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

RESEARCH QUESTION: **Among COVID-19 patients, should sotrovimab be used for treatment?**

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RECOMMENDATION

Recommendation	Certainty of Evidence	Strength of Recommendation
We suggest against the use of sotrovimab among children and adult patients with COVID-19.	Very low	Weak

Consensus Issues

The consensus panel unanimously voted against the use of sotrovimab in the treatment of both children and adults with COVID-19, based on the drug's ineffectiveness against Omicron variants and the drug's prohibitive cost. Although current evidence showed that sotrovimab had benefit on the composite outcome of death or hospitalization and all-cause hospitalization among non-hospitalized unvaccinated adults at risk for disease progression, recent in-vitro studies demonstrated that similar with other monoclonal antibodies, sotrovimab is ineffective against Omicron variants, particularly BA.2, BA.4 and BA.5. Given that Omicron remains to be the predominant variant locally, this was well considered by the panel, hence the recommendation. Since the drug has not been granted emergency use authorization (EUA) in the Philippines, it is not yet available locally. A full treatment course was estimated to cost US$2,100 (₱115,000), which the panel deemed more costly than other effective and locally available drugs against COVID-19.

KEY FINDINGS

- Two (2) RCTs investigated the effect of sotrovimab as treatment for COVID-19 compared to standard of care or placebo.
- There was no significant benefit in all-cause mortality, composite outcome of disease progression or mortality, need for mechanical ventilation, clinical improvement, nor virologic clearance with sotrovimab for COVID-19.
- Sotrovimab was shown to have significant effect in the reduction in the composite outcome of hospitalization or all-cause mortality among non-hospitalized COVID-19 patients at risk for progression when administered within 5 days of symptom onset.
- Sotrovimab was also shown to have benefit for all-cause hospitalization among non-hospitalized patients.
- Sotrovimab had no significant difference for adverse and serious adverse events compared to placebo.
- The overall certainty of evidence was rated very low because of imprecision, heterogeneity, and indirectness.

INTRODUCTION

Sotrovimab, also known as VIR-7831, is a monoclonal antibody which neutralizes SARS-CoV-2, originating from S309 which was isolated from a patient with SARS-CoV-1 [1,2]. This targets the spike (S) glycoprotein which is instrumental in host entry of the virus. It is hypothesized that sotrovimab works by preventing a yet undefined step after viral attachment but before fusion of viral and cell membranes [1,2,3]. Monoclonal antibodies have been investigated as treatment against COVID-19, however, with the emergence of the omicron variant, reports of lack of in vitro activity for monoclonal antibodies against this variant surfaced. Sotrovimab is one of the antibodies noted to have retained partial neutralization activity against initial variants of omicron, albeit with less potency compared to its initial activity [4].

REVIEW METHODS

A systematic search was done until October 29, 2022 using Medline, Cochrane Library, and Google Scholar using a combined MeSH and free text search using the terms sotrovimab, COVID-19, SARS COV2, Searches for randomized controlled trials, meta-analysis, systematic review in the title, abstract, and publication type were also done. We also looked at the COVID-NMA Living Data and ongoing studies in the NIH Clinical trials.gov and Cochrane. Preprints were searched using medrixiv, biorxiv. Handsearching was also done from references of related texts. Only randomized controlled trials that compared sotrovimab against placebo or standard of care were included in this review. In vitro studies were not included. Studies comparing sotrovimab to other experimental interventions were also not included. Only randomized controlled trials were included in the review. No limits were placed on age, COVID-19 severity, and administration method of sotrovimab. Subgroup analysis by severity, vaccination status, and age was planned. Results of the search are found in Appendix 2.

RESULTS

The search yielded 4 articles. After review of search output, 2 RCTs [5,6], and 2 meta-analysis [7,8] was retrieved. The two RCTs were included in the 2 meta-analyses, as well as the in the COVID-NMA Living Data [7,8,9].

A total of 1,424 patients were included in this review. Both RCTs were multicenter studies. COMET-ICE was carried out in 57 centers across 5 countries (US, Canada, Pero, Brazil and Spain) [5] while the Therapeutics for Inpatients with COVID-19 (TICO) was carried out at 43 hospitals across 4 countries in the USA and Europe [6]. Both studies included patients 18 years old and above with confirmed COVID-19. One study included non-hospitalized patients with COVID-19 at high risk of progression. Risk factors included age of 55 years or older, diabetes requiring medication, obesity (body mass index >30; calculated as weight in kilograms divided by height in meters squared), chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m^2), congestive heart failure (≥New York Heart Association class II), chronic obstructive pulmonary disease, or moderate to severe asthma [5]. The other RCT included patients with progressive disease who are hospitalized for manifestations of COVID-19 [6]. Patients in both RCTs were given sotrovimab at a dose of 500mg intravenously over an hour as a single dose. The control groups for both studies received placebo and standard of care which may include antivirals and steroids. In ACTIV/TICO, 96% of patients in the sotrovimab group and 94.5% of patients in the control group received remdesivir throughout the observation period. Vaccination status was not reported among non-hospitalized patients [5], while among hospitalized patients 8% and 6% in the sotrovimab and placebo groups, respectively received at least one dose of COVID-19 vaccine. Both studies took place prior to the emergence of Omicron as the predominant circulating variant - August 2020 to March 2021 [5] and December 2020 to March 2021 [6]. The characteristics of included studies are summarized in Appendix 3.

Overall certainty of evidence

The overall certainty of evidence was rated very low because of imprecision, inconsistencies, and indirectness. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Efficacy

Patients given sotrovimab did not improve all-cause mortality compared to those given placebo/standard of care (RR 0.87, 95%CI 0.36-2.08, I^2=0%). Subgroup analyses based on hospitalization status are inconclusive for both non-hospitalized (RR 0.20 95% CI 0.01-4.16) and hospitalized patients (RR 0.99, 95% CI 0.40-2.45).

