimab compared to placebo (RR 0.91, 95% CI 0.65-1.29; $I^2 = 0$). Most adverse events were mild. There was no incidence of anaphylaxis nor life-threatening adverse events. There was no evidence of dose-related increase in toxicity. There was no occurrence of any adverse event causing discontinuation of treatment.[2,3]

In the Phase 1 trial, adverse events reported included diarrhea (13.3% of patients given regdanvimab), flank pain (6.6%), insomnia (6.6%), productive cough (6.6%), palpitations (6.6%), dysphagia (6.6%), Candida infection (unspecified location, 6.6%), increased ALT (13.3%), and increased blood creatine phosphokinase (6.6%). One patient had grade 3 hepatocellular injury (6.6%). One patient (6.6%) had baseline obesity and hypertriglyceridemia and had worsening of hypertriglyceridemia after being given regdanvimab. However, the investigators stated that all the adverse events were considered unrelated to the study drug.[2]

In the Phase 2/3 trial, the most frequently reported adverse event was hypertriglyceridemia but the number of patients affected was not reported. One patient had infusion-related reaction, described as fever and dyspnea, which resolved on the same day after paracetamol and oxygen therapy.[3]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian COVID-19 Guidelines (as of November 26, 2021) [4]	Recommends against the use of monoclonal antibody regdanvimab for the treatment of COVID-19 outside of randomized trials with appropriate ethical.

NIH COVID-19 Guidelines (as of October 19, 2021)	No statement on the recommendation of regdanvimab as treatment for COVID-19.[5-8]
Surviving Sepsis Campaign Guidelines (as of January 29, 2021)	
Infectious Diseases Society of America (as of November 18, 2021	
World Health Organization (WHO) Living Guidelines (as of September 24, 2021)	
Korean Society of Infectious Diseases/National Evidence-based Healthcare Collaborating Agency Guidelines (as of June 18, 2021) [11]	Anti-SARS-CoV-2 monoclonal antibody may be considered in patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19. (*Low level of evidence; Grade of recommendation: B, conditional)* Anti-SARS-CoV-2 monoclonal antibody is not recommended for patients with severe COVID-19. These treatments may be considered for clinical trials of patients with severe COVID-19 requiring supplemental oxygen but not high flow oxygen or invasive mechanical ventilation. *(Low level of evidence; Grade of recommendation: C, not recommended)* Anti-SARS-CoV-2 monoclonal antibody pertains to bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, and regdanvimab.

Research Gaps

There is one (1) ongoing study on regdanvimab, also funded by the manufacturer. It is a Phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study, which aimed to evaluate the efficacy and safety of regdanvimab in combination with standard of care, in patients hospitalized with COVID-19.[3] It has already completed recruitment as of October 20, 2021, but results were not published yet. As of writing, there are no independent trials studying the efficacy of regdanvimab for COVID-19 infections.

References

[1] Kim C, Ryu DK, Lee J, et al. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. Nat Commun. 2021;12(1):288. doi: 10.1038/s41467-020-20602-5.

[2] Kim JY, Jang YR, Hong JH, et al. Safety, Virologic Efficacy, and Pharmacokinetics of CT-P59, a Neutralizing Monoclonal Antibody Against SARS-CoV-2 Spike Receptor-Binding Protein: Two Randomized, Placebo-Controlled, Phase I Studies in Healthy Individuals and Patients With Mild SARS-CoV-2 Infection. 18 Aug 2021. Available from https://doi.org/10.1016/j.clinthera.2021.08.009

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[5] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 4 December 2021.

[6] Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: FIrst Update, Accessed 4 December 2021.https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

[7] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.2.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 4 December 2021.

[8] World Health Organization. Therapeutics and COVID-19 Living Guidelines. 6 July 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2. Accessed 4 December 2021.

[9] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 3 December 2021. Available from https://covid19.who.int.

