Pharmacokinetic and safety study of co-administration of albendazole, diethylcarbamazine, Ivermectin and azithromycin for the integrated treatment of Neglected Tropical Diseases

Lucy N. John[1,2,3], Catherine Bjerum[4], Pere Millat Martinez[5], Rhoda Likia[5], Linda Silus[5], Chilaka Wali[2], Arthur Elizah[5], Yashpal S. Chhonker[6], Veenu Bala[6], Christopher L. King[4], Daryl J. Murry[6,7], Oriol Mitja[2,3] Michael Marks[8,9]

[1]*National Department of Health, Port Moresby, Papua New Guinea,*

[2] *Barcelona Institute for Global Health - University of Barcelona, Barcelona, Spain,*

[3]*School of Medicine and Health Sciences, University of Papua New Guinea, Port Moresby, Papua New Guinea*

[4]*Case Western Reserve University School of Medicine and Veterans Affairs Medical Center, Cleveland, OH, United States,*

[5] *Lihir Malaria Elimination Program, Newcrest Lihir, New Ireland Province, Papua New Guinea*

[6] *Clinical Pharmacology Laboratory, Dept. of Pharmacy Practice and Science, Nebraska University Medical Center, Omaha, NE, United States,*

[7] *Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE, USA,*

[8] *London School of Hygiene and Tropical Medicine, London, United Kingdom,*

[9]*Hospital for Tropical Diseases, London, United Kingdom*

Corresponding author:

L. N. John National Department of Health P.O.BOX 807, Waigani NCD *lucyninmongojohn@gmail.com* or lucy_john@health.gov.pg

Summary:
Pharmacokinetic data are needed to support co-administration of drugs used in the elimination of neglected tropical diseases. We demonstrate that ivermectin, diethylcarbamazine, albendazole and azithromycin can be co-administered without significant drug-drug interactions. This data will facilitate large scale co-administration studies.

Accepted Manuscript

© The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

ABSTRACT

***Background*.** Pharmacokinetic data are a pre-requisite to integrated implementation of large-scale mass drug administration (MDA) for neglected tropical diseases (NTDs). We investigated the safety and drug interactions of a combination of azithromycin (AZI) targeting yaws and trachoma, with the newly approved ivermectin, albendazole, diethylcarbamazine (IDA) regime for Lymphatic Filariasis.

***Methodology*.** An open-label, randomized, 3-arm pharmacokinetic interaction study in adult volunteers was carried out in Lihir Island, Papua New Guinea. Healthy adult participants were recruited and randomized to (I) IDA alone, (II) IDA combined with AZI, (III) AZI alone. The primary outcome was lack of a clinically relevant drug interaction. The secondary outcome was the overall difference in the proportion of AEs between treatment arms.

Results. Thirty-seven participants, eighteen men and nineteen women, were randomized and completed the study. There were no significant drug-drug interactions between the study arms. The GMR of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for IVM, DEC, ALB-SOX, and AZI were within the range of 80–125% (GMR for $AUC_{0-\infty}$ for IVM, 87.9; DEC, 92.9; ALB-SOX, 100.0; and AZI, 100.1). There was no significant difference in the frequency of AEs across study arms (AZI and IDA alone arms 9/12 (75%), co-administration arm 12/13 (92%); p = 0.44). All AEs were grade 1 and self-limiting.

Conclusions. Co-administration of AZI with IDA did not show evidence of significant drug-interactions. There were no serious AEs in any of the study arms. Our data support further evaluation of the safety of integrated MDA for NTDs.

Clinical Trials Registration. NCT03664063

Keywords: yaws, lymphatic filariasis, mass drug administration, co-administration

Accepted Manuscript

BACKGROUND

Mass drug administration (MDA) is the mainstay of control programs for many neglected tropical diseases (NTDs) including lymphatic filariasis (LF), soil-transmitted helminths (STH), trachoma and yaws [1–3]. In many countries, including Papua New Guinea (PNG), most NTD control programs run separately and deliver separate MDA campaigns for each targeted disease. However, conducting separate MDA campaigns for each NTD involves added complexity and increases economic and logistic costs. Studies in other settings have explored combining MDA for LF and schistosomiasis, which appears to be safe and allows programs to achieve considerable cost-savings [4]. Expanding opportunities for integration of MDA campaigns is therefore an attractive strategy for Ministries of Health and partner organizations for both logistical and economic reasons.

Lymphatic filariasis is an endemic nematode infection, most commonly caused by *Wuchereria bancrofti,* and affects 120 million people worldwide. For the last 20 years, the main LF elimination strategy has consisted of repeated rounds of MDA with albendazole (ALB) and either diethylcarbamazine (DEC) or ivermectin (IVM). However, recent studies have shown that single-dose combination therapy with all three drugs, IVM, DEC, ALB (IDA) is superior to the previous two-drug combinations, and may help accelerate LF elimination [1]. In light of this emerging data on both, safety and efficacy, WHO has provided alternative guidelines recommending IDA based MDA in countries endemic for LF outside sub-Saharan Africa [5].

