

Phase IV studies of anti-malarial drugs: the Indepth Experience

INDEPTH EFFECTIVENESS AND SAFETY STUDIES (INESS)

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For the INESS Partnership



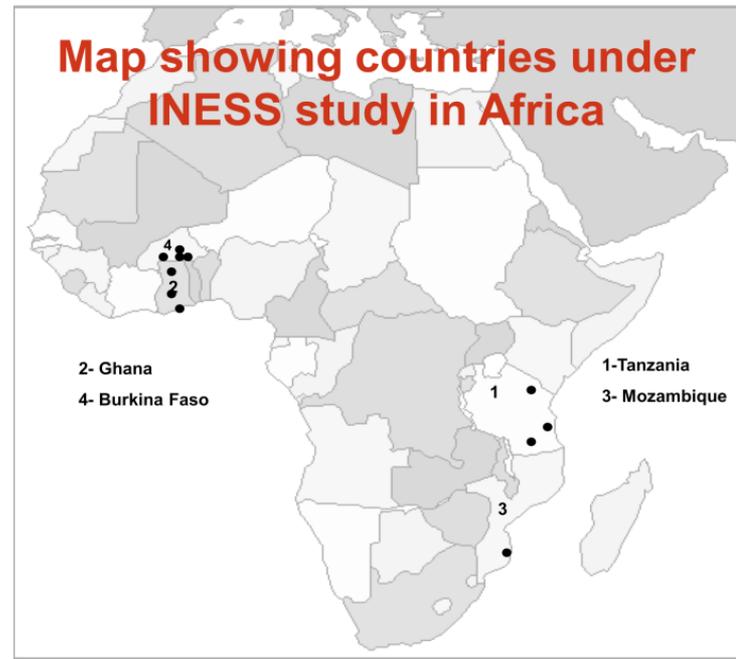
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Studies of Antimalarials in Africa

ISC 2015 Addis Ababa Ethiopia

INESS Partners

- INDEPTH-Network
- School of Public Health, University of Ghana Legon
- Swiss Tropical & Public Health, Basel, Switzerland
- Center for Disease Control, Atlanta
- MMV & Sigma Tau



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Goal

To provide national, regional and international health decision makers with independent and objective evidence on the safety and effectiveness of new anti-malarial drugs as a basis for malaria treatment policy.

Objectives

- To develop and maintain a Phase IV Safety and Effectiveness Studies Platform in Africa
- To assess the Effectiveness of new malaria treatments and its determinants in real life health systems in Africa
- To evaluate Safety of new malaria treatments through comprehensive pharmacovigilance in an African health systems context.

