Preliminary results for LF study

The efficacy of Rifampicin 35mg/kg/d plus Albendazole 400mg/d given for 7 or 14 days against Lymphatic filariasis

Safety Profile

Background

Lymphatic filariasis remains a significant public health concern in tropical regions (WHO, 2022). The ASTAWOL project aimed to evaluate the therapeutic potential of rifampicin (RIF) combined with albendazole (ALB) for treating Lymphatic filariasis, focusing on the ability of this combination treatment to clear *W. bancrofti* CFA from the blood of an infected person.

Objectives

The objectives of this study were:

- To assess efficacy (reduction in CFA levels) of the combination of Rifampicin plus Albendazole compared to treatment with Albendazole only and 'no treatment' (other than Ivermectin) against lymphatic filariasis using Og4C3 antigen test 18 months after treatment onset (where day 0 is start of drug administration).
- To analyse the safety profile of the combination of RIF plus ALB in the treatment of lymphatic filariasis
- To select the best therapy strategy and dosing regimen with regard to safety and efficacy

Results

Participants flow and recruitment

Figure 1 provides a detailed flowchart illustrating the progress of participants throughout the trial. All participants received their assigned treatment regimen and underwent follow- up evaluations at intervals of 4-, 6-, 12- and 18 months post-treatment**.** Additionally, ivermectin was administered to all participants at six months as part of the standard care protocol.