Results for the composite outcome of disease progression (based on WHO progression score level 7 or above) or mortality also revealed inconclusive results among patients who received sotrovimab compared to placebo (RR 0.37, 95% CI 0.03-5.00, I^2=65%) with significant heterogeneity. Subgroup analysis by hospitalization status shows no significant benefit for both non-hospitalized (RR 0.08, 95% CI 0.00-1.36) and hospitalized patients (RR 0.99, 95% CI 0.25-3.92).

Among non-hospitalized patients, sotrovimab showed significant benefit for eventual all-cause hospitalization among patients at high risk of progression (RR 0.21, 95% CI 0.09-0.50) and for the composite outcome of eventual hospitalization or mortality compared to placebo (RR 0.20, 95% 0.08-0.48, 1 study, n=1,057 [5].

Sotrovimab had no significant effect on the need for mechanical ventilation for COVID-19 patients (RR 0.52, 95% CI 0.05-6.04, I^2=58%), with moderate heterogeneity. Subgroup analysis based on hospitalization status show that there is no significant effect were seen in both non-hospitalized patients (RR 0.11, 95% CI 0.01-2.06) and hospitalized patients (RR 1.33, 95% CI 0.3-5.84).

For the symptom response, non-hospitalized COVID-19 patients in the sotrovimab group reported greater mean difference in symptoms by from day 0 to day 7 compared to placebo (least mean square difference, -1.07, (95%CI -1.38 to -0.76, p<0.001) using FLU-PRO Plus score, n=811, 1 study. The FLU-PRO Plus score is a 5-point scoring system wherein 0 is symptom-free while 5 means severe symptoms [5]. Among hospitalized COVID-19 patients, there is no significant difference in the clinical improvement of symptoms by day 90 for sotrovimab compared to placebo (RR 1.05, 95% CI 0.97-1.15, 1 study, n=367) [6].

Based on one study sotrovimab did not improve virologic clearance by day 8 (RR 0.81, 95% CI 0.51-1.30, n=127) nor on day 28 (RR 0.68, 95% CI 0.17-2.74, n=145) compared to placebo/standard of care.

Stratification based on vaccination was planned however, there was no data to subgroup patients based on their vaccination statuses.

Adverse events

The point estimate for any adverse events shows no significant difference between patients given sotrovimab and placebo (RR 0.97, CI 95% 0.81-1.17, I^2=0%). The most common adverse events reported include diarrhea, nausea, headache [5], and administration site, gastrointestinal, respiratory, metabolic and nutritional events, as well as nervous system events [6]. Results were inconclusive for serious adverse events (SAEs) (RR 0.49, 95%CI 0.23-1.03, I^2= 50%).

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
Australian COVID-19 Guidelines (version 70.1, as of 12/20/2022) [18]	***Adults*** Consider using within 5 days of symptom onset in unvaccinated adults who do not require oxygen and who have one or more risk factors for disease progression	Conditional recommendation
	Consider among immunocompromised regardless of vaccination status	Consensus recommendation
	High risk of disease on the basis of age and multiple risk factors	Consensus recommendation
	Children Consider using, in exceptional circumstances, sotrovimab for the treatment of COVID-19 within 5 days of symptom onset in **children and adolescents aged 12 years and over and weighing at least 40kg** who do not require oxygen and who are at high risk of deterioration.	Consensus recommendation
	Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration.	Only in research settings
	*If Omicron BA.2, BA.4, or BA.5 is confirmed or considered likely, use of sotrovimab should only be considered where other treatments are not suitable or available	
World Health Organization Living Guidelines (as of 01/13/2023) [19]	Several other therapeutic options for patients with non-severe COVID-19 at highest risk of hospitalization are available: • The GDG considered *in vitro* data demonstrating that neutralization of currently circulating variants of SARS-CoV-2 and their subvariants with sotrovimab is diminished. • There was consensus among the panel that the meaningful reduction of *in vitro* neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab. • There was also consensus regarding the need for clinical trial evidence in order to confirm clinical effectiveness of new monoclonal antibodies that reliably neutralize circulating strains *in vitro.*	Strong recommendation against
NIH COVID-19 Guidelines (as of 12/28 /2022) [20]	Recommends against The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of anti-SARS-CoV-2 mAbs for the treatment of COVID-19 **(AIII)** because the	

	dominant Omicron subvariants in the United States are not expected to be susceptible to these products.	
Infectious Diseases Society of America (IDSA) Treatment and Management of Patients with COVID-19 (as of 5/23/2022) [21]	Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests treatment with anti-SARS-CoV-2 monoclonal antibodies with activity** against the predominant regional variants* within 7 days of symptom onset rather than no anti-SARS-CoV-2 monoclonal antibodies. *The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.*	Conditional recommendation (no specific recommendation for sotrovimab, recommendation is for monoclonal antibodies in general), Moderate certainty of evidence

ONGOING STUDIES AND RESEARCH GAPS

There are currently no available clinical trials on the in vivo efficacy of sotrovimab for these emerging variants. Additionally, no data on the effect of sotrovimab efficacy with vaccination is currently available. Upcoming studies also aim to investigate efficacy among children aged 12 years and older and among immunocompromised patients.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

Economic analyses were done based on data from COMET-ICE [11,12]. One was a within-trial analysis of cost of healthcare resources among those treated with sotrovimab versus placebo using data from COMET-ICE[11] using the perspective of the US payer. In this analysis, sotrovimab yielded savings of around ₱130,000 or $2,325 for total hospitalization cost compared to placebo (placebo - ₱159,000 or $2,850; sotrovimab - ₱29,000 or $525). Of note, this analysis did not consider the cost of the medication and administration, which was estimated as ₱115,000 or $2,100.00 per 500mg, and ₱25,000 or $450 for administration, for a total of ₱140,000[11]. Another analysis done by ICER showed that with the healthcare provider perspective, comparing with usual care, sotrovimab costs more than ₱4 million or $76,000/QALY gained or more than ₱3.5 million ($63,000)/life year gained and will lead to ₱6 million or $108,000 inpatient hospitalization cost averted [12].