Trachoma is caused by *Chlamydia trachomatis* infection and is the leading infectious cause of blindness worldwide. The macrolide antibiotic azithromycin (AZI) has been demonstrated to be highly safe and effective as MDA for trachoma [6], and now forms a cornerstone of the WHO SAFE strategy [2]. Recently single doze AZI has also been shown to be effective against yaws and is now recommended by WHO for this indication[3,7].

Pharmacokinetic (PK) data are needed to ensure that there are no significant drug-drug interactions that might impact either the safety or efficacy of co-administration of the new IDA regimen and AZI. PK data formed an important part of the safety data collected prior to large scale field studies of the IDA regimen and have shown no clinically important effect on any of the drug levels [8,9]. Previous PK studies examining the interaction between IVM, ALB and AZI have not identified clinically meaningful drug-drug interactions and small-scale field implementation studies have suggested co-administration is safe [10–12]. There is no PK data on co-administration of DEC and AZI with or without the addition of IVM or ALB. We therefore conducted a PK study amongst healthy volunteers to assess the safety and drug interactions of co-administration of AZI alongside IDA in PNG.

Accepted Manuscript

METHODS

Study setting and participants

We undertook an open-label, parallel-group, randomized study with 3 treatment arms at the Lihir Medical Centre between Sept 15 and Oct 15, 2018. Participants were recruited from Kunaye 1, Kunaye 2, Putput and Zuen villages of Lihir Island, New Ireland Province, PNG. All individuals provided written informed consent to participate in the study. The Medical Research Advisory committee of PNG (MRAC 17.19) and the institutional Review Board of Case Western University approved the study. The trial was registered at ClinicalTrials.gov (NCT03664063).

Eligible participants were adult healthy volunteers aged 18–70 years who reported no significant past medical history and no current acute illnesses. At enrollment participants underwent a standardized medical examination and blood and urine tests. Exclusion criteria were alanine transaminase (ALT), aspartate transaminase (AST), or creatinine >1.5 times the upper limit of normal; hemoglobin levels <7 gm/dL; abnormal (>++) urine leucocytosis or glucosuria and pregnancy.

Randomization and masking

Eligible participants were randomly assigned by use of a computer generated randomization sequence stratified by sex to receive one of three treatment regimens: (ARM-I) IVM 200 µg/kg + DEC 6 mg/kg + ALB 400 mg, or (ARM-II) IVM 200 µg/kg + DEC 6 mg/kg + ALB 400 mg + AZI 30 mg/Kg, or (ARM-III) AZI 30 mg/Kg. Randomization was done in permuted blocks of six and in a 1:1:1 ratio. The allocation was concealed from investigators by use of opaque, sealed and sequentially numbered envelopes that were opened after the study team decided to enroll the participant. Laboratory technicians were unaware of participants' treatment allocation. All participants received directly observed treatment, but masking was not possible for logistical reasons.

Procedures

The primary outcome was lack of a clinically relevant pharmacokinetic drug interactions, defined as geometric mean ratios (GMRs) within the conventional acceptance range of 80-125 for the Cmax, $AUC_{0\text{-}t}$, and $AUC0_{-\infty}$ between treatment arms. GMR was used as previous studies have shown the pharmacokinetics of IVM, DEC, and ALB to be highly variable (CV greater than 30%). The secondary outcome was the difference in the overall proportion of AEs between treatment arms.

The study team conducted local visits to communities to explain the purpose and the procedures involved in the study and volunteers were provided detailed information. For the purpose of the study, all participants were admitted the day before treatment administration for a period of 72 hours for blood collections and close monitoring of adverse event (AE). At baseline we tested for malaria antigen (CareStart® Malaria PF/PAN rapid diagnostic test, ACCESSBIO), syphilis serology (DPP® syphilis screen & confirm Assay, CHEMBIO), *W. bancrofti* antigen (Alere® Filarial Test Strips, ABBOTT), for liver function fests, kidney function fests, full blood count, and urinalysis (Multistix 10 SG, Bayer/Seimens). Female participants had a pregnancy test performed. Participants were fasted

Accepted Manuscript

overnight and medication was administered at 0700h after breakfast. Blood draws for PK testing were performed at baseline, 1, 2, 3, 4, 6, 8, 12 hours (using intravenous cannulas) and at 24, 48, and 72 hours using venipuncture in keeping with previous similar studies [2,8]. Participants were monitored for AEs on the basis of physical examinations including recording blood pressure (BP), pulse rate, respiratory rate and temperature every 6 hours for the first 24 hours and then every 12 hours up to 72 hours after drug administration. We tested for full blood count, liver and kidney function, and urinalysis daily for the 72 hours. We conducted an additional safety visit in the community at day 7.

