CO103

Real-world effectiveness of sotrovimab for the early treatment of COVID-19: evidence from the National COVID Cohort Collaborative (N3C)

Christopher Bell[1]; Priyanka Bobbili[2]; Raj Desai[2]; Daniel C. Gibbons[3]; Vishal Patel[3*]; Maral DerSarkissian[4]; Myriam Drysdale[3]; Helen Birch[3]; Emily Lloyd[3]; Adina Zhang[2]; Mei Sheng Duh[2]

[1]GSK, Research Triangle Park, NC, USA; [2]Analysis Group, Boston, MA, USA; [3]GSK, Brentford, Middlesex, UK; [4]Analysis Group, Los Angeles, CA, US

*at time of study

Background

- Sotrovimab is a dual-action human IgG1κ mAb derived from the parental mAb S309, a potent neutralizing mAb directed against the spike protein of SARS-CoV-2[1–4]
- While clinical trials have demonstrated the safety and efficacy of sotrovimab[5], it was deauthorized by the FDA on April 5th 2022 following the emergence of the Omicron BA.2 sub-variant.[6]
- There is a need for real-world effectiveness data especially in light of the rapidly changing COVID-19 environment
- The primary aim of the current study was to compare real-world outcomes for sotrovimab-treated versus untreated patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, during a period of Delta, Omicron BA.1, and early Omicron BA.2 predominance

Methods

- This retrospective cohort study used electronic health records from N3C (Limited Dataset) to identify US patients aged ≥12 years diagnosed with COVID-19 (positive test or ICD-10: U07.1 during the period 27 September 2021 to 30 April 2022) in an ambulatory setting who met EUA high-risk criteria
- Patients were assigned to one of two cohorts:
  - Sotrovimab cohort: patients receiving sotrovimab in an outpatient or ER setting within 10 days of COVID-19 diagnosis, where index date was defined as date of sotrovimab administration
  - Untreated cohort: patients with no evidence of authorized mAb (early or prophylaxis treatment) or antiviral treatment for COVID-19 in an outpatient or ER setting, where index date was imputed based on the time distribution between diagnosis and sotrovimab treatment for the sotrovimab cohort as well as calendar month of the COVID-19 diagnosis
- The baseline period was defined as the 1 year prior to index for assessment of demographics and clinical characteristics with the exception of vaccination status, which used all available patient data up to 14 days prior to index date
- The primary outcomes of interest were all-cause hospitalization, all-cause mortality and the composite of all-cause hospitalization or all-cause mortality; these were evaluated during the 29-day post-index follow-up period and reported as descriptive rates and adjusted (via IPTW) ORs and 95% CIs
- Sub-group analyses included stratification of the primary endpoint by age at index, variant predominance (based on date as viral sequencing data was not available), vaccination status, and high-risk status

Results

- Of nearly 2.9 million patients diagnosed with COVID-19 in the N3C data set, 4,992 met the inclusion criteria for the sotrovimab cohort and 541,325 were included in the untreated cohort
- **Table 1** presents baseline demographics and clinical characteristics
  - Prior to weighting, an absolute standard difference of more than 10% was noted for most categories, indicating imbalance between the sotrovimab and untreated cohorts,
  - After weighting, these imbalances were addressed for most of the categories, although some imbalances remained; Black/African American race, Quan-CCI, and several of the EUA categories.

Primary endpoint

- **Table 2** shows data from the descriptive analysis (overall and by month)
  - The overall 29-day all-cause hospitalization or mortality rates were 3.5% and 4.5% in the sotrovimab and untreated cohorts, respectively
- **Table 3** shows the unadjusted and adjusted comparative analysis of primary endpoints
  - The adjusted odds of all-cause hospitalization or mortality was reduced by 25% in the sotrovimab group compared with the untreated cohort (OR=0.75)

Sub-group analyses

- **Figure 1** shows forest plots for the sub-group analyses, summarizing the likelihood of all-cause hospitalization or mortality in the sotrovimab cohort compared with the untreated control group.

