Regdanvimab in patients with mild-to-moderate SARS-CoV-2 infection: A propensity score–matched retrospective cohort study

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ABSTRACT

Background: Regdanvimab (CT-P59) is a neutralizing antibody authorized in Republic of Korea for the treatment of adult patients with moderate or mild-COVID-19 who are not on supplemental oxygen and have high risk of progressing to severe disease (age $\geq$ 50 years or comorbidities). This study evaluated the clinical efficacy, safety and medical utilization/costs associated with real-world regdanvimab therapy.
Methods: This non-interventional, retrospective cohort study included adult patients with confirmed mild-to-moderate SARS-CoV-2 infection. Patients treated with regdanvimab were compared with controls who had received other therapies. The primary endpoint was the proportion of patients progressing to severe/critical COVID-19 or death due to SARS-CoV-2 infection up to Day 28. Propensity score matching was applied to efficacy analyses.
Results: Overall, 552 patients were included in the Safety and Efficacy Sets (regdanvimab, n = 156; control, n = 396) and 274 patients in the propensity score–matched (PSM) Efficacy Set (regdanvimab, n = 113; control, n = 161). In the PSM Set, the risk of severe/critical COVID-19 or death was significantly lower in the regdanvimab group (7.1% vs 16.1%, $P = 0.0263$); supplemental oxygen was required by 8.0% and 18.6% of patients in the regdanvimab and control groups, respectively ($P = 0.0128$). There were no unexpected safety findings in the regdanvimab group. Medical utilization analysis showed an overall cost reduction with regdanvimab compared with control treatments.
Conclusions: Regdanvimab significantly reduced the proportion of patients progressing to severe/critical disease or dying of SARS-CoV-2 infection. This study shows the potential benefits of regdanvimab in reducing disease severity and improving medical utility in patients with COVID-19.

1. Introduction

To date, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused >265 million confirmed cases of coronavirus disease 2019 (COVID-19) and >5.2 million COVID-19–related deaths globally [1]. A highly successful, mass immunization program is currently being rolled out worldwide, but this represents a huge undertaking and it will be a number of years before the virus is controlled on a global scale [2]. Infection and mortality rates continue to increase in many regions, particularly in developing countries where immunization rates are lower owing to the lack of vaccine supply/uptake and scarcity of public health infrastructure and primary care facilities [3]. While the COVID-19

vaccines have been developed extremely quickly using new technologies, their effectiveness appears to wane over time [4,5]. Limited duration of protection requires booster doses, yet the emergence of SARS-CoV-2 variants may reduce the effectiveness of existing vaccines against new viral strains [6,7]. The emergence of new SARS-CoV-2 variants with higher transmissibility is therefore likely to present many ongoing challenges to public health services resulting from the consequent increase in COVID-19 cases, hospitalizations and deaths [3,8,9].

The urgent need for effective new treatments has led to an unprecedented research effort, with clinical evaluation of many potential therapeutic candidates, including antiviral drugs, anti-inflammatory agents, anticoagulants, antifibrotics and targeted immunomodulatory therapies [10]. One possible therapeutic approach involves targeting of the SARS-CoV-2 spike (S) protein, which is responsible for entry of the coronavirus into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor located on epithelial and endothelial cells [11,12]. Indeed, proof of principle for the use of antibody therapy that targets the SARS-CoV-2 S protein has been demonstrated in several studies [13–16], and clinical studies have reported reduced hospitalizations, clinical symptoms and viral titers in patients with SARS-CoV-2 infection administered antibodies to the S protein [12,17–19].

Regdanvimab (CT-P59) is a potent neutralizing antibody against various SARS-CoV-2 isolates (including the D614G S-protein variant) that blocks the interaction regions of the SARS-CoV-2 S-protein receptor-binding domain for the ACE2 receptor [20] (Fig. 1). Preclinical data suggest that regdanvimab is active against several variants of SARS-CoV-2 (B.1.351 [the Beta variant], B.1.526, B.1.525, B.1.617 and B.1.617.2 [the Delta variant]) [21–23].

Regdanvimab has demonstrated antiviral activity and clinical efficacy, along with good tolerability and safety, in a Phase 1 single-dose study in patients with mild SARS-CoV-2 infection [24] as well as in a Phase 2/3 randomized, placebo-controlled, double-blind study in outpatients with mild-to-moderate SARS-CoV-2 infection, including high-risk patients [25,26]. A reduced need for hospitalization or oxygen therapy up to Day 28 was demonstrated with regdanvimab in the Phase 2/3 study and led to full marketing authorization being granted by the South Korean Ministry of Food and Drug Safety on September 17, 2021, for the treatment of patients aged at least 50 years, or with at least one underlying medical condition with mild symptoms of COVID-19, and of adult patients with moderate symptoms of COVID-19 [27]. On November 12, 2021, regdanvimab was granted marketing authorization by the European Medicines Agency for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of

their disease becoming severe [28]. Regdanvimab has also been selected by the European Commission as a preferred treatment as part of the EU strategy against COVID-19 [29]. Emergency use authorization was granted by the Indonesian National Agency for Drug and Food Control (Badan Pengawas Obat dan Makanan) [30] and the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária) [31] in July and August 2021, respectively, for the indication of mild-to-moderate COVID-19. Provisional approval was granted by the Therapeutic Goods Administration (TGA) of Australia on Dec 2021, for the indication of mild-to-moderate COVID-19 [32].