RESISTANCE

Other considerations for sotrovimab is that current in vitro studies have emerged on the resistance of Omicron to monoclonal antibodies such as sotrovimab. While sotrovimab was able to retain its neutralizing activity against Omicron, this was less efficient than its response for the B.1 spike [13]. Additionally, sotrovimab was shown to have a 46-fold and 16.8-fold decrease in potency for BA.2 and BA.5 compared to ancestral A.2.2 in vitro [14].

Observational studies done during the initial Omicron surges showed varying results. Picciacacco et al. reported that sotrovimab is effective in reducing hospitalization in the first 29 days compared to control (OR 0.28, 95% CI 0.11-0.71). However, in this cohort, there were more patients who were older in age, and had more cardiac conditions, as well as were unvaccinated in the control group. No analyses were done to subgroup vaccinated and non-vaccinated patients in this analysis. Additionally, data from this cohort later showed that BA.2 comprised less than 2% of the variant in this cohort [15]. On the other hand, data from Aggarwal et. al. showed that there was no difference in hospitalization or mortality between those who received sotrovimab versus control with an OR 0.82 (95% CI 0.55-1.19). In this cohort, BA.1/BA1.1 was the predominant variant. There may be benefit however for members of the population who are at highest risk of progression [16].

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Sotrovimab currently is not yet FDA approved locally, nor has it been granted an EUA in the Philippines [17].

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=4/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (4)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate (2)	Small (1)	Trivial (1)			• Results were inconclusive for overall mortality , as well as progression to WHO Progression Score of at least 7 or mortality among COVID-19 patients. • Sotrovimab shows a reduction in death or hospitalization compared to placebo among non-hospitalized cases at risk for progression RR 0.2 (95% CI 0.08-0.48). It has also shown benefit in averting hospitalization for non-hospitalized patients at high risk of progression RR 0.21 (95%CI 0.09-0.50[5].
Harm	Large	Moderate (1)	Small	Trivial (2)	Varies	Uncertain (1)	• Pooled results were inconclusive the occurrence of SAEs for sotrovimab group compared to placebo RR 0.49 (CI 95% 0.23-1.02). Results also show equivalence with placebo for any adverse events RR 0.97 (CI 95% 0.81- 1.17)[5,6].
Certainty of Evidence	High	Moderate	Low (3)	Very low (1)			• Certainty of evidence for this review is very low to low. For outcomes on mortality, progression and adverse events, studies are of moderate to high risk of bias mostly due to imprecision, inconsistency, and indirectness. Issues on attrition are also noted in outcomes for symptom relief and viral clearance.
Balance of effects	Favors intervention	Probably favors intervention (1)	Does not favor intervention or no intervention (1)	Probably favors no intervention	Favors no intervention	Varies (2)	• Results were inconclusive for overall mortality, as well as progression to WHO Progression Score of at least 7 or mortality among COVID-19 patients. For non-hospitalized patients with COVID-19 with high risk of progression, sotrovimab has shown benefit in decreasing mortality or hospital admission[5] compared to placebo. Pooled results for serious adverse events are inconclusive, while there is no significant difference for the outcome of adverse events.
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (1)	Probably no important uncertainty or variability	No important uncertainty or variability			

Resources Required	Uncertain	Large cost (4)	Moderate Cost	Negligible cost or savings	Moderate savings	Large savings	• In the US, it costs approximately $2100.00 (₱115,000) per 500mg for the medication, and $450 (₱25,000) for the administration.
Certainty of evidence of required resources	No included studies (1)	Very low	Low (1)	Moderate (2)	High		• Healthcare costs in the perspective of a US payer were considered and collected through an **analysis of insurance claims** for unit cost per COVID-19 care-related resource use, and then the unit costs obtained was applied to resource use observed for the within-trial economic analysis.
Cost effectiveness	No included studies	Favors using the comparison	Probably favors the comparison (1)	Does not favor either the intervention or the comparison (1)	Varies (1)	Unclear (1)	• For non-hospitalized patients, receipt of sotrovimab seems to show decreased health resource costs incurred compared to no sotrovimab received. Data from the within trial economic analysis shows that **sotrovimab affords savings of ₱130,000 ($2,325) for total hospitalization cost compared to placebo ₱159,000 ($2,850)** • Evidence review by the Institute for Clinical and Economic Review (ICER) showed that using the healthcare provider perspective, for non-hospitalized COVID-19 patients, **sotrovimab costs more than ₱4 million ($76,000) per QALY gained**, **₱3.5 million ($63,000) per life year gained**, and **₱6 million ($108,000) inpatient hospitalization averted**
Equity	Uncertain	Varies	Probably reduced (2)	Reduced	Probably no impact (1)	Probably Increased (1)	
Acceptability	Uncertain	Varies (3)	No (1)	Probably no	Probably yes	Yes	• No EUA in the Philippines
Feasibility	Uncertain	Varies	No (1)	Probably no (2)	Probably yes (1)	Yes	
Recommendation	For (1)	Against (3)					
Strength	Weak (4)	Strong					

Other considerations:

