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CLARIFICATION MEMO

DATE: January 11, 2023

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5404 Protocol Team

SUBJECT: Clarification Memo #1 for Protocol A5404

The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarification(s) contained in this memo should be implemented immediately.

The main reasons for this CM are to inform A5404 study sites that the study will end follow-up earlier than expected, that several Secondary Objectives were moved to Other Objectives, and to inform participants and sites about an increased risk of myocarditis and pericarditis in individuals vaccinated with some COVID-19 vaccines containing S- antigen. Participant follow-up will end at the Day 365 visit, and not at Day 730 as initially planned. Please note that the change in some Secondary Objectives to Other will not impact the data that have already been collected nor does it require sites to take any action. Information on an increased risk of myocarditis and pericarditis should be communicated with study participants via a *Dear Participant Letter* that the A5404 team will provide to study sites.

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The following are clarifications (noted in bold and strikethrough) to Protocol A5404, Version 2.0, 07May2021, titled, "SARS-CoV-2 Immune Responses after COVID-19 Therapy and Subsequent Vaccine." These clarifications will be included in the next version of the A5404 protocol if it is amended at a future date.

1. Shortening participant follow-up to end at the Day 365 study visit instead of at the Day 730 visit: (Protocol sections impacted: SCHEMA (sections "DESIGN" and "DURATION"); section 3.0 (Study Design), section 6.1 (Schedule of Evaluations), and section 6.2.3 (Post-Entry Evaluations).

2. Secondary Objectives (section 1.2): The team re-prioritized the analysis of secondary objectives and moved several to Other Objectives (section 1.3). As a result, section 1.2 was updated to move Secondary Objectives 1.2.2–1.2.5 to section 1.3—now reflected as Other Objectives 1.3.1–1.3.4. Remaining Other Objectives in this section were renumbered accordingly. Associated changes were made to section 10.2.2 (Secondary Outcome Measures) and a new section 10.2.3 was added for Other Outcome Measures.

Refer to item #3 for changes that were made to section 10.6 (Analyses), which relate to the re-prioritization of objectives.

The following updates resulted from this change:

1.2 Secondary Objectives~~s~~

1.2.1 To explore the safety of mRNA-based COVID-19 vaccines among participants with prior COVID-19 who received investigational therapy or its comparator for COVID-19 and persons who are SARS-CoV-2 naïve.

~~1.2.2 To explore the difference in humoral and cellular **immune** responses to **mRNA-based COVID-19 vaccines** among participants with prior **COVID-19 who received** investigational therapy compared to participants without prior investigational therapy (**placebo or** corresponding active comparator) exposure **and persons who are SARS-CoV-2 naïve**.~~

~~1.2.3 To explore the difference in humoral and cellular **immune** responses, including NAb levels, B and T cell responses, and serologic responses to **COVID-19 vaccination** by duration of time of vaccination from prior investigational therapy versus active comparator/placebo exposure and **compared to persons who are SARS-CoV-2 naïve**.~~

~~1.2.4 To explore whether **investigational** therapy **drug** levels at time of first **COVID-19** vaccination is associated with humoral and cellular responses **in participants with prior COVID-19 who received investigational therapy or its comparator for COVID-19.**~~

~~1.2.5 To explore B and T cell exhaustion before and after **COVID-19** vaccination in persons with prior COVID-19 who received investigational therapy or corresponding comparator for COVID-19 **and persons who are SARS-CoV-2 naïve**.~~

1.3 Other Objectives

1.3.1 To explore the difference in humoral and cellular immune responses to mRNA-based COVID-19 vaccines among participants with prior COVID-19 who received investigational therapy compared to participants without prior investigational therapy (placebo or corresponding active comparator) exposure and persons who are SARS-CoV-2 naïve.

1.3.2 To explore the difference in humoral and cellular immune responses, including

NAb levels, B and T cell responses, and serologic responses to COVID-19 vaccination by duration of time of vaccination from prior investigational therapy versus active comparator/placebo exposure and compared to persons who are SARS-CoV-2 naïve.

1.3.3 To explore whether investigational therapy drug levels at time of first COVID-19 vaccination is associated with humoral and cellular responses in participants with prior COVID-19 who received investigational therapy or its comparator for COVID-19.

1.3.4 To explore B and T cell exhaustion before and after COVID-19 vaccination in persons with prior COVID-19 who received investigational therapy or corresponding comparator for COVID-19 and persons who are SARS-CoV-2 naïve.

10.2.2 Secondary Outcome Measures

10.2.2.1 Relative pre-vaccine to post-vaccine change in NAb response defined as the ratio of post-vaccine level/pre-vaccine level. The pre-vaccine NAb measurement will be obtained before the first dose of the vaccine, and the post-vaccine measurement will be obtained at least 56 days after the first dose of the vaccine.

10.2.2.2 New Grade 3 or higher AE, or SAE, or AE leading to change or discontinuation in vaccine receipt from first dose of the mRNA-based COVID-19 vaccine and through 140 days after the first dose of vaccine.

10.2.2.3 Grade 1 or higher allergic reaction from first dose of the mRNA-based COVID-19 vaccine through the visit 56 days after the first dose of the vaccine.

10.2.2.4 Grade 2 or higher injection site reaction from first dose of the mRNA-based COVID-19 vaccine through the visit 56 days after the first dose of the vaccine.