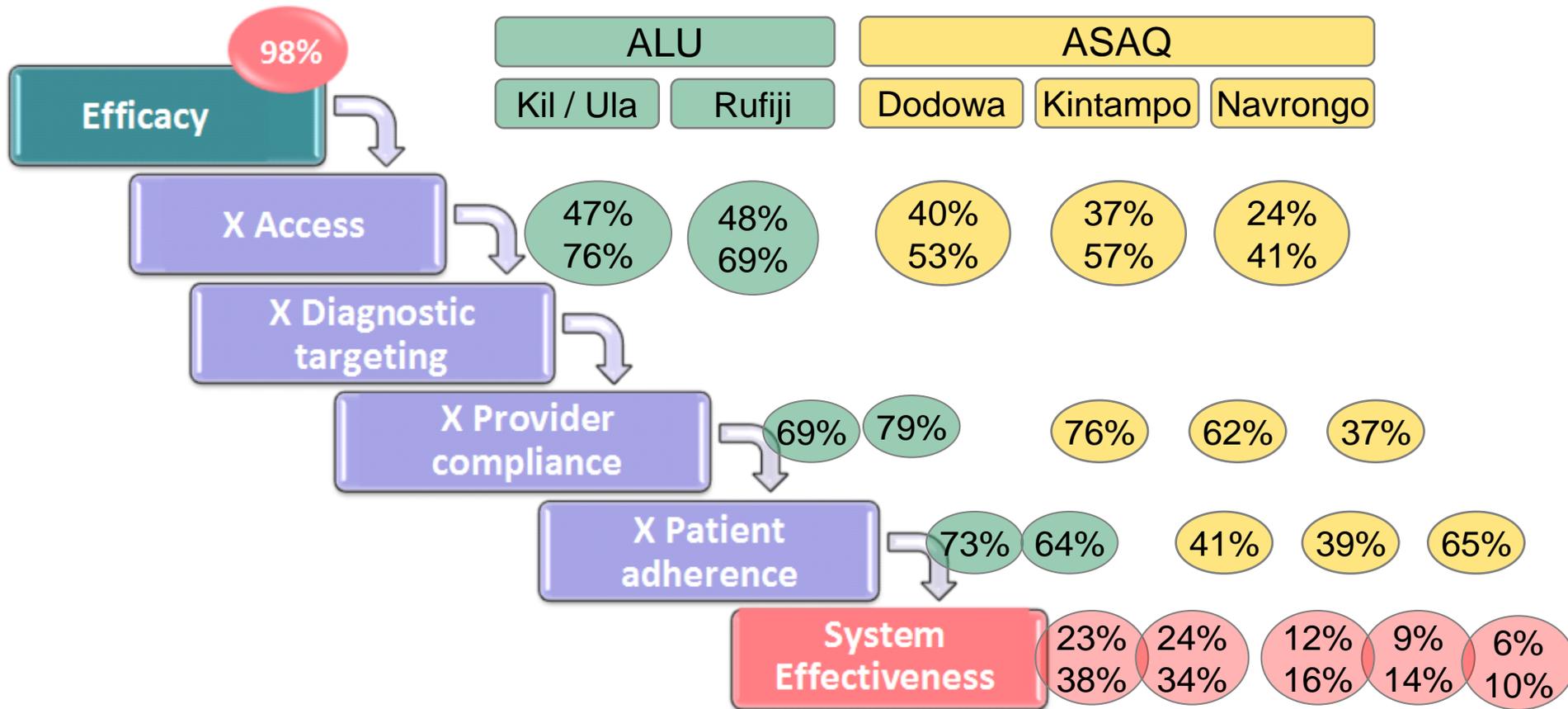
Data linkage Module: Health data

Mobile biometrics solution for health care

✓ Healthcare Application Solution:

- The healthcare application would be integrated with the DSS application linking the DSS and the six health centres using biometric data
- The health application is subdivided into the Reception, Laboratory, Consultation for normal clinical visits and clinical trials.
- Data collected includes, study numbers, anthropometric, immunization records, clinical data and outcomes including ICD10 codes
- Patients enrolled in the DSS would be easily identified and verified using the fingerprint scanners at the health centres.
- For children under the age of 12 years a “buddie” system for biometrics data capture has been implemented