Table 1: Baseline demographics and clinical characteristics

	Unweighted				IPTW			
	Sotrovimab (*n* = 4,992)	Untreated (*n* = 541,325)	P-value	Absolute standardized difference[1]	Sotrovimab (*n* = 4,805)	Untreated (*n* = 4,992)	P-value	Absolute standardized difference[1]
Mean (SD) age, y	60 (17.4)	53.6 (19.2)	<0.001	34.7% #	52.4 (19.2)	53.7 (19.2)	0.014	6.6%
Race, n (%)								
White	4,186 (83.9)	405,279 (74.9)	<0.001	23.3% #	3,426 (71.3)	3,742 (75.0)	0.002	8.2%
Black / African American	436 (8.7)	74,186 (13.7)	<0.001	15.8% #	861 (17.9)	682 (13.7)	<0.001	11.7% #
Asian / Pacific Islander	56 (1.1)	11,179 (2.1)	<0.001	7.5%	128 (2.7)	103 (2.1)	0.129	4.0%
Other / unknown	314 (6.3)	50,406 (9.3)	<0.001	11.5% #	390 (8.1)	466 (9.3)	0.157	4.3%
Female sex, n (%)	3,002 (60.1)	336,752 (62.2)	0.003	4.3%	3,170 (66.0)	3,105 (62.2)	0.001	7.9%
Mean (SD) time to sotrovimab infusion from diagnosis, days	1.6 (1.8)	1.3 (2.0)	<0.001	16.7% #	1.3 (1.6)	1.3 (2.0)	0.891	0.3%
Mean (SD) Quan-CCI	1.6 (2.3)	0.9 (1.6)	<0.001	39.0% #	1.1 (1.8)	0.9 (1.6)	<0.001	13.7% #
Vaccination status, n (%)								
Fully vaccinated[2]	2,311 (46.3)	194,387 (35.9)	<0.001	21.2% #	1.576 (32.8)	1,797 (36.0)	0.002	6.8%
Partially vaccinated	204 (4.1)	17,933 (3.3)	0.002	4.1%	196 (4.1)	165 (3.3)	0.073	4.0%
Unknown	2,477 (49.6)	329,005 (60.8)	<0.001	22.6% #	3,034 (63.1)	3,030 (60.7)	0.024	5.0%
Mean (SD) number of EUA criteria	3.1 (2.2)	2.2 (1.7)	<0.001	45.1% #	2.5 (1.8)	2.2 (1.7)	<0.001	13.1% #
1 EUA criterion, n (%)	1,435 (28.7)	256,049 (47.3)	<0.001	38.9% #	1,921 (40.0)	2,354 (47.2)	<0.001	14.5% #
2 EUA criteria, n (%)	1,001 (20.1)	118,274 (21.8)	0.002	4.4%	1,124 (23.4)	1,090 (21.8)	0.131	3.7%
≥3 EUA criteria, n (%)	2,556 (51.2)	167,002 (30.9)	<0.001	42.3% #	1,760 (36.6)	1,548 (31.0)	<0.001	11.9% #

[1]For each variable, an absolute standardized difference more than 10% was considered to be an imbalance between the two cohorts and denoted with "#"; [2]Received 2 or more vaccinations during assessment period with an mRNA vaccine, or a single dose of viral vector vaccine

Table 2: Descriptive analysis of primary endpoints (unweighted cohort)

			All-cause hospitalization[1]			All-cause mortality[1]			All-cause hospitalization or mortality[1]		
	Sotrovimab cohort[2]	Untreated cohort[2]	Sotrovimab[3] (*n* = 4,992)	Untreated[3] (*n* = 541,325)	P-value[6]	Sotrovimab[2] (*n* = 4,992)	Untreated[2] (*n* = 541,325)	P-value[6]	Sotrovimab[2] (*n* = 4,992)	Untreated[2] (*n* = 541,325)	P-value[6]
Overall, n (%)	4,992	541,325	167 (3.3)	22,572 (4.2)	0.004*	15 (0.3)	2,811 (0.5)	0.041*	176 (3.5)	24,163 (4.5)	0.002*
Month											
September 2021[4]	8 (0.2)	8,338 (1.5)	0	449 (5.4)	N/A	0	81 (1.0)	N/A	0	493 (5.9)	N/A
October 2021	84 (1.7)	51,187 (9.5)	2 (2.4)	2,358 (4.6)	N/A	0	334 (0.7)	N/A	2 (2.4)	2,559 (5.0)	N/A
November 2021	296 (5.9)	54,390 (10.0)	12 (4.1)	2,781 (5.1)	0.488	1 (0.3)	433 (0.8)	N/A	13 (4.4)	3,012 (5.5)	0.464
December 2021	800 (16.0)	111,368 (20.6)	27 (3.4)	5,129 (4.6)	0.116	2 (0.2)	686 (0.6)	N/A	28 (3.5)	5,466 (4.9)	0.079
January 2022	1,924 (38.5)	226,766 (41.9)	74 (3.8)	7,703 (3.4)	0.308	6 (0.3)	867 (0.4)	N/A	78 (4.1)	8,213 (3.6)	0.343
February 2022	1,304 (26.1)	54,271 (10.0)	46 (3.5)	2,488 (4.6)	0.082	6 (0.5)	311 (0.6)	N/A	49 (3.8)	2,690 (5.0)	0.056
March 2022	530 (10.6)	17,019 (3.1)	6 (1.1)	927 (5.4)	N/A	0	68 (0.4)	N/A	6 (1.1)	970 (5.7)	N/A
April 2022	46 (0.9)	17,227 (3.2)	0	708 (4.1)	N/A	0	30 (0.2)	N/A	0	730 (4.2)	N/A
May 2022[5]	–	759 (0.1)	–	29 (3.8)	N/A	–	1 (0.1)	N/A	–	30 (4.0)	N/A

[1]Hospitalizations defined from N3C's algorithm mapping visits to macrovisits; [2]Overall sample size of cohort was presented; sample size by month and its proportion of the overall cohort was presented; [3]Number and proportion of patients with hospitalization presented overall and monthly; [4]Only patients with index date on or after September 27 2021 were included; [5]No patients with index dates in May 2022 were observed in the sotrovimab cohort; [6]Statistical significance for p-values <0.05 is denoted with * (p-values reported as N/A due to insufficient sample size)

