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Viral resistance analysis in the COMET-PEAK study: sotrovimab treatment in participants with mild-to-moderate COVID-19

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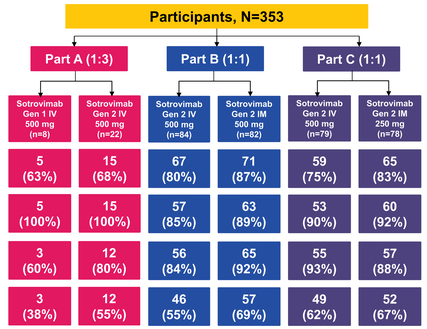
Background

- Sotrovimab is a dual-action monoclonal antibody targeting a conserved region of the SARS-CoV-2 S protein
- 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 current marketing authorization in Europe, and current provisional, temporary, or conditional marketing in many countries, including the UK, Japan, and Australia[3–6]
- COMET-PEAK was a 3-part, phase 2 study that evaluated intravenous (500 mg) and intramuscular (250 mg and 500 mg) administration of sotrovimab in outpatients with mild-to-moderate COVID-19
- We assessed amino acid substitutions in the SARS-CoV-2 S protein and circulating VOC/VOI in COMET-PEAK participants (enrolled February–July 2021)

Methods

- Mid-turbinate (Part A) or nasopharyngeal (Parts B and C) samples were obtained from all participants at baseline and post-baseline visits (**Figure 1**)
- Next-generation sequencing of the SARS-CoV-2 S gene was conducted using Illumina MiSeq with a ≥5% allelic frequency cut-off for samples with a viral load above 3.0 $\log_{10}$ copies/mL
- Baseline, post-baseline and treatment-emergent (TE) substitutions were assessed, and prevalence of VOC/VOI was evaluated
- Clinical progression was defined as having an SAE of requiring hospitalization for COVID-19
- Phenotypic analysis was conducted to evaluate the susceptibility of epitope substitutions to sotrovimab *in vitro*
  - Amino acid substitutions detected in the epitope of sotrovimab in COMET-PEAK participants were introduced into the SARS-CoV-2 spike coding sequence and assessed in a SARS-CoV-2 pseudotyped virus neutralization assay

Figure 1: Study population



Two formulations of sotrovimab were employed for this study (Gen1 and Gen2). Gen1 = sterile solution for IV infusion, 25 mg/mL concentration, 20 mM histidine, 8% sucrose (w/v), 0.04% PS80 (w/v), 5 mML-methionine at pH 6.0. Gen2 = sterile solution for IV infusion/IM injection, 62.5 mg/mL concentration, 20 mM histidine, 7% sucrose (w/v), 0.04% PS80 (w/v), 5 mML-methionine at pH 6.0.

Results

- In total, 282/353 participants had sequencing results for ≥1 visit (253 baseline, 248 post-baseline; **Figure 1**)
- 219 (78%) participants had paired baseline and post-baseline sequences
- 266 (94%) participants were infected with VOC/VOIs

TE substitutions

- A summary of epitope substitutions detected at ≥5% allelic frequency is presented in **Table 1**
- Of the 219 participants with paired sequences, 149 (68%) had TE substitutions in the S protein, with 26 (12%) in the epitope (**Table 2**)
- E340K was the predominant TE substitution in the epitope (15/219 [7%])

Table 1: Epitope substitutions (≥5% allelic frequency)

Amino acid position	Part A					
	Gen1 (500 mg IV; N=8), n		Gen2 (500 mg IV; N=22), n		Total Part A (N=30), n	
	Baseline	Post-baseline	Baseline	Post-baseline	Baseline	Post-baseline
P337H	0	0	1	0	1	0
E340V	0	0	0	2	0	2
R509I	0	0	0	1	0	1
Amino acid position	**Part B**					
	Gen2 (500 mg IV; N=84), n		Gen2 (500 mg IM; N=82), n		Total Part B (N=166), n	
	Baseline	Post-baseline	Baseline	Post-baseline	Baseline	Post-baseline
P337H	0	0	1	0	1	0
P337L	0	4	0	0	0	4
G339D	0	1	0	1	0	2
E340K	0	4	0	2	0	6
R346I	0	0	1	0	1	0
R346K	1	1	5	6	6	7
R357G	0	0	0	1	0	1
N360S	0	0	0	1	0	1
N440K	3	4	1	2	4	6
Amino acid position	**Part C**					
	Gen2 (500 mg IV; N=79), n		Gen2 (250 mg IM; N=78), n		Total Part C (N=157), n	
	Baseline	Post-baseline	Baseline	Post-baseline	Baseline	Post-baseline
P337L	0	2	0	4	0	6
E340A	0	0	0	1	0	1
E340K	0	5	0	4	0	9
E340V	0	2	0	0	0	2
R346I	0	0	0	1	0	1
R346K	0	0	3	2	3	2
N354S	0	0	0	1	0	1

N = the total number of participants in each treatment group.