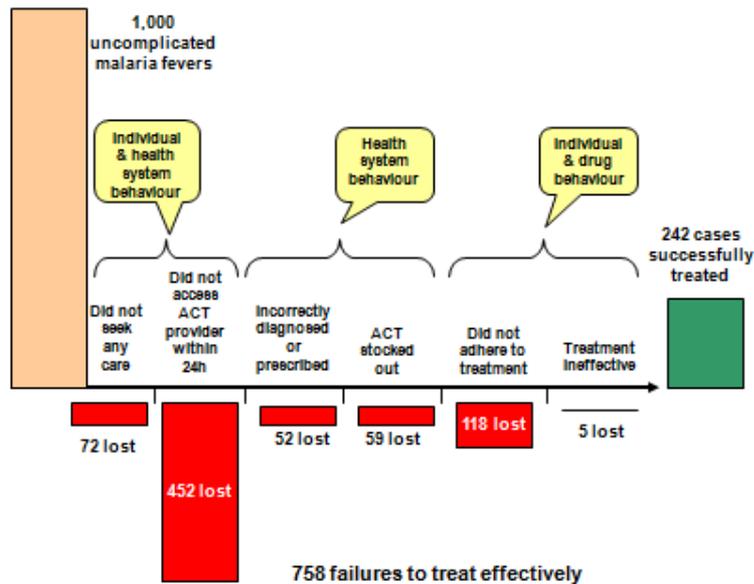
Systems effectiveness ALU & ASAQ



Summary results

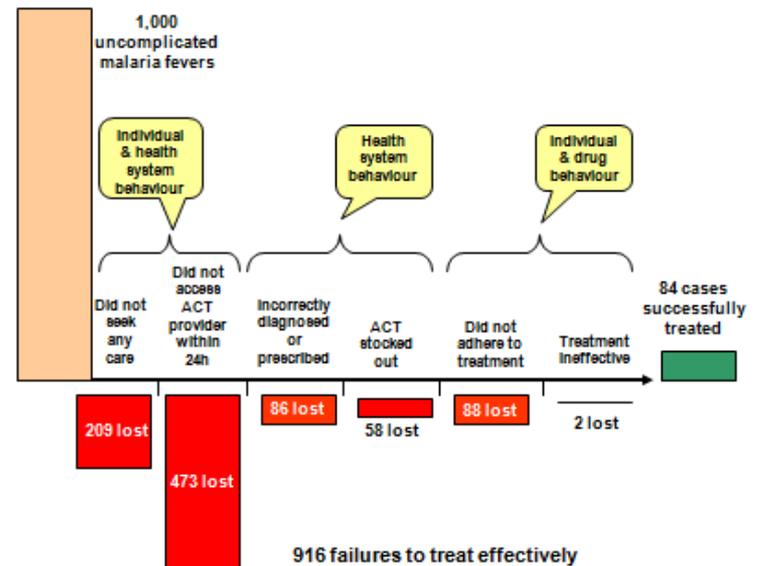
Tanzania

System effectiveness of ALU in Tanzania

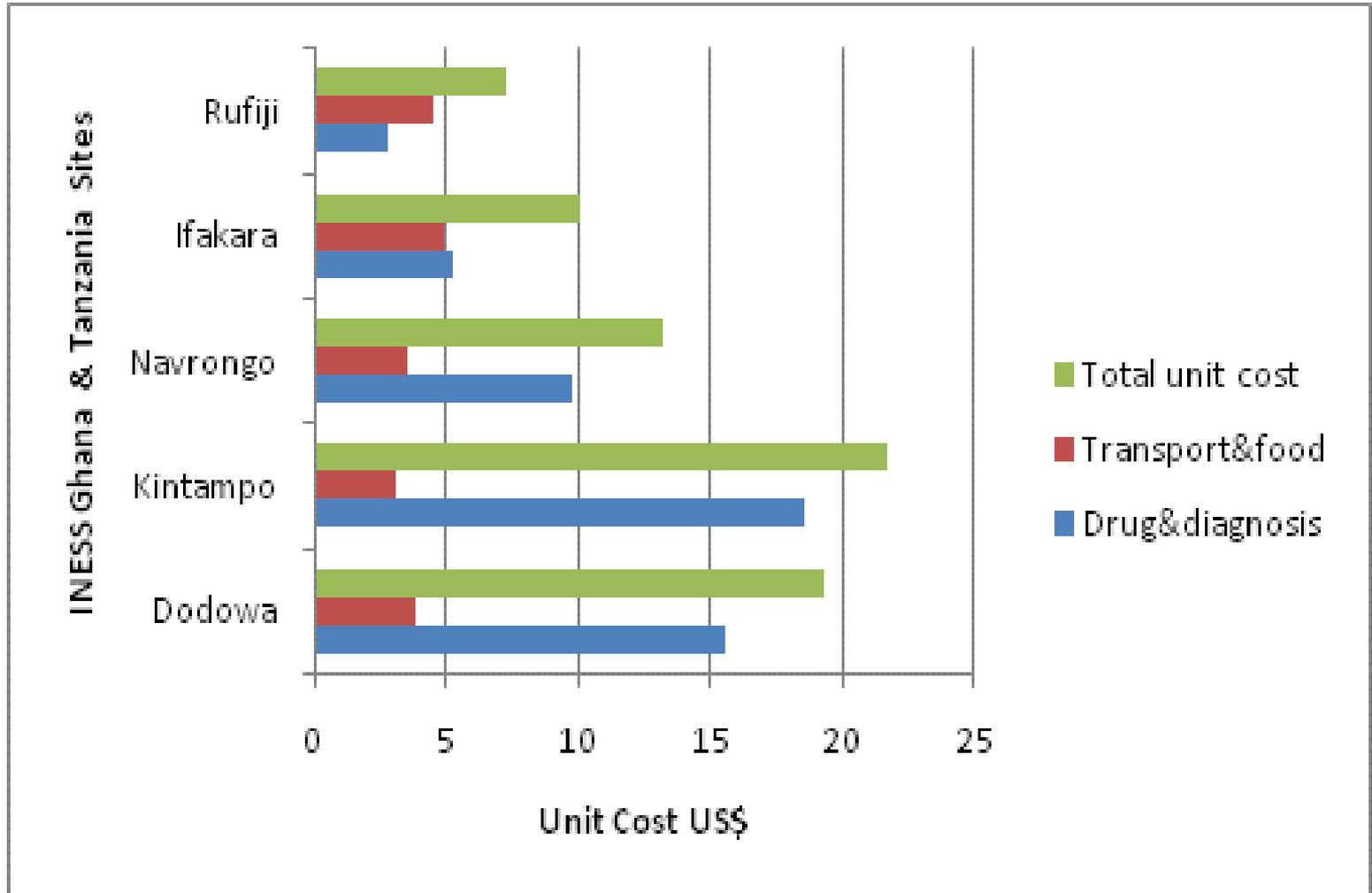


Ghana

System effectiveness of ASAQ in Ghana



Average Costs of treating Fever episode in Tanzania & Ghana



Basic vital statistics from the INESS HDSS sites, 2009,2010,2011

‡2009, †2010, ↓2011

	Dodowa†	Kintampo↓	Navrongo†	Ifakara‡	Rufiji†	Manhiça†	Nouna†
Population	111,976	142,524	153,293	112,521	84,095	87,500	88,328
Crude birth rate	23.5	25.9	25.0	32.5	31.1	42.3	39.4
Total fertility rate	2.7	3.6	3.8	4.4	4.8	5.5	5.8
Crude death rate	6.5	6.1	10.0	8.2	9.9	15.3	8.8
Neonatal mortality rate	8.8	23.0	31.4	28	20.3	21.6	6.8
Post neonatal mortality rate	11.1	15.4	18.7	31.5	21.1	30.9	21.6
Infant mortality rate	19.8	33.4	31.8	58.7	41.4	58.8	28.5
Under 5 mortality rate	35.7	60.5	60.8	87.8	73.8	100.6	80.3
In-migration rate	125.4	159.4	63.5	142	164.6	69.8	44.1
Out-migration rate	127.3	162.4	70.4	141	146.8	117.4	39.0