[10] Republic of the Philippines Department of Health. COVID-19 Case Tracker. 6 December 2021. Available from https://doh.gov.ph/covid-19/case-tracker

[11] Kim SB, Kim J, Huh, K, et al. Korean Society of Infectious Diseases/National Evidence-based Healthcare Collaborating Agency Recommendations for Anti-SARS-CoV-2 Monoclonal Antibody Treatment of Patients with COVID-19. 6 December 2021. Available from https://www.icjournal.org/DOIx.php?id=10.3947/ic.2021.0304.

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					
Benefits	Large	Moderate	Small (2)	Uncertain (3)			• Regdanvimab showed trend towards benefit in terms of clinical recovery at Day 14 and Day 28. • Inconclusive evidence in terms of other critical outcomes such as all-cause mortality, need for hospitalization, and oxygen therapy requirement.
Harm	Large	Small (2)	Uncertain (3)				• No significant difference in adverse events between patients treated with regdanvimab compared to placebo (RR 0.91, 95% CI 0.65-1.29) • Adverse events: hypertriglyceridemia, increased ALT, 1 infusion-related (fever, dyspnea), cough, diarrhea
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			• Very low due to serious risk of bias, imprecision in some critical outcomes, and high probability of publication bias
Balance of effects	Favors drug	Does not favor drug (1)	Uncertain (4)				• Minimal net potential benefit (in terms of clinical recovery), with no significant harm
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (4)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• Regdanvimab is currently not available in the Philippines. • Its estimated cost is PHP 25,000 / course
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		
Cost effectiveness	No included studies (4)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention			
Equity	Uncertain (3)	Reduced (2)	Probably no impact	Increased			
Acceptability	Uncertain (5)	No	Yes				
Feasibility	Uncertain (2)	No (3)	Yes				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(regdanvimab OR CT-P59 OR (regdanvimab[tiab]) OR (CT-P59[tiab])) AND (((COVID-19[MeSH Terms]) OR (coronavirus[MeSH Terms])) OR ((COVID-19 [tiab]) OR (coronavirus [tiab]))) AND (((((((COVID-19[MeSH Terms]) OR (coronavirus[MeSH Terms])) OR (sars-cov-2[MeSH Terms])) OR (nCoV [tiab])) OR (COVID-19)) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-CoV-2 [tiab]))	Dec 5, 2021	11	1
CENTRAL	(regdanvimab OR CT-P59) AND (COVID-19 OR SARS-Cov-2 OR coronavirus)	Dec 5, 2021	1	1
Google Scholar	Regdanvimab OR CT-P59 AND COVID-19 OR SARS-Cov-2	Dec 5, 2021	109	5
COVID-NMA initiative	Regdanvimab OR CT-P59	Dec 5, 2021	10	0
ClinicalTrials.gov	Regdanvimab OR CT-P59	Dec 4, 2021 10:00 AM	1	1
Chinese Clinical Trial Registry	Regdanvimab OR CT-P59	Dec 4, 2021 10:05 AM	0	0
EU Clinical Trials Register	Regdanvimab OR CT-P59	Dec 4, 2021 10:10 AM	0	0
Republic of Korea - Clinical Research Information Service	Regdanvimab OR CT-P59	Dec 4, 2021 10:15 AM	1	1
Japan Primary Registries Network/ NIPH Clinical Trials Search	Regdanvimab OR CT-P59	Dec 4, 2021 10:20 AM	0	0
CenterWatch	Regdanvimab OR CT-P59	Dec 4, 2021 10:25 AM	0	0
chinaxiv.org	(Regdanvimab OR CT-P59) AND (COVID-19 OR SARS-Cov-2)	Dec 5, 2021	0	0
Medrxiv.org	(Regdanvimab OR CT-P59) AND COVID-19	Dec 5, 2021	4	0
Biorxiv.org	(Regdanvimab OR CT-P59) AND COVID-19	Dec 5, 2021	13	0