Table 2: Summary of participants with TE amino acid S substitutions

	Part A		Part B		Part C	
	Gen1 (500 mg IV; N=8)	Gen2 (500 mg IV; N=22)	Gen2 (500 mg IV; N=84)	Gen2 (500 mg IM; N=82)	Gen2 (500 mg IV; N=79)	Gen2 (250 mg IM; N=78)
Participants with paired sequence data[a], n (%)	3 (38)	12 (55)	46 (55)	57 (70)	49 (62)	52 (67)
TE S protein substitution, n (%)[b]	1 (33)	9 (75)	34 (74)	38 (67)	34 (69)	3 (63)
TE epitope substitution, n (%)[b]	0	2 (17)	7 (15)	3 (5)	6 (12)	8 (15)
TE epitope substitution identified (n)	0	E340V (2) R509I (1)	P337L (4) G339D (1) E340K (4)	G339D (1) E340K (2) R357G (1)	P337L (2) E340K (5) E340V (2)	P337L (4) E340A (1) E340K (4) R346I (1) N354S (1)

Part A: MT samples; Part B and C: NP samples.
N = the total number of participants in each treatment group.
[a]Participants with paired baseline and post-baseline sequence data available for analysis.
[b]Calculated as a % of participants with paired sequence data.

Sotrovimab effectiveness versus epitope substitutions

- In the *in vitro* phenotypic analysis, sotrovimab effectively neutralized 7/12 of the available epitope substitutions tested
- P337L and E340A/K/V conferred significantly reduced susceptibility to sotrovimab *in vitro* (**Table 3**)
- None of the 7 participants with clinical progression in COMET-PEAK had epitope substitutions

Table 3: Neutralization activity of sotrovimab against individual epitope substitutions

Epitope substitutions detected in COMET-PEAK participants	Average fold change in EC_{50} relative to wild-type[a]
G339D, R346I, R346K, R357G[b], N354S, N360S, N440K	<3
P337H	5.13
P337L, E340A, E340K, E340V	>100
R509I[c]	ND

[a]Fold change in EC_{50} calculated relative to wild type sequence YP-009724390.1
[b]Substitution R357G was evaluated in Vero E6-TMPRSS2 cells
[c]Substitution R509I could not be evaluated due to poor expression of the S protein containing this substitution

Sotrovimab effectiveness versus VOC/VOI

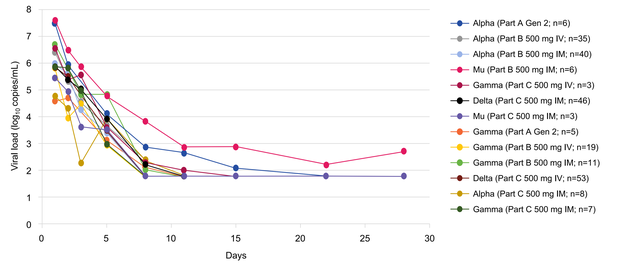
- Of those with a VOC/VOI, the most frequent were Alpha (Part A, 8/16 [50%]; Part B, 75/128 [59%]) and Delta (Part C, 99/122 [81%]) variants (**Table 4**)
- Of 7 participants with clinical progression, 3 had Alpha, 3 had Delta, and 1 had Gamma VOC/VOI; none had epitope substitutions in the S protein
- Sotrovimab retains neutralization activity against pseudotyped virus expressing VOC/VOIs detected in COMET-PEAK participants[7]
- Viral load decline was similar between patients with each VOC/VOI (**Figure 2**)

Table 4: Summary of VOC/VOI

	Part A		Part B		Part C		Participants with clinical progression
	Gen1 (500 mg IV) (N=8, n=4)	Gen2 (500 mg IV) (N=22, n=12)	Gen2 (500 mg IV) (N=84, n=61)	Gen2 (500 mg IM) (N=82, n=67)	Gen2 (500 mg IV) (N=79, n=58)	Gen2 (250 mg IM) (N=78, n=64)	
	MT	MT	NP	NP	NP	NP	
Alpha (B.1.1.7)	2	6	35	40	1	8	3
Beta (B.1.351)	0	0	0	0	0	0	0
Gamma (P.1)	1	5	19	12	3	7	1
Delta (B.1.617.2)	0	0	1	1	53	46	3
Eta (B.1.525)	0	0	0	1	0	0	0
Iota (B.1.526)	0	1	1	1	0	0	0
Kappa (B.1.617.1)	0	0	0	0	0	0	0
Lambda (C.37)	0	0	1	1	0	0	0
Mu (B.1.621)	0	0	1	6	0	3	0
Epsilon (B.1.427/B.1.429)	0	0	0	0	0	0	0
Omicron (B.1.1.529/BA.1)	0	0	0	0	0	0	0

Part A: MT samples; Part B and C: NP samples
N = the total number of participants in each treatment group; n = the number of participants with VOC/VOIs
Participants were infected with other VOC/VOIs which are not included in Table 4, such as K417N, S447N and E484K

Figure 2: Median viral load by VOC/VOI



Conclusions

- The prevalence of treatment-emergent epitope substitutions in the S protein was 12%
- There was no evidence that sotrovimab epitope substitutions were associated with clinical progression
- *In vitro* testing of VOC/VOI and epitope substitutions observed in COMET-PEAK demonstrated that sotrovimab retained neutralizing activity against the VOC/VOIs detected in study participants, and effectively neutralized 7/12 of the TE epitope substitutions tested
- These data are consistent with those from the COMET-ICE study, where detection of sotrovimab epitope substitutions was not correlated with progression in treated patients[8]

Abbreviations

EC_{50}, half maximal effective concentration; EUA, emergency use authorization FDA, Food and Drug Administration; IM, intramuscular; IV, intravenous; MT, mid-turbinate; ND, not determined; NP, nasopharyngeal; S, spike; SAE, serious adverse event; TE, treatment-emergent; VOC, variant of concern; VOI, variant of interest.

Disclosures

JM, JH, AS, AP, and JTW are employees of and/or hold stocks/shares in GSK. PYJ was an employee of GSK at the time of study. GS, ALC, and MA are employees of and/or hold stocks/shares in Vir Biotechnology.

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