Herein, we report 28-day results from a non-interventional, retrospective cohort study of regdanvimab for the treatment of patients with mild-to-moderate SARS-CoV-2 infection, including patients considered to be at high risk of severe disease. Using propensity score matching, the primary objective was to compare the real-world proportion of patients treated with regdanvimab versus standard of care who progress to severe/critical COVID-19 or die of SARS-CoV-2 infection.

2. Methods

2.1. Study design and participants

This non-interventional, retrospective cohort study included patients with confirmed mild-to-moderate SARS-CoV-2 infection who were admitted to and received medical treatment at one of three hospitals in the Republic of Korea (Kyungpook National University Chilgok Hospital, Kyungpook National University Hospital or Pusan National University Hospital). The first patient with COVID-19 reported in Korea occurred in January 2020, and the date of the first patient admitted to the hospital among analyzed patients in this study was March 2020. Regdanvimab acquired conditional marketing approval on February 5, 2021 in Korea. From March 3, 2020 to February 4, 2021 before acquiring conditional marketing authorization, only the patients in control group were enrolled in this study. After approval of conditional marketing authorization of regdanvimab in Korea, both control and regdanvimab patients were enrolled in the study and the last patient was enrolled on July 15, 2021. The protocol and all applicable amendments were reviewed and approved by local institutional review boards (IRBs) prior to study initiation. In accordance with Article 16 of the Bioethics and Safety Act of the Republic of Korea, formal informed consent was not required for this retrospective analysis [33]. The medical records of all patients admitted to the study centers were reviewed to determine eligibility for the study. Data were recorded electronically for all eligible patients and anonymized on electronic data capture forms.

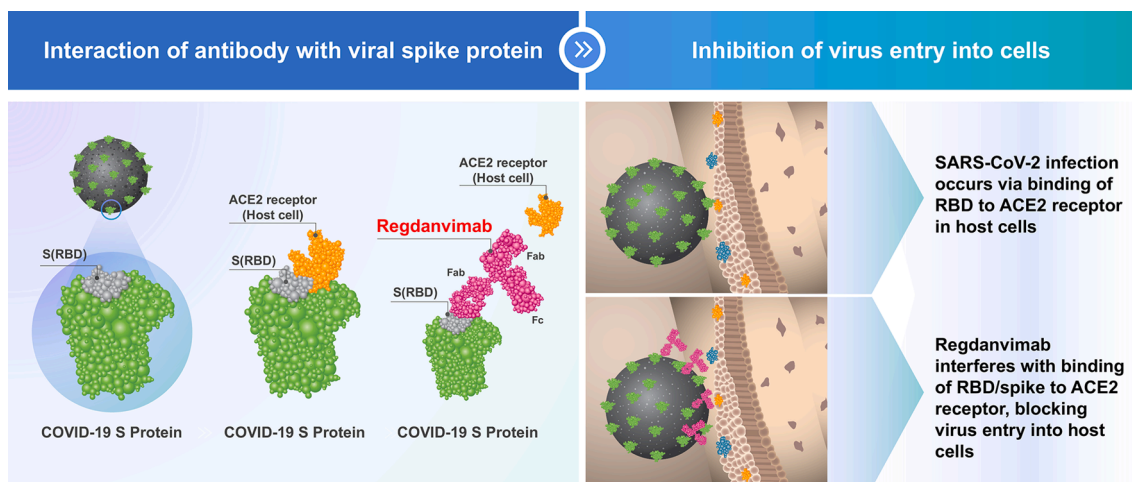**Fig. 1.** Schematic representation of regdanvimab binding to the receptor-binding domain of SARS-CoV-2. Steric hindrance caused by regdanvimab prevents SARS-CoV-2 binding to the angiotensin-converting enzyme 2 receptor on host cells, blocking virus entry. ACE2, angiotensin-converting enzyme 2; Fab: fragment antigen binding; Fc: fragment crystallizable; RBD, receptor-binding domain; S, spike protein.