Appendix 3. Characteristics of Included Studies

Author	Study Design	Country	Population	Intervention	Control	Outcomes
Kim et al. 2021	RCT	South Korea, Romania	Part 1.1: Age 19 to 55 years, without SARS-CoV-2 infection, weigh ≥50 kg, BMI 18-29.9 (not included in this review) Part 1.2: Age 18-70 years, with mild SARS-Cov-infection (based on WHO) diagnosed by RT PCR, with O2 sats >94%, and symptom onset within 7 days before drug administration	Regdanvimab at 3 doses (20 mg/kg, 40 mg/kg and 80 mg/kg) as IV infusion, single dose	Placebo (0.9% NaCl)	Adverse events, vital signs, ECG, physical exam, laboratory tests, radiography; Pharmacokinetics; Incidence of antidrug antibodies (ADA); Time to clinical recovery; Proportion of patients with clinical recovery up to day 14
Eom et al. 2021 (pre-print)	RCT	South Korea, Romania, Spain, USA	Age ≥ 18 years, with SARS-Cov-2 infection diagnosed by rapid SARS-Cov-2 test or RT-PCR, with O2 sats >94%, mild to moderate infection (based on WHO), and symptom onset within 7 days before drug administration	Regdanvimab at 2 doses (40 mg/kg and 80 mg/kg) as IV infusion, single dose	Matching placebo	Time to conversion to negative RT PCR; Time to clinical recovery; Proportion of patients with clinical recovery; Proportion of patients requiring hospitalization, oxygen therapy, mechanical ventilation, ICU admission, or rescue therapy; All cause mortality; Proportion of patients with conversion to negative RT PCR

Appendix 4. Study Appraisal

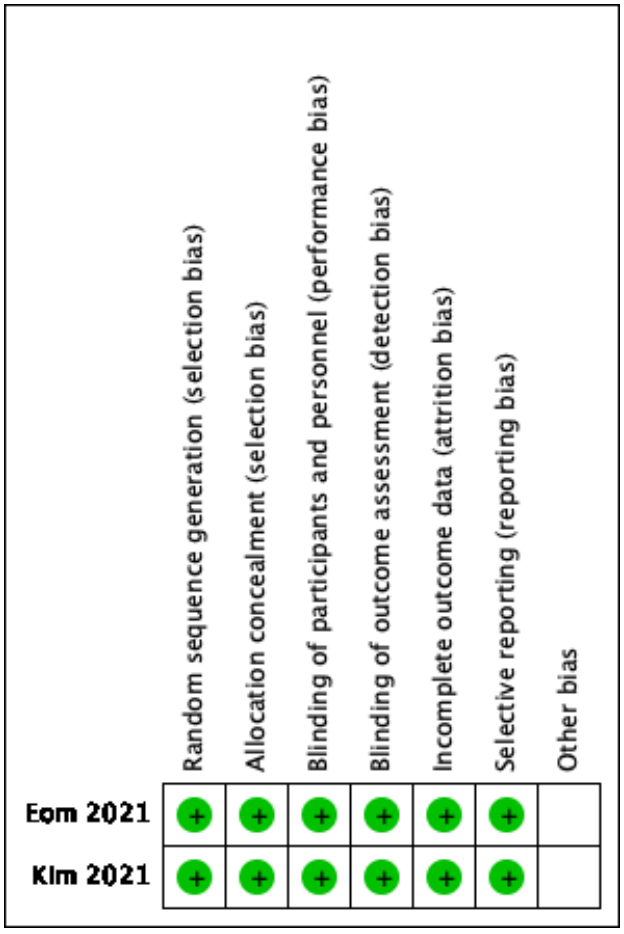

Fig. 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Furqaan Lim, April Padua-Zamora
Question: Should Regdanvimab be used to treat patients with COVID-19?
Setting: South Korea, Romania
Bibliography: Kim JY, Jang YR, Hong JH, et al. Safety, Virologic Efficacy, and Pharmacokinetics of CT-P59, a Neutralizing Monoclonal Antibody Against SARS-CoV-2 Spike Receptor-Binding Protein: Two Randomized, Placebo-Controlled, Phase I Studies in Healthy Individuals and Patients With Mild SARS-CoV-2 Infection. 18 Aug 2021. Available from https://doi.org/10.1016/j.clinthera.2021.08.009

