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Safety, Tolerability, and Viral Pharmacodynamics of the Monoclonal Antibody Sotrovimab Administered via Intramuscular Injection for the Treatment of Early Mild-to-Moderate COVID-19

Anil Gupta[1]; Maria Teresa Perez-Rodríguez[2]; Yaneicy Gonzalez-Rojas[3]; Moti Ramgopal[4]; Almena Free[5]; Jennifer Han[6]; Jennifer Moore[7]; Rudrani Banerjee[8]; Phillip J. Yates[9]; Jill T. Walker[6]; Mary Beth Connolly[10]; Gretja Schnell[11]; Andrea L. Cathcart[11]; Varsha Imber[7]; Rabia Anselm[7]; Lindsay Winograd[12]; Scott Segal[6]; Andrew Skingsley[7]; Melissa Aldinger[11]; Amanda Peppercorn[6]; Jaynier Moya[13]

[1]Albion Finch Medical Centre, Ontario, Canada; [2]Hospital Álvaro Cunqueiro, Vigo, Pontevedra Galicia sur Health Research Institute, Spain; [3]Optimus U Corp, Miami, FL, USA; [4]Midway Immunology and Research Center, Fort Pierce, FL, USA; [5]Pinnacle Research Group, LLC, Anniston, AL, USA; [6]GSK, Collegeville, PA, USA; [7]GSK, Brentford, UK; [8]GSK India Global Service Private Ltd, Bangalore, India; [9]GSK, Stevenage, UK; [10]GSK, Research Triangle Park, NC, USA; [11]Vir Biotechnology Inc, San Francisco, CA, USA; [12]GSK, Mississauga, Ontario, Canada; [13]Pines Care Research Center LLC, Pembroke Pines, FL, USA

Background

- Sotrovimab is a pan-sarbecovirusdual-action neutralizing monoclonal antibody that has been shown to be efficacious in the early treatment of mild to moderate COVID-19 in patients at high risk of clinical progression.
- Sotrovimab 500 mg IV was authorized by the FDA under EUA from May 2021 to April 2022 for treatment of patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease or death.[1,2]
- Sotrovimab 500 mg IV holds holds current marketing authorization in Europe, and current provisional, temporary, or conditional marketing in many countries, including the UK, Japan, and Australia[3–6]
- In the COMET-ICE Phase 3 clinical trial, a 500 mg IV infusion of sotrovimab resulted in a statistically significant 79% reduction in relative risk (RR: 0.21, 95% CI: 0.09, 0.50) of COVID-19 progression through Day 29 (defined as all-cause >24-hour hospitalization or death due to any cause[7]) in non-hospitalized participants compared to placebo.
- Given the evolving landscape of SARS-CoV-2 variants and variability in vaccine effectiveness and uptake, there is a continued need for therapeutics for the treatment of COVID-19.
- Sotrovimab 500 mg IM has been demonstrated to be non-inferior to sotrovimab 500 mg IV, which may enable broader use across a variety of healthcare delivery settings compared to an IV infusion.[8]
- The objective of COMET-PEAK was to evaluate the safety, tolerability, and viral pharmacodynamics of sotrovimab administered via IV infusion or IM injection as treatment for adults ≥18 years with early mild/moderate COVID-19.

Methods

COMET-PEAK is a randomized, parallel group, multicenter three-part study evaluating the safety, tolerability, PK, and viral PD of sotrovimab for early treatment of non-hospitalized adults aged ≥18 years with mild-to-moderate COVID-19.

- PK results are not included in this poster and are planned to be presented in the future.

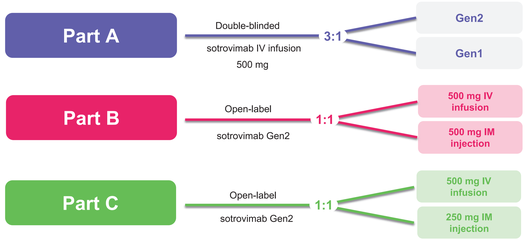
In Part A, the safety, tolerability, virology, and PK of generation 1 (Gen1) and generation 2 (Gen2) sotrovimab administered as a single 500 mg IV infusion were evaluated (**Figure 1**).

- Gen1 and Gen2 sotrovimab have been shown to have a high degree of analytical and bioanalytical comparability, with Gen2 being produced from a master clonal cell bank.
- The primary objective was to assess the safety and tolerability of Gen1 and Gen2 IV sotrovimab through Day 29.

In Parts B and C, the safety, tolerability, PK, and viral PD of Gen2 sotrovimab administered as a single 500 mg IV infusion or as a single 500 mg or 250 mg IM injection, respectively, were evaluated (**Figure 1**).