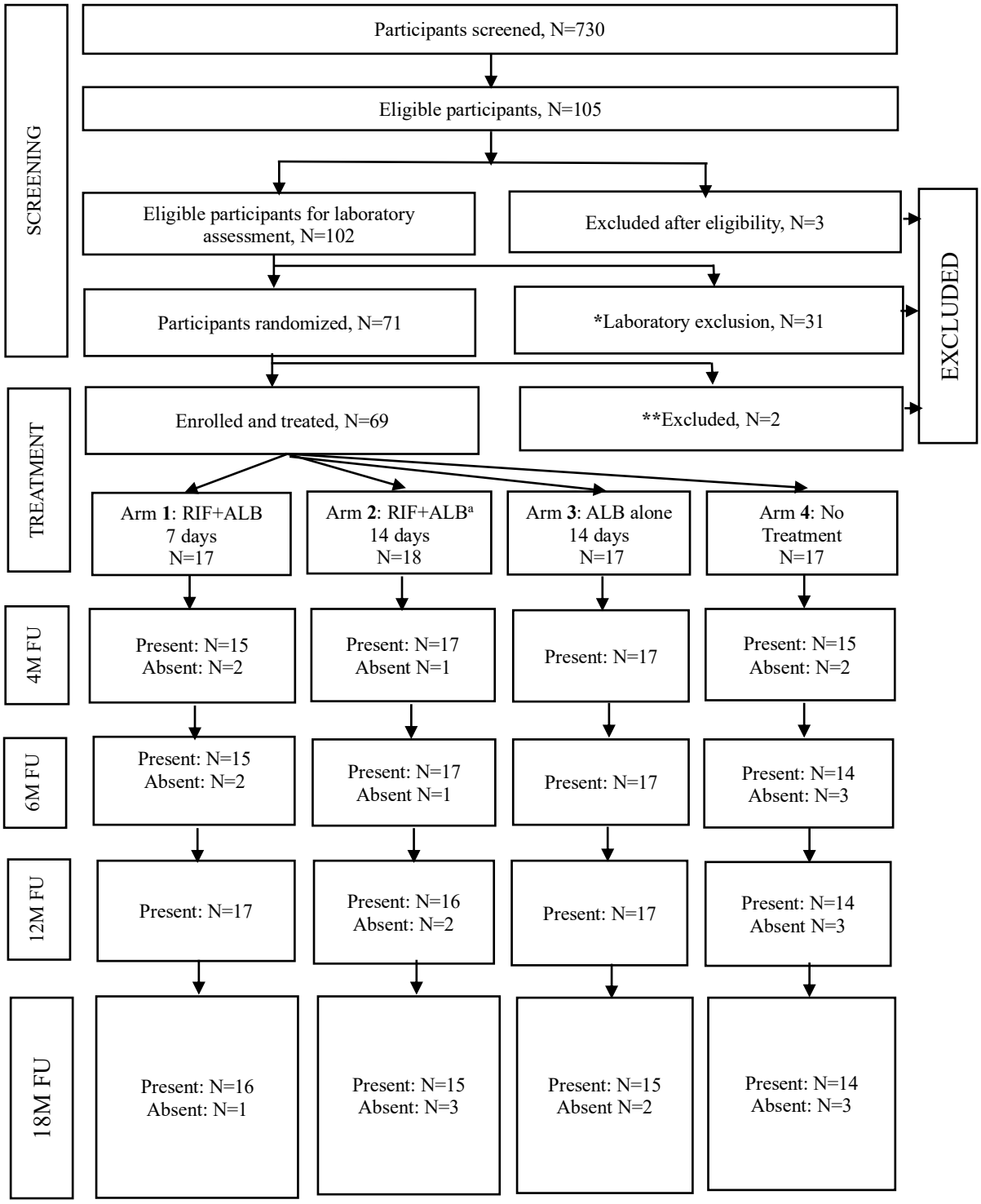

Figure 1: Participant flow chart, showing the number of participants screened, randomized, treated and followed up

