CADTH COVID-19 PANDEMIC

COVID-19 CADTH Health Technology Review

Casirivimab-Imdevimab: Evidence Review and Appraisal

This report is current as of February 23, 2021.

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

This report reviews the current scientific evidence on the potential benefits and harms of casirivimab-imdevimab.

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Key Messages

Casirivimab (REGN10933) and imdevimab (REGN10987) are 2 virus-neutralizing monoclonal antibodies that are used against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The combination product is also known as REGN-COV2, and more recently as REGEN-COV.

Casirivimab-imdevimab (CAS-IMD) is not approved for use in any country. However, the US Food and Drug Administration (FDA) granted an emergency use authorization (EUA) for patients with mild or moderate COVID-19 on November 21, 2020.

The literature search identified 1 randomized controlled trial (RCT) that met the inclusion criteria. As the trial is ongoing, the publication of this phase I to phase III RCT is based on an interim analysis of 275 patients enrolled during phase I and phase II. In this multi-centre, randomized, double-blind, placebo-controlled trial, patients were randomly assigned in a 1:1:1 ratio to CAS-IMD 2.4 g (low-dose group), CAS-IMD 8.0 g (high-dose group), or placebo. Equal doses of CAS and IMD were administered as a single IV infusion over 1 hour.

The trial population comprised ambulatory adult patients with confirmed SARS-CoV-2 infection. There was an equal proportion of men and women; the majority were White and the median age was approximately 44 years.

Two end points were reported in the publication: the time-weighted average change in viral load from day 1 (baseline) to day 7 and the proportion of patients with at least 1 Covid-19–related medically attended visit through day 29. Medically attended visits included telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalization. Safety outcomes were also reported.

Although patients treated with CAS-IMD had greater reductions in viral load and fewer medically attended visits compared with patients in the placebo group, there was no formal hypothesis testing performed and these were very early data. Therefore, further evidence is needed to confirm treatment efficacy. Very few adverse events and serious adverse events were reported. The trial data are limited in that the results are based on an interim analysis with several methodological issues. Therefore, the results of the interim analysis may or may not be reflective of the results of the final analysis.

The US FDA issued an EUA for CAD-IMD based on a larger set of unpublished data on 799 patients from the same ongoing trial reviewed in this report. The US FDA Fact Sheet included results that indicated that CAD-IMD may be beneficial in preventing medical visits due to COVID-19. The US authorized dose for adults and children is 1.2 g of CAS and 1.2 g of IMD (total of 2.4 g, which is identical to the low-dose treatment regimen in the publication).

In summary, there is limited trial evidence to date regarding the efficacy and safety of CAS-IMD. As such, additional RCTs are required to determine the potential place of CAS-IMD in the treatment of COVID-19.

Introduction

REGN-COV2 is a combination of 2 virus-neutralizing monoclonal antibodies: casirivimab (REGN10933) and imdevimab (REGN10987). They target the receptor-binding domain of the spike protein on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, thereby blocking the virus' attachment and entry into human cells.[1,2] REGN-COV2 is administered as a single IV infusion with a 1:1 concentration of each antibody.[1] REGN-COV2's proprietary name was changed to REGEN-COV in the US in February 2021.[3]

On November 21, 2020, REGEN-COV was granted an emergency use authorization (EUA) by the US Food and Drug Administration (FDA). The European Medicines Agency (EMA) issued an Advice on February 26, 2021.

In the US, REGEN-COV is indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 and/or hospitalization. It is *not* authorized for use in patients "who are hospitalized due to COVID-19, who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity."[3] Each REGEN-COV dose pack contains vials of casirivimab (CAS) and imdevimab (IMD), which must be administered as a single IV infusion over 1 hour. The US authorized dose for adults and children is 1.2 g of CAS and 1.2 g of IMD.[3] The regulatory status in various jurisdictions is shown in Table 1.

This report reviews the current scientific evidence on the potential benefits and harms of CAS-IMD.