- Randomization for participants in Part C was stratified based on prior exposure to an authorized/approved SARS CoV-2 vaccine.
- IM administration in Part B was via two injections, one in each dorsogluteal muscle.
- In Part C, IM administration was via either the dorsogluteal muscle (one injection) or the deltoid muscles (two injections, one in each muscle).
- The primary objective was to compare the virologic response of sotrovimab IM to IV, with an endpoint of mean AUC of SARS-CoV-2 viral load as measured by qRT-PCR from Day 1 to Day 8 ($AUC_{D1–8}$) in nasopharyngeal swabs and with predefined 90% CI limits of 0.5–2.0 indicating equivalence.
- The secondary objective was to evaluate the safety and tolerability profile of sotrovimab Gen2 administered via IV infusion and IM injection through Day 29.

Figure 1: COMET-PEAK Study design



Results

- A total of 30, 167, and 157 participants were enrolled in Parts A, B, and C, respectively, from February 2021 to July 2021.
- The median age of participants ranged from 41 to 50 years depending on treatment group. Approximately ~50% of each population had at least one risk factor for progression to severe disease, with the most common risk factor being obesity (BMI>30 kg/m^2), followed by age ≥55 years (**Table 1**).

Table 1: Summary of risk factors for COVID-19 progression

	Part A Total (N=30)	Part B Total (N=166)	Part C Total (N=157)
Conditions as risk factor for COVID-19 progression[a], n (%)			
Any Condition	15 (50%)	85 (51%)	70 (45%)
Obesity (BMI >30 kg/m^2)	12 (40%)	54 (33%)	46 (29%)
Aged ≥55 (years)	7 (23%)	37 (22%)	30 (19%)
Chronic obstructive pulmonary disease	2 (7%)	1 (<1%)	1 (<1%)
Diabetes requiring medication	2 (7%)	13 (8%)	9 (6%)
Moderate to severe asthma	N/A	5 (3%)	4 (3%)
Number of COVID-19 risk factor conditions met, n (%)			
0	15 (50%)	81 (49%)	87 (55%)
1	9 (30%)	62 (37%)	51 (32%)
2	4 (13%)	21 (13%)	18 (11%)
3	2 (7%)	2 (1%)	1 (<1%)

Note: Subjects may occur more than once in the list of risk factors. aMedical conditions present as risk factors at screening.

- In Part A, the viral load was numerically lower in saliva samples compared to NMT. In the virology population (n=22; Gen1 = 6, Gen2 = 16), which included participants with a quantifiable sample at baseline, viral load declined from baseline in both saliva and NMT samples across the Gen1 and Gen2 groups. Mean change in viral load from baseline to Day 8 was –1.705 log_{10} copies/mL and –2.703 log_{10} copies/mL in NMT samples in the Gen1 group and the Gen2 group, respectively. Sotrovimab was well-tolerated, with 3 AEs reported in the Gen2 arm (Grade ≤2, none related to study treatment). There were no SAEs reported.
- For Parts B and C, the nasopharyngeal viral load at baseline and through Day 29 of follow-up for each arm is shown in **Figure 2a** and **Figure 2b**. The decrease in mean viral load from baseline (log_{10} copies/mL) was comparable between the 500 mg IV and 500 mg IM groups through Day 29 for Part B, and between the 500 mg IV and 250 mg IM groups through Day 29 for Part C. The primary objective was met for both study parts: the ratio of the least square geometric mean viral load $AUC_{D1–8}$ of sotrovimabIM vs IV was 1.04 (90% CI, 0.98, 1.09) and 1.02 (90% CI, 0.94, 1.11), for Parts B and C, respectively (**Table 2**).

Figure 2a: Plot of mean (±SD) SARS-CoV-2 viral load (log_{10} copies/mL) as measured by qRT PCR from NP swab samples through Day 29: Part B (Viral pharmacodynamic population)

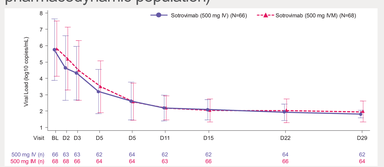


Figure 2b: Plot of mean (±SD) SARS-CoV-2 viral load (log_{10} copies/mL) as measured by qRT PCR from NP swab samples through Day 29: Part C (Viral pharmacodynamic population)

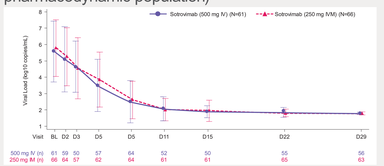


Table 2: Analysis of mean $AUC_{D1–8}$ of SARS-CoV-2 viral load (log_{10} copies/mL) as measured by qRT-PCR from NP swab samples (Viral pharmacodynamic population)

	Sotrovimab IM		Sotrovimab IV		Sotrovimab IM vs IV	
	n	LS Geometric Mean (SE logs)	n	LS Geometric Mean (SE logs)	Ratio (SE logs)	90% CI
Part B	***Sotrovimab (500 mg IM)***		***Sotrovimab (500 mg IV)***			
	65	25.28 (0.022)	64	24.40 (0.022)	1.04 (0.031)	(0.98, 1.09)
Part C	***Sotrovimab (250 mg IM)***		***Sotrovimab (500 mg IV)***			
	62	26.72 (0.034)	55	26.20 (0.036)	1.02 (0.049)	(0.94, 1.11)