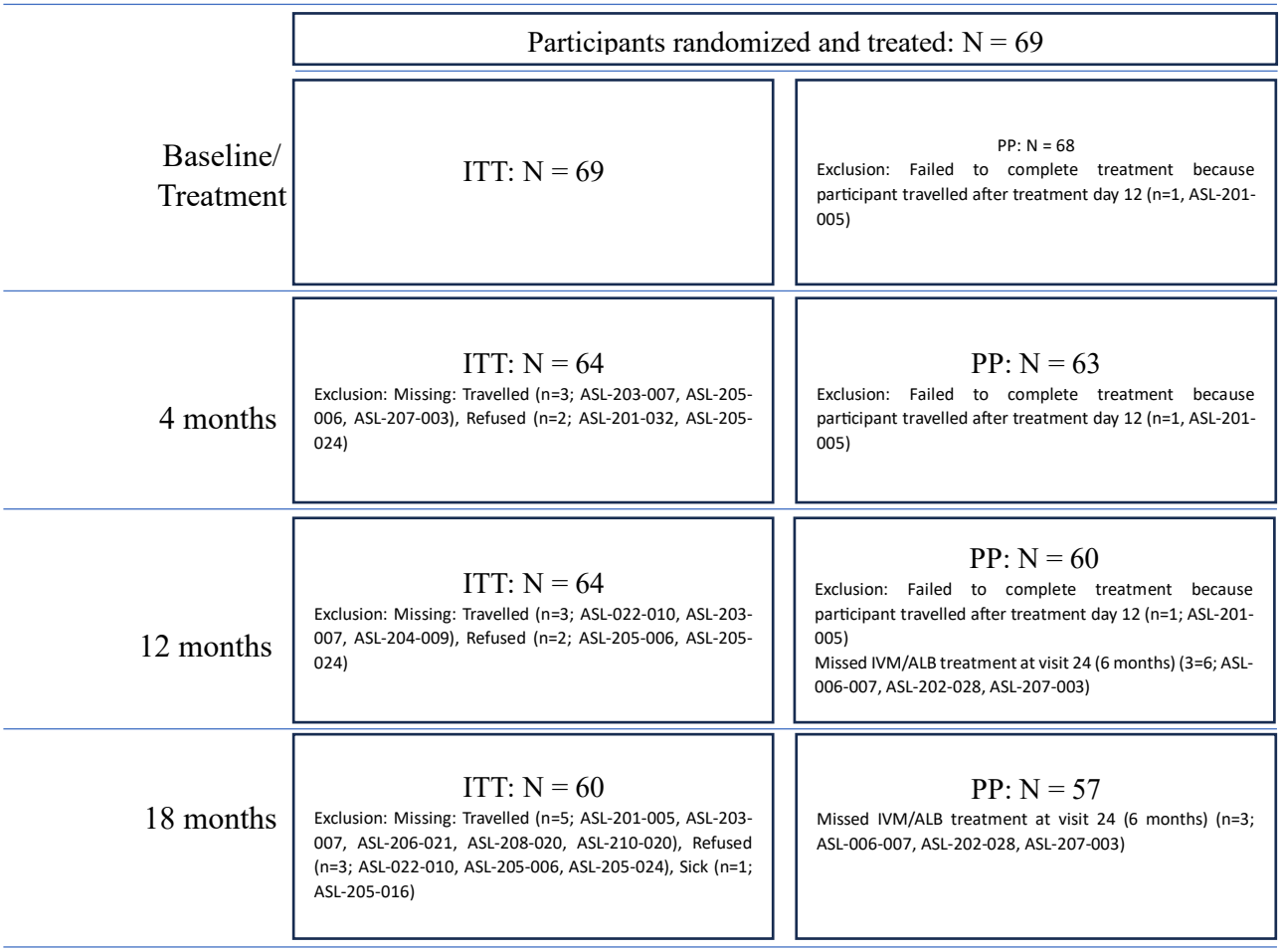

Figure 2: Flowchart illustrating the allocation of participants to treatment groups, their presence/absence during follow-up visits, and their inclusion in the intention-to-treat (ITT) and/or per-protocol (PP) analysis sets at each time point. Reasons for absence from follow-up or exclusion from the PP analysis are also indicated. Abbreviations: ITT= intention-to-treat; PP=per-protocol

Baseline characteristics of participants enrolled on the study

A total of 69 FTS-CFA positive participants were enrolled for the clinical trial. Table 1 below provides an overview of the participants' features. The majority (43.5%, n = 30) were from the Nabdam district. The four treatment arms were generally well-balanced, with 17 participants in each, except for the "RIF+ALB-14Days (TA2)" arm, which had 18 participants. Females constituted 52.2% of the 69 participants enrolled on the study. While only 4 participants (5.8%) had never received MDA before, the majority (53.6%) had completed five or more rounds. The average age of the participants was 42.46 years (SD = 8.46), and on average, they had lived in endemic areas for 39.68 years (SD = 9.80) and had an average body weight of 60.4 kg (SD = 9.3). There were no significant differences in the distribution across treatment arms in terms of gender, district, or the number of MDA rounds received. Similarly, the distribution of different CFA-positive grades across treatment groups showed no statistical difference. Using the TropBio ELISA test, 34.8% (n=24) of the 69 enrolled FTS-CFA positive participants tested positive for the CFA per the TropBio ELISA test and the distribution of these 24 Og4C3 CFA positive participants among the treatment arms was not different statistically.

Safety assessments

Adverse events (AEs) were assessed during treatment. Of the 69 participants enrolled and treated at baseline, the follow-up rates were generally high, 87% or more and the follow-up success rate for all the four treatment arms were above 80% across all the time-points. All participants, except one, successfully completed the treatment, resulting in a compliance rate of 98.6%. A total of 48 AEs were reported during treatment, majority (68.8%) of which were reddish discolouration of urine which occurred only in treatment arm 1 and 2. Headache was recorded among 14.6% of the participants and it was the only AE to have been recorded across all the 4 treatment arms (Table 2).

Table 1: Demographic characteristics of participants enrolled on the study

Variable	Category	RIF+ALB-7Days (TA1)	RIF+ALB-14Days (TA2)	ALB alone-14Days (TA3)	No Treatment (TA4)	Total	P-value
Randomized and treated		17	18	17	17	69	
Sex	Male, n (%)	7 (41.2)	9 (50.0)	11 (64.7)	6 (35.3)	33 (47.8)	0.373[a]
	Female, n (%)	10 (58.8)	9 (50.0)	6 (35.3)	11 (64.7)	36 (52.2)	
District	Nabdam	7 (41.2)	8 (44.4)	7 (41.2)	8 (40.1)	30 (43.5)	0.469[a]
	Kassena/Nankana West, n (%)	5 (29.4)	7 (38.9)	4 (23.5)	4 (23.5)	20 (29.0)	
	Kassena/Nankana East, n (%)	5 (29.4)	3 (16.7)	6 (35.3)	5 (29.4)	19 (27.5)	
Age (years)	Mean (SD)	44.82 (8.66)	45.22 (7.85)	40.35 (6.86)	39.29 (9.32)	42.46 (8.46)	0.080[b]
	Min-Max	29-55	26-55	32-55	25-53	25-55	
Weight (kg)	Mean (SD)	60.5 (12.1)	59.6 (8.2)	62.8 (7.7)	58.8 (9.0)	60.4 (9.3)	0.634[b]
	Min-Max	46.5-89.0	48.0-76.0	52.0-82.5	48.5-75.0	46.5-89.0	
Years in endemic areas	Mean (SD)	42.82 (9.40)	40.50 (11.00)	38.29 (8.58)	37.06 (9.87)	39.68 (9.80)	0.232[c]
	Min-Max	26-55	10-52	20-55	25-53	10-55	
FTS-CFA	Grade 1, n (%)	12 (70.6)	12 (66.7)	12 (70.6)	13 (76.5)	49 (71.0)	0.934[a]
	Grade 2, n (%)	4 (23.5)	6 (33.3)	5 (29.4)	4 (23.5)	19 (27.5)	
	Grade 3, n (%)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	
Og4C3 CFA	Positive, n (%)	5 (29.4)	6 (33.3)	8 (47.1)	5 (29.4)	24 (34.8)	0.709[a]
	Negative, n (%)	12 (70.6)	12 (66.7)	9 (52.9)	12 (70.6)	45 (65.2)	
IVM rounds	0 round, n (%)	1 (5.9)	0 (0.0)	1 (5.9)	2 (11.8)	4 (5.8)	0.758[a]
	1-4 rounds, n (%)	8 (47.1)	6 (33.3)	8 (47.1)	6 (35.3)	28 (40.6)	
	≥ 5 rounds, n (%)	8 (47.1)	12 (66.7)	8 (47.1)	9 (52.9)	37 (53.6)	