- No FDA, no EUA in the Philippines
- Question 2 number of subjects

Appendix 2: Search Yield and Results

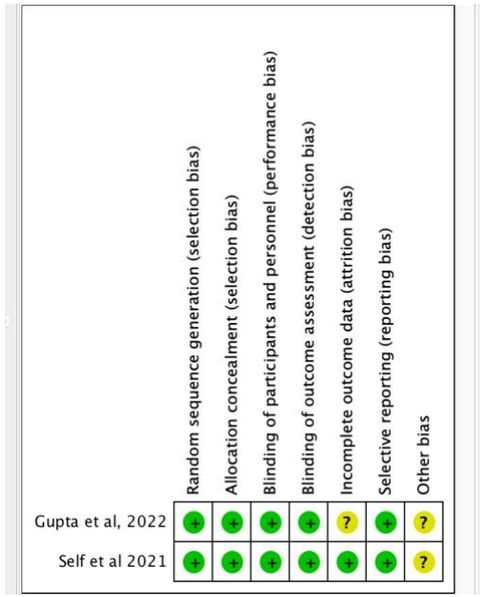
DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	("sotrovimab"[Supplementary Concept] OR "sotrovimab"[All Fields]) AND (("covid 19"[MeSH Terms] AND "sars cov 2"[MeSH Terms]) OR ("sars cov 2"[MeSH Terms] OR "covid 19"[MeSH Terms] OR "covid"[Text Word])) AND ("randomized controlled trial"[Title/Abstract] OR "randomized controlled trial"[Publication Type] OR ("meta analysis"[Publication Type] OR "meta analysis as topic"[MeSH Terms] OR "meta analysis"[All Fields] OR "metaanalysis"[Title/Abstract] OR "meta analysis"[Publication Type] OR ((("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields]) AND "systematic review"[Title/Abstract]) OR "systematic review"[Publication Type])))	10/18/2022 13:05	16	4
CENTRAL	Sotrovimab	10/29/22 10:35	28	21 trials 3 reviews
Cochrane COVID-19 Study Register	Sotrovimab (limit: interventional)	10/29/22 21:30	15	2 trials
COVID-NMA Initiative	Sotrovimab	10/29/22 10:00	5	2
Biorxiv	Sotrovimab and COVID-19	10/25/22 22:50	123	0
MedRxiv	Sotrovimab and COVID-19	10/26/22 1:55	108	2
ClinicalTrials.gov	Sotrovimab	10/29/22 10:54	22	2
Chinese Clinical Trial Registry	Sotrovimab	10/29/22 10:55	0	0
EU Clinical Trials Register	Sotrovimab	10/29/22	8	0
WHO International Clinical Trials Registry Platform (ICTRP)	Sotrovimab	10/29/22 12:00	28	2
Google Scholar	sotrovimab and covid-19 and “randomized control trial”	10/26/22	395	2
Reference search		10/29/22		1

Appendix 3: Characteristics of Included Studies

Author	Study design	Population (n)	Inclusion criteria	Exclusion criteria	Intervention	Outcomes
Gupta et al., 2022	Randomized controlled trial	RT-PCR or antigen confirmed COVID-19 patients aged 18 years and above *recruitment August 2020 to March 2021 *No mention of vaccination status	Symptom onset within the prior 5 days Patients at high risk for COVID-19 progression requiring hospitalization or death (at least 1 of the following risk factors) - Age 55 years or older - Diabetes requiring medication - Obesity (BMI>30) - Chronic kidney disease (eGFR < 60 mL/min/1.73m2) - Congestive heart failure (NYHA Class 2 at least) - Chronic obstructive pulmonary disease - Moderate to severe asthma	Hospitalized patients, Had signs or symptoms of severe COVID-19 such as - shortness of breath at rest, - oxygen saturation < 94%, or required supplemental oxygen - Severely immunocompromised patients such as patients on immunosuppression, immunotherapy or those who have received transplant within the past 3 months	Experimental: sotrovimab 500 mg IV over 1 hour Control: placebo (0.9% NSS)	Primary Progression through day 29 (all cause hospitalization >24 hrs or death) - All cause hospitalization by day 29 - Death by day 21 Secondary Progression to severe/ critical COVID-19 at D29 All-cause mortality at D 29 Mean change in symptom severity and duration (FLU-PRO Plus) Change in viral load by RT-PCR at day 8 Exploratory outcome Total hospital stay Total ICU length of stay Total number of days of mech vent Detection of SARS-CoV-2 nasal secretions D 29 Adverse events Infusion related reactions Antibody dependent enhancement Any AE or SAE including hospitalizations and deaths regardless of relationship to COVID-19
Self et al., 2022	Randomized controlled trial	RT-PCR or antigen confirmed COVID-19 patients aged 18 years and above admitted for COVID-19 *recruitment Dec 2020 to March 2021 *Only 6.9% received at least 1 dose of COVID-19 vaccine.	Symptoms less than or equal to 12 days Require inpatient hospital acute medical care for COVID-19 manifestations	Prior receipt of SARS-CoV-2 hIVIG. SARS-CoV-2 nMAb at any time prior to hospitalization For early futility analysis: On high flow oxygen via nasal cannula, non-invasive ventilation or invasive mechanical ventilation, with acute organ failure or major extrapulmonary manifestations of COVID-19, (on vasopressor, on mechanical circulatory support, on renal replacement therapy)	Control group: placebo + standard of care- may have received remdesivir and/or corticosteroids Experimental group: Sotrovimab 500mg IV over 1 hour	Primary Time from randomization to sustained recovery to day 90 Secondary Mortality, all cause D90 Composite of time to sustained recovery and mortality Time to discharge for initial hospitalization Days alive out of a short term facility* Ordinal outcomes (pulmonary and pulmonary +) D1-7, 14, 28 * Development of organ failure or severe infection D28 Safety and tolerability0 composite safety outcomes D5, 28, 90 Change in antibody profile (D1,3,5,28, 90)

Lokhandwala, et al.	Post hoc within-trial economic analysis	RT-PCR or antigen confirmed COVID-19 patients aged 18 years and above	Symptom onset within the prior 5 days Patients at high risk for COVID-19 progression requiring hospitalization or death (at least 1 of the following risk factors) - Age 55 years or older - Diabetes requiring medication - Obesity (BMI>30) - Chronic kidney disease (eGFR < 60 mL/min/1.73m2) - Congestive heart failure (NYHA Class 2 at least) - Chronic obstructive pulmonary disease - Moderate to severe asthma	Hospitalized patients, Had signs or symptoms of severe COVID-19 such as - shortness of breath at rest, - oxygen saturation < 94%, or required supplemental oxygen Severely immunocompromised patients such as patients on immunosuppression, immunotherapy or those who have received transplant within the past 3 months	Sotrovimab versus placebo	Economic analysis comparing longer than 24- hour hospitalization costs and total healthcare costs associated with COVID-19 care

Appendix 4: Methodological Assessment of Included Studies



Gupta et al, 2022
- Incomplete outcome data for outcomes on viral clearance and symptom scores