Note: Analysis performed using an ANCOVA model with covariates of treatment and baseline log_{10} viral load, and prior exposure to authorized or approved SARS-CoV-2 vaccine (part C). A ratio >1 indicates a larger AUC was seen in the IM subjects. Baseline log_{10} viral load was defined as the non-missing assessment taken at Day 1 excluding the "NEG" and "<2.08" results

- Through Day 29 of follow-up in Parts B and C, the most common adverse event was ISRs in the IM arms. A total of 10 (11%) participants in the 500 mg IM group and 4 (5%) (two each in dorsogluteal and deltoid injection sites) participants in the 250 mg IM group experienced an ISR. All of the ISRs were Grade 1, and most were related to injection site pain +/- tenderness. SAEs were uncommon and related to COVID-19 progression, including one death in the 250 mg IM arm (**Table 3a** and **Table 3b**).

Table 3a: Serious adverse events: Part B

Participant	Age (years)/ Sex (M/F)/ Race	SAE (preferred term)	Time to SAE from dose (days)	Outcome	Maximum grade	Related to study treatment?	Relevant medical history and COVID-19 risk factors
Sotrovimab (500 mg IV)							
1	63/M/Asian	COVID-19 pneumonia	2	Recovered/ Resolved	3	No	Age
Sotrovimab(500 mg IM)							
2	54/F/White	COVID-19 pneumonia	4	Recovered/ Resolved	3	No	Overweight
3	50/F/White	Bilateral pneumonia	3	Recovered/ Resolved	4	No	Obesity, asthma
		Dehydration	2	Recovered/ Resolved	3	No	
		Acute respiratory failure	3	Recovered/ Resolved	4	No	

Table 3b: Serious adverse events: Part C

Participant	Age (years)/ Sex (M/F)/ Race	SAE (preferred term)	Time to SAE from dose (days)	Outcome	Maximum grade	Related to study treatment?	Relevant medical history and COVID-19 risk factors
Sotrovimab (500 mg IV)							
1	62/M/White	COVID-19 pneumonia	11 hours	Recovered/ Resolved	1	No	Age
Sotrovimab (250 mg IM)							
2	27/M/White	COVID-19 pneumonia	4	Recovered/ Resolved	4	No	Obesity
3	60/F/White	COVID-19 pneumonia	3	Recovered/ Resolved	3	No	Age, diabetes mellitus, hypertension
4	67/M/White	COVID-19 pneumonia	3	Fatal	5	No	Age, hypertension

- There were few treatment-related AEs, and none were serious: 2 of 84 (2%) participants in the IV group and 8 of 82 participants (10%) in the IM group had treatment-related AEs in Part B. No participant in the 500 mg IV group and 4 of 78 participants (5%) in the 250 mg IM group had treatment-related AEs in Part C.

Conclusions

- In both Part B and C, the equivalence with respect to mean $AUC_{D1–8}$ of SARS-CoV-2 viral load between the treatment groups was met.
- Sotrovimab 500 mg IM has been demonstrated to be non-inferior to sotrovimab 500 mg IV in the COMET-TAIL Ph3 clinical trial, which may enable broader use across a variety of healthcare delivery settings compared to an IV infusion.[8]
- The viral PD results seen in the present study demonstrated equivalence between 500 mg IV and 250 mg IM. In the context of the COMET-TAIL study, clinical data suggest that nasopharyngeal viral load changes may not be a robust clinical surrogate measure for COVID-19 disease progression.
- Sotrovimab IM injection was found to be well-tolerated and other than injection site reactions associated with the route of administration, no other safety concerns were identified with IM administration. Overall, the AE profile of sotrovimab was consistent with the natural history of the underlying disease and the known safety profile of IV sotrovimab.
- IM administration of sotrovimab may improve patient access to therapy by offering physicians an alternative route of administration.

Abbreviations

AE, adverse event; ANCOVA, analysis performed using an analysis of covariance; AUC, area under the curve; BL, baseline; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease; IM, intramuscular; ISR, injection-site reaction; IV, intravenous; NMT, nasal mid-turbinate; NP, nasopharyngeal; PD, pharmacodynamics; PK, pharmacokinetics; qRT-PCR, quantitative polymerase chain reaction; RT-PCR, quantitative reverse transcriptase polymerase chain reaction; SAE, serious adverse events; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error.

Disclosures

Conflicts of interest: JM, JH, AS, AP, JTW, VI, MBC, RB, RA, LW: employees of GSK and hold stocks/shares in the company.

PJY, NH: Former employees (retired) of GSK and hold stocks/shares in the company.

GS, AC, MA: Employees of Vir Biotechnology and may hold shares/stock in the company.

AG: Vir Biotechnology consultant, speaker, contracted researcher.

MR: consultant, speaker ViiVHealthcare, and holds stocks / shares in the company.

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