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LETTER OF AMENDMENT #1

DATE: June 22, 2023

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

FROM: A5362 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5362, Version 2.0

The following information affects the A5362 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) should be implemented immediately, prior to IRB/EC approval, to eliminate immediate hazard to participants.

The following information also affects the Sample Informed Consent (SIC). A letter informing participants about the contents of this LOA and an addendum to the SIC were provided electronically to sites on 16Jun2023.

Sites should implement the LOA immediately and inform IRB/EC and any other applicable regulatory entities of the LOA. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). 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.

In April 2023, the study temporarily closed to screening and accrual due to an unanticipated trend in outcome events, which triggered review by the National Institute of Allergy and Infectious Diseases (NIAID) Therapeutic and Prevention Data and Safety Monitoring Board (DSMB), which met on 01Jun2023 to review all available safety and efficacy data from A5362. The DSMB recommended that A5362 permanently close to accrual because of the high rate of treatment failure and TB recurrence. There were no other safety concerns related to study regimen. The A5362 team, NIAID and DAIDS leadership, and ACTG leadership concur with the following DSMB recommendations for implementation:

- Permanently close A5362 to accrual.

- Participants currently receiving treatment in the experimental arm (Arm 1) should finish their 3-month experimental regimen [rifapentine/isoniazid/pyrazinamide/ethambutol/clofazimine (PHZEC)] and then be placed on an additional 3 months of continuation phase rifampicin/isoniazid (RH) regimen.
- Participants in Arm 1 who have already finished the experimental regimen in Arm 1 without an unfavorable outcome, should be followed closely for the duration of the trial. The DSMB suggests that the investigators consider strategies for more intensive follow-up of these participants to ascertain recurrences, and that those diagnosed with recurrence be referred for 6 months of SOC treatment.
- Participants in Arm 1 follow-up will be extended to 117 weeks, as outlined below.

As referenced in the investigator and IRB/EC letters sent to A5362 sites on 16Jun2023, this LOA formally outlines changes to Version 2.0 of A5362, dated 08Jul2022, given the abovementioned DSMB recommendations.

There are no changes to the Sample Informed Consent (SIC) in this LOA. Refer to the SIC addendum for the updated information to provide to participants and for reconsenting participants.

This LOA also includes revisions from the 26Sep2022 DSMB review, in which the DSMB requested that the team specify the monitoring of the unfavorable composite outcome per definition 10.2.4A.

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The following are changes (noted in bold or strikethrough) to A5362, Version 2.0, 08Jul2022, titled A "Phase IIc Trial of Clofazimine- and Rifapentine-Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study." These changes will be included in the next version of the A5362 protocol if it is amended at a future date. Changes that have already been made (Clarification Memo #1) have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

1. Section SCHEMA, DESIGN

   The following information has been added to reference the change in study design due to a DSMB review.

   Per the June 1, 2023 DSMB review, and permanent closure of accrual, the follow-up schedules for Arm 1 participants will be revised as follows:

   - **Participants currently on Arm 1 study treatment should complete the 3-month regimen and then be placed on an additional 3 months of continuation phase rifampicin/isoniazid (RH). Based on the DSMB recommendations, an additional 3 months of treatment is necessary to decrease the likelihood of treatment failure and TB relapse in study participants.**

   - **Participants who have already completed Arm 1 treatment should be seen for a follow-up visit within the next 4 weeks of the date of this LOA, at a scheduled or unscheduled visit, to assess whether further treatment is needed.**

   - **Additional extended follow-up visits for participants in Arm 1 will be added at weeks 30, 38, 60, 91 and 117 unless the participant has already been referred for, or already received, 6 months of SOC through the local TB program. The additional visits at weeks 30, 38, and 60 may be performed by telephone only; these calls are to assess the participant's TB symptoms and determine if it is clinically indicated that the participant should come in for an in-person visit to assess the need for possible poor treatment response (PPTR) assessments and/or referral to SOC treatment.**

   - **If the site investigator diagnoses TB recurrence at any time during Arm 1 follow up, the participant should be referred to 6 months of SOC treatment by the national TB program. For study purposes, such participants should continue to be followed in the study for outcome determination, unless the participant withdraws consent.**

   Participants in Arm 2 and Arm C should complete their treatment and follow-up schedule as planned; no additional visits are planned for these groups.

2. Section SCHEMA, DURATION

Arm 1:

- **Up to 117 weeks.**
- **65 weeks for participants who are or have been diagnosed with TB treatment failure or recurrence and are or have been referred to six months of local SOC treatment by the national/local TB program.**

Arm 2: 65 weeks

Arm C: 65 weeks

3. Section SCHEMA, REGIMEN

The following paragraph has been included to add three months of rifampicin/isoniazid for Arm 1 participants who are currently receiving the experimental 3-month treatment regimen as of 16Jun2023. The treatment regimen for all other participants will remain the same.

Arm 1 participants receiving the experimental 3-month treatment regimen as of 16Jun2023:
rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) + clofazimine (CFZ) 300 mg once daily for 2 weeks; then PHZE + CFZ 100 mg once daily for 6 weeks; then rifapentine/isoniazid/pyrazinamide (PHZ) + CFZ 100 mg once daily for 5 weeks; then rifampicin/isoniazid (RH) for 13 weeks for a total of 26 weeks of study treatment.