Eligible participants were adults (aged ≥ 18 years) with mild-to-moderate disease as defined by National Institutes of Health (NIH) guidance [34], who had been diagnosed with SARS-CoV-2 infection at screening by means of reverse transcription–polymerase chain reaction. Individuals were required to have oxygen saturation of > 94% on room air, no need for supplemental oxygen, and onset of symptoms ≤ 7 days before study drug administration or admission for COVID-19 treatment. High-risk patients were included among the study population; in accordance with the Korean prescribing information of regdanvimab at the time of IRB submission, high risk was defined as age ≥ 60 years or having mild disease with underlying medical conditions (≥1 of the following: cardiovascular disease, chronic respiratory disease, diabetes or hypertension) [35].

Patients who had received a COVID-19 vaccine or who had severe or critical illness at screening (per US National Institutes of Health [NIH] classification [34]) were excluded from the study.

Regdanvimab was administered according to the dose and schedule approved by the Korean Ministry of Food and Drug Safety at the time when patients received treatment: 40 mg/kg as an intravenous infusion over 90 min, not later than 7 days after symptom onset [35].

2.2. Study objectives

The primary study objective was to evaluate the clinical efficacy of regdanvimab compared with a propensity score–matched control cohort receiving standard of care in a real-world setting, according to the proportion of patients progressing to severe/critical COVID-19 or death due to SARS-CoV-2 infection. Secondary objectives were to evaluate mortality, oxygen therapy and rescue treatment, and safety endpoints related to regdanvimab. Medical utilization of regdanvimab was evaluated as an exploratory objective.

2.3. Study endpoints

The primary efficacy endpoint was the proportion of patients developing severe or critical disease (based on the NIH severity categories for SARS-CoV-2 infection) [34] or death due to SARS-CoV-2 infection, up to Day 28. The NIH definitions are as follows: severe illness – individuals who have SpO_2 of < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of < 300 mmHg, respiratory frequency > 30 breaths/minute or lung infiltrates > 50%; and critical illness – individuals who have respiratory failure, septic shock and/or multiple organ dysfunction [34].

Secondary efficacy endpoints (analyzed up to Day 28 except where noted) were: proportion of patients developing severe or critical disease or death due to SARS-CoV-2 infection, up to Day 10; proportion of patients requiring mechanical ventilation due to SARS-CoV-2 infection; duration of mechanical ventilation in each patient due to SARS-CoV-2 infection; proportion of patients requiring supplemental oxygen due to SARS-CoV-2 infection; duration of supplemental oxygen therapy in each patient due to SARS-CoV-2 infection; duration of hospitalization in survivors (i.e., patients who survived up to Day 28), including patients transferred to other hospitals; proportion of patients requiring corticosteroid therapy due to SARS-CoV-2 infection; proportion of patients requiring remdesivir due to SARS-CoV-2 infection; duration of fever (defined as body temperature > 38 °C); and proportion of patients with all-cause mortality (at any time throughout the study).

Safety was analyzed according to reported adverse events (AEs), including serious AEs, infusion-related reactions (IRRs) and pregnancy test analyses. AEs were classified using the Common Terminology Criteria for Adverse Events, Version 5.0. Medical utilization and costs were also analyzed as exploratory endpoints. The medical utilization and cost endpoints were length of inpatient stay for each patient and total medical costs for each patient during hospitalization.

2.4. Statistical analysis

The proposed sample size was approximately 450 patients; this was based on the estimated number of patients admitted for COVID-19 at the study centers during the data collection period who would meet enrollment criteria, rather than a formal statistical hypothesis. The intention was for the final ratio of study participants (regdanvimab:no regdanvimab) to be approximately 1:2. Patients in the "no regdanvimab" group (hereafter referred to as the control cohort) were propensity score–matched to the "regdanvimab" cohort, using the following factors: sex, age, body mass index (BMI), Charlson Comorbidity index score and presence of pneumonia upon admission. Patients were also equally matched according to study center.

All statistical analyses were conducted using Statistical Analysis System (SAS) software, Version 9.4 (SAS Institute Inc., Cary, NC). The analysis populations were the Propensity Score–Matched (PSM) Efficacy Set (patients who received a full dose of regdanvimab or who were admitted for the treatment of COVID-19, had at least one post-admission evaluation for efficacy, and met the criteria for propensity score matching), the Safety Set (all patients who received a full or partial dose of regdanvimab or who were admitted for the treatment of COVID-19), and the Medical Utilization Set (all patients in the PSM Efficacy Set for whom information on medical billing was available).

Efficacy endpoints were summarized by cohort (regdanvimab and control groups) using descriptive statistics or frequency tables. For categorical variables, the chi-squared test or Fisher exact test was used. For continuous variables, the Student *t* test was used. A *P* value of < 0.05 was determined to indicate statistical significance. Medical utilization results were summarized by cohort (regdanvimab and control groups) using descriptive statistics or frequency tables.

