**Regulatory Progress Report for Dr. Teresa Kinyari**
**Quarterly Report for the period: Jan 2024 to Oct 2024**

**Title of Proposal:** A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ASTEGOLIMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

**Principal Investigator(s):** Teresa Kinyari

**Centre:** University of Nairobi Clinical Research Centre

**ECCT No.:** 23/08/01
**(Tick the appropriate identifier)**

1) **Date of Regulatory approval (KPPB):** 06 Dec 2023

    i) **Date the study stopped collecting data where applicable:**
    - ✓ Date for the last participant was recruited (and enrolment): **15 May 2024**
    - ✓ Date the last follow-up was made.: **Ongoing**

**2. The copy of the last continuing review approval or initial approval if this is the first request for renewal:** Initial Approval enclosed

**3. Project period covered:** This approval is valid for one year from 06 Dec 2023 and the expiry day is 06 Dec 2024.

4. **Research objectives:** Briefly describe the purpose of the study.

This study will evaluate the efficacy and safety of Astegolimab compared with placebo in participants with COPD who are former or current smokers and have a history of frequent exacerbations.

5. **Research progress summary:** Briefly describe the progress made during the reporting period, highlighting key findings and achievements during the period. Include the number of new study participants enrolled/recruited into the study, the number of study participants continuing participation the number of new study participants expected to enroll or leave the study during this period, and reasons for their departure. Summarize ongoing activities.

**KNH-UoN ERC Approval date: 25 Jul 2023**
***Trainings/Updates:***

- **Site Training** and Initiation Visit: Site initiation training was completed on 28 Nov 2023 and 25 Jan 2024
- **Protocol Refresher training** conducted on 04th, 5th and 7th April 2024
- **Training:** Vitalograph training and certification on activation of new Compact – Ruth Mungai and Alice Njoroge Feb 2024
- **Updates:** ARNASA_GB44332_New Investigator's Brochure Version 9.0 dated 26 Apr 2024

- **Training:** ARNASA_GB44332_New Investigator's Brochure Version 9.0 dated 26 Apr 2024 and Retention Materials
- **Online training** on Invoice by Sindi on 12 Jun 2024
- **Follow up:** Decentralized Clinical Trial (DCT) Training for Africa EC and RA Partners by Thinaboyo Mphafudi on 3rd July 2024
- **Follow-Up:** Update on EDC Query- (Discussion) – By Amma Twum-Banner dated 12 Jul 2024
- **Training:** Interim Monitoring Follow-Up GB44332, 22-Apr-2024 - 12-Jul-2024
- **Training:** Interim Monitoring Visit Follow-up letter GB44332, 24-25 July 2024
- **Training:** ARNASA/GB44332 – End of Treatment/ End of Study Guidance v3 dated 26 Jul 2024
- **Training:** Vitalograph training and certification on activation of new Compact – Teresa Kinyari on 03 Sep 2024
- **Training Update:** Vitarograph Pre Week 52 refresher training for EMEA and Latin America sites – 26 Sep 2024-
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Date of first enrollment: **28 Feb 2024**
How many authorized to enroll: **5**
How many have been consented: **8**
How Many Screened so far: **8**
How Many Rescreened: **4**
How Many enrolled: **4**
Number withdrawn**: 1**
**Number Discontinued on IMP administration: 1**
N/A lost to follow-up: **0**
Deaths: **2**
How many have Completed the visit: **0**
How many active/ongoing: **2**
How many screened Failed: **4**

6. **Amendments:** Indicate any amendments made and approved during the reporting period e.g. changes in the research site, increase in study sites, sample size, procedure, recruitment plan, investigators, start/end date, modification of informed consent documents, or any other deviation from the original, approved study or protocol violations, etc.
**-Amendment:**
Non-Substantial Amendment Investigator Brochure V9

***Submissions are already done to Local ERC*:**

a) -Phase III Open-Label Extension Study to Evaluate the Long-Term Safety of Astegolimab in Patients with Chronic Obstructive Pulmonary Disease- Approved on **26 Aug 2024**
b) Approval of Substantial Amendment: Revised Main ICF V2, Optional Mobile Nursing Approved **on 20 Sep 2024**

c) Non-Substantial Amendment Investigator Brochure V9 with Participant Face Materials.

d) SUSARS:: 70 SUSARs and 4 SAEs have been submitted to Ethics.

Suspected and Unexpected Severe Adverse Reactions (SUSARs) December 2023 to October 2024 for the above ongoing study for your information. Also attached are the updated forms for the above-referenced SUSAR.

