Resistance Analysis in the COMET-TAIL Study: Participants With Mild-to-Moderate COVID-19 Treated With Intramuscular or Intravenous Sotrovimab

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Background

- Sotrovimab (VIR-7831) is an engineered human monoclonal antibody that targets a conserved region of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein and contains the "LS" modification to increase half-life
- Sotrovimab neutralizes most spike protein variants *in vitro*, including Alpha, Beta, Gamma, Delta, Epsilon, and Omicron (B.1.1.529/BA.1). A 16-fold shift was observed for the Omicron BA.2 variant[1]
- Sotrovimab 500 mg intravenous (IV) was authorized by the US Food and Drug Administration under emergency use authorization from May 2021 to April 2022 for the treatment of patients with mild-to-moderate coronavirus disease 2019 (COVID-19) who are at high risk of progression to severe disease or death[2,3]
- Sotrovimab 500 mg IV holds current marketing authorization in Europe, and current provisional, temporary, or conditional marketing in many countries, including the United Kingdom, Japan, and Australia[4-7]
- COMET-TAIL (ClinicalTrials.gov Identifier: NCT04913675) is a Phase 3, randomized, multicenter, open-label, non-inferiority study to evaluate intramuscular (IM) versus IV administration of sotrovimab for the early treatment of mild-to-moderate COVID-19 in participants at high risk of disease progression

Objective

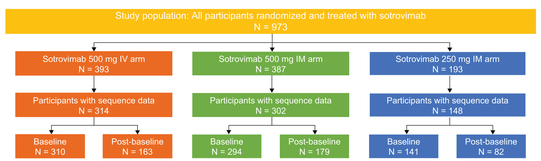
- In this virology resistance analysis, the study objectives were to identify SARS-CoV-2 variants of concern or variants of interest (VOC/VOI) and characterize amino acid substitutions in the SARS-CoV-2 spike gene in COMET-TAIL participants

Methods

Study Design

- Participants were randomized to receive sotrovimab as a single 500 mg IV infusion, a single 500 mg IM injection, or a single 250 mg IM injection (**Figure 1**). Enrollment occurred between June and August 2021[8]

Figure 1: Participant Enrollment and SARS-CoV-2 Spike Sequence Availability by Treatment Arm



mAb, monoclonal antibody; IV, intravenous; IM, intramuscular.
Participants with samples that were unavailable or had viral load below the limit of the sequencing assay (3.0 $\log_{10}$ copies/mL) were not included in sequence analysis. Of participants with baseline sequence data available, 45 participants (500 mg IV: n = 15; 500 mg IM: n = 20; 250 mg IM: n = 10) had a Day 3 sample substituted for Day 1.

Sequence Analysis

- Nasopharyngeal swab samples were collected at baseline (Day 1 or Day 3, if Day 1 was unavailable) and post-baseline (Day 5-Day 29) visits. Next-generation sequencing was conducted using Illumina MiSeq with primers derived from the Centers for Disease Control and Prevention protocol.[9] Amino acid substitutions were reported against reference sequence Wuhan-Hu-1 (GenBank: MN908947.3) using a threshold of ≥5% allelic frequency (AF)
  - Prevalence of VOC/VOI in COMET-TAIL participants was assessed using characteristic spike amino acid substitutions as defined by the World Health Organization[10]
  - Baseline, post-baseline, and treatment-emergent substitutions at sotrovimab epitope positions were evaluated (spike amino acids 332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, and 509)

Phenotypic Analysis

- Phenotypic analyses of sotrovimab epitope substitutions detected in COMET-TAIL participants were conducted using a SARS-CoV-2 vesicular stomatitis virus pseudotyped virus neutralization assay

Results

VOC/VOI Detected in COMET-TAIL Participants

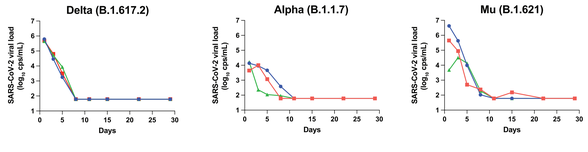
- Among 764 COMET-TAIL participants with sequence results, 98.0% (749/764) were infected with a VOC/VOI (**Table 1**; **Figure 2**). The Delta (B.1.617.2) variant was predominant, detected in 88.2% (674/764) of participants
  - Sotrovimab retains *in vitro* neutralization activity against pseudotyped virus expressing VOC/VOIs[1] and single substitutions of interest (reported in **Table 1**) detected in COMET-TAIL participants
  - Of the participants harboring VOC/VOIs, 3.5% (26/749) met the primary endpoint for clinical progression of hospitalization for >24 hours or death due to any cause through Day 29 (**Table 1**). Of the participants infected with the Alpha, Delta, or Mu variants, 3.2% (1/31), 3.6% (24/674), and 4.2% (1/24), respectively, met the primary clinical endpoint for progression, supporting that the clinical efficacy was not impacted by the presence of specific VOC/VOIs