3. Results

3.1. Patient population and baseline characteristics

A total of 627 patients with a confirmed COVID-19 diagnosis were admitted to one of the three study centers between March 3, 2020, and July 17, 2021 (Fig. 2). After exclusions, 552 patients were eligible for regdanvimab therapy, and of these, 156 received regdanvimab and 396 received other treatments for COVID-19 and were included in the Efficacy and Safety Sets. The PSM Efficacy Set consisted of 274 patients (113 treated with regdanvimab and 161 treated with other COVID-19 medication; Fig. 2). The Medical Utilization Set also comprised 113 patients treated with regdanvimab and 153 treated with other COVID-19 medication(s).

Baseline demographic and disease characteristics are summarized for the PSM Efficacy Set in Table 1 and for the Efficacy and Safety Sets in **Supplementary Table S1**. Although the regdanvimab group tended to be older (median age: 66 vs 61 years), with a higher BMI (mean: 24.0 vs 23.3 kg/m²) and higher prevalence of pneumonia at baseline (37.8% vs 12.6%), due to propensity score matching, the differences between the regdanvimab and control groups were not statistically significant for the efficacy analyses, except for the presence of pneumonia (*P* = 0.0263). Therefore, baseline characteristics in the PSM Efficacy Set were well balanced across the two treatment groups (Table 1); overall, 116 (42.3%) patients were female, the median age was 63.5 years (range: 25–97) and the mean BMI was 24.0 kg/m² (standard deviation: 3.46). Eighty (29.2%) patients had moderate disease and no patients had severe or critical disease.

3.2. Efficacy

All efficacy analyses were conducted using the PSM Efficacy Set unless otherwise specified.
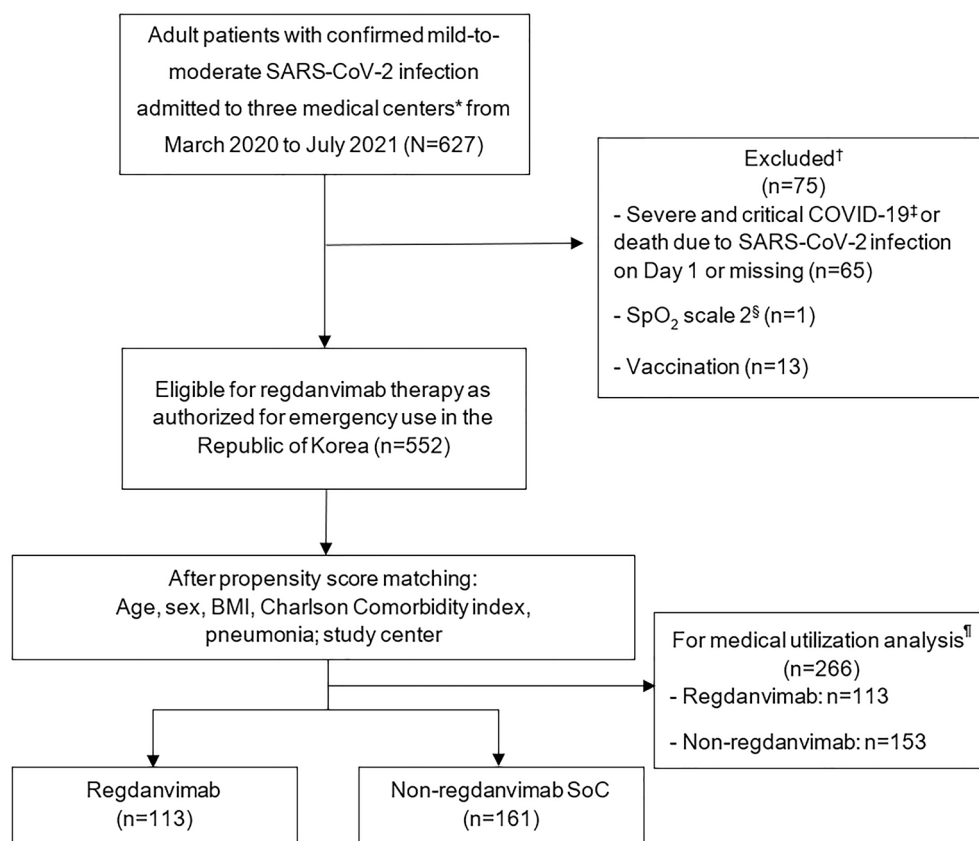
Fig. 2. Patient flow diagram. *The three medical centers were Kyungpook National University Chilgok Hospital, Kyungpook National University Hospital and Pusan National University Hospital. ‡Some patients were excluded based on more than one factor. ‡Severe illness – individuals with oxygen saturation (SpO_2) < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mmHg, respiratory frequency > 30 breaths/minute or lung infiltrates > 50%; and critical illness – individuals with respiratory failure, septic shock and/or multiple organ dysfunction. §SpO_2 is for use in patients with hypercapnic respiratory failure who have clinically recommended oxygen saturation of 88–92%. BMI, body mass index; SoC, standard of care. ¶Patients without medical cost information were excluded from the medical utilization analysis.