Top 20 causes of death 2009, 2010 and 2011 in Rufiji HDSS

2009 (N= 631)		2010 (N=674)		2011 (N = 354)* (*incomplete)	
Disease	Percent	Disease	Percent	Disease	Percent
Malaria	30.38	Malaria	54.23	Malaria	31.36
Tuberculosis	6.49	Birth asphyxia, or other respiratory disease	9.86	Hypertensive diseases	9.89
Senility/Oldage	6.17	Pneumonia	7.75	Human immunodeficiency virus [HIV]	6.21
Hypertensive diseases	6.01	Prematurity and low birth weight	5.63	Pneumonia	5.65
Human immunodeficiency virus [HIV]	5.38	Fetus or newborn affected by maternal factors	3.52	Senility/Oldage	4.52
Cerebrovascular diseases	4.75	Human immunodeficiency virus [HIV]	3.52	Tuberculosis	4.52
Unspecified/Undetermined causes	3.32	Other intestinal infectious diseases	2.82	Cerebrovascular diseases	3.95
Pneumonia	2.53	Disorders of the skin and subcutaneous	2.11	Other intestinal infectious diseases	3.11
Birth asphyxia, or other respiratory disease	2.22	Bacterial sepsis of newborn	1.41	Diabetes mellitus	2.82
Other diseases of circulatory system	1.9	Malnutrition	1.41	Unspecified/Undetermined causes	2.54
Other intestinal infectious diseases	1.9	Other respiratory and cardiovascular diseases	1.41	Asthma	1.69
Prematurity and low birth weight	1.9	Accidental poisoning	0.7	Bacterial sepsis of newborn	1.41
Asthma	1.74	Complication of labor and delivery	0.7	Birth asphyxia, or other respiratory disease	1.41
Diabetes mellitus	1.42	Disorders of the kidney	0.7	Hyperplasia of prostate	1.41
Hyperplasia of prostate	1.42	Eclampsia	0.7	Other diseases of circulatory system	1.41
Malnutrition	1.42	Meningitis	0.7	Disorders of the kidney	1.13
Hernias	1.27	Other maternal disorders predominantly	0.7	Duodenal Ulcer	1.13
Sickle-cell disorders	1.27	Other neoplasms	0.7	Epilepsy	1.13
Disorders of the kidney	1.11	Remainder of infectious and parasitic diseases	0.7	Other anemias	1.13
Transport accidents	1.11	Unspecified/Undetermined causes	0.7	Accidental drowning and submersion	0.85



Mortality data/Health data integration

- Timeliness of Mortality data was not improved and hence could not be incorporated in the effectiveness outcomes.
- Health data integration was also not complete in any one site, could not be added to the platform

DISASTER



Objective 3: To evaluate safety of new malaria treatments through comprehensive pharmacovigilance in an African health systems context.

Safety Monitoring

- **Yellow card system; reporting to NRA**
- **Linked database** approach and validation of innovative approaches/systems
- **Cohort Event Monitoring**
 - Adherence
 - Home visits
 - Phone contacts
 - Drug efficacy monitoring

Indicators

- **SAERs**
 - Number of reports received and submitted to national authorities
 - Number of events
- **CEM**
 - Number of participants recruited and followed up
 - Adverse events
 - Incidence, types
 - Information on drug utilization
 - Risk factors



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Summary reports on SAER & CEM

Sites on INESS platform	Serious Adverse Reaction Reports	Total SAERs (all cases reported to regulator)	CEM patients recruited	Total number of patients reporting events
Dodowa	4	95	4165	1194
Kintampo	23	58	3879	254
Navrongo	1	33	3335	310
Ifakara	10	41	3658	15
Rufiji	14	29	6034	3
Total	52	256	21091	1776

Primary Objective

Evaluate the **safety** of Eurartesim[®] when used in uncomplicated malaria cases confirmed by a parasitological diagnosis (Microscopy/RDT)



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Regulatory approvals

- **Dossier submitted between July and October, 2012** in Ghana, Burkina Faso, Tanzania & Mozambique
- Timelines expected for full registration in all 4 countries by Nov/Dec 2012
- Regulatory processes longer than expected (**about 8 to 12 months**)

Approvals

- in Ghana **January 2013** (Navrongo, Kintampo & Dodowa)
- Burkina Faso in **March 2013** (Nouna, Nanoro)
- Tanzania **April 2013** (Rufiji)
- Mozambique **September 2013** (Manhica)