Table 1: Regulatory Status

Regulatory body	Jurisdiction	Status	Indication
Health Canada	Canada	Under review (February 24, 2021)	NA
FDA[4]	US	EUA (November 21, 2020)	For the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 and/or hospitalization
European Medicines Agency[5,6]	European Union	Rolling review (started February 1, 2021) EMA Advice issued (February 26, 2021)	For the treatment of confirmed COVID-19 in patients aged 12 years and older who do not require supplemental oxygen for COVID-19 and are at high risk of progressing to severe COVID-19
AIFA[7]	Italy	EUA (February 5, 2021)	Patients with mild-to-moderate disease who are at risk of their condition worsening
SUKL[8]	Czech Republic	Under review by the Minister of Health	NA

AIFA = Agenzia Italiana del Farmaco; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; NA = not applicable; SUKL = State Institute for Drug Control.

Clinical Evidence

Literature Search Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[9]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was REGN-Cov2, or at least 1 of CAS or IMD mentioned. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was limited by a publication date of January 1, 2019 or later, and English or French language. Conference abstracts were excluded from the search results.

The initial search was completed on January 18, 2021. Regular alerts updated the database literature searches and clinical trial registries search until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[10] and CADTH COVID-19 Grey Literature Resources (https://covid.cadth.ca/literature-searching-tools/), which includes the websites of regulatory agencies, HTA agencies, drug and device regulatory approvals, advisories and warnings, and databases. Google was used to search for additional internet-based materials. Preprints (preliminary reports that are not peer reviewed) were also searched. The grey literature search was updated before the completion of the report.

Selection Criteria

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. Studies of interest were selected for review according to the criteria outlined in Table 2.

Non-randomized studies, single-arm trials, case series, case reports, conference reports, editorials, letters to the editor, and press releases were excluded from the evidence review.

Table 2: Selection Criteria

Criteria	Description
Population	Patients with SARS-CoV2 infection or uninfected people who are at high risk of exposure to a COVID-19 patient
Intervention	Casirivimab (REGN10933) and imdevimab (REGN10987) administered together as a single dose
Comparators	• Placebo • Standard of care • Other pharmacotherapies
Outcomes	• Efficacy • Safety
Study design	Randomized controlled trials published in full (excluding preprints)

Literature Search Results

The literature search identified 1 randomized controlled trial (RCT) that met the inclusion criteria.[11] As the trial is ongoing, the publication of this phase I to phase III RCT is based on an interim analysis of 275 patients enrolled during phase I to phase II. Of note, the US FDA had access to a larger set of unpublished data for this same RCT (799 patients) that was used to support their EUA.[3]

Other ongoing trials of CAD-IMD are presented in CADTH Emerging Health Technology for COVID-19: Virus-Neutralizing Monoclonal Antibodies Against SARS-CoV-2 (p. 23–25).[12]

Study Characteristics

The characteristics of the study of interest to this report are summarized in Table 3.

Table 3: Characteristics of the Included RCT and Its Interim Analysis

Characteristic	Weinreich et al.[11]
Designs and populations	
NCT Number	04425629
Status	Recruiting
Estimated study completion date	August 28, 2021 (according to NCT record)
Funding	Regeneron Pharmaceuticals, and the Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services
Study design (interim analysis)	Phase I to II, MC, DB, PC
Study design (final analysis)	Phase I to III, MC, DB, PC
Locations (interim analysis)	US (number of centres NR)
Locations (final analysis)	US and Romania (97 centres)
Randomized, N (interim analysis)	275
Randomized, N (final analysis)	NA
Inclusion criteria	• 18 years and older • Non-hospitalized • Confirmed SARS-CoV-2 infection: positive results no more than 72 hours before randomization • Symptomatic (all phases): symptoms consistent with COVID-19 with onset ≤ 7 days before randomization • Asymptomatic (phase II only): no symptoms of COVID-19 < 2 months prior to randomization, no positive SARS-CoV-2 test results from a sample collected > 7 days prior to randomization, and no known contact with an individual with COVID-19 or positive SARS-CoV-2 test result > 14 days prior to randomization • Oxygen saturation ≥ 93% on room air
Exclusion criteria	• Admitted to a hospital prior to randomization, or is hospitalized at randomization, due to COVID-19 • Participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIG ≤ 3 months or < 5 half-lives of the investigational product (whichever is longer) prior to screening • Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or Covid-19 Emergency Use Authorization approved treatments • Known allergy or hypersensitivity to components of study drug • Discharged, or is planned to be discharged, to a quarantine centre • Pregnant or breastfeeding women • Continued sexual activity in women of childbearing potential, or sexually active men who are unwilling to practice highly effective contraception