3.2.1. Primary endpoints

Table 2 summarizes the incidence of severe/critical COVID-19 (NIH-defined) or death due to SARS-CoV-2 infection, up to Day 28. Compared with controls, patients treated with regdanvimab had a significantly lower risk of severe/critical disease or death (7.1% vs 16.1%, $P = 0.0263$). The incidence of severe/critical COVID-19 (NIH-defined) or death due to SARS-CoV-2 infection, up to Day 28, was also lower for the regdanvimab group versus the control group when analyzed prior to propensity score matching (7.7% vs 12.6%, respectively [$P = 0.1023$]; **Supplementary Table S2**).

3.2.2. Secondary endpoints

Secondary endpoint data were analyzed up to Day 28 (except where noted) and are summarized in Table 3. Up to Day 10, 7 (6.2%) patients in the regdanvimab group experienced severe/critical COVID-19, death due to SARS-CoV-2 infection, or death from any cause, compared with 21 (13.0%) patients in the control group ($P = 0.0654$). No patients in the regdanvimab group required mechanical ventilation, compared with 1 (0.6%) patient in the control group. Supplemental oxygen was required by 8.0% and 18.6% of patients in the regdanvimab and control groups, respectively ($P = 0.0128$). There was a trend toward the duration of supplemental oxygen therapy being longer in the control group, but this did not reach statistical significance. The mean duration of hospitalization was significantly shorter in the regdanvimab group than in the control group (12.4 vs 14.6 days, $P < 0.0001$). Significantly lower percentages of patients in the regdanvimab arm than the control arm required treatment with a corticosteroid or with remdesivir. The mean duration of fever was 2.3 days in the regdanvimab group versus 2.5 days in the control group ($P = 0.5252$). No patients in the regdanvimab group died during the study, compared with 2 (1.2%) patients in the control group.

3.3. Safety

All safety analyses were conducted using the Safety set unless otherwise specified. In the regdanvimab group, 7 (4.5%) patients experienced treatment-emergent AEs (TEAEs). All TEAEs were mild in severity (Grade 1) and patients recovered within 2 days of onset. Two IRRs (Grade 1 hypoxia and Grade 1 hypertension, both possibly treatment related) were observed separately in two patients who had received regdanvimab. No pregnancies were recorded in patients who had received regdanvimab. No new safety events were identified that would have affected the safety profile of regdanvimab.

3.4. Medical utilization

Medical utilization differed significantly between treatment groups (Table 4). Mean total medical costs per patient during hospitalization were 7,449,060.64 Korean Won (₩; 6260.77 US dollars [$]) in patients who had received regdanvimab and ₩9,536,197.84 ($8014.96) in those who had received other therapies for COVID-19 ($P = 0.0032$). The mean duration of hospitalization used for estimating medical utilization comprised the total length of hospitalization for patients (i.e., including patients hospitalized for >28 days); this differed from the estimation of the secondary efficacy endpoint of "duration of hospitalization up to Day 28", which did not count days over Day 28. There was a statistically significant difference between the two groups, with a mean duration of hospitalization per patient of 12.7 days in patients receiving regdanvimab versus 15.4 days in patients receiving other therapies for COVID-19 ($P = 0.0011$).

Table 1
Baseline demographics and disease characteristics (Propensity Score–Matched Efficacy Set).

Characteristic	Regdanvimab (n = 113)	Control (n = 161)	P value[*]
Age, years			
Median (range)	64.0 (26–90)	63.0 (25–97)	0.9221
Female, n (%)	41 (36.3)	75 (46.6)	0.0894
BMI, kg/m^2			
Mean (SD)	24.2 (3.41)	23.9 (3.50)	
<25, n (%)	67 (59.3)	92 (57.1)	0.9873
25–29, n (%)	27 (23.9)	40 (24.8)	
>29, n (%)	9 (8.0)	14 (8.7)	
Missing, n (%)	10 (8.8)	15 (9.3)	
CCI, mean (SD)	2.8 (1.95)	2.7 (1.93)	0.7522
Severity of disease, n (%)			
Asymptomatic or pre-symptomatic	0	10 (6.2)	NA
Mild disease	74 (65.5)	110 (68.3)	
Moderate disease	39 (34.5)	41 (25.5)	
Symptom incidence, n (%)			
Feeling feverish	24 (21.2)	34 (21.1)	NA
Shortness of breath or difficulty breathing	35 (31.0)	49 (30.4)	
Cough	48 (42.5)	59 (36.6)	
Diarrhea	0	2 (1.2)	
Sputum	20 (17.7)	21 (13.0)	
Sore throat	18 (15.9)	30 (18.6)	
Loss of taste of smell	2 (1.8)	3 (1.9)	
Fatigue	0	3 (1.9)	
Myalgia	8 (7.1)	19 (11.8)	
Widespread pain	2 (1.8)	2 (1.2)	
Nausea or vomiting	1 (0.9)	1 (0.6)	
Others	7 (6.2)	21 (13.0)	
Presence of pneumonia, n (%)	39 (34.5)	36 (22.4)	0.0263