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean change in viral titers (20 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	5	3	-	MD **2.11 lower** (3.97 lower to 0.25 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Mean change in viral titers (40 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	5	3	-	MD **0.76 lower** (2.57 lower to 1.05 higher)	⨁⨁◯◯ LOW	IMPORTANT
Mean change in viral titer (80 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	5	3	-	MD **1.29 lower** (2.78 lower to 0.19 higher)	⨁⨁◯◯ LOW	IMPORTANT
Time to recovery, mild infection (20 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	publication bias strongly suspected[a]	5	3	-	MD **0.82 lower** (8.69 lower to 7.05 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Clinical recovery at day 7 (20 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	4/5 (80.0%)	2/3 (66.7%)	**RR 1.20** (0.48 to 2.99)	**133 more per 1,000** (from 347 fewer to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT
Clinical recovery at day 14 (20 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	publication bias strongly suspected[a]	5/5 (100.0%)	2/3 (66.7%)	**RR 1.47** (0.66 to 3.25)	**313 more per 1,000** (from 227 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Author(s): Furqaan Lim, April Padua-Zamora
Question: Should Regdanvimab be used to treat patients with COVID-19?
Setting: South Korea, Romania, Spain, USA
Bibliography: Eom, JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebocontrolled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. 15 March 2021. Available from https://www.researchsquare.com/article/rs-296518/v1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical recovery at day 28 (40 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	83/95 (87.4%)	70/98 (71.4%)	**RR 1.22** (1.06 to 1.42)	**157 more per 1,000** (from 43 more to 300 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Clinical recovery at day 28 (80 mg/kg Regdanvimab)												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	79/92 (85.9%)	70/98 (71.4%)	**RR 1.20** (1.03 to 1.40)	**143 more per 1,000** (from 21 more to 286 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Requirement for hospitalization (40 mg/kg Regdanvimab) for mild-moderate infection												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	4/101 (4.0%)	9/103 (8.7%)	**RR 0.45** (0.14 to 1.42)	**48 fewer per 1,000** (from 75 fewer to 37 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for oxygen therapy (40 mg/kg Regdanvimab) for mild-moderate infection												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	4/101 (4.0%)	9/103 (8.7%)	**RR 0.45** (0.14 to 1.42)	**48 fewer per 1,000** (from 75 fewer to 37 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization or oxygen therapy (40 mg/kg Regdanvimab) for moderate infection												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	4/62 (6.5%)	9/57 (15.8%)	**RR 0.41** (0.13 to 1.25)	**93 fewer per 1,000** (from 137 fewer to 39 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization or oxygen therapy (40 mg/kg Regdanvimab) for moderate infection, age≥50 years												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	3/40 (7.5%)	9/38 (23.7%)	**RR 0.32** (0.09 to 1.08)	**161 fewer per 1,000** (from 216 fewer to 19 more)	⨁⨁◯◯ LOW	CRITICAL
Requirement for hospitalization (80 mg/kg Regdanvimab) for mild-moderate infection												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	5/103 (4.9%)	9/103 (8.7%)	**RR 0.56** (0.19 to 1.60)	**38 fewer per 1,000** (from 71 fewer to 52 more)	⨁⨁◯◯ LOW	CRITICAL

Requirement for oxygen therapy (80 mg/kg Regdanvimab) for mild-moderate infection

1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	4/103 (3.9%)	9/103 (8.7%)	**RR 0.44** (0.14 to 1.40)	**49 fewer per 1,000** (from 75 fewer to 35 more)	⨁⨁◯◯ LOW	CRITICAL

Requirement for hospitalization or oxygen therapy (80 mg/kg Regdanvimab) for moderate infection