~~10.2.2.5 CD4+ and CD8+ T cell responses to SARS-CoV-2 spike protein and IgG and IgM serologic responses to SARS-CoV-2 spike protein at receptor binding domain (RBD) and N terminal domain (NTD) and Matrix (M) protein at study entry/Day 0 and 56 days after the first vaccine dose.~~

~~10.2.2.6 Flow cytometry of PBMC for markers of exhaustion on B and T cells at study entry/Day 0 and 56, and 140 days after the first vaccine dose.~~

~~10.2.2.7~~ **10.2.2.5** Relative pre-vaccine to post-vaccine change in NAb response defined as the ratio of post-vaccine level/pre-vaccine level by received vaccine, i.e., Moderna versus Pfizer. The pre-vaccine NAb measurement will be obtained before the first dose of the vaccine, and the post-vaccine measurement will be obtained at least 56 days after the first dose of the vaccine.

10.2.3 Other Outcome Measures

10.2.3.1 CD4+ and CD8+ T cell responses to SARS-CoV-2 spike protein and IgG serologic responses to SARS-CoV-2 spike protein at receptor binding domain (RBD) and N terminal domain (NTD) at study entry/Day 0 and 56 days after the first vaccine dose.

10.2.3.2 Flow cytometry of PBMC for markers of exhaustion on B and T cells at study entry/Day 0, 56, and 140 days after the first vaccine dose.

3. Section 10.2 (Outcome Measures) was expanded to include revisions to the analysis plan

addressing mitigation strategies that will be implemented should study accrual be low and insufficient to provide meaningful estimates. In the case that accrual is too low to produce meaningful estimates, analyses will instead be reported as descriptive estimates within participant groups rather than as comparisons between groups. Further revisions related to this change are reflected in section 10.4 (Sample Size) first paragraph and section 10.6 (Analyses) second paragraph, as detailed below.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to **https://**ClinicalTrials.gov. **Outcome measures will be analyzed as originally pre-specified if accrual is sufficiently high to provide meaningful estimates. Otherwise, analyses will instead be reported as descriptive estimates within participant groups rather than as comparisons between groups. Additional details are pre-specified in the primary Statistical Analysis Plan.**

10.4 Sample Size

The following considers sample size for a comparison of responses among participants who previously received an investigational agent versus among participants who previously received placebo. Similar considerations apply if instead the comparison is of responses among participants who previously received an investigational agent versus among participants who previously received an active control. **It was originally intended to consider the following sample sizes: 50, 70, and 90 for each investigational therapy group separately. Due to lower than anticipated enrollment numbers, revisions to the protocol and Statistical Analysis Plan (SAP) now consider combining the active arms from some investigational therapy groups together for comparisons against the pooled placebo group or active comparator (sample sizes: 10, 20, 30, 50, and 70).**

10.6 Analyses

Statistical analysis plans will be developed describing analyses to address the primary and secondary objectives of the study.

The primary outcome analysis is descriptive and **was originally intended to** be carried out separately for each investigational therapy and associated combined placebo group or investigational agent and associated active comparator group. **Due to lower than anticipated enrollment into the study, the primary outcome analysis may be amended to be carried out in a combined group of participants exposed to particular ACTIV-2/A5401 investigational agents. Additional details are described in the Statistical Analysis Plan.** The analysis will combine **participants regardless of which** mRNA-based COVID-19 vaccine **they received.** An exploratory analysis **may** be carried out separately for each mRNA-based COVID-19 vaccine **if sample size permits.**

Risk of Myocarditis and Pericarditis

4. In response to FDA comments on recent available data regarding an increased risk of myocarditis and pericarditis reported in individuals vaccinated with some COVID-19 vaccines containing S-antigen, the following language was included in a *Dear Participant Letter* that will be provided to the 43 participants that have been enrolled into the study:

There is an increased risk of myocarditis and pericarditis after getting the study-provided Moderna mRNA-1273 COVID-19 vaccine. Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the lining around the heart. In both cases, the body's immune

system is causing inflammation in response to the vaccine. Symptoms can include chest pain, shortness of breath, or palpitations. Symptoms usually start within a few days after receipt of the Moderna mRNA-1273 COVID-19 vaccine. Most individuals who have sought medical care have responded well to medications and rest, and symptoms have resolved for most persons who experienced this side effect. It is not known if either myocarditis or pericarditis from the vaccine causes long-term health effects.

Myocarditis and pericarditis have been reported in greatest numbers in males under the age of 40 years following a second dose of mRNA vaccines (including the COVID-19 vaccine), but cases have been reported in older males and in females as well, and also following other doses. Risk for myocarditis and pericarditis has been observed to be highest in males between 12 to 17 years of age. While some cases required intensive care support, data suggests that symptoms got better in most people with some management. Information is not yet available about the potential long-term affects of myocarditis and pericarditis in these people. While there is limited data on the risk of myocarditis and pericarditis in children younger than 12 years old (especially compared to the risk data that is available in adolescents and adults), it is an area of science that is currently being studied.

Please let a member of the study staff know if you experience any of the following symptoms of myocarditis or pericarditis, following vaccination provided through the study:

- **Chest pain**
- **Shortness of breath**
- **A fast heartbeat, fluttering, or pounding heart**

Study staff will provide you with appropriate contact information so that you can reach out should you experience any of these symptoms.