BMI, body mass index; CCI, Charlson Comorbidity Index; NA, not available; SD, standard deviation.

[*] P value for covariates after propensity score matching, calculated from Student t test for continuous variables and chi-squared test for categorical variables.

Table 2
Primary efficacy endpoint analysis (Propensity Score–Matched Efficacy Set).

	Regdanvimab (n = 113)	Control (n = 161)	Difference	P-value[*]
Patients with severe/critical disease or death due to SARS-CoV-2 infection up to Day 28, n (%) [95% CI]	8 (7.1) [3.6%,13.4%[†]]	26 (16.1) [11.3%, 22.6%[†]]	−9.1% [−16.7%, −0.6%[‡]]	0.0263

CI, confidence interval.

[*] P values derived from Fisher's exact test.
[†] Wilson (score) 95% CI is presented.
[‡] Farrington and Manning score exact 95% CI for proportion difference is presented.

4. Discussion

4.1. Study overview

This non-interventional, propensity score–matched, retrospective cohort study of Korean patients demonstrates that regdanvimab is effective in the treatment of mild-to-moderate COVID-19. The primary analysis showed that regdanvimab significantly reduced the proportion of patients progressing to severe or critical disease severity or dying of SARS-CoV-2 infection. Regdanvimab was associated with significant reductions in the percentages of patients requiring treatment with

Table 3
Secondary efficacy endpoint data (Propensity Score–Matched Efficacy Set).

Endpoint	Regdanvimab (n = 113)	Control (n = 161)	P value[*]
Patients with severe symptoms or death due to SARS-CoV-2 infection up to Day 10, n (%)	7 (6.2)	21 (13.0)	0.0654
Patients requiring mechanical ventilation up to Day 28, n (%)	0	1 (0.6)	1.0000[†]
Duration of mechanical ventilation, days, mean (SD)	0	22.79 (NC)	NC
Patients requiring supplemental oxygen therapy up to Day 28, n (%)	9 (8.0)	30 (18.6)	0.0128
Duration of supplemental oxygen therapy, days, mean (SD)	4.7 (7.1)	8.6 (6.1)	0.1070
Duration of hospitalization up to Day 28[‡], days, mean (SD)	12.4 (3.7)	14.6 (5.6)	<0.0001
Patients requiring corticosteroid therapy up to Day 28, n (%)	0	20 (12.4)	<0.0001
Patients requiring remdesivir therapy up to Day 28, n (%)	1 (0.9)	23 (14.3)	0.0001
Duration of fever, days, mean (SD)	2.3 (1.1)	2.5 (1.7)	0.5252
Patients dying of any cause, n (%)	0	2 (1.2)	0.5136[†]

NC, not calculated; SD, standard deviation.

[*] P-value is derived from Student t-test for continuous variables and chi-squared test for categorical variables.
[†] P-value derived from Fisher's exact test, since chi-squared test may not be valid due to 50% of the cells having expected counts<5.
[‡] Two patients in the control group who died were not included for the purpose of this endpoint (regdanvimab = 113; control = 153). Duration of hospitalization for patients hospitalized over Day 28 was calculated as being hospitalized for 28 days. Patients transferred to other hospitals were included in this analysis, with duration calculated as the duration of admission at the study site.

Table 4
Medical utilization data, by treatment group (Medical Utilization Set[**]).

Endpoint	Regdanvimab (n = 113)	Control (n = 153)	P value
Mean duration of hospitalization,[*] days	12.67	15.42	0.0011
Mean total cost of medical bills per patient during hospitalization, ₩	7,449,060.64	9,536,197.84	0.0032

₩, Korean Won.
[*] The mean duration of hospitalization used for estimating medical utilization comprised the total length of hospitalization for patients (i.e., including those hospitalized for>28 days); this differed from the estimation of the secondary efficacy endpoint "duration of hospitalization up to Day 28", which did not count days over Day 28. Two patients who died during the study were not included in the calculation of duration of hospitalization.
[**] Patients with no information on medical billing in the PSM Efficacy Set were excluded from the Medical Utilization Set.

supplemental oxygen, corticosteroids or remdesivir. In addition, a modest but statistically significant reduction in the duration of hospitalization was observed with regdanvimab, with no notable safety issues.