-Other bias:

publication bias possible: trial was sponsored by industry, authors declaration of COIs- noted affiliations with industry, Industry also with a hand at the design, data analysis and final manuscript; but had no power to veto publication

Trial stopped early for efficacy but with limited events

Self et al, 2021
- Noted role of industry in provision of drugs, and COI declarations with the

Appendix 5: GRADE Evidence Profile

Author(s): Ong, Faustine Richelle; Esteban-Ipac, Natasha
Question: Sotrovimab compared to Placebo for COVID-19
Setting:
Bibliography: Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Rodrigues Falci D, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL, Parra S, Sager JE, Austin D, Peppercorn A, Alexander E, Yeh WW, Brinson C, Aldinger M, Shapiro AE; COMET-ICE Investigators. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2022 Apr 5;327(13):1236-1246. doi: 10.1001/jama.2022.2832. PMID: 35285853; PMCID: PMC8922199.ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 2022 May;22(5):622-635. doi: 10.1016/S1473-3099(21)00751-9. Epub 2021 Dec 23. PMID: 34953520; PMCID: PMC8700279.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sotrovimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 28 days; assessed with: mortality)												
2	randomised trials	not serious[a]	not serious	serious[b]	serious[c]	none	9/712 (1.3%)	11/712 (1.5%)	**RR 0.87** (0.36 to 2.08)	**2 fewer per 1,000** (from 10 fewer to 17 more)	⨁⨁◯◯ Low	
WHO Progression Score 7 or above or mortality												
2	randomised trials	not serious[a]	serious[d]	serious[b]	serious[e]	none	4/712 (0.6%)	10/712 (1.4%)	**RR 0.37** (0.03 to 5.00)	**9 fewer per 1,000** (from 14 fewer to 56 more)	⨁◯◯◯ Very low	
Need for mechanical ventilation												
2	randomised trials	not serious[a]	serious[d]	serious[b]	serious[e]	none	4/712 (0.6%)	7/712 (1.0%)	**RR 0.52** (0.05 to 6.04)	**5 fewer per 1,000** (from 9 fewer to 50 more)	⨁◯◯◯ Very low	
Serious adverse events (SAE)												
2	randomised trials	not serious	not serious	not serious	serious[f]	none	20/712 (2.8%)	44/712 (6.2%)	**RR 0.49** (0.23 to 1.03)	**32 fewer per 1,000** (from 48 fewer to 2 more)	⨁⨁⨁◯ Moderate	
Any Adverse event (AE)												
2	randomised trials	not serious	not serious	not serious	serious[f]	none	169/712 (23.7%)	174/712 (24.4%)	**RR 0.97** (0.81 to 1.17)	**7 fewer per 1,000** (from 46 fewer to 42 more)	⨁⨁⨁◯ Moderate	
Hospitalization or Mortality (follow-up: 29 days)												
1	randomised trials	not serious	not serious	serious[b]	not serious		6/528 (1.1%)	30/529 (5.7%)	**RR 0.20** (0.08 to 0.48)	**45 fewer per 1,000** (from 52 fewer to 29 fewer)	-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sotrovimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Virologic clearance (Day 8) (follow-up: 8 days; assessed with: RT-PCR)												
1	randomised trials	serious[g]	not serious	not serious	serious[f]		19/59 (32.2%)	27/68 (39.7%)	**RR 0.81** (0.51 to 1.30)	**75 fewer per 1,000** (from 195 fewer to 119 more)	-	

CI: confidence interval; **RR:** risk ratio

Explanations

a. 1 Trial stopped enrollment early due to efficacy (5) but with less than 500 events
b. Studies took place August 2020 to March 2021 and December 2020 to March 2021, variants predominant at that time may not be the same as now.
c. 1 study had very wide confidence interval, also crosses 1 (no events in treatment)
d. heterogeneity I2 >50%
e. wide confidence interval, crosses 1
f. crosses 1
g. Concerns for attrition (only 59 of those who received treatment and 68 of those who received the control had results for this outcome)

Appendix 6: Forest Plots

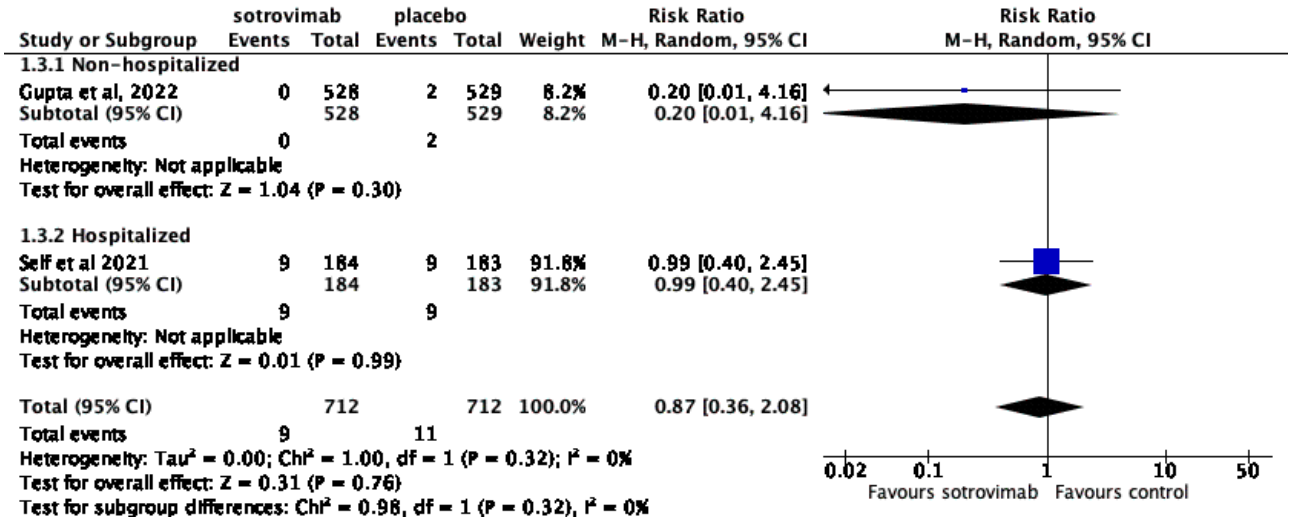


Figure 1. All-cause mortality (D28)