Characteristic	Weinreich et al.[11]
Drugs	
Interventions	REGN-COV2 2.4 g IV in 250 mL of normal saline solution infused over 1 hour OR REGN-COV2 8.0 g IV in 250 mL of normal saline solution infused over 1 hour Each antibody of REGN-COV2, casirivimab and imdevimab, are given in equal doses in the cocktail
Comparator	Normal saline infused over 1 hour
Duration	
Phase	
Treatment duration	One dose
Follow-up	29 days
Outcomes	
Primary end point	To be determined
Secondary end points (interim analysis)	Clinical: • percentage of patients with at least one COVID-19–related medically attended visit[a] through day 29 Laboratory: • time-weighted average change in the viral load from baseline (day 1) through day 7 Safety
Notes	
Publications	Weinreich et al.[11]

EAU = Emergency Use Authorization; FDA = Food and Drug Administration; IVIG = intravenous immunoglobulin; mAbs = monoclonal antibodies; NA = not applicable; NCT = National Clinical Trial; NR = not reported.

[a] Includes telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalization.

Study Design Characteristics

Weinreich et al.

Weinreich et al. described an on-going, phase I to phase III, multi-centre, randomized, double-blind, placebo-controlled trial.[11] The current publication includes an interim analysis (data cut-off, September 4, 2020) of the first 275 patients enrolled in the phase I and phase II portions of the trial (72 patients in phase I and 203 patients in phase II). Phase I and phase II of the trial were identical, although phase I included additional pharmacokinetic analyses. The population of patients in the current publication was pooled from both phases.

Patients were randomly assigned in a 1:1:1 ratio to CAS-IMD 2.4 g (low-dose group), CAS-IMD 8.0 g (high-dose group), or placebo. Equal doses of CAS and IMD were administered as a single IV infusion over 1 hour. Non-hospitalized adult patients with a confirmed SARS-CoV-2 infection, a positive test result within 72 hours before randomization, and symptom onset within 7 days before randomization were included in the trial. Patients were required to maintain an oxygen saturation of 93% or greater on room air. Patients were excluded if they had been admitted to a hospital before randomization, or were hospitalized at randomization, due to COVID-19. They were also excluded if they had participated, were currently participating, or were planning to participate in a clinical research study of other COVID-19 treatments.

All patients were tested for SARS-CoV-2 antibodies (IgA anti-S1 domain of spike protein, IgG anti-S1 domain of spike protein, and IgG anti-nucleocapsid protein). Patients underwent randomization irrespective of their baseline antibody status. Patients who tested negative for all 3 antibodies were evaluated first in the efficacy analysis. Patients who tested positive to any of the antibodies were considered serum antibody–positive. Those who were not tested or for whom the results were borderline were characterized as unknown serum antibody status.

The end points for the interim analysis were the time-weighted average change in viral load from baseline (day 1) to day 7 and the proportion of patients with at least 1 Covid-19–related medically attended visit through day 29 (including telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalization). A subgroup analysis based on the baseline serum antibody status (i.e., negative, positive, unknown) was reported for these end points. Safety outcomes were also reported.[11]

The details of the inclusion and exclusion criteria are provided in Table 3. Details of the statistical analysis are provided in Appendix 1.

Evidence Results

Patient Disposition

Weinreich et al.

The patient disposition for the study by Weinreich et al. is shown in Appendix 2. Of 306 patients who were screened for eligibility, 275 patients underwent randomization, with 92 patients assigned to low-dose CAD-IMD, 90 patients assigned to high-dose CAD-IMD, and 93 patients assigned to placebo. Of these, 80 patients, 84 patients, and 88 patients in the low-dose CAD-IMD, high-dose CAD-IMD, and placebo groups, respectively, completed the trial by the data cut-off date.[11]

Baseline Characteristics

Weinreich et al.