[a]*Fisher-Freeman-Halton Exact test;* [b]*Analysis of variance (ANOVA) test;* [c]*Kruskal-Wallis test, n: Number, SD: Standard deviation, RIF: Rifampicin, ALB: Albendazole, TA: Treatment Arm*

Table 2: Safety assessments

Adverse events (AE)	RIF+ALB-7Days (TA1)	RIF+ALB-14Days (TA2)	ALB alone-14Days (TA3)	No Treatment (TA4)	Total
Reddish discolouration of urine	17 (81.0)	16 (76.2)	0 (0.0)	0 (0.0)	33 (68.8)
Headache	2 (9.5)	1 (4.8)	2 (100.0)	2 (50.0)	7 (14.6)
Body itch	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (4.2)
Reddish discolouration of Stool	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (2.1)
Body pains	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (2.1)
Malaise	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Fever	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (2.1)
Malaria	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (2.1)
TOTAL	21 (100.0)	21 (100.0)	2 (100.0)	4 (100.0)	48 (100.0)

RIF: Rifampicin, ALB: Albendazole, TA: Treatment Arm

Change in CFA status across the study time-points within the various treatment groups

Compared to baseline, all treatment arms had decreased number of FTS-CFA positives at all the follow up time-points. The highest rate of reduction in the number of FTS-CFA positives occurred in “treatment arm A (RIF+ALB-7Days)” across all follow ups while “treatment arm B (ALB alone-14Days)” correspondingly had the lowest rate of decrease in number of FTS-CFA positives. However, the rate of decrease in the number of FTS-CFA positives did not differ statistically across the treatment arms at any of the follow up time-points. It is also notable that the rate of decrease in the number of FTS-CFA positives was highest at the 18-month post-treatment follow up, and this was true for all the treatment arms.

Importantly, 34.8% (n=24) of the 69 baseline FTS-CFA positive participants tested positive for the CFA by the use of Og4C3 TropBio ELISA. These 24 baseline Og4C3 CFA positive cases consistently decreased in number along the follow-ups to 7 at the 18-month follow-up. A similar trend was observed across all treatment arms, with all groups—except the "no treatment arm"—showing the lowest proportion of Og4C3 CFA positives at the 18-month follow-up. However, the number of Og4C3 CFA positives did not differ significantly between the treatment arms at any of the follow-up time-points. Notably, in treatment arm B (RIF+ALB-14Days), all participants who were Og4C3 CFA positive at baseline had turned negative by the 18-month follow-up, a statistically significant change from baseline (p=0.031).

Changes in Og4C3 antigen levels in the treatment arms across the study time-points

No statistically significant differences were observed in antigen levels either at baseline or at any of the follow-up points across the treatment arms. However, the "RIF+ALB-7Days" and "RIF+ALB-14Days" treatment arms had significantly lower antigen levels at all follow-up points compared to baseline. In contrast, the "ALB-alone-14Days" and the "no treatment" arms showed significant reductions in antigen levels only at the 12-month and 18-month follow-up.