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Investigators meeting & training session on the Eurartesim study



Interaction between investigators, INDEPTH Board Chair, Center Directors and INESS PI

Procedures

Main study

- RDT positive
- Enrolled & 1st dose under supervision,
- **Active follow up (telephone/physically) on day 5 ± 2 days, passively up to day 28**
- **All AEs, SAEs, & AESI documented after intake of the 1st dose**

Nested cohort

- RDT positive & microscopically confirmed plasmodium infection
- All 3 doses of Eurartesim[®] taken under supervision
- **ECG done: Baseline, day 3 pre & post dose and day 7 + Pka sampling, other labs**
- **Active follow up on days 3 & 7 and passively up to day 28 for any AEs AESI SAE**



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ECG & Pka samples

ECG procedure

- Baseline (triplicate)
- Day 3 pre-dose 3 (single)
- Day 3 post-dose 3 (triplicate)
- Day 7 (single)

All ECGs were sent electronically to Cardiabase (> 500,000 USD for 7000 ECGs)

4 serum samples per patient for PKa

- Baseline
- Day 3 Pre-dose 3
- Day 3 post-dose 3
- Day 7

NB: All samples were taken immediately after ECG



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Reporting and documentation of SAEs in Eurartesim safety study

All SAEs were reported to the following

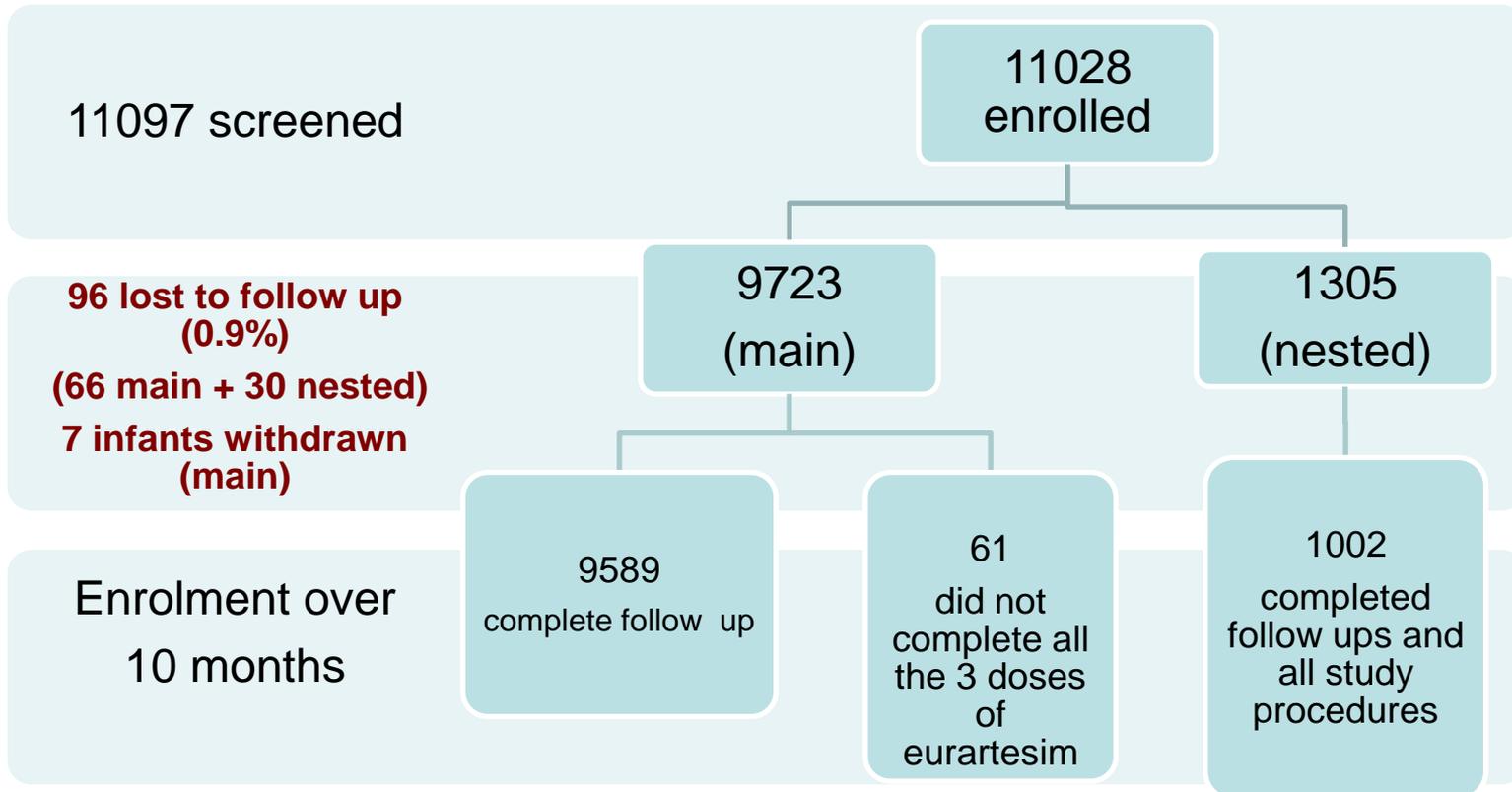
- Institutional IRB
 - National IRB
 - Site CRA
 - National Regulatory authorities
 - INESS
 - Sigma Tau/MMV
-
- All SAEs on the Eurartesim study have full documentation with INESS team in Accra including copies of source documents.