Table 1: Prevalence of VOC/VOI and Single Substitutions of Interest Detected in COMET-TAIL Participants

Variant	n (%)[a] 500 mg IV (N = 314)	500 mg IM (N = 302)	250 mg IM (N = 148)	Total (N = 764)	Participants meeting primary clinical endpoint[b]
VOC/VOI					
Alpha (B.1.1.7)	9 (2.9)	14 (4.6)	8 (5.4)	31 (4.1)	1 (500 mg IM)
Delta (B.1.617.2)	282 (89.8)	268 (88.7)	124 (83.8)	674 (88.2)	24 (500 mg IV: 4, 500 mg IM: 9, 250 mg IM: 11)[c]
Gamma (P.1)	5 (1.6)	3 (1.0)	1 (0.7)	9 (1.2)	0
Iota (B.1.526)	1 (0.3)	0	1 (0.7)	2 (0.3)	0
Lambda (C.37)	1 (0.3)	1 (0.3)	0	2 (0.3)	0
Mu (B.1.621)	6 (1.9)	9 (3.0)	9 (6.1)	24 (3.1)	1 (500 mg IV)
Delta (B.1.617.2) and Alpha (B.1.1.7)[d]	1 (0.3)	1 (0.3)	1 (0.7)	3 (0.4)	0
Delta (B.1.617.2) and Mu (B.1.621)[d]	0	3 (1.0)	1 (0.7)	4 (0.5)	0
Beta, Eta, Kappa, Epsilon, Zeta, Omicron, and B.1.1.519	0	0	0	0	N/A
Total VOC/VOI	305 (97.1)	299 (99.0)	145 (98.0)	749 (98.0)	26[c]
Single amino acid substitutions of interest[e]					
E484K	0	1 (0.3)	0	1 (0.1)	0
L452R	4 (1.3)	0	1 (0.7)	5 (0.7)	0
N501Y	1 (0.3)	0	0	1 (0.1)	0
Total (all variants)	310 (98.7)	300 (99.3)	146 (98.6)	756 (99.0)	26[c]

VOC/VOI, variant of concern/variant of interest; IV, intravenous, IM, intramuscular; N/A, not applicable.
[a]n: number of participants with each VOC/VOI or single substitution; N: number of participants with sequence results.
[b]The primary clinical endpoint for progression was defined as hospitalization for >24 hours for acute management of any illness or death from any cause through Day 29.
[c]1 participant in the 250 mg IM arm who met the primary endpoint for clinical progression was excluded from the primary analysis efficacy population, as this individual was immunocompetent and fully vaccinated against SARS-CoV-2 and met a key exclusion criteria; however, this participant received sotrovimab and was included in viral-resistance analyses.
[d]Participants with >1 VOC/VOI detected (Delta and Alpha or Delta and Mu) contained all of the characteristic spike substitutions for each variant. Variants may have been detected in the same visit or across baseline and post-baseline visits.
[e]Participants with single amino acids of interest did not have the spike substitutions characteristic of any VOC/VOI.

Figure 2: Median Viral Load Profiles for Participants with VOC/VOI Detected at ≥2% Prevalence in COMET-TAIL



VOC/VOI, variant of concern/variant of interest; IV, intravenous; IM, intramuscular.
Median viral load profiles for participants infected with Delta (500 mg IV: n = 282; 500 mg IM: n = 268; 250 mg IM: n = 124), Alpha (500 mg IV: n = 9; 500 mg IM: n = 14; 250 mg IM: n = 8), and Mu (500 mg IV: n = 6; 500 mg IM: n = 9; 250 mg IM: n = 9) variants.

