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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. Risks Associated with AZD7442 (new paragraphs 7-9)
   In two studies of AZD7442 called the PROVENT study and the TACKLE study a small number of serious events happened involving heart or blood vessel problems such as heart attack or heart failure. More people who got AZD7442 had these events than participants that got placebo in these studies. In the PROVENT study, 23 out of the 3,461 people who got AZD7442 had one of these events compared to 5 of the 1,736 people who got placebo. In the TACKLE study there were 2 of these type of events in the group that got AZD7442 and 1 in the placebo group.

   All of those that had these events were at high risk for heart-related events. Most had heart problems before they started the study. We don't know if these events were caused by AZD7442 or not and they happened at different times after people got the drug or placebo. These events did not happen in another AZD7442 study called STORMCHASER.

   In the PROVENT study, AZD7442 worked very well at stopping COVID-19. Looking at the good and bad, the FDA approved an Emergency Use Authorization (EUA) for this drug for stopping COVID-19 on December 8, 2021. The FDA saw the data about these events before they approved it.

   b. Effect on Future Vaccination
   There is a chance that AZD7442 could interfere with how your body responds to a COVID-19 vaccine while it is in your system. Studies show AZD7442 can remain in the body for more than 90 days. However, the US Centers for Disease Control and Prevention (CDC) currently recommends that COVID-19 vaccination does not need to be delayed following receipt of monoclonal antibodies like AZD7442. ~~The US Centers for Disease Control and Prevention (CDC) currently recommends that people wait at least 90 days after receiving antibody treatment before receiving a COVID-19 vaccine, because some antibodies remain in the body for about 90 days, and there is a chance that these antibodies could interfere with how your body responds to the vaccine during those 90 days. Some of the antibodies in this study including AZD7442 are designed to remain in the body for longer than 90 days. Although there is no further guidance available, there is a chance that these longer-lasting monoclonal antibodies could~~

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

   a. Risks Associated with AZD7442 (new paragraphs 8-10)
   In two studies of AZD7442 called the PROVENT study and the TACKLE study a small number of serious events happened involving heart or blood vessel problems such as heart attack or heart failure. More people who got AZD7442 had these events than participants that got placebo in these studies. In the PROVENT study, 23 out of the 3,461

people who got AZD7442 had one of these events compared to 5 of the 1,736 people who got placebo. In the TACKLE study there were 2 of these type of events in the group that got AZD7442 and 1 in the placebo group.

All of those that had these events were at high risk for heart-related events. Most had heart problems before they started the study. We don't know if these events were caused by AZD7442 or not and they happened at different times after people got the drug or placebo. These events did not happen in another AZD7442 study called STORMCHASER.

In the PROVENT study, AZD7442 worked very well at stopping COVID-19. Looking at the good and bad, the FDA approved an Emergency Use Authorization (EUA) for this drug for stopping COVID-19 on December 8, 2021. The FDA saw the data about these events before they approved it.

b. Effect on Future Vaccination

There is a chance that AZD7442 could interfere with how your body responds to a COVID-19 vaccine while it is in your system. Studies show AZD7442 can remain in the body for more than 90 days. However, the US Centers for Disease Control and Prevention (CDC) currently recommends that COVID-19 vaccination does not need to be delayed following receipt of monoclonal antibodies like AZD7442. ~~The US Centers for Disease Control and Prevention (CDC) currently recommends that people wait at least 90 days after receiving antibody treatment before receiving a COVID-19 vaccine, because some antibodies remain in the body for about 90 days, and there is a chance that these antibodies could interfere with how your body responds to the vaccine during those 90 days. Some of the antibodies in this study including AZD7442 are designed to remain in the body for longer than 90 days. Although there is no further guidance available, there is a chance that these longer-lasting monoclonal antibodies could interfere with how your body responds to the vaccine even if you wait at least 90 days for the vaccine.~~

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. New introductory paragraphs

NOTE: This revised sample informed consent is intended for participants that enrolled under protocol V7 and were randomized to SAB-185 or casirivimab plus imdevimab.

You received either ~~A study drug that you might be assigned to in this study is one of two doses of the~~ **SAB-185 or** ~~the placebo~~ **casirivimab plus imdevimab (also known as REGEN-COV) as part of the ACTIV-2/A5401 study. The purpose of this consent form is to share new information with you that is important for you to know.** ~~Each dose of SAB-185 is considered a separate study drug in the trial.~~

There is now a new variant (type) of the SARS-CoV-2 virus that has become very common around the world, the Omicron variant. A variant means that parts of the virus have changed. As a result of these changes, casirivimab plus imdevimab is not expected to work against the Omicron virus and is no longer authorized by the FDA for treatment of COVID-19 in parts of the US where Omicron is common. Because of this, the ACTIV-2 study was changed to no longer give casirivimab plus imdevimab to participants.

On February 28, 2022, a planned review of the study was conducted by a Data and Safety Monitoring Board, a group of experts separate from the study team that reviews how the study is going. Information from 734 participants who received either SAB-185 or casirivimab plus imdevimab was reviewed. They found that because there have been so few hospitalizations and deaths in the study, even if more people participate in the study, it would not be possible to know if SAB-185 works to prevent hospitalizations and deaths for COVID-19. For this reason, the study will not continue to enroll up to the original 1200 planned for the study. The expert monitoring group did not find any safety concerns (new or worrisome risks for serious side effects). We ask that you continue to follow up with visits for the study so that the study staff and study team can continue to monitor for side effects and understand if the drugs received in the study help other symptoms, such as late or long-lasting symptoms from COVID-19.

b. IF YOU ARE IN THE SECOND PART OF THE STUDY (PHASE III~~, COMPARISON TO PLACEBO~~) **AND RECEIVED SAB-185** (new section title)

c. Study Visit on Day 28 **and Week 24**
   - You will have blood drawn. This blood will be used for the following tests:
     - levels of the drug
     - levels of antibodies to the drug (your body's immune response to the drug)

d. WHAT ARE THE RISKS OF **THE STUDY DRUGS** ~~SAB-185~~? (new section title)

e. Effect on Future Vaccination **for Both SAB-185 and Casirivimab Plus Imdevimab**
   The US Centers for Disease Control and Prevention (CDC) recently changed their guidance (as of February 11, 2022) to say that people who have received antibody treatment for COVID-19 can receive a COVID-19 vaccine at any time, and do not have to wait for a period after receiving the antibody treatment. It is possible that the levels of antibodies generated by vaccination may be lower in people who received an antibody treatment before vaccination than in people who did not receive an antibody treatment before vaccination, but it is not known if this means you will not be as protected from future COVID-19, and the CDC recommends proceeding with vaccination. SAB-185 **and casirivimab plus imdevimab** ~~is an~~ **are** experimental antibody treatment**s** and it is not known if receiving ~~SAB-185~~ **either of them** affects how you will respond to COVID-19 vaccines.

f. ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING **FOR SAB-185**? (new section title)

8. APPENDIX XIX SIGNATURE PAGE – STUDY DRUGS

   a. Consent ~~forms~~ **addenda** for the following study drugs were reviewed (initial if reviewed with you):

   b. _____ (initials) SAB-185 **OR CASIRIVIMAB PLUS IMDEVIMAB** INTRAVENOUS ADMINISTRATION

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