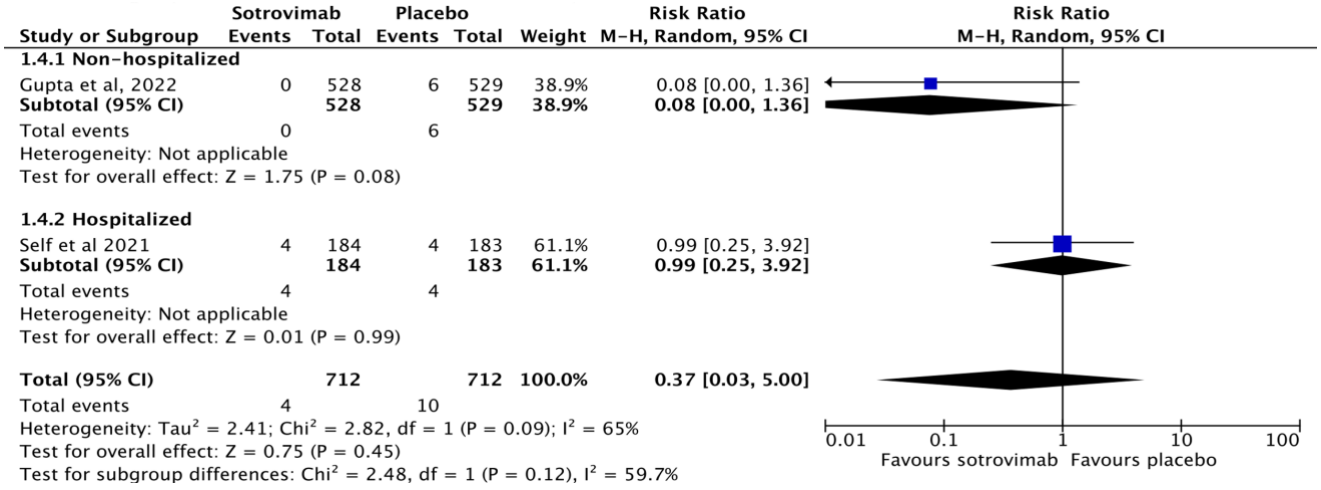


Figure 2. WHO Progression Score 7 or mortality (D28)