Blood samples for PK analysis were stored at a temperature of -15 ^{0}C at site laboratory and were then shipped on dry ice to the University of Nebraska Medical Center. Plasma concentrations of DEC, ALB, ALB-SOX (Albendazole-Sulphoxide), ALB-SON (Albendazole-sulphone) and IVM were determined using a validated liquid chromatography-mass spectrometric (LC-MS/MS) methods as previously reported[8,9]. AZI plasma concentrations were determined using a validated LC-MS/MS assay (under preparation for publication). The PK parameters of DEC, ALB, ALB-SOX, ALB-SON, IVM and AZI were calculated using non-compartmental analysis (NCA) using Phoenix WinNonlin-8.1 (Certara, Princeton, NJ, USA). The maximum concentration (C_{max}), and time to C_{max} (T_{max}) were determined directly from the plasma concentration-time data. The area under the curve ($AUC_{0\text{-}inf}$), was estimated using the trapezoidal method from 0 to t_{last} and extrapolation from t_{last} to infinity ($AUC_{0-\infty}$) based on the observed concentration at the last time point divided by the terminal elimination rate constant (λ_z). The half-life (t ½) was calculated using the formula of 0.693/ λ_z. Apparent volume of distribution (Vz/F) and clearance (CL/F) for each drug was calculated using standard equations. Values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were normalized to mg/kg doses of 4 mg/kg for ALB, 6.0 mg/kg for DEC (or 3.0 mg/kg after salt normalization), 200 µg/kg for IVM and 30 mg/kg for AZI, to reduce variability in PK parameters resulting from the differing mg/kg doses administered to each subject.

Adverse Events were defined as any one of the following: an increase in ALT, AST, or creatinine >1.5 times the upper limit of normal, tympanic temperature >37.8°C, or BP <90/60. Subjective AEs were assessed by interviews and were defined as any new symptoms and worsening of pre-existing symptoms. Severity was assessed using the GRADE system established in the Common Terminology Criteria for Adverse Events. In all participants reporting a grade $\geq$2 AE, a targeted physical examination was conducted by a study clinician. If appropriate, additional diagnostic testing and treatment was provided through the Lihir Medical Centre. Any medical treatment required was provided free of charge to participants. All data was collected using standardized data collection forms. Data was double entered into a REDCap database.

Pharmacokinetic and Pharmacodynamic Analysis

Power calculations indicated that 42 participants (14 subjects per arm) would give a power of 80% to test the hypothesis that the primary outcome of a bioequivalence between test groups between 80-120% of geometric mean ratio (see below) based on previous PK modelling studies [8] and European Medicines Agency guidelines [13] with the assumption that 10% of participants would be lost to follow-

Accepted Manuscript

up. For analysis of the primary outcome (lack of clinically relevant pharmacokinetic interactions), we estimated one-sided 90% CI for the geometric mean ratios (GMRs) of the experimental regimen and the reference regimens. Descriptive comparisons of PK parameters between arms were performed using the Kruskal-Wallis test using the JMP software (Ver. 14.0, Cary, NC, USA) and comparison of GMRs of the main PK parameters and 90% CI were estimated, after log transformation of within-subject using Phoenix WinNonlin-8.1 (Certara, Princeton, NJ, USA). The data obtained in this study were compared according to Food and Drug Administration and European Medicines Agency guidelines (EMA) (90% CI, 80%–125% for $AUC_{0-\infty}$ and Cmax)[13,14]. According to the EMA guideline, the wider equivalence range could be considered for highly variable drugs (intra-subject coefficient of variation > 30%). Previous studies have shown the substantial PK variability with coefficient of variations for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} greater than 30% for DEC, IVM and AZI and C_{max} greater than 50% for ALB and its active metabolite [12,13].

Statistical Analysis

For analysis of the AEs outcomes, we calculated the frequency of each AE by study arm. We grouped diarrhea, abdominal pain and nausea together into a single AE category. Differences between arms were assessed using a Chi-Square test. All statistical analysis was conducted in R version 3.4.2 (The R Foundation for Statistical Computing) [15].

RESULTS

Study Enrolment and Flowchart

Forty-two individuals were screened for inclusion into the study. Three participants were excluded (pregnant n = 1, acute febrile illness n = 1, unable to obtain venous access n = 1; **Figure 1**). Thirty-nine (39) participants met study inclusion and 37 completed the full study. Two participants were excluded after screening (n = 1 in ARM-II, consumed alcohol following treatment; n = 1 in ARM-III withdrew and did not receive study drugs). The three study arms were well balanced with regards to demographic characteristics. The mean age (years+/-SD) of the 37 participants that completed the study was 29.2 (10.6) and 19 (51.4%) were female (**Table 1**). Overall 10 (27%) participants had serological evidence of yaws, and 8 (21.6%) had serological evidence of lymphatic filariasis.