Epitope Substitutions Detected in COMET-TAIL Participants

Frequency of Epitope Substitutions

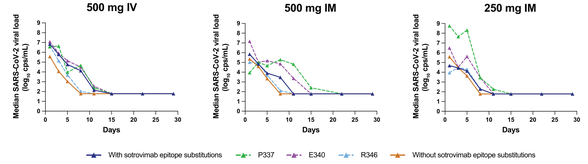
- Epitope substitutions (**Table 2**; **Figure 3**) were detected at baseline and post-baseline in 10.7% (82/764) of participants overall at any visit
- Predominant epitope substitutions detected at baseline included R346K (3.5% [26/745]; associated with the Mu variant), and post-baseline included P337L and E340A/K/V (10.8% [46/424]), and R346K (3.5% [15/424]; associated with the Mu variant)
  - Of the 82 participants with an epitope substitution detected at any visit, 48 participants had a substitution detected at amino acid positions 337 or 340
- Treatment-emergent epitope substitutions were detected in 12.3% (50/405) of participants with paired baseline and post-baseline sequences (**Table 3**). Predominant treatment-emergent substitutions included P337L and E340A/K/V (11.1% [45/405]), which confer reduced susceptibility to sotrovimab *in vitro* (**Table 4**)
- Post-baseline (**Table 2**) and treatment-emergent (**Table 3**) epitope substitutions were detected in a higher proportion of participants in the 500 mg IV arm compared to the 500 mg IM and 250 mg IM arms

Table 2: Summary of Epitope Substitutions Detected at ≥5% Allelic Frequency in COMET-TAIL Participants at Baseline or Post-baseline

No. of participants	Amino acid substitution[a] 500 mg IV Baseline	500 mg IV Post-baseline	500 mg IM Baseline	500 mg IM Post-baseline	250 mg IM Baseline	250 mg IM Post-baseline
Total, % (n/N)[b]	3.2% (10/310)	22.7% (37/163)	5.1% (15/294)	9.5% (17/179)	7.1% (10/141)	9.8% (8/82)
1	C336R, P337S, E340STOP, R346I	T333I	P337L, G339C, E340K, R509G	N354K, N360S, N440K	N440K	P337L, E340V
2	-	-	N440K	-	-	E340K
3	-	E340V	-	E340A, E340V	-	-
≥4 (n)	R346K (7)	R346K (5), G339D (6), E340A (7), P337L (9), E340K (19)	R346K (10)	P337L (4), E340K (7), R346K (4)	R346K (9)	R346K (6)

IV, intravenous; IM, intramuscular.
[a]Participants with >1 epitope substitution detected at baseline or post-baseline visits were counted in the total count for each substitution.
[b]n: number of participants with a baseline or post-baseline epitope substitution; N: number of participants with baseline or post-baseline sequence data.

Figure 3: Median Viral Load Profiles for Participants with Sotrovimab Epitope Substitutions



IV, intravenous; IM, intramuscular.
All participants with sotrovimab epitope substitutions at positions P337 (500 mg IV: n = 10; 500 mg IM: n = 4; 250 mg IM: n = 1), E340 (500 mg IV: n = 27; 500 mg IM: n = 10; 250 mg IM: n = 3), and R346 (500 mg IV: n = 8; 500 mg IM: n = 12; 250 mg IM: n = 10) are included in the sotrovimab epitope substitutions group (500 mg IV: n = 42; 500 mg IM: n = 27; 250 mg IM: n = 13) shown in dark blue as well as their respective subgroups shown in dashed lines. Participants with multiple epitope substitutions at positions P337, E340, and R346 are included for each position where a substitution was detected and may be included in >1 subgroup (**Table 2**; **Table 3**). Participants without sotrovimab epitope substitutions (500 mg IV: n = 272; 500 mg IM: n = 275; 250 mg IM: n = 135) are shown in orange.

Table 3: Summary of Treatment-emergent Substitutions at Epitope Positions Detected in COMET-TAIL Participants

Treatment arm	Participants with TE epitope substitutions, % (n/N)[a]	Single TE epitope substitutions (n)[b]	Multiple TE epitope substitutions (n)[b]
500 mg IV	20.8 (33/159)	T333I (1), P337L (5), G339D (1), E340A (4), E340K (10), E340V (2)	P337L and E340K (3); G339D and E340K (3); E340A and E340K (1); E340K and E340V (1); G339D, E340A, and E340K (1); P337L, G339D, and E340A (1)
500 mg IM	7.6 (13/171)	P337L (2), E340A (1), E340K (2), E340V (1), R346K (1), N354K (1)	E340A and E340K (2); E340K and E340V (1); E340K and N360S (1); P337L, E340K, and E340V (1)
250 mg IM	5.3 (4/75)	E340K (1), E340V (1), R346K (1)	P337L and E340K (1)