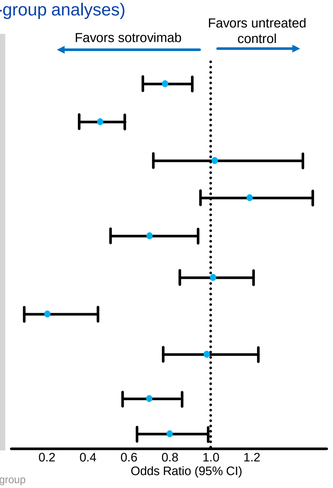
Table 3: Comparative analysis of primary endpoints

	Sotrovimab (*n* = 4,992)	Untreated (*n* = 541,325)	P-value
All-cause hospitalization or mortality			
Unadjusted OR (95% CI)	0.78 (0.67, 0.91)	Reference	0.001*
Doubly-robust IPTW-adjusted[1] OR (95% CI)	0.75 (0.61, 0.92)	Reference	0.005*
All-cause hospitalization			
Unadjusted OR (95% CI)	0.80 (0.68, 0.93)	Reference	0.004*
Doubly-robust IPTW-adjusted[1] OR (95% CI)	0.77 (0.63, 0.95)	Reference	0.016*

[1]IPTW-weighted logistic regression model further adjusted for covariates with a standardized difference of >10% after weighting, which included race, Quan-CCI, pregnancy status, and immunosuppressive disease, using a doubly robust approach
Statistical significance for p-values < 0.05 is denoted with *

Figure 1: Forest plot summarizing the overall likelihood of all-cause hospitalization or mortality (unadjusted sub-group analyses)

	N	OR (95% CI)[1]	P-value
Overall	546,317	0.78 (0.67, 0.91)	<0.01*
Age 65+	187,555	0.46 (0.36, 0.58)	<0.001*
Age 55–64	90,816	1.02 (0.72, 1.45)	0.90
Age 12–54	267,946	1.19 (0.95, 1.50)	0.14
Delta variant period	226,471	0.70 (0.51, 0.94)	0.02*
Omicron BA.1 period	284,265	1.01 (0.85, 1.21)	0.87
Omicron BA.2 period	35,581	0.20 (0.09, 0.45)	<0.001*
Fully vaccinated	196,698	0.98 (0.77, 1.24)	0.86
Unknown vacc. status	331,482	0.70 (0.57, 0.86)	<0.001*
High risk[2]	121,041	0.80 (0.64, 0.99)	0.04*



Statistical significance for p-values < 0.05 is denoted with *
[1]Unadjusted ORs and p-values are reported by overall and for each subgroup
[2]patients who had at least one of the following during the baseline period: Hodgkin's lymphoma, Non-Hodgkin lymphoma, leukemia, solid cancers, HIV, autoimmune disease, solid organ transplant, allogenic stem cell transplant, and/or immunosuppressive treatment

Conclusions

- **This study demonstrates that there are distinct differences in baseline characteristics of patients diagnosed with COVID-19 that warrant careful consideration when designing comparative effectiveness studies**
- **In this study, sotrovimab demonstrated (in descriptive and adjusted analyses) clinical effectiveness in preventing hospitalization and/or mortality during the period Sept 2021–April 2022, when Delta and Omicron (BA.1/BA.2) were the predominant variants**

Abbreviations

CCI, Charlson Comorbidity Index; CI, confidence interval; EUA, emergency use authorization; ER, emergency room; FDA, Food and Drug Administration; mAb, monoclonal antibody; IPTW, inverse probability of treatment weighting; IQR, interquartile range; N/A, not applicable; OR, odds ratio

Disclosures

CB, DG, VP, MD, HB, EL: employees and/or hold stocks/shares in GSK
PB, RD, MD, AZ, MSD: employees of Analysis Group; Analysis Group received funding from GSK to conduct the study

Acknowledgments

This study was funded by GSK (study ID: 219020) in collaboration with Vir Biotechnology. Editorial support (in the form of writing assistance, collating and incorporating authors' comments for each draft, assembling tables, grammatical editing and referencing) was provided by Tony Reardon of Luna, OPEN Health Communications, in accordance with Good Publication Practice (GPP) guidelines (www.ismpp.org/gpp-2022), and was funded by GSK and Vir Biotechnology
The analyses described in this presentation were conducted with data or tools accessed through the NCATS N3C Data Enclave https://covid.cd2h.org and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NCATS U24 TR002306, Axle Informatics Subcontract: NCATS-P00438-B. This research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists who have contributed to the on-going development of this community resource (https://doi.org/10.1093/jamia/ocaa196)

References

(1) Gaudinsk MR et al. PLoS Medicine 2018;15(1):e1002493
(2) Ko SY et al. Nature 2014;514:642–5
(3) Cathcart AL et al. BioRxiv 2021; https://doi.org/10.1101/2021.03.09.434607
(4) Pinto D et al. Nature 2020;583:290–5
(5) Gupta A et al. JAMA 2022;327:1236–46
(6) https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs