Emergency Use Authorization (EUA) for Sotrovimab 500 mg
Center for Drug Evaluation and Research (CDER) Memorandum on
Fact Sheet Update

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number	EUA 000100, SDN 43
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	EUA Sponsor GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK GSK US Point of Contact Debra H. Lake, M.S. Sr. Director Global Regulatory Affairs GlaxoSmithKline 5 Moore Drive PO Box 13398 Research Triangle Park, NC 27709-3398 Email: (b) (6) Phone: (b) (6)
Manufacturer	GlaxoSmithKline, Parma.
Submission Date	July 9, 2021
Receipt Date	July 9, 2021
Review Completion Date	August 16, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Sarita Boyd, Clinical Reviewer Kimberly Struble, Clinical Team Lead Eric Donaldson, Clinical Virology Reviewer Julian O'Rear, Clinical Virology Team Lead Tony Nicasio, Clinical Pharmacology Reviewer Su-Young Choi, Clinical Pharmacology Team Lead Scott Komo, Statistics Reviewer Thamban Valappil, Statistics Team Lead Mayumi Takahashi, Product Quality Reviewer Koung Lee, OBP Labeling Assessor Debra Birnkrant, Division Director, DAV John Farley, Office Director, OID
Proprietary Name	None

Established Name/Other names used during development	Sotrovimab (VIR-7831)
Dosage Forms/Strengths	Sterile solution for injection, 500mg/8 mL vial
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Population	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

I. Review of Fact Sheet Revisions

The Applicant's proposed updates based on population pharmacokinetic (PK) analyses will not be reviewed at this time. Therefore, the proposed updates to Sections 2.3, 11.4, 11.5, and 11.6, as well as some updates to Section 14.2 will not be implemented. The proposed changes do not impact the overall safety profile that warrant prompt review of the PK datasets.

The following proposed updates to the long version of the Fact Sheet (FS) for Healthcare Providers were reviewed. Corresponding changes were made in the short version.

A. Dose Preparation and Administration (2.4)

The Applicant proposed the use of 5% Dextrose Injection for dilution of sotrovimab in polyvinyl chloride (PVC) or polyolefin (PO) IV bags for IV administration.

> The Applicant provided in-use stability data supporting the use of sotrovimab, diluted in aqueous 5% Dextrose Injection, in PVC bags for IV infusion under the EUA. The Applicant also requested the use of 5% Dextrose Injection with PO IV bags. However, in the absence of in-use stability data supporting the Applicant's use of sotrovimab in 5% Dextrose Injection in PO IV bags, which are of significantly different composition than PVC bags, the use of sotrovimab in PO IV bags with 5% Dextrose Injection is not allowed under the EUA at this time. The Applicant acknowledged the FDA's restriction and has withdrawn the use of sotrovimab in 5% Dextrose Injection in PO IV bags from the EUA FS. Should the Applicant intend to use 5% Dextrose Injection for dilution of sotrovimab in PO IV bags under the EUA, in-use compatibility study should be performed with sotrovimab diluted with 5% Dextrose in PO IV bags.

B. Overall Safety Summary: Clinical Trials Experience (6.1)

The Applicant updated the safety results for COMET-ICE to include the full safety population (n=1049).

Hypersensitivity reactions related to study drug occurred in 9/523 (2%) and 5/526 (1%) participants treated with sotrovimab and with placebo, respectively. All were Grade 1 or 2, and none led to pausing or discontinuation of the infusion.

The percentage of participants in the sotrovimab arm who experienced an adverse event of rash decreased from 2% to 1% because no additional rash events were reported in participants included after the interim analysis. However, the percentage of participants who experienced diarrhea increased from 1% to 2%, all of which were Grade 1 or 2.

The proposed changes to the content of this section are acceptable with minor edits.

C. Microbiology/Resistance Information (15)

The Applicant updated the nomenclature for describing SARS-CoV-2 variants to include reference to the WHO nomenclature and additional information regarding new SARS-CoV-2 variants was added. In addition, the language used to describe SARS-CoV-2 spike protein substitutions was revised for clarity to use the term ‘substitution’ instead of ‘variant’.

An additional sentence was added in the introductory paragraph advising Health Care Professionals to consult the CDC website to determine which regions of the US are being impacted by specific SARS-CoV-2 variants to determine which EUA mAb therapy will likely have the greatest impact in their region. Of note, currently sotrovimab retains antiviral activity against all SARS-CoV-2 variants assessed to date in a pseudotyped virus-like particle assay or in microneutralizaton assay using authentic SARS-CoV-2.