A crucial attribute of any COVID-19 treatment is preventing disease deterioration and death in patients with moderate disease. Increased disease severity is associated with worsened outcomes and increased healthcare and economic burden. In one study of hospitalized patients with COVID-19, the mortality rate among those who required mechanical ventilation was 88.1%, compared with 11.7% in individuals not requiring ventilation [36]. A second study, also conducted in hospitalized patients with COVID-19, showed marked increases in in-hospital mortality, length of hospital stay and hospital charges in patients who required admission to the intensive care unit (ICU) or invasive

mechanical ventilation (IMV) [37].

Identifying patterns in the course of COVID-19 disease deterioration may highlight optimal timepoints for interventions to prevent deterioration, and a Chinese observational study of patients hospitalized for moderate COVID-19 has provided important information in this regard. Among patients who deteriorated to severe or critical status, the median time to deterioration was 11 days from symptom onset; exacerbation to a critical condition occurred after a median of 3 days in a severe condition [38]. Initiating treatment early in the disease course before patients experience disease deterioration would therefore appear to be advantageous, and this is supported by the efficacy observed across both arms of our study, in which patients were required to have symptom onset within 7 days of study drug administration.

Numerous therapeutic candidates for COVID-19 have been evaluated in clinical trials and several are under evaluation for EU marketing authorization as treatments for COVID-19, including anakinra, baricitinib, and tocilizumab. However, the only drug that has so far been approved in the US and European Union (EU) for the treatment of COVID-19, besides monoclonal antibody (mAb) treatment, is remdesivir [39,40]. Clinical studies evaluating the efficacy of remdesivir have not consistently demonstrated a statistically significant difference in comparison with control in terms of mean time to clinical improvement and mortality [41,42]. The large, international, Solidarity study, conducted by the WHO, found in-hospital mortality rates with remdesivir and control to be comparable, and that remdesivir treatment did not reduce initiation of ventilation or the duration of hospitalization, as compared with control [43]. As a result, the WHO has recommended against the use of remdesivir for treatment of COVID-19, citing insufficient supporting evidence [44]. More recently, in December 2021, nirmatrelvir with ritonavir and molnupiravir, become the first oral antiviral treatments for SARS-CoV-2 to be issued emergency use authorizations by the US FDA [45]. However, some caution is still needed with these agents as they may not be suitable for all patients. Hepatotoxicity has been observed with ritonavir [46] and metabolism of the co-administered agent nirmatrelvir is highly dependent on CYP3A enzymes. The nirmatrelvir with ritonavir combination is therefore contraindicated with certain medications that are dependent on hepatic clearance [46]. Molnupiravir may affect bone and cartilage growth in adolescents and cause fetal harm in pregnant women [47].

Unlike these antiviral drugs, the safety of antibody drugs have been well demonstrated in both clinical studies and accumulating real world data. Several antibody treatments including casirivimab/imdevimab and sotrovimab have received EU Marketing Authorizations based on evidence of efficacy in preventing progression, reducing mortality or accelerating recovery from COVID-19 [48,49]. Additionally, data on the therapeutic effectiveness and safety of antibody drugs has been accumulated through real world data, including studies of bamlanivimab and casirivimab/imdevimab [50–55], and this has influenced key regulatory decisions in this setting. With these strengths, mAb prescription remains feasible in patients with limited capacity for oral drugs.

4.2. Evaluation of medical utilization

A medical utilization framework developed in the US suggests that treatments that reduce mortality in hospitalized patients with COVID-19 are likely to be cost-effective [59]. In this study, the incidence of mortality was too low to come to a definitive conclusion (n = 2, both in the control group) regarding whether regdanvimab reduced mortality. [60] COVID-19 has greatly increased the medical cost burden, especially when ICU admission and IMV have been required. In 2020, median hospital charges in the US (from a US COVID-19 database comprising records for almost 174,000 patients), per hospitalized patient, were $34,634 for patients without ICU admission and IMV, and $198,394 for those admitted to the ICU and who had received IMV. Likewise, median hospital costs (i.e., costs incurred by hospitals) were six-fold higher for patients with ICU admission and IMV usage ($9,504 vs $54,402,