4. Section 1.4, Exploratory Objectives

The following objective has been added to align with the addition of Drug-Susceptibility Testing and Sputum AFB Smear and Culture at weeks 91 and 117:

1.4.8 To explore long term outcomes in Arm 1 participants through 117 weeks after randomization.

5. Section 3.0, STUDY DESIGN

The following update to the Arm 1 regimen and follow-up has been added to the end of the section:

<u>Updates following the DSMB reviews in April and June 2023</u>
Following the DSMB reviews in April and June 2023, and the premature closure to accrual of the study, Arm 1 treatment duration and follow-up was revised for participants who are currently on or have completed Arm 1 study treatment without experiencing treatment failure or TB recurrence, and have not already been referred to six months local SOC treatment. Participants in Arm 1 who have not already been referred to six months local SOC treatment will have follow-up extended through week 117.

6. Section 6.1, Schedule of Evaluations

A new Table 6.1-2 has been inserted for the additional visits and assessments for Arm 1 after week 26. The SOE table for Arm C has been renumbered to Table 6.1-3.

Table 6.1-2: Schedule of Evaluations for Arm 1 Who Have Not Been Referred to Local SOC, Additional Visits and Assessments After Week 26

Evaluation	Follow-up									After Week 65	
	Visit Window is ±7 days							Visit Window is ±14 days		Time of Suspected Treatment Failure or Recurrence or Poor Treatment Response	Premature Treatment/Study Discontinuation
	30[4]	34	38[4]	42	52	60[4]	65	91	117		
Targeted Physical Exam	(X)	Refer to Table 6.1-1	(X)	Refer to Table 6.1-1	Refer to Table 6.1-1	(X)	Refer to Table 6.1-1	X	X	X	X
Concomitant Medications	(X)		(X)			(X)		X	X	X	X
Pregnancy Testing	As clinically indicated										
Sputum AFB Smear and Culture[1]	(X)	Refer to Table 6.1-1	(X)	Refer to Table 6.1-1	Refer to Table 6.1-1	(X)	Refer to Table 6.1-1	X	X	X	X
Molecular Assay to Detect *Mtb* INH- and RIF-Resistance	(X)		(X)			(X)		X	X	X	X
Whole Genome Sequencing[2]										X	X
Drug-Susceptibility Testing[3]	(X)		(X)			(X)		X	X	X	X
TB Symptom Assessment (See Section 6.3.18)	X		X			X					

(X) = If clinically indicated.

1 Two sputum samples for AFB smear microscopy and culture in liquid and solid media will be collected at each time point. Sputum specimens and culture isolates will be stored for targeted deep sequencing and phenotypic drug-susceptibility testing in the event of TB treatment failure or TB recurrence.
2 For participants with suspected recurrence, whole genome sequencing performed on the baseline and recurrent isolate pair.
3 See section 6.3.9.
4 Telephone visit for Arm 1 participants who did not receive 6 months of SOC. If concerning symptoms are reported in the opinion of the site investigator, the patient should be seen in person and the conditional evaluations noted in the SOE performed.

7. Section 6.2.3 Post-Entry Evaluations

   The revision below has been made to update the study duration for follow-up:

   Post-Treatment Evaluations
   Arm 1: The window for study visits during weeks 17-26 is ±3 days. The window for study visits during weeks 34-65 is ±7 days. **The window for study visits during weeks 66 - 117 is ±14 days.**

8. Section 6.3, Instructions for Evaluations

   The following evaluation has been added:

   6.3.18 TB Symptom Assessment

   At weeks 30, 38, and 60, participants in Arm 1, who have not already been referred for 6 months of SOC, will have telephone follow-up visits to assess participants' TB symptoms and determine if it is clinically indicated that the participant should come in for an in-person visit and further TB treatment. If the participant has symptoms concerning for TB in the opinion of the site investigator, an unscheduled in-person visit should be conducted within 1 week to determine if PPTR reporting and evaluations are appropriate, and whether the participant should be referred to the local TB program for 6 months of SOC treatment.

9. Section 10.5.1, Interim Monitoring Guidelines

   The first and last sentences have been updated as follows:

   Unfavorable Composite Outcome Monitoring in Arm 1
   Monitoring for unfavorable composite **clinical efficacy** outcome **(per definition 10.2.4A)** will begin approximately 1 month after the first participant completes treatment in Arm 1 and will continue approximately monthly and for each DSMB review until the end of the study. Two-sided 95% confidence bands for the cumulative probability of unfavorable outcome over time will be generated. If the lower confidence band for the cumulative probability exceeds 12% at any time, this will trigger a DSMB review. **At all DSMB reviews, the DSMB will also be provided with the cumulative probability of unfavorable composite outcome (and corresponding two-sided 95% confidence interval) according to definition 10.2.4B.**

10. Section 10.5.2, Interim Analysis Plan

    The first and third sentences have been revised to read:

    Confidence Bands for Unfavorable Composite Outcome Probabilities
    Monitoring of the unfavorable composite outcome will **be according to definition 10.2.4A.** ~~only include treatment failures, treatment extensions, loss to follow-up while culture positive, recurrences, and deaths.~~ Two-sided 95% confidence bands will be

generated for the cumulative unfavorable composite outcome probability in Arm 1. Since Arm 2 data will be lagging 3 months behind Arm 1, the **data** will be presented alongside historical unfavorable proportions for SOC on the REMox, OFLOTUB, and RIFAQUIN trials, and A5362 SOC data as it becomes available. There will be no adjustment to the confidence bands for multiple looks.