The patient baseline demographic and clinical characteristics are presented in Appendix 3. The median age was 43.0 (interquartile range [IQR], 33.5 to 51.0) years, 44.0 (IQR, 36.0 to 53.0) years, and 45.0 (IQR, 34.0 to 54.0) years for the low-dose CAD-IMD, high-dose CAD-IMD, and placebo groups, respectively. More than 80% of the population was White, 49% were male, and 42% were obese (body mass index of greater than 30). The median time from symptom onset to randomization was approximately 3 days.[11]

Efficacy

Weinreich et al.

The efficacy outcome results for Weinreich et al. are reported in Table 4.[11]

- Time-weighted average change in viral load from day 1 to day 7
  - From the modified full analysis set, the least squares mean differences from placebo were −0.25 $\log_{10}$ copies/mL (95% confidence interval [CI], −0.60 to 0.10) and −0.56 $\log_{10}$ copies/mL (95% CI, −0.91 to −0.21) in the low-dose CAS-IMD and high-dose CAS-IMD groups, respectively.
  - In patients who were antibody-negative, the least squares mean differences from placebo were −0.52 $\log_{10}$ copies/mL (95% CI, −1.04 to 0.00) and −0.60 $\log_{10}$ copies/mL (95% CI, −1.12 to −0.08) in the low-dose CAS-IMD and high-dose CAS-IMD groups, respectively.
  - In patients who were antibody-positive, the least squares mean differences from placebo were 0.00 $\log_{10}$ copies/mL (95% CI, −0.48 to 0.49) and −0.39 $\log_{10}$ copies/mL (95% CI, −0.89 to 0.11) in the low-dose CAS-IMD and high-dose CAS-IMD groups, respectively.
  - In patients with an unknown antibody status, the least squares mean differences from placebo were 0.54 $\log_{10}$ copies/mL (95% CI, −1.20 to 2.28) and −0.49 $\log_{10}$ copies/mL (95% CI, −2.27 to 1.30) in the low-dose CAS-IMD and high-dose CAS-IMD groups, respectively.
- COVID-19–related, medically attended visit within 29 days
  - From the full analysis set, a total of 3 patients in each treated group (3% in the low-dose CAS-IMD group and 3% in the high-dose CAS-IMD group) and 6 patients (6%) in the placebo group had a medically attended visit. The absolute difference compared with placebo was −3% (95% CI, −18% to 11%) for either group.
  - In patients who were antibody-negative, 5% of patients in the low-dose CAS-IMD group, 8% in the high-dose CAS-IMD group, and 15% in the placebo group had a medically attended visit. The absolute difference compared with placebo was 10% (95% CI, −32% to 13%) and 8% (95% CI, −30% to 16%) for the CAS-IMD low-dose and high-dose groups, respectively.
  - In patients who were antibody-positive, 3% of patients in the low-dose CAS-IMD group, zero in the high-dose CAS-IMD group, and 2% in the placebo group had a medically attended visit.
  - None of the patients with an unknown antibody status had a medical visit within 29 days.

Table 4: Efficacy Outcomes for Weinreich et al.