Data Management and Data Sharing

- Major component & a huge task on data cleaning by 7 consultants from INDEPTH sites on the platform.
- Data was entered online from all the sites onto a central database in Accra using openclinica.
- Managed using stata 11 (about 1, 470 Variables checked and cleaned)
- Full database shared with all major stakeholders (at the middle of recruitment and the end of recruitment) including the 7 sites on the platform, MMV and the Gates Foundation before any publication from the dataset was made.

***Summary findings from the Eurartesim®
phase IV study***

Recruited cases



Status reported by 7 Sites for the Eurartesim
phase IV safety study
September 2013 to March 2014

Site	No. consented	No. enrolled into main	No enrolled into nested	No. withdrawn	No. of AESI	No. of SAEs
Dodowa	950	739	161	12	4	1
Kintampo	2157	1830	132	38	0	16
Navrongo	1894	1604	275	0	2	4
Nouna	1814	1688	125	30	3	1
Rufiju	1032	501	166	4	5	1
Nanoro	1081	885	194	10	9	1
Manhica	1194	1100	92	18	0	3
Total	10 122	8347	1145	112	23	27



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Adverse events reported for all cases (main and nested)

- ❑ 560/10,925 (5%) patients reported a total of 797 events of which 27 were classified as SAEs

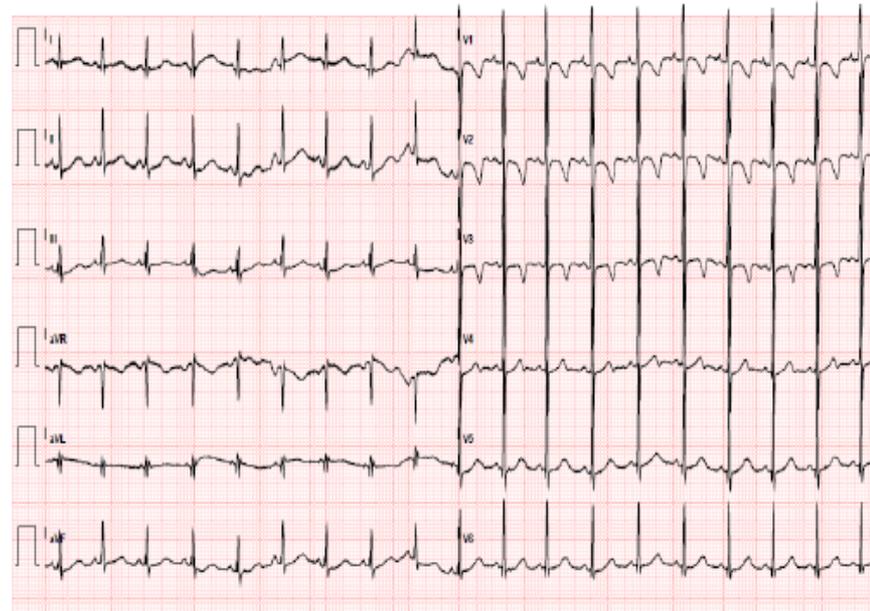
- ❑ Incidence rate (crude) was 7.3% (797/10,925)

- ❑ All AEs were classified by MedRA & most frequently reported events classified by SOC were
 - Infections and infestations (3.24%)
 - Gastrointestinal disorders (1.37%)
 - General disorders and administrative site conditions (0.76%)

ECG findings



Country Site # 3 30-09-2013 14:42:59 SINUS TACHYCARDIA WITH SHORT PR INTERVAL
T WAVE ABNORMALITY CONSISTENT WITH ANTERIOR ISCHEMIA (J-L-S-M-T WAVE IN V3/V4)
Screen # 3005 Initials AJ Ventr rate: 111 bpm
Patient # 3005 Initials AJ PR int: 118 ms
DOB 07.11.2008 Age 4yr QRS dur: 85 ms
Gender Male QT/QTc: 330/396 ms UNCONFIRMED REPORT
Visit Label DIPRE P-R-T axes: 01 58 35
WEBSD1192