11. Appendix I-C, ADDENDUM TO SAMPLE INFORMED CONSENT

    An addendum to the Sample Informed Consent has been added as Appendix I-C. Appendix I-C is included in this LOA on pages 9-12.

12. Protocol Signature Page (PSP)

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

APPENDIX I-C: ADDENDUM TO SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

For protocol A5362

A5362, FINAL Version 2.0, 08Jul2022, A Phase IIc Trial of Clofazimine- and Rifapentine-Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study

SHORT TITLE FOR THE STUDY: A5362, FINAL Version 2.0, 08Jul2022, Clofazimine and Rifapentine for Drug-Susceptible Tuberculosis

We have important information to share with you about the A5362 (CLO-FAST) study. This study is reviewed by the National Institute of Allergy and Infectious Diseases (NIAID) Therapeutic and Prevention Data and Safety Monitoring Board (DSMB) at least every 6 months. This Board is a group of people who are experts in the fields of medicine and statistics, none of whom are directly involved with the study. Their role is to review the conduct of the study and ensure the safety of participants.

The DSMB met on June 1, 2023 to review the A5362 study.

DSMB RECOMMENDATIONS

After looking at the information about how participants who were receiving the 3-month experimental treatment (Arm 1) were doing, the DSMB concluded that participants who were treated with 3-months of experimental treatment were not doing as well as people who were treated with standard of care [SOC] (Arm 2). Because of this, the DSMB recommended that the study close to enrollment, and recommended that participants currently receiving the 3-month experimental treatment continue to finish the treatment and then receive an additional 3 months of SOC rifampicin/isoniazid treatment. The Board did not find any safety concerns, so there is no concern about harm if you received the 3-month experimental treatment.

WHAT WILL HAPPEN TO ME NOW?

<u>Participants randomized to Arm 1 and are still on study treatment</u>

- **If you are currently completing the 13 weeks of study treatment, you will complete your current course of rifapentine/isoniazid/pyrazinamide/ethambutol (PHZE) + clofazimine (CFZ)**

300 mg for 2 weeks; then PHZE + CFZ 100 mg for 6 weeks; then rifapentine/isoniazid/pyrazinamide (PHZ) + CFZ 100 mg for 5 weeks, for a total of 13 weeks of study treatment.

- **Once you have completed the 13 weeks of study treatment, you will take rifampicin/isoniazid (RH) for 12 weeks.**
- **You will complete all study visits and follow-up through 117 weeks.**

<u>Participants randomized to Arm 1 and have completed study treatment</u>

- **You will be contacted by study staff to discuss how you are feeling and decide whether further TB treatment is needed.**
- **You will attend an additional 5 follow-up visits through 117 weeks. Three of these visits will be conducted by telephone.**

<u>Participants randomized to Arm 2</u>

- **Study treatment and follow-up visit schedule is not changing.**
- **You will complete your current course of rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) for 8 weeks; then rifampicin/isoniazid (RH) for 18 weeks, for a total of 26 weeks of study treatment. Thus, the standard of care for TB treatment.**
- **You will complete all study visits and follow-up through 65 weeks.**

<u>Participants randomized to Arm C</u>

- **Study treatment and follow-up visit schedule is not changing.**
- **You will complete your course of rifapentine/isoniazid/pyrazinaminde/ethambutol (PHZE) + clofazimine (CFZ) 100 mg daily for 4 weeks. This will be followed by standard of care TB treatment (received from your health care provider) that will include 4 weeks of rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) and 18 weeks of rifampicin/isoniazid (RH).**
- **You will complete all study visits and follow-up through 65 weeks.**

WHAT DO I HAVE TO DO IF I STAY ON THE STUDY?

If you are in Arm 1 and stay on study, you will have up to 5 additional follow up visits than you were previously scheduled for, to make sure you are safe and well. Three of these follow up visits may occur on the telephone. If you are on Arm 2 or Arm C, you will continue with the current study visits and follow-up schedule.

You may also choose to stop being followed on the study at any time as well, but we encourage you to discuss this with your health care provider. Once you leave the study, you will not be able to return to the study.

We appreciate your efforts and thank you for being a part of this study and for your continued participation.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study contact:

- ***Site add Name and telephone number for the investigator or other study staff.***

SIGNATURE PAGE

I have been notified of the new study findings and have discussed these findings and my treatment options.

Participant Name	**Participant Signature and Date**
Study Staff Conducting Consent Discussion	**Study Staff Signature and Date**
Witness Name	**Witness Signature and Date**

A Phase IIc Trial of Clofazimine- and Rifapentine-Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study

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