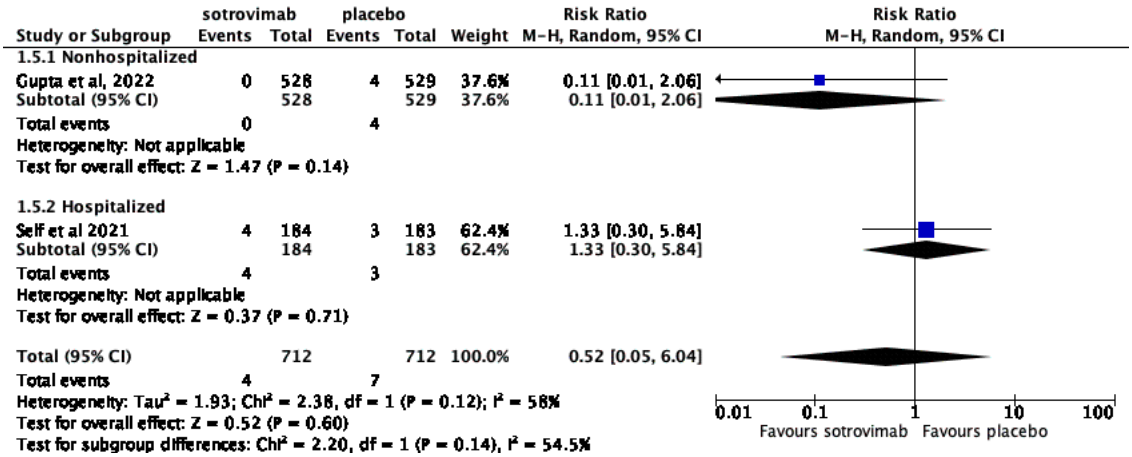


Figure 3. Need for mechanical ventilation

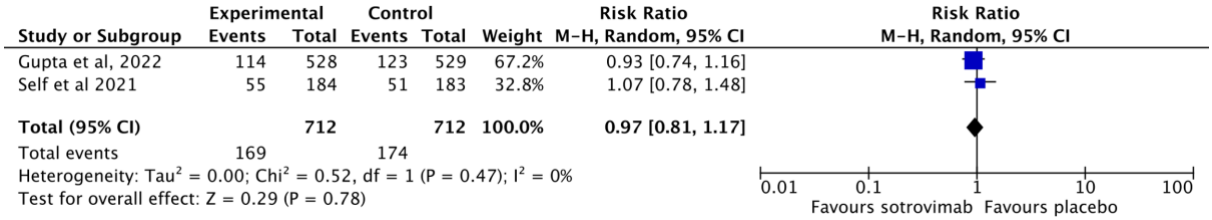


Figure 4. Adverse events

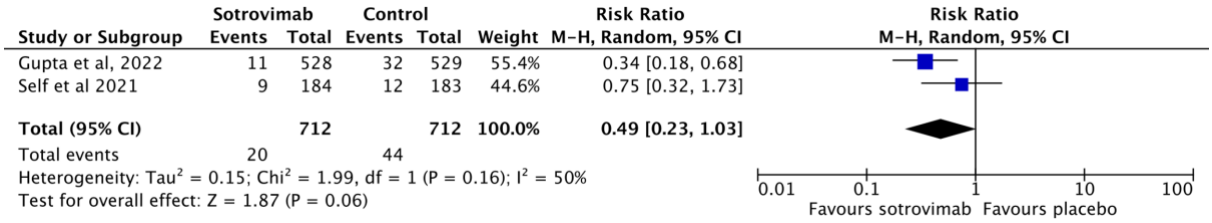


Figure 5. Serious adverse events

Appendix 7. Characteristics of Ongoing Studies

Title	Population	Interventions	Characteristics	Outcome Measures
NCT04870333 PROphylaxis for paTiEnts at Risk of COVID-19 infecTion -V PROTECT-V Recruiting, No results	Age more than 18 and a member of vulnerable population: - Kidney transplant, vasculitis, glomerulonephritis For sotrovimab arm: - absent or suboptimal response to Anti-SARS-CoV-2 vaccination antibody and immunocompromised	Sotrovimab Niclosamide Ciclesonide Versus placebo	N=5000 Study Type: Interventional Phase 2, 3 Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Prevention	Confirmed symptomatic COVID-19 infection during treatment Time to confirmed SARSCov-2 infection from the date of randomisation including asymptomatic cases Safety All-cause mortality Severity of COVID-19 disease
NCT04381936 Randomised Evaluation of COVID-19 therapy RECOVERY Ongoing, no results	Age more than 0, Clinically suspected or laboratory confirmed SARS-CoV-2 infection, hospitalized with viral pneumonia *Some arms for age 0-12 has been discontinued	LopinavirRitonavir Corticosteroid Hydroxychloroquine Azithromycin Convalescent plasma Tocilizumab Immunoglobulin Synthetic neutralising antibodies Aspirin Colchicine Versus standard of care	N= 50,000 Study Type: Interventional Phase: 2 and 3 Study Design: Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Duration of hospital stay Composite endpoint of death or need for mechanical ventilation or ECMO
EUCTR2021-004035-88-IT A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the	Age 12 years or older, not hospitalized, with mild or moderate COVID-19	Sotrovimab Bamlanivimab Etesevimab Casirivimab	N=400 Study type: interventional Phase: Yes Controlled: yes Randomised: yes	Disease progression: hospitalization in intensive care unit, oxygen desaturation = 4% and peripheral oxygen saturation = 92% during the follow-up period (30 days), incidence and severity of adverse events, proportion of patients admitted to the ED, all-cause mortality

efficacy and tolerability of Bamlanivimab and Etesevimab, Casirivimab and Imdevimab, and Sotrovimab versus Standard of Care in patients with mild to moderate COVID-19 disease (AntiCov) AntiCov Not recruiting	symptoms and risk for developing severe COVID	Versus standard of care	Open: yes Single blind: no Double blind: no Parallel group: yes Cross over: no	

Appendix 8: Characteristics of the Systematic Reviews Retrieved Through Citation Search

Study and Impact Factor	Country of authors	Cochrane review or not?	Is funding present?	Is there prospective registration or protocol publication?	Number of included studies in the review	Total sample size (number of participants included)	Are meta-analyses done?	Intervention	Comparison	Outcomes
Amani and Amani, 2022	Iran	No	No	None mentioned	2 RCTs 15 observational with control arm	27, 429	Yes	Sotrovimab	Any therapeutic intervention	Primary: Mortality, hospitalization rate, hospitalization or death rate Secondary: ICU admission, mechanical ventilation, disease progression, ED visits
Ao et al., 2021	China and Canada	No	No	Yes	2 RCTs 2 observational with control arm	3,866	Yes	Sotrovimab	Standard of care, placebo	Primary: Mortality, development of sever COVID-19

Appendix 9: Evaluation of the systematic reviews retrieved using AMSTAR-2 tool

AMSTAR 2 Questions	Ao et al., 2022	Amani and Amani, 2022
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Y	N
3. *Did the review authors explain their selection of the study designs for inclusion in the review?*	N	N
4. Did the review authors use a comprehensive literature search strategy?	PY	Y
5. Did the review authors perform study selection in duplicate?	Y	Y
6. Did the review authors perform data extraction in duplicate?	Y*	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	N	Y
8. Did the review authors describe the included studies in adequate detail?	Y	Y
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	N+	PY^
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Y	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N	Y
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Y	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N	Y
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N	Y
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Y	Y
Rate of overall confidence	Critically Low	Low

*Not indicated in the manuscript but was in the PROSPERO Registration
+While method to be used in the determination of risk of bias of studies was mentioned in the PROSPORO registration, there was no assessment given in the actual report
^ For the included RCTs only

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 10. Appraisal of Economic Article

Questions	Answers	Explanations Article 1	Answers	Explanations Article 2
1. Identify the study as an economic evaluation and specify the interventions being compared	Yes	Within trial economic analysis of resource use from COMET-ICE: a Phase 3 clinical trial evaluating sotrovimab for the treatment of patients with COVID-19 at high risk of progression	Not entirely	Institute for Clinical and Economic Review Special Assessment of Outpatient Treatments for COVID-19 – no mention of it being an economic review based on the article per se
2. Provide a structured summary that highlights context, key methods, results and alternative analyses	Yes	Structured abstract included	Yes	Provided an executive summary
3. Give the context for the study, the study question and its practical relevance for decision making in policy or practice	Yes	Primary objective: Comparing estimated hospitalization costs associated with COVID-19 care in the sotrovimab group vs the placebo group. Secondary objective: Estimated total health care costs	Yes	The report aims to present a full evaluation of clinical and economic outcomes of four treatments for mild to moderate COVID-19 among outpatients at high risk of progression to severe disease: sotrovimab, molnupiravir, Paxlovid and fluvoxamine
4. Indicate whether a health economic analysis plan was developed and where available	Yes	A plan was developed and described in the methods section. The plan has 2 steps, first was obtaining unit costs per COVID-19 care-related resource use from a retrospective analysis of administrative claims data, while Step 2 involved applying theses costs to the resources used during the first 29 days post-randomization of COMET-ICE. This is also shown in figure 1.		Yes, this was discussed in the part on Long-Term Cost effectiveness
5. Describe the characteristics of the study population	Yes	First Paragraph in Results under economic analysis describes the population of COMET-ICE. Figure 2 also includes the population from which unit costs were derived for step 1.	Yes	The review also discussed the study population
6. Provide relevant contextual information that may influence findings	Unsure		Yes	The review included information which may affect the results of the findings.
7. Describe the interventions and strategies being compared and chosen	Yes	The interventions of COMET-ICE were described.	Yes	The review included the interventions being compared
8. State the perspective(s) adopted by the study and why chosen	Yes	The abstract mentions that the perspective used is the US payer, but no reason as to why this was chosen	Yes	This was done in the perspective of the healthcare provider, modified societal perspectives as well
9. State the time horizon for the study and why appropriate	Yes	The time horizon was the 29 day- trial follow-up period.	Yes	Lifetime time horizon was used.
10. Report the discount rate(s) and reason chosen	Not relevant	No mention of discounting, but as the timeframe was only up to	Yes	Future costs and outcomes were discounted at 3% per year.