Efficacy outcome	CAS-IMD (low dose) n = 92	CAS-IMD (high dose) n = 90	Placebo n = 93
Time-weighted average change in viral load from day 1 to day 7[a]			
Modified full analysis set,[b] N	70	73	78
Least squares mean change, log_{10} copies/mL (SE)	–1.60 (0.14)	–1.90 (0.14)	–1.34 (0.13)
95% CI	–1.87 to –1.32	–2.18 to –1.62	–1.60 to –1.08
Difference vs. placebo at day 7			
Least squares mean change, log_{10} copies/mL (SE)	–0.25 (0.18)	–0.56 (0.18)	NA
95% CI	–0.60 to 0.10	–0.91 to –0.21	NA
Baseline serum antibody status: negative, n	34	35	28
Least squares mean change, log_{10} copies/mL (SE)	–1.89 (0.18)	–1.96 (0.18)	–1.37 (0.20)
95% CI	–2.24 to –1.53	–2.33 to –1.60	–1.76 to –0.98
Difference vs. placebo at day 7			
Least squares mean change, log_{10} copies/mL (SE)	–0.52 (0.26)	–0.60 (0.26)	NA
95% CI	–1.04 to 0.00	–1.12 to –0.08	NA
Baseline serum antibody status: positive, n	27	29	37
Least squares mean change, log_{10} copies/mL (SE)	–1.24 (0.19)	–1.63 (0.20)	–1.24 (0.16)
95% CI	–1.61 to –0.86	–2.03 to –1.24	–1.55 to –0.93
Difference vs. placebo at day 7			
Least squares mean change, log_{10} copies/mL (SE)	0.00 (0.24)	–0.39 (0.25)	NA
95% CI	–0.48 to 0.49	–0.89 to 0.11	NA
Baseline serum antibody status: unknown,[c] n	9	9	13
Least squares mean change, log_{10} copies/mL (SE)	–0.95 (0.56)	–1.98 (0.60)	–1.49 (0.63)
95% CI	–2.12 to 0.22	–3.22 to –0.73	–2.79 to –0.19
Difference vs. PB at day 7			
Least squares mean change, log_{10} copies/mL (SE)	0.54 (0.84)	–0.49 (0.86)	NA
95% CI	–1.20 to 2.28	–2.27 to 1.30	NA
At least 1 COVID-19–related, medically attended visit within 29 days[d]			
Full analysis set, N	92	90	93
Patients with ≥ 1 visit within 29 days, n (%)	3 (3)	3 (3)	6 (6)
Absolute difference vs. placebo, % (95% CI)	–3 (–18 to 11)	–3 (–18 to 11)	NA
Baseline serum antibody status: negative, n	41	39	33
Patients with ≥ 1 visit within 29 days, n (%)	2 (5)	3 (8)	5 (15)
Absolute difference vs. placebo, % (95% CI)	–10 (–32 to 13)	–8 (–30 to 16)	NA
Baseline serum antibody status: positive, n	37	39	47
Patients with ≥ 1 visit within 29 days, n (%)	1 (3)	0	1 (2)
Absolute difference vs. placebo, % (95% CI)	1 (–21 to 22)	–2 (–23 to 19)	NA

Efficacy outcome	CAS-IMD (low dose) n = 92	CAS-IMD (high dose) n = 90	Placebo n = 93
Baseline serum antibody status: unknown,[c] n	14	12	13
Patients with ≥ 1 visit within 29 days, n (%)	0	0	0

CAS-IMD = casirivimab-imdevimab; CI = confidence interval; NA = not applicable; SE = standard error; vs. versus.

[a] The time-weighted average change in viral load was based on an analysis-of-covariance model with treatment group, risk factor, and baseline serum antibody status as fixed effects and baseline viral load and treatment group–by–baseline viral load as covariates. Confidence intervals were not adjusted for multiplicity.

[b] The modified full analysis set excluded patients who tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by qualitative reverse-transcriptase polymerase chain reaction at baseline.

[c] An unknown serum antibody status indicates that the status could not be evaluated or that the results were borderline.

[d] Confidence intervals for the difference (CAS-IMD minus placebo) were based on the exact method and were not adjusted for multiplicity.

Harms

Weinreich et al.

The percentage of patients who experienced adverse events, serious adverse events, and adverse events leading to drug discontinuation are detailed in Table 5. Detailed harms are reported in Appendix 4.

Two patients (2.3%) in the low-dose CAS-IMD group experienced a serious adverse event of nausea or vomiting and 2 patients (2.2%) in the placebo group experienced a serious adverse event of hypertension or hypoxia. Patients in the high-dose CAS-IMD group experienced an adverse event of abdominal pain, pruritus, urticaria, chills, or flushing. There were no withdrawals from the trial due to an adverse event.[11]

Table 5: Summary of Harms (Safety Population)

Summary of harms	Weinreich et al.[11]		
	CAS-IMD (low dose) n = 88	CAS-IMD (high dose) n = 88	Placebo n = 93
Adverse events, n (%)	0	5 (5.7)	5 (5.4)
Serious adverse event, n (%)	2 (2.3)	0	2 (2.2)
Adverse events leading to drug discontinuation, n (%)	0	0	0

CAS-IMD = casirivimab-imdevimab.

Critical Appraisal

Weinreich et al.

Internal Validity

The RCT by Weinreich et al. is ongoing, manufacturer-sponsored, multi-centre, double-blind, placebo-controlled, and includes multiple clinical phases.[11] This report reviewed the interim results for the phase I and phase II portions of the trial, which included a sample size of 275 patients.