25 mm/s 10 mm/mV

INDEPTH / Site Nankongo Ghana

537 124 159

ECG summaries for day 1, day 3 pre and post dose, day 7

	PR	HR	QT	QTcB	QTcF	95% CI*	*P-value
Visit							
Day 1 (baseline)	134.2	104.6	331.9	429.6	393.3	-	-
Day 3 Pre-dose	138.3	92.5	355.4	434.2	411.2	-	-
Day 3 Post-dose	140.5	91.6	366.1	444.1	415.8	-	-
Day 7	137.6	94.2	346.2	428.2	398.6	-	-
Δ Day 1 to 3 Pre-dose	4.1	-12.1	23.5	4.6	17.9	16,19	<0.001
Δ Day 1 to 3 Post-dose	6.3	-13.1	34.2	14.6	22.5	21,24	<0.001
Δ Day 1 to 7	3.3	-10.3	14.2	-.31	5.3	4,7	<0.001



Participants with QTcF \geq 500ms and QTc prolongation \geq 60ms from the baseline (N= 1002)

QTcF (ms)	Day 1	Day 3 Predose	Day3 Postdose	Day 7
\leq 500	1002	1002	999	1000
>500	0	0	3*	2**
Total	1002	1002	1002	1002

QTcF(ms) prolongation greater than 60ms

Δ QTcF (ms)	Day 3 Pre – Day 1	Day 3 Post – Day 1	Day 7 – Day 1
\leq 60	932	914	995
>60	70	89	7
Total	1002	1002	1002

Elongation of >500ms: *Day 3 post dose: 3 male patients aged 8,19,24 yrs, 509, 501,538 ms, all returned to <500ms by day 7. **Day 7: 2 female patients 62,41 yrs suddenly recorded QTcF 501,532ms, both females. QTcF > 501ms, 532ms

Prolongation >60ms : Pre-dose 65/70 (93%) < 12yrs & Post-dose 75/89 (84%) cases were children less than 12 years , Day 7: 5/7 (never had prolongation on day 3 pre and post dose), but none was above 500ms.



Summary on PKa Sample breakdown for cohort with complete study procedures

- Over 4000 serum samples were collected and represents the largest in the world on ACTs (DHA+PQ) for Pka. 1002 participants had all 4 samples taken with breakdown as follows:
- Ghana: 3 sites collected 1,776 (45%) samples
- Burkina Faso: 2 sites collected 1176 (30%) samples
- Tanzania: 1 site collected 680 (17%) samples
- Mozambique: 1 site collected 356 (9%) samples

Pka Samples cont.....

- sex distribution is approximately 48% in males
- About 75% of the samples were collected in children below 13years of age.
- Samples shipped to The Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University in Thailand for analysis.
- Analysis in relation to food intake, concomitant medication, ECG changes , modelling etc will be done

Age, Sex, Site and Country Distribution of PK samples for Nested Cohort Participants who took all the 3 doses of Eurartesim®, had 4 samples of PKaand completed all the Study Procedures including Electrocardiogram on days 1, day 3 pre dose and post dose, and day 7. (N=1002)

Variable (N=1002)	Day 1		Day 3 Pre		Day 3 Post		Day 7	
	Taken	Processed	Taken	Processed	Taken	Processed	Taken	Processed
Age group (n (%))								
< 6	331(33.0)	331(33.0)	331(33.0)	331(33.0)	331(33.0)	331(33.0)	331(33.0)	331(33.0)
6 - <13	398(39.7)	398(39.7)	398(39.7)	398(39.7)	398(39.7)	398(39.7)	398(39.7)	398(39.7)
13- <18	112(11.2)	112(11.2)	112(11.2)	112(11.2)	112(11.2)	112(11.2)	112(11.2)	112(11.2)
> 18	161(16.1)	161(16.1)	161(16.1)	161(16.1)	161(16.1)	161(16.1)	161(16.1)	161(16.1)
Gender (n (%))								
Female	483(48.2)	483(48.2)	483(48.2)	483(48.2)	483(48.2)	483(48.2)	483(48.2)	483(48.2)
Male	519(51.8)	519(51.8)	519(51.8)	519(51.8)	519(51.8)	519(51.8)	519(51.8)	519(51.8)
Site (n (%))								
Dodowa	155(15.5)	155(15.5)	155(15.5)	155(15.5)	155(15.5)	155(15.5)	155(15.5)	155(15.5)
Kintampo	15(1.5)	15(1.5)	15(1.5)	15(1.5)	15(1.5)	15(1.5)	15(1.5)	15(1.5)
Navrongo	274(27.4)	274(27.4)	274(27.4)	274(27.4)	274(27.4)	274(27.4)	274(27.4)	274(27.4)
Nouna	102(10.2)	102(10.2)	102(10.2)	102(10.2)	102(10.2)	102(10.2)	102(10.2)	102(10.2)
Rufuji	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)
Manhica	89(8.8)	89(8.8)	89(8.8)	89(8.8)	89(8.8)	89(8.8)	89(8.8)	89(8.8)
Nanoro	197(19.6)	197(19.6)	197(19.6)	197(19.6)	197(19.6)	197(19.6)	197(19.6)	197(19.6)
Country (n (%))								
Burkina Faso	299(29.8)	299(29.8)	299(29.8)	299(29.8)	299(29.8)	299(29.8)	299(29.8)	299(29.8)
Ghana	444(44.3)	444(44.3)	444(44.3)	444(44.3)	444(44.3)	444(44.3)	444(44.3)	444(44.3)
Mozambique	89(8.9)	89(8.9)	89(8.9)	89(8.9)	89(8.9)	89(8.9)	89(8.9)	89(8.9)
Tanzania	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)	170(17.0)