Pharmacokinetics drug-drug Interactions

PK parameters for IDA alone (ARM-I), IDA+ AZI (ARM-II) or AZI alone (ARM-III) are shown in **Table 2**. The median elimination $t_{1/2}$ and time to peak concentration was similar for DEC, ALB-SOX, IVM and AZI when given alone or in combination. Median values for any comparison were not different between study arms ($p>0.05$). Ranges for each PK parameter are shown in **Supplementary Table 1**. Distribution of dose adjusted C_{max} and AUC_{0-t} of study drugs by study ARM with individual data points are shown in **Supplementary Figure 1**.

Accepted Manuscript

The mean plasma concentration–time profiles of ALB, ALB-SOX (the active metabolite of ALB), ALB-SON, DEC, IVM and AZI are shown in **Figure 2**. Geometric mean ratios (GMR) of parameters in the experimental arm (IDA + AZI) versus the reference arms (IDA and AZI alone) are presented with 90% confidence intervals (CIs) in **Figure 3**. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for each analyte were dose normalized. The GMR of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for DEC, IVM, ALB-SOX and AZI were within the range of 80–125%, and the 90% CIs partly overlap the range of 50–200% that reflects the inter subject variability. For ALB, which is rapidly metabolized to ALB-SOX, the GMR of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were within the range of 80–125% (data not shown).

Adverse Events

Overall, 30 (81.0%) of 37 participants developed at least 1 AE (Table 3). AEs were reported by 9/12 (75%) in ARM-I, 12/13 (92%) in ARM-II, and 9/12 (75%) in ARM-III, however this difference was not significant (p=0.44). All AEs reported in the study were Grade 1 and self-limiting. No serious AEs occurred in any of the study arms. No participants required treatment for any AE. A total of 372 AE assessments were conducted; the most common AEs were headache (11 episodes, 3.0%), GI upset (13 episodes, 3.5%), and asymptomatic transient hypotension (15 episodes, 4.0%) (Table 2). Biochemically, the highest recorded ALT and AST were 85iu/L and 76iu/L respectively at 24 hours post treatment and both resolved by 48 hours. The highest creatinine was 158umol/L at 24 hours which also resolved by 48 hours.

DISCUSSION

Our findings show that co-administration of AZI alongside the new triple-drug IDA regime for LF was tolerable and without any evidence of significant drug-drug interactions. The GMR values of PK parameters for IVM, DEC and ALB or ALB metabolites, were not significantly altered by the co-administration of AZI, and values were similar to those seen in previous studies[8,9,16]. These results suggest that AZI has no clinically relevant effect on the PK of IVM, DEC and ALB. Moreover, there was no change in the PK for AZI when administered in this combination regimen. There was considerable variability in plasma ALB and IVM drug levels among individuals as has been previously reported[8,9]. Evidence before this study showed that combinations for NTDs were safe in terms of PK interactions between AZI and IVM, IVM and ALB, IDA drugs, and IVM, ALB and AZI[8–11,16]. The added value of this study is that for the first time we report on the safety of a quadruple combination of IDA and AZI.

This study also showed no serious AEs in any of the 3 study arms. Mild AEs (grade 1) were frequent in all arms but self-limiting. Of participants who were treated with combined treatment 92% reported mild AEs that were mainly gastrointestinal, compared to 75% of participants who received IDA or AZI alone. Whilst, given the small sample size, we cannot preclude a risk of rarer more serious AEs due to co-administration, our data provides substantial reassurance that co-administration is well tolerated.

Accepted Manuscript

The main limitation of this study is the study sample size, which was only designed to exclude significant drug-drug interactions. A larger sample size is required to better understand whether the trend toward a higher rate of AEs with co-administration will be borne out and to assess for rarer AEs which may occur. Secondly, we did not assess the impact of co-administration on the efficacy of any of the drugs but given the absence of any significant drug-drug interactions it seems highly unlikely that co-administration would impact efficacy. Thirdly, we did not systematically measure acceptability on the challenge of swallowing a large number of tablets, but we observed that participants' acceptance was very high. Finally, our population was limited to adults. Data in paediatric populations would be of value to further support the case for integrated MDA, however we would not expect any significant interaction in children based on the results in adults, although optimal dosing in children may be more variable in MDA campaigns. It should be noted that IVM is currently not given to children <15 kg and/or <5 years of age.

