**STUDY PROTOCOL**

# IMART TRIAL

# IMPROVING TREATMENT OUTCOMES IN CHRONIC MYELOID LEUKAEMIA PATIENTS USING IMATINIB AND ARTESUNATE COMBINATION THERAPY.

**10th March, 2025**

Research Objectives

The general objective of this study is to evaluate the synergistic effect of imatinib and Artesunate on the clinical outcome of chronic phase and imatinib-resistant CML patients. The specific objectives are to:

a. Assess the safety of artesunate use beyond its traditional antimalarial dosing period in CML patients.

b. Compare treatment outcomes between patients on imatinib alone and patients on imatinib plus artesunate at 3, 6 and 12-months of follow-up.

c. Determine the effect of imatinib and artesunate combination on the achievement of major molecular remission [MMR] in CML patients with sub-optimal response to imatinib.

d. Determine the effect of artesunate on imatinib pharmacokinetics following coadministration of the two drugs.

Details

(a). Study population: The population will be consenting Philadelphia chromosome-positive (Ph+) or Breakpoint Cluster Region, Abelson murine Leukaemia (BCR-ABL) positive chronic phase CML patients accessing imatinib at the OAUTHC, Ile-Ife following Simon's design (Mander & Thompson, 2010)

Inclusion criteria: Newly diagnosed chronic phase CML patients between 18 years and 85 years with written informed consent and patients with sub-optimal response to imatinib therapy will be recruited for the study.

Exclusion criteria: Patients with documented hypersensitivity to artesunate, cardiovascular disease, pregnancy and inability to give consent will be excluded. Patients currently on any medication(s) that can interact with imatinib or affect its pharmacokinetics parameters (like rifampicin and ketoconazole) will be excluded.

(b). Study design: The study is a prospective randomized phase II clinical trial of artesunate and imatinib combination therapy in chronic phase CML patients. Patients will be recruited and followed up for at least 6 months of imatinib therapy. Newly diagnosed CML patients recruited for the study will be assigned to Group A or B by randomization already generated before recruitment starts using the Clinical Trial Randomization Tool.

- Group A: 25 newly diagnosed, imatinib naive, chronic phase CML (CP-CML) patients placed on a standard dose of imatinib [400mg daily] alone.
- Group B: 25 newly diagnosed, imatinib naive, CP-CML patients placed on standard-dose imatinib [400mg daily] plus artesunate [200mg daily for 14 days every month]
- Group C shall be 25 imatinib-exposed CML patients who have shown evidence of sub-optimal response to imatinib therapy. This group shall have standard-dose imatinib [400mg daily] plus artesunate [2mg/kg/day or 4mg/kg/day daily for 14 days

every month]. Patients will be randomized to either doses called Group C2 or Group C4.

Suboptimal response as defined by inability to achieve complete haematologic response (CHR) at 3months, major cytogenetic response (MCyR) at 6months, complete cytogenetic response (CCyR) at 12months or major molecular response (MMR) at 18months (Morotti et al., 2015).

(c). Tests: The following investigations will be conducted at the time of recruitment and as stated: Full blood count (monthly), Renal function test (monthly), Liver function test (monthly), and Bcr-Abl testing (every three months).

(d). Sample Collections for pharmacokinetics analysis and imatinib levels

Groups A: Baseline imatinib PK then imatinib levels monthly

Group B: Baseline imatinib PK then imatinib and artesunate levels monthly

Group C: Baseline imatinib PK then imatinib and artesunate levels monthly

2mls of blood samples will be withdrawn from all the patients at pre-determined time intervals (0min, 15min, 30mins, 60mins, 120mins & 360mins) into EDTA tubes this will be further processed to obtain plasma and this will be stored at -20oC.

(e). Pharmacokinetic analysis: A bio-analytical LC-MS/MS will be developed and validated according to ICH guidelines to simultaneously determine the amount of imatinib, its metabolite (N-desmethylimatinib) and artesunate and its metabolite (dihydroartemisin). This method will be used to quantify the amount of these drugs in the plasma of the patients at 3months, 6months and 12months of follow-up.

(f). Study End points: The primary endpoint will be the achievement of Major Molecular remission (MMR/MR3) with bcr/abl-1 gene transcript $\leq 0.1$ and deep molecular response (MR4) with bcr/abl-1 gene transcript $\leq 0.01$ at 12 months. The secondary endpoints will include plasma imatinib levels at 6 and 12 months, disease progression and adverse events relating to long-term use of artesunate.

(h). Statistical analysis: The cumulative incidence of molecular response rate at 12 months, the primary end point, will be estimated using the Kaplan–Meier method. Secondary endpoints regarding patient characteristics and safety indices will be estimated with the use of paired-sample tests. Confidence intervals will be estimated at the 95% confidence level and 2-sided $P < 0.05$ will be considered to indicate statistical significance.