Conclusion

❑ Adverse events

- Only 5% (590/10,925, of cases reported an Adverse event (main & Nested)

❑ ECG findings

- No patient had patient had QTcF > 500ms on day 3 pre-dose
- All 3 patients with prolonged QTcF > 500ms on day 3 post-dose returned to <500 ms on day 7
- 2 patients with increased QTcF on day 7 (day 1, day 3 pre and post dose QTcF were normal (QTcF < 500ms)
- Transient increase in Δ QTcF (ms) > 60ms in children (< 12yrs) may occur on day 3 post-dose but returns to nearly baseline on day 7

Conclusion II

- ❑ **DIHYDROARTEMISININ/PIPERAQUINE [DHA/PQP] is Safe DRUG for treating malaria in African settings.**
- ❑ **PIPERAQUINE is safe partner drug for developing other combinations therapies**

Analysis & Publication status

- ❖ Initial findings published

Prospective observational study to evaluate the clinical safety of the fixed-dose Artemisinin-based Combination Therapy Eurartesim® (dihydroartemisinin/piperaquine [DHA/PQP]) in public health facilities in Burkina Faso, Mozambique, Ghana and Tanzania

- ❖ Pka analysis started in Thailand and further analysis will be done

- ❖ Site are also working on papers for submission

Key Achievements

- INDEPTH - Established fully functional phase II – III Clinical Trials platform in Africa through MCTA which were used for phase IV studies
- INDEPTH - Set up 3 phase I/II facilities through MCTA
- INDEPTH – Established phase IV (pharmacovigilance) platform in sub-Saharan Africa through INESS
- INDEPTH- Has contributed the largest Pka sample on ACTs in the world
- ***INDEPTH has completed the entire loop of product evaluation in sub-Saharan Africa (Phase I-IV)***



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Some Lessons learnt

- Common protocol across all countries
- Standardized data collection tools, shared experience, improved data quality, common engagement with NRA.
- Trained national scientists for the current and future monitoring of new interventions
- NRA still using the old approach “police” engagement: Provide Risk Management Plan.
 - Now includes hefty fees for permission to conduct the studies.
 - Local collaboration between Scientists and NRA could be better so the population benefits.

Challenges

- Sigma Tau and MMV have provided some of the greatest challenges to deliver the Drugs to the sites. We must not undertake such studies if the drugs are not registered and available in the countries, so we can purchase off the counter.
- MAKE DATA COLLECTION INDEPENDENT OF MANUFACTURER OF THE DRUG
- Develop Local Capacity for ALL aspects of the data collection and Quality Control activities! (remember this a Phase IV activity)
- Cost of ECG readings not justified. Readings are as basic as we expected.
- DOCUMENTAION of SAE is Critical and currently poorly done. No incentives to do so
- Computing and analytical capacity at INESS secretariat extremely weak. We need assistance to be able to produce final reports and papers.
- Quality of data being produced by some of the Sites must improve. Site leaders must focus on the scientific rigor of the studies.



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End of grant period

- Grant period ended in March 2015
- Final report submitted to Gates in September 2015 and we are waiting for comments after review
- Focusing on analysis and publications (2009 -2015)
- Re-treatment with Eurartesim (cardiac effect)?
- New drug pyramax (ACT) just registered? May need a phase IV

Acknowledgements

- Governance Council (Chair Dr. Gabriel Upunda)
- Scientific Advisory Panel (Chair Prof. Peter Smith)
- International Safety Panel
- INDEPTH-Network Board of Management
- INDEPTH-Network Secretariat
- Nanoro, Nouna sites in Burkina Faso, Dodowa, Kintampo and Navrongo in Ghana, Rufiji site in Tanzania, Manhica site in Mozambique
- Hospital Superintendents, NMCP, in Ghana, Tanzania, Burkina Faso, Mozambique, Sierra Leone, Nigeria
- FDB (Ghana) TFDA (Tanzania), DF (Mozambique), Burkina Faso
- School of Public Health, University of Ghana Legon
- Swiss Tropical & Public Health, Basel, Switzerland
- Center for Disease Control, Atlanta, USA
- MMV in Geneva
- CARDIOBASE in Paris
- MMARCRO CRO team
- Sigma Tau in Italy
- WHO AFRO Brazzaville & sub-regional teams
- **Bill and Melinda Gates Foundation**



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Thank You