Our findings provide strong evidence on the lack of pharmacokinetic drug interactions and tolerability of co-administration of IDA with AZI. This data paves the way for integrated MDA programs targeting LF, STH, trachoma, scabies and yaws [18,19]. The benefits of MDA integration include increased coverage and geographic reach of national NTD programs, whilst achieving financial and programmatic savings. Integrated MDAs will be of particular value in countries such as Papua New Guinea where these diseases are co-endemic and where the cost of individual MDA is particularly high compared to other settings [17]. Field studies are now planned to further evaluate the safety of co-administration within a programmatic context.

Accepted Manuscript

Notes

Contributions. LJ, MM, CB, CK, OM conceived the study. LJ, CB, OM, MM, PM, RL, LS, CW and AE conducted the study. CK, YC, VB and DM performed the PK analysis. LJ, OM and MM drafted the manuscript. All authors contributed to revising the manuscript.

Acknowledgements. Participants who willingly participated in this study are acknowledged and thanked for their contribution. The Papua New Guinea National Department of Health and the Lihir Medical Centre are hereby thanked for their support in conducting this study.

***Financial support*.** Funding for the study was provided by the International Trachoma Initiative.

***Potential conflicts of interest*.** The authors declare no relevant conflict of interest.

Accepted Manuscript

REFERENCES

1. King CL, Suamani J, Sanuku N, et al. A Trial of a Triple-Drug Treatment for Lymphatic Filariasis. N Engl J Med **2018**; 379:1801–1810.

2. Emerson PM, Burton MJ, Solomon AW, Bailey R, Mabey DC. The SAFE strategy for trachoma control: using operational research for policy, and implementation. Bull World Health Organ **2006**; 84:613–619.

3. Mitjà O, Houinei W, Moses P, et al. Mass Treatment with Single-Dose Azithromycin for Yaws. N Engl J Med **2015**; 372:703–710.

4. Evans D, Mcfarland D, Adamani W, et al. Cost-effectiveness of triple drug administration (TDA) with praziquantel, ivermectin and albendazole for the prevention of neglected tropical diseases in Nigeria. Ann Trop Med Parasitol **2011**; 105:537–547.

5. WHO | Guideline – Alternative mass drug administration regimens to eliminate lymphatic filariasis. Available at: http://www.who.int/lymphatic_filariasis/resources/9789241550161/en/. Accessed 8 December 2019.

6. Solomon AW, Holland MJ, Alexander NDE, et al. Mass Treatment with Single-Dose Azithromycin for Trachoma. N Engl J Med **2004**; 351:1962–1971.

7. The World Health Organisation. Eradication of yaws - the Morges Strategy. Wkly Epidemiol Rec **2012**; 87:189–194.

8. Thomsen EK, Sanuku N, Baea M, et al. Efficacy, Safety, and Pharmacokinetics of Coadministered Diethylcarbamazine, Albendazole, and Ivermectin for Treatment of Bancroftian Filariasis. Clin Infect Dis **2016**; 62:334–341.

9. Bjerum CM, Ouattara AF, Aboulaye M, et al. Efficacy and Safety of a Single Dose of Ivermectin, Diethylcarbamazine, and Albendazole for Treatment of Lymphatic Filariasis in Côte d'Ivoire: An Open-label Randomized Controlled Trial. Clin Infect Dis Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz1050/5602915. Accessed 8 December 2019.

10. El-Tahtawy A, Glue P, Andrews EN, Mardekian J, Amsden GW, Knirsch CA. The Effect of Azithromycin on Ivermectin Pharmacokinetics—A Population Pharmacokinetic Model Analysis. PLOS Negl Trop Dis **2008**; 2:e236.

11. Amsden GW, Gregory TB, Michalak CA, Glue P, Knirsch CA. Pharmacokinetics of Azithromycin and the Combination of Ivermectin and Albendazole When Administered Alone and Concurrently in Healthy Volunteers. Am J Trop Med Hyg **2007**; 76:1153–1157.

12. Coulibaly YI, Dicko I, Keita M, et al. A cluster randomized study of the safety of integrated treatment of trachoma and lymphatic filariasis in children and adults in Sikasso, Mali. PLoS Negl Trop Dis **2013**; 7:e2221.

13. European Medicines Agency. Guideline on the Investigation of Bioequivalence. 2010; Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf.

14. Research C for DE and. Statistical Approaches to Establishing Bioequivalence. 2019. Available at: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence. Accessed 8 December 2019.

Accepted Manuscript

15. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2017. Available at: https://www.R-project.org/.

16. Awadzi K, Edwards G, Duke BOL, et al. The co-administration of ivermectin and albendazole--safety, pharmacokinetics and efficacy against Onchocerca volvulus. Ann Trop Med Parasitol **2003**; 97:165–178.