TE, treatment-emergent; IV, intravenous; IM, intramuscular.
[a]n: number of participants with a TE epitope substitution; N: number of participants with paired baseline and post-baseline sequence data. TE epitope substitutions were defined as any substitution detected in a post-baseline sample at ≥5% AF that was not detected in the corresponding baseline sample at ≥5% AF.
[b]Participants with single or multiple TE epitope substitutions are only counted once.

Table 4: Neutralization Activity of Sotrovimab Against Epitope Substitutions Detected in COMET-TAIL Participants

Epitope substitutions[a]	Average fold change in EC_{50} relative to wild-type[b]
T333I, P337S, G339C, G339D, R346I, R346K, N354K, N360S, N440K	<3[c]
P337L, E340A, E340K, E340V	>100[d]
C336R, E340STOP, R509G	ND[e]

EC_{50}, half-maximal effective concentration; ND, not determined.
[a]Epitope substitutions with or without the D614G substitution were introduced into the SARS-CoV-2 spike coding sequence and evaluated in a pseudotyped virus neutralization assay.
[b]Fold change in EC_{50} calculated relative to Wuhan-Hu-1 wild type (YP_009724390.1) or D614G for R346I.
[c]Sotrovimab retains activity against epitope substitutions with <3-fold change in EC_{50}.
[d]Substitutions result in a significant EC_{50} shift indicating reduced susceptibility to sotrovimab *in vitro*.
[e]Substitutions could not be evaluated due to poor expression of the spike protein containing these substitutions.

Clinical Outcomes

- Of the 82 participants with sotrovimab epitope amino acid substitutions at baseline and/or post-baseline visits, 2.4% (n = 2) met the primary endpoint for clinical progression of hospitalization for >24 hours or death due to any cause
  - 1 participant in the 500 mg IV arm had R346K (>99% AF) at Day 1 and Day 5 and was infected with the Mu variant of SARS-CoV-2
  - 1 participant in the 500 mg IM arm was infected with the Delta variant of SARS-CoV-2 and had both P337L (16.058% AF) and E340K (23.223% AF) detected at baseline (Day 3) and had P337L detected at Day 8 (85.964% AF). The presence of the P337L and E340K substitutions prior to treatment is unknown, as this participant did not have a Day 1 sample available for sequencing analysis
- Of the 424 participants with post-baseline sequence available, 3.2% (2/62) and 3.0% (11/362) of participants with or without epitope substitutions, respectively, met the primary clinical endpoint for progression
- No participant with treatment-emergent epitope substitutions met the primary clinical endpoint for progression

Conclusions

- Consistent with VOC/VOI circulation during the enrollment period of June to August 2021, the predominant VOC/VOI detected in COMET-TAIL participants was the Delta (B.1.617.2) variant (88.2% [674/764])
- Sotrovimab epitope substitutions at baseline were rare at amino acid positions 337 or 340 (0.4% [3/745])
- The predominant post-baseline and treatment-emergent epitope substitutions included P337L and E340A/K/V, which confer reduced susceptibility to sotrovimab *in vitro*
- Although post-baseline and treatment-emergent epitope substitutions were detected in a higher proportion of participants in the 500 mg IV arm, they were not associated with increased clinical progression
- Overall, detection of post-baseline or treatment-emergent epitope substitutions was not correlated with clinical progression in sotrovimab-treated COMET-TAIL participants

Disclosures

MLA, GS, JdI, LAG, MA, CMH, and **ALC** are employees of and hold stocks in Vir Biotechnology, Inc. **AK, AES,** and **EHS** are trial investigators in the COMET-TAIL study, sponsored by Vir Biotechnology, Inc., in collaboration with GlaxoSmithKline. **AK** served on advisory boards for Gilead, received grants from Gilead, and received clinical trial payments from Regeneron, Vir Biotechnology, Inc., GlaxoSmithKline, and Gilead. **EHS** received research support from AbbVie, Eli Lilly, Otsuka, Eisai, and Ironshore; and served on speaker bureaus for Janssen, Teva, and AbbVie. **DI, AP,** and **AS** are employees of and hold stocks in GlaxoSmithKline.

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