The baseline patient characteristics appeared to be balanced across treatment arms. The statistical plan stipulated that randomization was stratified by the presence or absence of COVID-19 symptoms (i.e., symptomatic versus asymptomatic), country, and risk factors for hospitalization due to COVID-19 (i.e., no risk factors for hospitalization due to COVID-19 or 1 or more risk factor for hospitalization due to COVID-19), such as age older than 50 years, obesity, cardiovascular disease, or chronic disease of the lung, kidney, or liver. However, the study sites to date have only included US sites and the details of the risk factors for hospitalization were not provided in the baseline characteristics (other than obesity).

The analyses based on baseline anti-SARS-CoV-2 antibodies status were pre-specified, but status was not stratified at randomization. Hence, it is unclear if randomization was maintained for the subgroups, which affects the interpretation of the results.

The use of concomitant medication, although collected, was not reported. Thus, it is unclear what background care was received in addition to CAS-IMD and if it was balanced between treatment groups.

The results presented in the publication were preliminary, based on an interim analysis. The investigators performing the interim analysis were distinct from the ongoing study team. No formal hypothesis testing was done. Hence, the results of the interim analysis should not be used to draw any statistical inference.

The protocol was amended on 5 different occasions before the interim analysis, with changes to the inclusion and exclusion criteria (for example, excluding patients with 1 or more symptoms of fever, cough, or shortness of breath) and study outcomes. On January 7, 2021 (after the interim analysis data cut-off), the protocol was amended to include children.

External Validity

The trial was conducted in multiple centres in the US. The included participants were adults, not hospitalized, with a confirmed SARS-CoV-2 infection. The trial population comprised an equal proportion of men and women; the majority were White and the median age was approximately 44 years. The results of the trial are generalizable to this population.

Although 2 doses of CAS-IMD were evaluated in this trial, the US FDA EUA is for the lower dose of 2.4 g (1.2 g for each active ingredient).

Discussion

Summary of Available Evidence

One trial with interim results was identified through the literature search and is the focus of this review. Weinreich et al. reported the findings of a combined phase I and phase II, manufacturer-sponsored, multi-centre, double-blind, placebo-controlled RCT.[11] The trial compared 2 different doses of CAD-IMD against placebo. The trial population comprised ambulatory adult patients with confirmed SARS-CoV-2 infection. There was an equal proportion of men and women; the majority were White and the median age was approximately 44 years.

Two end points were reported in the publication, the time-weighted average change in viral load from baseline (day 1) to day 7 and the proportion of patients with at least 1 Covid-19–related medically attended visit through day 29. Medically attended visits included telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalization.

Other ongoing trials of CAD-IMD are presented in the CADTH Emerging Health Technology for COVID-19: Virus-Neutralizing Monoclonal Antibodies Against SARS-CoV-2 (p. 23–25).[12]

Interpretation of Results

Efficacy

In Weinreich et al., interim results showed that patients treated with CAS-IMD had greater reductions in viral load and fewer medically attended visits compared with patients in the placebo group. No formal hypothesis testing was performed, and these were very early data. Therefore, further evidence is needed to confirm treatment efficacy.[11]

Harms

Weinreich et al. reported that 2% of patients in the low-dose CAS-IMD group and 2% in the placebo group experienced a serious adverse event. There were no serious adverse events reported with the high-dose CAS-IMD group. There were no withdrawals from the trial due to an adverse event.[11]

Other Evidence

The US FDA Fact Sheet included evidence for this same RCT as reported in Weinreich et al. but from a larger set of unpublished data (799 patients).[3] It showed that the time-weighted average change in viral load at day 7 for the treatment groups combined was significantly lower than with placebo (–0.36 $\log_{10}$ copies/mL; $P < 0.0001$). The proportion of patients with at least 1 COVID-19–related medically attended visit through day 29 was lower with CAS-IMD (2.8% for the combined low-dose and high-dose groups) compared with placebo (6.5%).[3]