17. Fitzpatrick C, Fleming FM, Madin-Warburton M, et al. Benchmarking the Cost per Person of Mass Treatment for Selected Neglected Tropical Diseases: An Approach Based on Literature Review and Meta-regression with Web-Based Software Application. PLoS Negl Trop Dis **2016**; 10:e0005037.

Accepted Manuscript

Table 1: Baseline Characteristics

	IDA Alone (ARM-I, N=12)	IDA and Azithromycin (ARM-II, N=13)	Azithromycin Alone (ARM-III, N=12)
Age			
Mean (SD)	25.6 (11.4)	32.3 (11.5)	29.3 (8.4)
Range	18.0 - 59.0	20.0 - 55.0	21.0 - 52.0
Sex			
Male	6 (50.0%)	6 (46.2%)	6 (50.0%)
Female	6 (50.0%)	7 (53.8%)	6 (50.0%)
Weight			
Mean (SD)	61.2 (9.2)	64.3 (13.3)	66.3 (15.7)
Range	46.0 - 73.0	51.0 - 92.0	41.0 - 93.0
BMI			
Mean (SD)	22.8 (3.3)	24.8 (5.1)	25.7 (5.8)
Range	18.7 - 29.2	19.1 - 35.8	17.3 - 36.3
DEC Dose			
Mean (SD)	366.7 (57.7)	380.8 (72.3)	NA
Albendazole Dose			
Mean (SD)	400	400	NA
Ivermectin Dose			
Mean (SD)	12.8 (2.3)	13.4 (2.3)	NA
Azithromycin Dose			
Mean (SD)	NA	1750 (204.1)	1770.8 (270.9)
DPP Result			
Negative	6 (50.0%)	6 (46.2%)	9 (75.0%)
Treponema Positive and Non-Treponema Negative	1 (8.3%)	2 (15.4%)	3 (25.0%)
Treponema Positive and Non-Treponema Positive	5 (41.7%)	5 (38.5%)	0 (0.0%)
Filariasis Test Strip Result			
Negative	8 (66.7%)	11 (84.6%)	10 (83.3%)
Positive	4 (33.3%)	2 (15.4%)	2 (16.7%)

Accepted Manuscript

Table 2: Pharmacokinetic parameters of the study drugs when administered in either a three drug (IDA), a four drug combination (IDA+AZI) or AZI alone.

Parameter	ALB-SOX		DEC		IVM		AZI	
	IDA	IDA+AZI	IDA	IDA+AZI	IDA	IDA+AZI	AZI	IDA+AZI
C_{max} (ng/mL)	391.6	443.6	1368.9	1539.1	96.6	83.6	1190.6	1648.8
T_{max} (hr)	5	6	3	4	6	6	3.5	4
Half-life ($t_{1/2}$)	7.3	8.1	10.7	9.9	24.3	33.1	32.1	29.9
AUC_{0-t} (ng*hr/mL)	5484	5902.2	22967.6	21227.6	1856.1	1576.1	11332.8	14532
$AUC_{0-\infty}$ (ng*hr/mL)	5487.8	5921.6	23299.3	21397.3	2178.9	2019.9	13950.2	17298.6
$V_{z/F}$ (L)	788.5	783.4	127.2	136.6	213.9	332.6	5484.2	5504.3
Cl/F (L/hr)	73	68.2	7.7	9.2	5.6	6	129.5	101.2
C_{max} adjusted to dose (ng/mL)	222.3	278.7	1420.8	1542.9	96.7	78.9	1312.5	1905.9
AUC_{0-t} adjusted to Dose (ng*hr/mL)	3103.7	4712.8	22750.8	23147.9	1746	1567.2	12511	14778
$AUC_{0-\infty}$ adjusted to dose(ng*hr/mL)	3151.3	4731.3	23079.6	23333.6	2047.5	1962.8	16706.8	17208

Data presented are the median values for each pharmacokinetic parameter.

Data are median. $T_{1/2}$ terminal half-life, T_{max} time of maximum plasma concentration, C_{max} maximum plasma concentration, AUC area under the concentration-time curve, Vz/F apparent volume of distribution, CL/F apparent clearance.

ALB-SOX, albendazole sulfoxide, DEC, diethylcarbamazine, IVM, ivermectin, AZI, azithromycin.

IDA, three drug combination (DEC 6mg/kg+ IVM 200ug/kg + ALB 400mg); IDA+AZI, four drug combination (IVM 200µg/kg + DEC 6mg/kg+ ALB 400mg +AZI 30mg/kg); or AZI (AZI alone 30mg/kg).

Accepted Manuscript

Table 3: Adverse events experienced in each of the three study arms (IDA, IDA+AZI, AZI alone).