D. Clinical Trial Results and Supporting Data for EUA (18)

Primary Endpoint

The Applicant updated COMET-ICE results to include the full analysis Intent to Treat (ITT) population (n=1057). Topline data in this population, including demographics, baseline characteristics, primary endpoint results, and all-cause mortality up to Day 29, were reviewed during the original EUA submission. The final results submitted to support this FS revision as well as the proposed changes to this section are consistent with the information previously reviewed. Please refer to the original EUA review for more details.

Inclusion of the primary efficacy endpoint for the full ITT population in the FS is acceptable but without the p-value. Because no formal statistical testing was planned and performed in this population, the p-value would be open to misinterpretation. Instead, a description of the interim analysis results will be retained as a footnote to Table 2 along with the adjusted relative risk estimate, 97.24% CI, and p-value.

Secondary Clinical Endpoints

The Applicant proposed to add secondary endpoint results, including disease progression defined by an emergency room visit, hospitalization, or death and progression to severe and/or critical respiratory COVID-19. We will include only the primary endpoint and the secondary endpoint of all-cause mortality, given its extension from the primary endpoint, in the EUA FS.

Symptom-based Endpoint

The Applicant proposed the addition of symptom resolution results, displayed as the mean change in FLU-PRO Plus total score (AUC through Day 7). Inclusion of the mean change in FLU-PRO Plus total score is not acceptable and is inconsistent with the advised patient reported outcome (PRO)-based endpoints discussed with the IND Sponsor. Symptom resolution results will not be included in the EUA FS at this time.

Virologic Endpoint

For the virology population, the Applicant submitted additional SARS-CoV-2 viral load results (n=754). The data in total comprise >99% of the expected nasopharyngeal swabs taken through Day 29. Viral load at baseline remained similar across treatment arms. The difference in change from baseline with sotrovimab compared to placebo was numerically greater at Day 5 than at Day 8 (Table 1).

Table 1: Change from Baseline in Viral Load in Nasal Secretions by qRT-PCR Through Day 8 (Virology Population) (n=754)

	Placebo	**Sotrovimab**
Baseline (log 10 copies/mL)		
n	385	369
Mean (standard deviation)	6.645 (1.6632)	6.535 (1.6331)
Median (Min, Max)	6.824 (3.367, 9.941)	6.609 (3.373, 9.985)
Day 5 change from baseline (log 10 copies/mL)		
n	331	323
Mean (standard deviation)	-1.488 (1.4971)	-1.925 (1.3113)
Median (Min, Max)	-1.542 (-5.210, 3.455)	-1.894 (-5.251, 3.306)
Day 8 change from baseline (log 10 copies/mL)		
n	323	316
Mean (standard deviation)	-2.444 (1.5076)	-2.625 (1.4609)
Median (Min, Max)	-2.451 (-5.875, 4.615)	-2.682 (-5.981, 2.328)

Source: Information Amendment 09Jul2021 - Day 29 Data Displays, Table 112.1
Note: Values less than the lower limit of detection (LLD=1493 copies/mL) are imputed to 0.5 x LLD, detectable values less than lower limit of quantification (LLQ=2228 copies/mL) are imputed to LLQ – (0.5 x (LLQ-LLD)) prior to taking the log 10 value.

The least square (LS) mean change from baseline (SE) at Day 5 was -1.442 (0.0679) with placebo and -1.916 (0.0685) with sotrovimab, for a difference of -0.474 (0.0965) [95% CI (-0.663, -0.285)]. The LS mean change from baseline (SE) at Day 8 was -2.358

(0.0589) with placebo and -2.610 (0.0593) with sotrovimab, for a difference of -0.251 (0.0835) [95% CI (-0.415, -0.087)].

The inclusion of mean decline from baseline in viral load at Day 8 in the FS is acceptable with edits.

E. How Supplied/Storage Handling (19)

The proposed change to the in-use storage of the diluted solution of sotrovimab (up to 6 hours at room temperature (up to 25°C [up to 77°F]) is acceptable.

II. Recommendations

The proposed revisions to the Fact Sheet for Healthcare Providers are acceptable with edits and with the exception of recommendations based on population PK analyses and results for secondary clinical and symptom-based endpoints.

The agreed upon FS updates do not alter the benefit-risk analysis or conclusion in the initial review to support authorization of EUA 100.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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