respectively) [37]. In addition, the disability caused by the duration and severity of COVID-19 may incur further social and economic burdens and may represent up to 30% of the total health burden [61]. According to the South Korean National Health Insurance Service, the average cost of treating patients with mild COVID-19 disease in hospital was ₩4.78 million ($4,176), whereas the cost was ₩70 million ($62,197) for treating patients with severe disease [62,63]. At the time of our study, treatment guidelines in the Republic of Korea recommended the hospitalization of patients with non-severe COVID-19 (Patients with COVID-19 infection are hospitalized regardless of their severity). Evidence continues to accumulate demonstrating regdanvimab's effect in decreasing the risk of progression to severe disease [60]; however, this is the first study which has also analyzed medical utilization cost in propensity score matched cohorts. Regdanvimab proved to be cost-effective over control by reducing the duration of hospitalization, as well as the proportion of patients progressing to severe/critical disease or death. In this study, mean total medical costs per patient during hospitalization were ₩7,449,060.64 ($6,260.77) in patients who had received regdanvimab compared with ₩9,536,197.84 ($8,014.96) in the control group. With regards to other COVID-19 therapies, the Institute for Clinical and Economic Review (ICER) in the US has commented that remdesivir is cost-effective at a benchmark price of $4580 to $5080, but there have been conflicting results regarding the cost-effectiveness of remdesivir in practice [64–66]. As more COVID-19 treatment options become available, ICER is planning to assess the health and economic outcomes of several available therapies and therapies under development for treatment of mild-to-moderate COVID-19 (casirivimab/imdevimab, sotrovimab, molnupiravir, PF-07321332/ritonavir, fluvoxamine) [65,67].

4.3. Strengths and limitations

Limitations of this study include the non-interventional, retrospective study design; the specific nature of the patient population (Korean patients admitted to one of three hospitals for treatment of mild-to-moderate SARS-CoV-2 infection; although the research institutes are representative hospitals in each region, patients were only recruited from two hospitals, not from multiple institutions) and the relatively short follow-up of 28 days. In addition, no information on SARS-CoV-2 variants was collected during the study.

The key strengths of our study are the large number of patients analyzed and the real-world setting. Propensity score matching adjusted for differences between the two treatment groups and ensured that the study groups were well balanced, thus reducing the risk of confounding factors. Therefore, we consider our results to be highly applicable to real-world clinical practice in Korea. The inclusion of cost and medical utilization data is another strength, enabling the financial implications of using regdanvimab to be evaluated.

4.4. Conclusions

In conclusion, this retrospective analysis demonstrates that regdanvimab reduces the risk of severe/critical disease or death due to SARS-CoV-2 infection among patients with high risk mild-or-moderate COVID-19. Propensity score matching ensured that the study groups were well balanced and therefore that the outcomes were robust. The study results are consistent with those of a randomized Phase 2/3 outpatient study in showing the potential benefits of regdanvimab in the treatment of COVID-19. Additionally, we demonstrated that medical utilization costs were significantly lower in patients who received regdanvimab than in patients who did not receive regdanvimab. Regdanvimab may help to ease the considerable burden of SARS-CoV-2 on healthcare systems.

Data sharing

All data are available upon request. Please contact the corresponding author Ki Tae Kwon for enquiries.

Ethics approval

The Daegu Joint IRB (DGIRB 2021–07-002) and Pusan NU IRB (2109–012-107) reviewed and approved the study protocol.

Declaration of interest

SWL, SOL and JEL have been an investigator for clinical trials sponsored by Daewoong Pharmaceutical Co., Ltd., Pfizer, Chong Kun Dang Pharmaceutical and Shin Poong Pharmaceutical Co., Ltd., outside the scope of the submitted work.

K-HK has been an investigator for clinical trials sponsored by SD Biosensor, Inc., Abbott and Kogene Biotech Co., Ltd, outside the scope of the submitted work.

SHL has been an investigator for clinical trials sponsored by GlaxoSmithKline plc., Gilead Sciences, and Merck Sharp & Dohme Corp., outside the scope of the submitted work.

SYH and KTK have been investigators for clinical trials sponsored by Pfizer, Chong Kun Dang Pharmaceutical, SK Bioscience Co., Ltd. and Celltrion, Inc., outside the scope of the submitted work.

SW-K, YJK and SHB have been investigators for clinical trials sponsored by Dong Wha Pharmaceutical Co., Ltd., Daewoong Pharmaceutical Co., Ltd., ImmunMed, Inc., Green Cross Corporation, Shin Poong Pharmaceutical Co., Ltd. and Gilead Sciences, outside the scope of the submitted work.

H-HC has been an investigators for clinical trials sponsored by Green Cross Corporation, Celltrion, Inc., Shin Poong Parmaceutical Co., Ltd., and Gilead Sciences, outside the scope of the submitted work and also reports consulting fees from Green Cross Corporation.

A-SK declares no conflict of interest.

Funding

Authors Contribution

SOL, SWL and KTK contributed to the hypothesis, data gathering, and revising of the final manuscript before submission. Especially, KTK contributed to correspondence. All the authors reviewed and confirmed the manuscript before submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2022.108570.

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