1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	5/63 (7.9%)	9/57 (15.8%)	**RR 0.50** (0.18 to 1.41)	**79 fewer per 1,000** (from 129 fewer to 65 more)	⨁⨁◯◯ LOW	CRITICAL

Requirement for hospitalization or oxygen therapy (80 mg/kg Regdanvimab) for moderate infection, age≥50 years

1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	4/40 (10.0%)	9/38 (23.7%)	**RR 0.42** (0.14 to 1.26)	**137 fewer per 1,000** (from 204 fewer to 62 more)	⨁⨁◯◯ LOW	CRITICAL

Requirement for mechanical ventilation (80 mg/kg Regdanvimab)

1	randomised trials	not serious	not serious	not serious	very serious[c]	publication bias strongly suspected[a]	1/103 (1.0%)	0/103 (0.0%)	**RR 3.00** (0.12 to 72.80)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Requirement for rescue therapy (40 mg/kg Regdanvimab)

1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	7/101 (6.9%)	15/103 (14.6%)	**RR 0.48** (0.20 to 1.12)	**76 fewer per 1,000** (from 117 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL

Requirement for rescue therapy (80 mg/kg Regdanvimab)

1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	11/103 (10.7%)	15/103 (14.6%)	**RR 0.73** (0.35 to 1.52)	**39 fewer per 1,000** (from 95 fewer to 76 more)	⨁⨁◯◯ LOW	CRITICAL

Author(s): Furqaan Lim, April Padua-Zamora
Question: Should Regdanvimab be used to treat patients with COVID-19?
Setting: South Korea, Romania, Spain, USA
Bibliography:

1) Kim JY, Jang YR, Hong JH, et al. Safety, Virologic Efficacy, and Pharmacokinetics of CT-P59, a Neutralizing Monoclonal Antibody Against SARS-CoV-2 Spike Receptor-Binding Protein: Two Randomized, Placebo-Controlled, Phase I Studies in Healthy Individuals and Patients With Mild SARS-CoV-2 Infection. 18 Aug 2021. Available from https://doi.org/10.1016/j.clinthera.2021.08.009
2) Eom, JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebocontrolled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. 15 March 2021. Available from https://www.researchsquare.com/article/rs-296518/v1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regdanvimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Time to recovery, mild infection (40 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	43	49	-	MD **1.9 lower** (4.96 lower to 1.15 higher)	⨁⨁◯◯ LOW	IMPORTANT
Time to recovery, mild infection (80 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	45	49	-	MD **1.58 lower** (4.29 lower to 1.14 higher)	⨁⨁◯◯ LOW	IMPORTANT
Clinical recovery at day 7 (40 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	57/100 (57.0%)	39/101 (38.6%)	**RR 1.46** (1.08 to 1.97)	**178 more per 1,000** (from 31 more to 375 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Clinical recovery at day 7 (80 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	51/97 (52.6%)	39/101 (38.6%)	**RR 1.34** (0.98 to 1.81)	**131 more per 1,000** (from 8 fewer to 313 more)	⨁⨁◯◯ LOW	IMPORTANT
Clinical recovery at day 14 (40 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	78/100 (78.0%)	64/101 (63.4%)	**RR 1.23** (1.02 to 1.47)	**146 more per 1,000** (from 13 more to 298 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Clinical recovery at day 14 (80 mg/kg Regdanvimab)												
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	77/97 (79.4%)	64/101 (63.4%)	**RR 1.25** (1.04 to 1.49)	**158 more per 1,000** (from 25 more to 310 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Total adverse events												
2	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	68/230 (29.6%)	35/113 (31.0%)	**RR 0.91** (0.65 to 1.29)	**28 fewer per 1,000** (from 108 fewer to 90 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Limited trials available are sponsored by manufacturing company
b. The outcome has imprecision because the results include the line of null effect and has a wide confidence interval.
c. The outcome includes the line of null effect and has a very wide confidence interval.