The US FDA Fact Sheet reported safety information based on the same RCT as reported in Weinreich et al., also from a larger set of unpublished data on 799 patients.[3] Serious adverse events were reported in 1.6% of patients in the CAS-IMD low-dose group, 0.8% in the CAS-IMD high-dose groups, and 2.3% in the placebo group. Serious adverse events that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea, and vomiting in the low-dose group; intestinal obstruction and dyspnea in the high-dose group; and COVID-19 pneumonia and hypoxia with placebo. Two patients in the high-dose group had to discontinue the infusion due to an infusion-related reaction.[3]

Conclusions

One RCT provided interim results on 275 patients regarding the efficacy and safety of CAS-IMD. The trial was conducted in non-hospitalized adults with a confirmed infection with SARS-CoV-2. Although patients treated with CAS-IMD had greater reductions in viral load and fewer medically attended visits compared with patients in the placebo group, there was no formal hypothesis testing performed and these were very early data. Therefore, further evidence is needed to confirm treatment efficacy. Very few adverse events and serious adverse events were reported. There were no withdrawals from the trial due to an adverse event. The trial data are limited in that the results are based on an interim analysis with several methodological issues. Therefore, the results of the interim analysis may or may not be reflective of the results of the final analysis.

The US FDA issued an EUA for CAD-IMD based on unpublished data on 799 patients from the same ongoing trial reviewed in this report. The US FDA Fact Sheet included results that indicated that CAD-IMD may be beneficial in preventing medical visits due to COVID-19. As these additional results are not published in full, it is challenging to interpret these findings.

In summary, there is limited trial evidence to date regarding the efficacy and safety of CAS-IMD. As such, additional RCTs are required to determine the potential place of CAS-IMD in the treatment of COVID-19.

Appendix 1: Statistical Analysis

Table 6: Statistical Analysis of Efficacy End Points

Study	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
Weinrich et al.[11]	The sample size for phase II is based on the primary virologic end point of time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, using a 2-sample t-test at a 2-sided significance of alpha = 0.05.	The time-weighted average change from baseline through day 7 was calculated for each patient as the area under the concentration–time curve and analyzed with an analysis-of-covariance model with treatment group, risk factor, and baseline serum antibody status as fixed effects and baseline viral load and treatment group–by–baseline viral load as covariates. Confidence intervals were not adjusted for multiplicity. The proportion of patients with medically attended visits due to worsening COVID-19 were compared between groups using stratified CMH test at 2-sided 0.05 level based on FAS for each cohort separately.	Analysis positive PCR results below the lower limit of quantification were imputed as half the lower limit of quantification (357 copies/mL) and negative PCR results were imputed as 0 log_{10} copies/mL. PCR results greater than the upper limit of quantification were not imputed.	There was no formal hypothesis testing and no adjusting for multiplicity.	Patients who were serum antibody–negative and serum antibody–positive Analyses were pre-specified in the statistical analysis plan to focus on the serum antibody–negative subgroup.	The FAS included all randomized patients and was based on the treatment allocated (as randomized). The mFAS included all randomized patients with positive SARS-CoV-2 test at randomization and was based on the treatment allocated (as randomized). Efficacy end points were analyzed using the FAS (for clinical) or mFAS (for laboratory). The safety analysis set included all randomized patients who received any study drug; it was based on the treatment received (as treated).

Study	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
		P values and 95% stratified Newcombe confidence intervals with CMH weights for the treatment difference were presented.				

CMH = Cochran Mantel-Haenszel; FAS = full analysis set; mFAS = modified full analysis set.

Appendix 2: Patient Disposition

Table 7: Patient Disposition for Weinreich et al.

Patient disposition	Total	CAS-IMD (low dose)	CAS-IMD (high dose)	Placebo
Screened, N	306	—	—	—
Randomized, N	275	—	—	—
Received treatment, N (%)	269 (97.8)	—	—	—
Discontinued from study, N (%)	6 (2.2)	—	—	—
Reasons for discontinuation, N (%)		—	—	—
Withdrew	5 (1.8)	—	—	—
Discontinued due to randomization error	1 (0.4)	—	—	—
Treatment assignment, n	—	92	90	93
Completed trial, n (%)	—	80 (86.9)	84 (93.3)	88 (94.6)
Did not complete trial, n (%)	—	12 (13.0)	6 (6.7)	5 (5.4)
Reasons for not completing trial, n (%)				
Trial is ongoing	—	3 (3.3)	2 (2.2)	1 (1.1)
Lost to follow-up	—	3 (3.3)	1 (1.1)	4 (4.3)
Withdrawn by sponsor[a]	—	1 (1.1)	0	0
Withdrew	—	4 (4.3)	3 (3.3)	0
Unknown	—	1 (1.1)	0	0

CAS-IMD = casirivimab-imdevimab.