**Protocol Deviations**

1. The protocol sequence of assessments requires that study drug dosing is the last activity at a study visit however, ePROs for subject 20824 were completed after IP administration on Day 1 in error.
   *-Corrective measures:* The Site has been retrained to follow the sequence for assessments in the protocol and to timely communicate challenges to RCRA.

2. 2 participants missed their Dose of IMP Assignments dated -(PID No. 209977- Missed Visit 5 IMP due date: 02 May 2024, PID No. 20968 - Missed Visit 5 IMP due date: 06 May 2024.
   *Reason:* This was due to a lack of IMP at our site due to floods at the Jomo Kenyatta International Airport.
   *-Corrective measure:* Later the IMP assigned to our site were conferred safe for use and the two participants received their IMP assignments for Visit 6 as advised through ePIP communications.
3. Participant PID No. 20968 was recorded in the IXRS as a former smoker yet he was a current smoker
   *-Corrective Measure: The relevant changes have been made on Medidata, but the error still exists on IXRS.*
4. Participant PID 20824 had SAE. There was a Protocol deviation due to the delay in submitting the Initial written AE report to the KNH ERC office within the first Seven days from the time the AE was reported.
   *-Corrective Measure:* The AE forms were filled and delivered as required by the study team
5. Subject 20997: ECG and post-bronchodilator procedures were not done on 19-Jun-2024- at Visit 8 (Week 12) due to a faulty Vitalograph COMPACT
   *-Corrective measure:* The Vitalograph Site support provided the site with a new Vitalograph compact machine on 21 Aug2024
6. Subject 21322: ECG and post-bronchodilator procedures were not done on 19-Jun-2024 -at Visit 8 (Week 12) due to a faulty Vitalograph COMPACT
   *-Corrective measure:* The Vitalograph Site support provided the site with a new Vitalograph compact machine on 21 Aug2024

7. Subject 21322: The participant was discontinued from treatment on 30 Jul 2024. The PI submitted ePIP on 07 Aug 2024 to seek guidance on the procedures to be performed and as such, the ePROs to be completed on the day of the visit per the protocol, for Week 12 (Visit 8) were not completed although the daily diaries were completed as required for 7 days.
8. Participant 21322 at enrollment indicated that the PI considered vitiligo as the subject's medical records were not available for review. Biopsy confirmed early mycosis fungoides on 11 Jan 2024 but this was not disclosed until PI reviewed the medical records post enrollment. A diagnosis of cutaneous T cell lymphoma was made awaiting staging of the disease. The CT chest done at screening did not reveal any visceral disease but showed centrilobular emphysema.

   -*Corrective Measures:* The participant was referred to the haemato-oncologist on 07 Jun 2024 to begin chemotherapy for mycosis fungoides and has been discontinued from study treatment due to unknown drug interaction of IP and immunomodulatory Retinol A treatment (Exclusion Criteria 15).

   9. XRS IMP MIX 20997 AND 20968: On O5 Sep 2024, Participant 20968 came to the study site for his study IMP assignment Visit week 24, The study staff by error registered Participant 20997 for the IMP in the ALMAC instead of 20968. Participant 20997 had come on 26 August for his visit and was not due for any visit on 05 Sep 2024. Therefore Participant 20968 received his IMP as assigned on 05 Sep 2024.

   -*Corrective measure:*

   The PI, Dr. Kinyari contacted the ALMAC team about the error on the same day. On 13 Sep 2024, the Almac team advised the PI, to register a new visit for Participant 20968 so that they can correct the system error. In the process, the Participant was assigned a new IMP on the same date which was not issued to him.

   Almac team was to confirm whether the treatment ARMs for both Participant 20997 and 20968 were the same so that the treatment IMP assignments for Participant 20997 could be swiped over to Participant 20968 and correct the error in the system. The swiping of the IMP is still pending. The error in the system is also still pending and the IMP treatment assigned to Participant 20968 on 13 Sep 2024 is still in quarantine. Participant 20997 passed on, on 09 Sep 2024.

   *On 17 Oct 2024, the Sponsor informed the site that the incident should be reported as a major protocol deviation and that it should be* ***registered as a special situation AE in EDC as per eCRF completion -- guidelines*** *from page 24. The Site was also advised to make a follow-up on Participant- 20968; to inform him about the IMP administration error and assess him for any AE related to the IMP administration error and the appropriate treatment management given. The participant was informed about the error that the administered kit was assigned to a different patient and was only noticed after dosing however there shouldn' t be any cause for alarm. A follow-up on the participant has been ongoing since the IMP error occurred and there is no new AE Observed. He had reported bloating, dermatitis and hypopigmentation since enrollment. He is now asymptomatic for corpulmonale and some of the concomitant medications have been stopped. On 19 Sep 2024 the study staff together*

*with the CRA team and online discussion and trained on how to avoid reoccurrence of the same and will sign a training log as evidence of the same.*

7. **Adverse events reports:** If applicable, report any adverse events – expected or unexpected e.g. related to a drug or a product/procedure being tested that may have occurred during the reporting period, the proportion of the study participants involved, the severity, and how the events were handled.