	IDA Alone (ARM-I, N=12)	IDA+AZI (ARM-II, N=13)	AZI Alone (ARM-III, N=12)	Total (N=37)	p value
Fever	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (2.7%)	0.39
Headache	3 (25.0%)	2 (15.4%)	3 (25.0%)	8 (21.6%)	0.80
GI Upset	2 (16.7%)	5 (38.5%)	2 (16.7%)	9 (24.3%)	0.34
Myalgia	0 (0.0%)	2 (15.4%)	0 (0.0%)	2 (5.4%)	0.14
Itch	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0.34
Cough	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (2.7%)	0.39
Hypotension*	5 (41.7%)	1 (7.7%)	3 (25.0%)	9 (24.3%)	0.14
AKI (Creat 1.5*ULN)$	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (2.7%)	0.39
Hepatotoxicity[$] (ALT or AST 1.5*ULN)	0 (0.0%)	2 (15.4%)	1 (8.3%)	3 (8.1%)	0.37
Glycosouria	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (2.7%)	0.39
Proteinuria	2 (16.7%)	2 (15.4%)	1 (8.3%)	5 (13.5%)	0.81
Haematuria	0 (0.0%)	1 (7.7%)	1 (8.3%)	2 (5.4%)	0.60
Other	2 (16.7%)[#]	3 (23.1%)^	0 (0.0%)	5 (13.5%)	0.22
Any Adverse Event	9 (75.0%)	12 (92.3%)	9 (75.0%)	30 (81.1%)	0.44

GI Gastrointestinal, AKI Acute kidney Injury

[$] Change in Creatinine / ALT / AST relative to baseline

*All cases of hypotension were asymptomatic and none required treatment

[#] 1 Patient reported 'eyes feeling tired' and 1 patient reported pain at the IV catheter site

^ 2 Patients reported subjectively feeling cold without objective change in temperature and 1 patient developed phlebitis at the IV catheter site.

Accepted Manuscript

Figure Legends

Figure 1: Study enrolment flowchart

Figure 2: Drug concentration vs time curve plots for subjects on the IDA, IDA+AZI and AZI alone study arms.

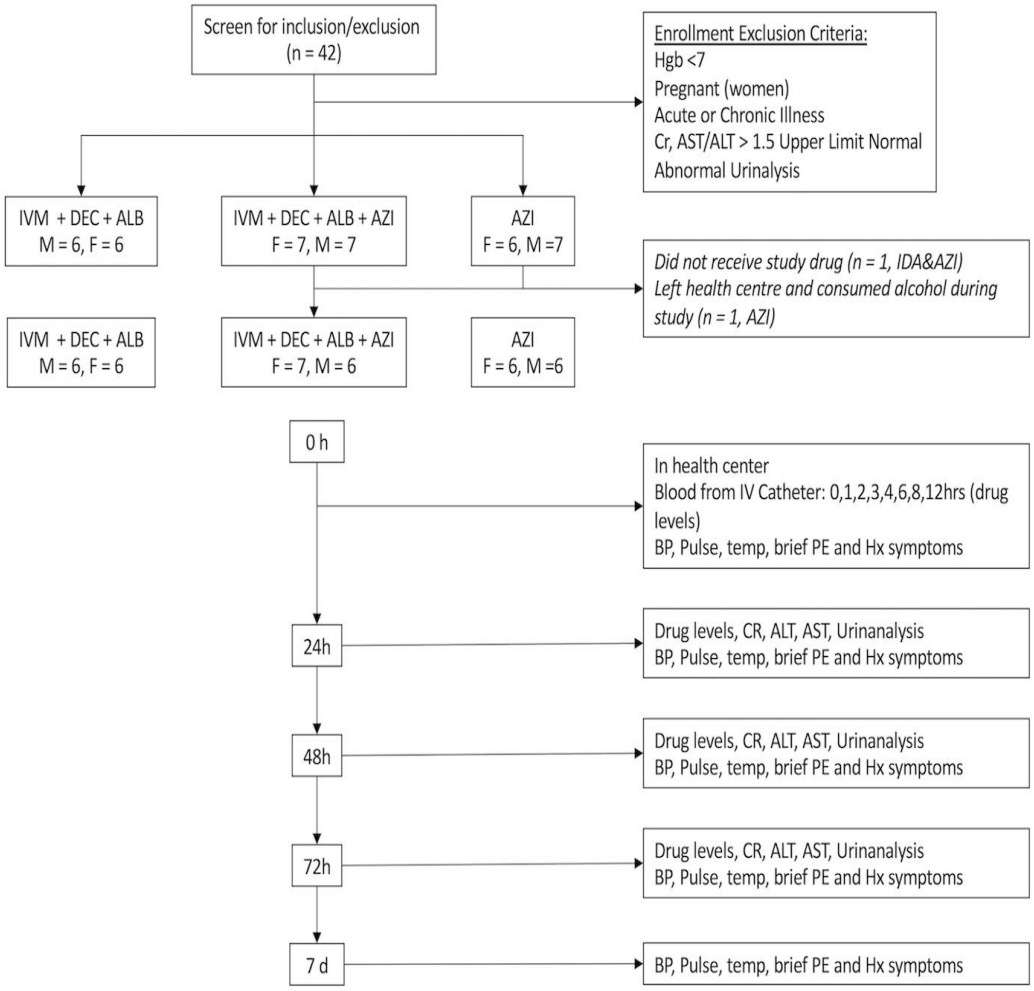
Overlay of mean (±SD) plasma concentration-time profiles of (a) **ALB**, (b) **ALB -SOX** (c) **ALB-SON**, (d) **DEC (e) IVM, and (f) AZI** after a single dose separated by study ARM (IDA, n= 12, IDA+AZI, n=13, AZI, n= 13).