[a] Patient underwent randomization in error, and sponsor requested that the patient withdraw from the trial.

Appendix 3: Baseline Characteristics

Table 8: Demographic and Clinical Characteristics of Patients at Baseline for Weinreich et al.

Demographic and clinical characteristics	CAS-IMD (low dose) n = 92	CAS-IMD (high dose) n = 90	Placebo n = 93
Age, median years (IQR)	43.0 (33.5 to 51.0)	44.0 (36.0 to 53.0)	45.0 (34.0 to 54.0)
Men, n (%)	46 (50)	38 (42)	50 (54)
Hispanic or Latino ethnic group, n (%)	52 (57)	55 (61)	46 (49)
Race, n (%)			
White, n (%)	74 (80)	78 (87)	72 (77)
Black or African American, n (%)	15 (16)	6 (7)	14 (15)
Asian, n (%)	0	1 (1)	2 (2)
American Indian or Alaska Native	0	0	2 (2)
Unknown	0	(1)	2 (2)
Not reported	3 (3)	4 (4)	1 (1)
Weight, median kg (IQR)	85.65 (72.20 to 97.10)	86.25 (72.60 to 98.30)	83.90 (72.90 to 97.70)
BMI, mean (SD)	30.39 (6.58)	30.63 (7.2)	29.73 (7.15)
Obesity (BMI > 30), n (%)	39 (42)	42 (47)	34 (37)
Positive baseline qualitative RT-PCR, n (%) [a]	73 (79)	74 (82)	81 (87)
Baseline serum antibody status, n (%)			
Negative	41 (45)	39 (43)	33 (35)
Positive	37 (40)	39 (43)	47 (51)
Unknown [b]	14 (15)	12 (13)	13 (14)
Time from symptom onset to randomization, median days (range)	3.5 (0 to 7)	3.0 (0 to 8)	3.0 (0 to 8)
At least 1 risk factor for hospitalization, n (%) [c]	57 (62)	61 (68)	58 (62)

BMI = body mass index; CAS-IMD = casirivimab-imdevimab; IQR = interquartile range; kg = kilogram; SD = standard deviation.

[a] A positive result was defined as a viral load greater than or equal to the lower limit of detection (714 copies/mL [2.85 $\log_{10}$ copies/mL]).

[b] Status could not be evaluated, or the results were borderline.

[c] Risk factors for hospitalization included age > 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromise (immunosuppression or receipt of immunosuppressants).

Appendix 4: Harms Data

Table 9: Harms Outcomes for Weinreich et al.

Harms outcomes	CAS-IMD (low dose) n = 88	CAS-IMD (high dose) n = 88	Placebo n = 93
Adverse events, n (%)			
Adverse events	0	5 (5.7)	5 (5.4)
Gastrointestinal disorders			
Abdominal pain	0	1 (1)	0
Vomiting	0	0	1 (1)
Nausea	0	0	1 (1)
Skin and subcutaneous tissue disorders			
Pruritus	0	1 (1)	0
Urticaria	0	1 (1)	0
Rash	0	0	1 (1)
General disorders and administration site conditions			
Chills	0	1 (1)	0
Vascular disorders			
Flushing	0	1 (1)	0
Nervous system disorders			
Dizziness	0	0	1 (1)
Headache	0	0	1 (1)
Serious adverse events, n (%)			
Serious adverse events	2 (2)	0	2 (2)
Gastrointestinal disorders			
Vomiting	1 (1)	0	0
Nausea	1 (1)	0	0
Vascular disorders			
Hypertension	0	0	1 (1)
Respiratory, thoracic, and mediastinal disorders			
Hypoxia	0	0	1 (1)

CAS-IMD = casirivimab-imdevimab.

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