1 Participant 20824: Had a local Injection reaction on 28 Feb 2024 which cleared on the same day without any intervention.

2 Participant 20824: He was admitted with Severe COPD exacerbation on 5 Mar 2024 and was discharged on 12 Mar 2024 in a stable health condition, on COPD and concomitant medications.

3 Participant 20824: On 13 Apr 2024, he had Severe COPD exacerbation and was evacuated to the KNH KPCC in an ambulance. His SPO2 was initially at 50% but had stabilized at 94% on arrival. He was admitted into Ward 10A with acute kidney injury as a comorbidity and was noted deteriorating succumbing on 14 Apr 2024 on the morning at 12. 40am. The event was assessed as not related to the IMP and procedures.

1 Participant 20997: Had Acute Right-Sided Heart Failure (22 May 2024). An Echocardiogram showed a normal ejection fraction of 55%, dilated ventricles with severe pulmonary arterial hypertension (PAH), and functional severe mitral and tricuspid regurgitation

2 Participant 20997: Severe COPD Exacerbations that occurred on 22 Aug 2024 resulted in hospitalization on 24 Aug 2024. The Participant was discharged home on 04 Sep 2024 in a stable health condition, on COPD and concomitant medications.

3 Participant 20997: On 09 Sep 2024, he developed severe COPD exacerbation, while en route to the study site clinic for his Scheduled Visit 14 and was pronounced dead on arrival at Kenyatta National Hospital Accident and Emergency Department on the same date at 8.15 AM. The event was assessed as not related to the IMP and procedures

8**. Violations:** Report any violations that occurred during the reporting period and corrective measures.

-None reported

9. **Projects outputs:** State if there were any publications, abstracts, a product, patent application, etc. during the last calendar year reporting period, please list these and provide details. Please attach any study output for the reporting period.

-None Reported

10. **Constraints:** State any constraints experienced during the reporting period, and whether or not they adversely affected project progress. Constraints may include lack of funding, transport, personnel, space, etc.

1. The study pharmacist passed on in November 2023. A new pharmacist was invited to join the study team and his documents were approved by the PPB.
2. Delay in funds disbursement for startup
3. Printing of documents
4. Delay in funds disbursement due to incorrect invoicing. The study team was trained and invoices were corrected.
5. Weekly Gen Z protests which coincided with participant visits on Tuesdays and Thursdays. Study team rescheduled visits within the 3-day window as per protocol
6. Faulty Vitalograph COMPACT that was replaced on 21 Aug 2024
7. Lack of funds to purchase participants' COPD Concomitant medications that were a challenge to the participant's care and treatment.

11. **Any other relevant information:** Include any information that might be relevant to this report but not captured in the items listed e.g. if there has been new literature in the field that may or may not affect the conduct of the study or the risk/benefit status of the study. State whether or not a continuation approval is required for the project.

-GB44332 (ARNASA) iDMCs recommendation following review of safety data that the Sponsor continue with the study without modification

**Approvals:**

1. GB332 ARNASA Annual Renewal, approved on **18 July 2024** – Received on **29 July 2024**
2. Phase III Open-Label Extension Study to Evaluate the Long-Term Safety of Astegolimab in Patients with Chronic Obstructive Pulmonary Disease- Approved on **26 Aug 2024**
3. 
4. Approval of Substantial Amendment: Revised Main ICF V2, Optional Mobile Nursing- Approved **on 20 Sep 2024**

12. **Plans for the next project year:** State project activities planned for the coming year or continuing into the next year. Indicate if this is the last project year.

- Participant follow-up ongoing until **06 Mar 2025**
-Implement Revised Main ICF V2, Optional Mobile Nursing
- Roll over to phase III Open Label Extension ALNASA study after **week 52**

**Checklist for documents submitted by the Principal Investigators:**

| DOCUMENT | CONFIRM |
|---|---|
| Cover letter | □ 19 Sep 2024 |
| Continuing Review Report (CRR) | 19 Sep 2024 |
| The last KNH UoN ERC approval letter | 30 Jul 2024 |
| Current approved Protocol | Version 4 |