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**LETTER OF AMENDMENT**

DATE: March 18, 2022

TO: A5401 Principal Investigators and Site Staff

FROM: A5401 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5401 Version 8.0

**The following information affects the A5401 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.**

**The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.**

**Your site will receive this LOA along with the PPD notification letter with instructions for implementation at your site. Please provide PPD with the signed LOA. Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, please provide the approvals to PPD. PPD will provide an amendment follow-up letter to your site prior to implementation.**

**PPD will submit a LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center on behalf of the sites. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.**

The following are changes (noted in bold or strikethrough) to A5401, Version 8.0, dated 25Feb2022, titled "Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)". These changes will be included in the next version of the A5401 protocol if it is amended at a future date.

On February 28, 2022, a planned review of the study was conducted by the study's external Data and Safety Monitoring Board (DSMB). Information from 734 participants who received either SAB-185 or casirivimab plus imdevimab was reviewed. The DSMB found that because there have been so few hospitalizations and deaths in the study, even if more people participated in the study to meet the planned sample size of 1200 were enrolled, it would not be possible to know if SAB-185 works to prevent hospitalizations and deaths for COVID-19. Based on this, the DSMB recommended to stop enrollment to the phase III evaluation of SAB-185 for operational futility, and the NIH (the Sponsor) accepted this recommendation. In addition, with the current epidemiology of COVID-19, it was determined by the Sponsor and the protocol team that the phase III evaluation of SNG001 would not be pursued within the ACTIV-2/A5401 platform; alternative platforms to continue investigation of SNG001 will instead be explored, Thus, this LOA is being implemented to note that the study will close to further enrollment. Participants that are currently enrolled and on study should continue to be followed through end of study (Week 72), as per the protocol.

1. Section 6.3.8, Vital Status Checks

   Vital status contacts and other reported information ~~should be recorded on the eCRFs~~ **will be documented in the study chart at each timepoint per the SOE. The outcome of the final vital status check at which the participant's status of alive, hospitalized, or dead is verified must be recorded on the eCRFs**.

2. APPENDIX II: SAMPLE INFORMED CONSENT – PHASE III, MAIN PROTOCOL, new first paragraph

   **NOTE: No additional participants will be enrolled into ACTIV-2/A5401. This version of the consent is retained for archival purposes.**

3. APPENDIX VIII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

   a. [redacted]

4. APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

   a. [redacted]

[redacted]

5. APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001), first paragraph

   **NOTE: Phase III evaluation of SNG001 will ~~be initiated under a future protocol version and not protocol Version 8.~~ not be initiated in ACTIV-2/A5401.**

6. APPENDIX XV: SAB-185 ANTI-SARS-COV-2 HUMAN IMMUNOGLOBULIN INTRAVENOUS (TC BOVINE-DERIVED), new first paragraph

   **NOTE: Following the first interim analysis and DSMB review of the phase III evaluation of SAB-185 under protocol version 8, further enrollment to SAB-185 phase III has been terminated due to operational futility. Previously enrolled participants will continue to be followed through end of study as per the protocol.**

7. APPENDIX XVI: SAMPLE INFORMED CONSENT FOR **PARTICIPANTS RANDOMIZED TO** STUDY DRUG SAB-185 **OR CASIRIVIMAB PLUS IMDEVIMAB** (new section title)

   a. [redacted]

   [redacted]

[redacted]

The US Centers for Disease Control and Prevention (CDC) recently changed their guidance (as [redacted]

9. A Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____Date: _____
Name/Title