		the first 29 days, discounting may not be relevant.		
11. Describe what outcomes used as the measure(s) of benefit(s) and harm(s)	Yes	The methods/ study variables shows the outcomes measured – primary endpoint as the cost associated with longer-than- 24-hour hospitalizations per patient for COVID-19, secondary endpoint as total health care costs, defined as outpatient and inpatient costs associated with COVID-19 care.	Yes	Outcomes included hospitalization or death, mortality and change in viral load, as well as outcomes on adverse events
12.Describe how outcomes used to capture benefit(s) and harm(s) were measured	Yes	The methods section narrates how the costing was done for step one, and how they were applied for step 2.	Yes	The outcomes used were based on the results of the studies which was also discussed in the appraisal
13. Describe the population and methods used to measure and value outcomes	Yes	The methods described the population including the definition of outcome measures	Yes	The population and the studies included were discussed in the report.
14. Describe how costs were valued	Yes	The methodology described the source study, the database used.	Yes	The sources for costs were described in Supplement E.
15. Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion	Yes	The methods specified the year of currency (2020 USD) and the timeframe as well of the costing for step 1 .	Yes	Costs were updated to the 2021 US dollar.
16. If modelling is used, describe the detail and why used. Report if model is publicly available and where it can be accessed	No mention	No mention of model used. Article mentioned that modeling was not used for the costing, rather the costs were directly based on the COMET-ICE trial.	Yes	The models used were described in supplement E.
17. Describe methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used	Yes	The statistical methods employed were discussed in the data analysis portion. No model validation was done. Sensitivity analysis was done	Yes	Details of model validation were mentioned in supplement E.
18. Describe any methods used for estimating how the results of the study vary for subgroups	Yes	Possible subgrouping was determined prior, and analysis was done using the pre-determined subgrouping.	Yes	Subgroups were analyzed for race, vaccination status, variant of concern, time since randomization, serum antibody status, individual risk for progression.
19. Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations	None mentioned		None mentioned	
20. Describe methods to characterize any sources of uncertainty in analysis	None mentioned		Yes	Issues on generalizability were discussed as the review included only one RCT. Additionally, issues on the efficacy of sotrovimab against

				the Omicron variant was also raised.
21. Describe any approaches to engage patients or service recipients, the general public, communities. Or stakeholders (such as clinicians or payers) in the design of the study	None mentioned		Yes	The review also included stakeholders perspectives, including patients, physician-scientist, NGOs.
22. Report all analytical inputs including uncertainty or distributional assumptions	Yes	Mean >24 hour hospitalization cost was USD 2827 in the placebo group versus USD 485 for sotrovimab, difference of USD 2,342 (95% CI 1071-3786). Mean total hospitalization cost USD 2850 for placebo versus USD 525 for sotrovimab, mean difference 2325 (CI 95%, USD 1056 to 3776). Also figures 3 and 4; tables 1 and 2 show the results obtained.	Yes	Table 4.3 shows the results for the base case, health care sector perspective; wherein sotrovimab will incur a total cost of $ 300,700, 15.9648 QALYs; and comparing with usual care, sotrovimab costs $76,000 per QALY gained, $63,000 per life year gained, $73,000 per evLY gained, and $108,000 inpatient hospitalization averted.
23. Report mean values for categories of costs and outcomes of interest and summarize them in the most appropriate overall measure	Yes	As above	Yes	As above
24. Describe how uncertainty about analytic judgements, inputs or projections affect findings. Report the effect of choice of discount rate and time horizon	None noted			
25. Report on any difference patient/service recipient, general public, community or stakeholder involvement made to the approach or findings of the study	None reported		Yes	Public comments and new evidence lead to the changes including incorporation of new evidence around the percent of infections among those vaccinated, approach for how excess deaths averted are calculated in the modified societal perspective and added a scenario analysis without future unrelated costs
26. Report key findings, limitations, ethical or equity considerations not captured and how these could affect patients, policy, practice	Yes	The discussion related the outcomes to the setting, as well as discussed limitations of the study, such as that the analysis does not take into account acquisition and administration cost (USD 2100 and 450 respectively), as well as the follow-up timeframe.	Yes	These may be seen in section 5.Contextual considerations were noted as well as potential other benefits or disadvantages.
27. Describe how the study was funded	Yes	Disclosures were reported, and the role of the funding sponsor	Yes	This can be found in the introduction on ICER. Funding

and any role of the funder in the identification, design, conduct and reporting of the analysis		(GSK, Vir Biotechnology) which includes study design, collection, analysis, interpretation, writing report, and decision to submit.		came from government grants and non-profit foundations, largest single funder also noted. No funding also came from health insurers, pharmacy, benefit managers, and life science companies.
28. Report author conflicts of interest according to ICMJE	Cannot say	Conflicts of interests reported but no mention if it follows ICMJE.	Yes	Disclosures from authors are listed

*Comment: The study was done using COMET-ICE data. This trial is industry-sponsored. The authors of the article disclosed their relationship with the industry and the involvement of the sponsor in the manuscript.

Tool: Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health. 2022 Jan;25(1):10-31. doi: 10.1016/j.jval.2021.10.008. Erratum in: Value Health. 2022 Jun;25(6):1060. PMID: 35031088.