Appendix 6. Forest Plots

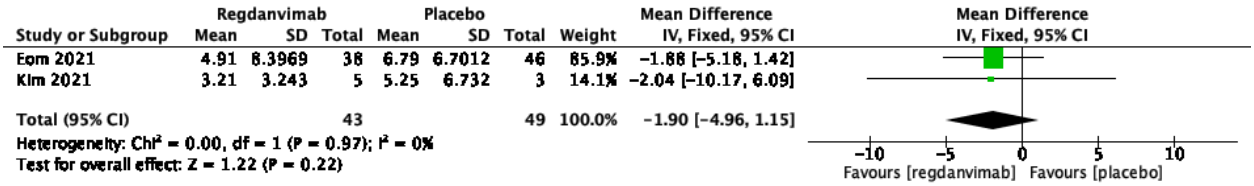

Figure 1. Time to recovery (40 mg/kg regdanvimab vs placebo)

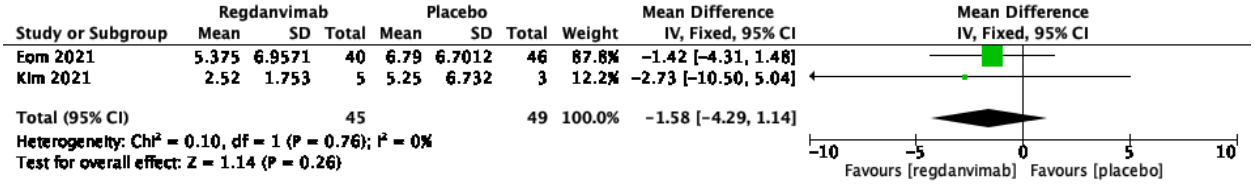

Figure 2. Time to recovery (80 mg/kg regdanvimab vs placebo)

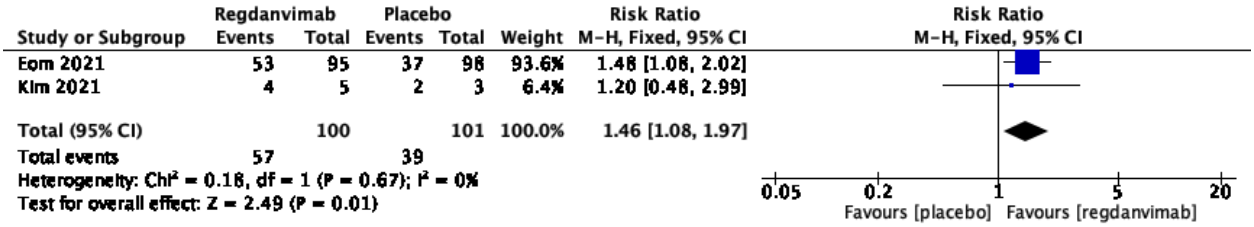

Figure 3. Patients with clinical recovery at day 7 (40 mg/kg regdanvimab vs placebo)

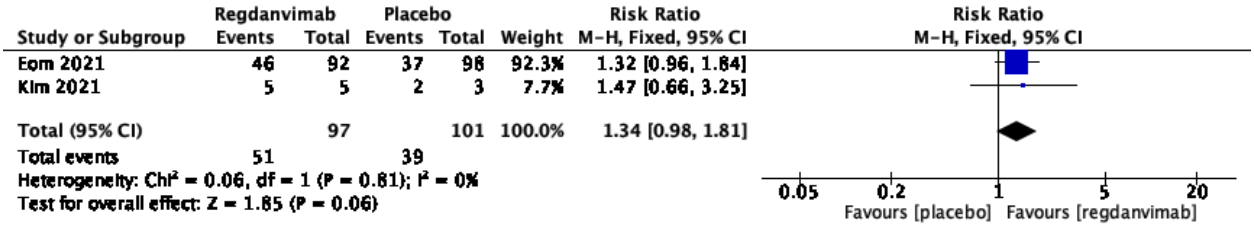

Figure 4. Patients with clinical recovery at day 7 (80 mg/kg regdanvimab vs placebo)