Figure 3. **Forest plots of the geometric mean ratios (±90% confidence intervals [CI]) of the drug administered for the experimental regimen and the reference regimens for logarithmically transformed C_{max} and AUC_{0-t} and AUC_{0-t} and $AUC_{0-\infty}$.**

The vertical dashed lines represent the EMA and US FDA criteria of 80 to 125% for assuming no effect boundary.

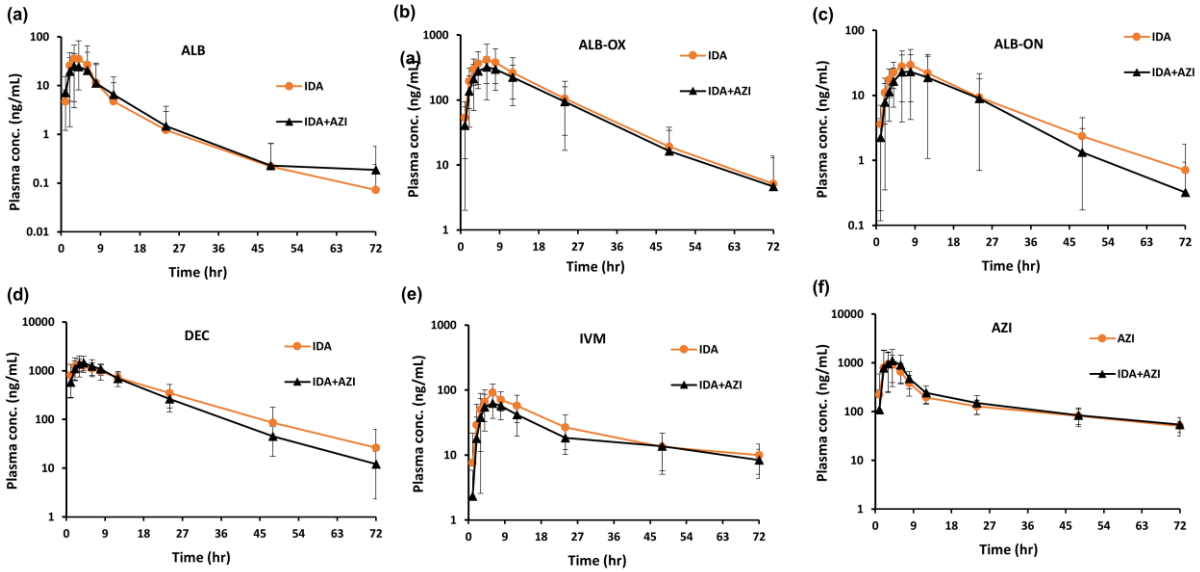
Accepted Manuscript

Figure 1



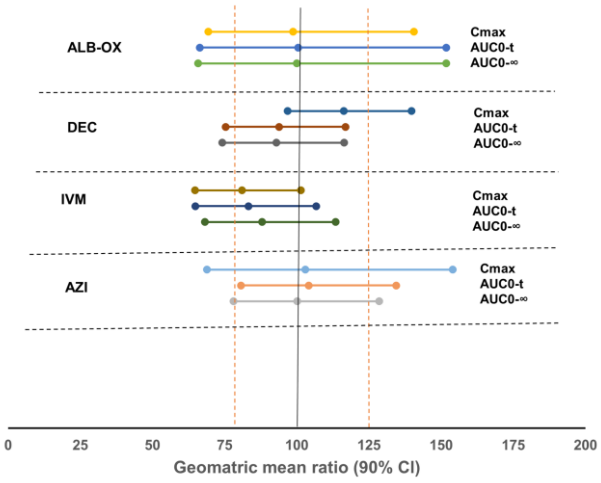
Accepted

Figure 2



Accepted Manus

Figure 3



Accepted Manuscript