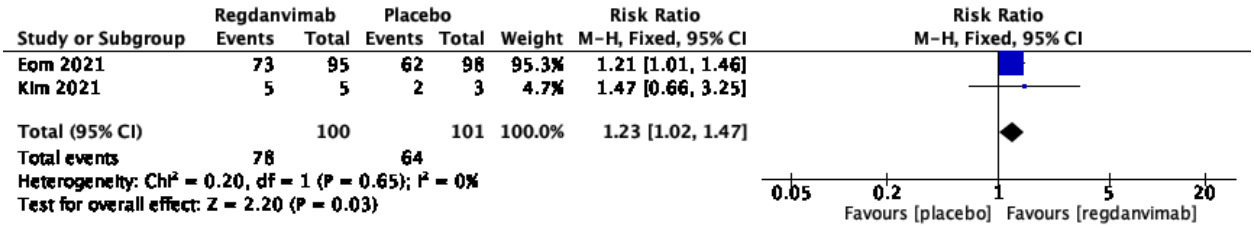

Figure 5. Patients with clinical recovery at day 14 (40 mg/kg regdanvimab vs placebo)

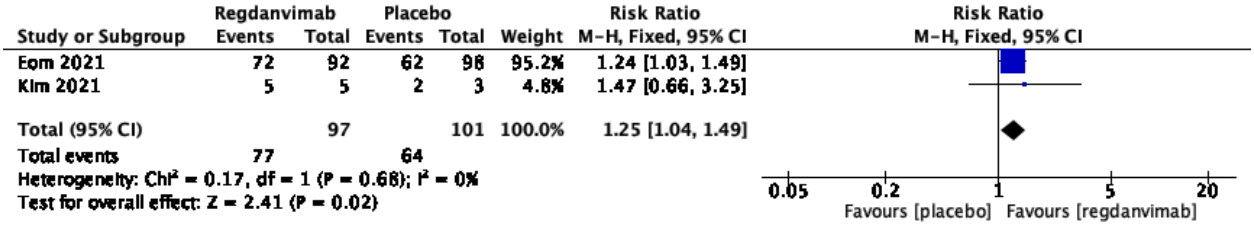

Fig. 6. Patients with clinical recovery at day 14 (80 mg/kg regdanvimab vs placebo)

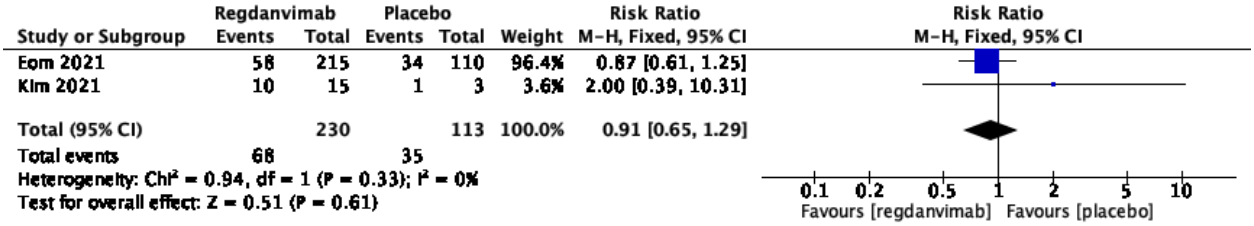

Fig. 7. Adverse events in patients (all doses of regdanvimab vs placebo)

Appendix 7. Ongoing Studies

Randomized Controlled Trials

Study ID	Setting	Title	Intervention	Control	Outcomes
NCT04602000	Multi-country (unspecified)	A Phase 2/3, Randomized, Parallel-group, Placebo-controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection	Regdanvimab	Placebo	Effect of CT-P59 on clinical symptoms requiring hospitalization, oxygen therapy, or mortality