PEDIATRIC PRAZIQUANTEL CONSORTIUM

The Pediatric Praziquantel Consortium

Helping children with Schistosomiasis

Dr Elly Kourany-Lefoll

Swiss TPH Winter Symposium
Helminth Infection – from Transmission to Control
7-8 December 2017

Background

High Prevalence

High Medical need

Pre-school aged children neglected

The Current Praziquantel tablet formulations (500 and 600mg) cannot be readily administered to pre-school aged children

→ clear **unmet medical need** for a suitable pediatric formulation for the **children aged 3 month to 6 years**!

Praziquantel Pediatric Consortium: Vision & Mission

Our **vision** is to reduce the global disease burden of schistosomiasis by addressing the medical need of infected preschool-age children including infants and toddlers.

Our **mission** is to develop, register and provide access to a suitable pediatric praziquantel formulation for treating schistosomiasis in preschool-age children.

Consortium formed in 2012
Two African partners will join beginning 2018

International non-profit R&D Consortium with a focus on extended partnership into endemic countries

In kind or in cash contribution or both

Continually seeking funding and help from external experts and partners who wish to join

International Expert Panel (World Health Organization) as observer

BILL & MELINDA GATES foundation

4 Grants received
- 2013: Bill & Melinda Gates
-2014 to 2016: GHIT Fund.

GHIT Fund
Global Health Innovative Technology Fund

MERCK

astellas

Swiss TPH

Consortium Board (chaired by Merck)

Consortium Team led by Merck

farmanguinhos
Instituto de Tecnologia em Fármacos

SIMCYP

SCI
Schistosomiasis Control Initiative

lygature

Simcyp exited the Consortium in Oct. 2017

The Consortium is developing two new innovative pediatric orodispersible tablets (ODTs), one of them will be selected in Q2 2018

L-PZQ ODT Formulation

150 mg

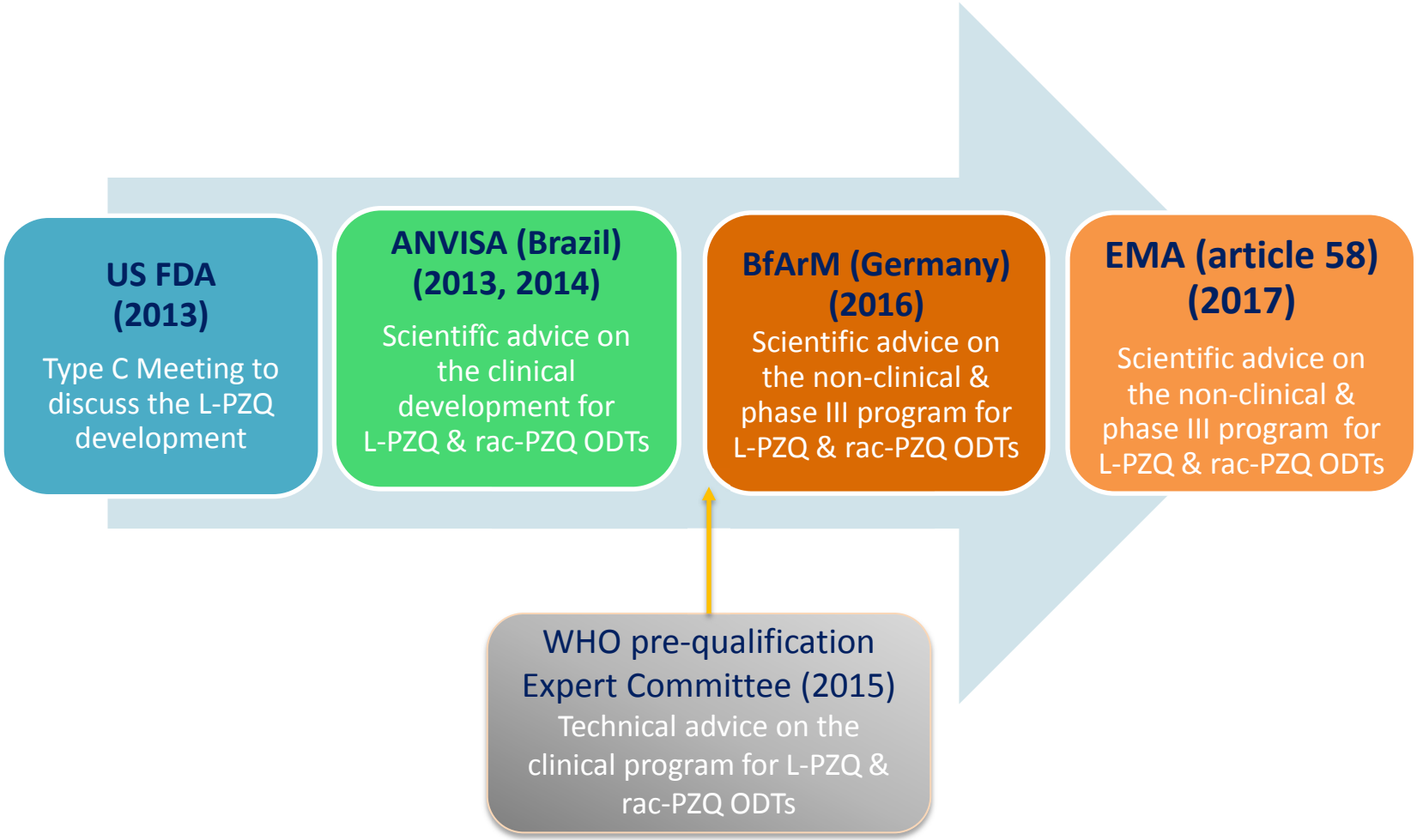
- Child friendly formulation with improved palatability
- Devoid of the biologically inactive D-PZQ enantiomer
- Reduced dosage expected per treatment as compared to Racemate
- Improved safety profile vs Racemate PZQ

Racemate PZQ ODT Formulation

150 mg

- Child friendly formulation with improved palatability/ease of use

Non-clinical & clinical program designed based on consultations with health authorities & WHO PQP



Clinical Program ongoing, targeting the 1st regulatory submission in 2019

Completed

Two Phase I Studies in South Africa (Rac-PZQ ODTs and L-PZQ ODTs)

Relative Bioavailability study in healthy male adults between the current PZQ formulation registered by Merck (Praziquantel 500mg) and the new 150mg ODT tablet (n = 32 for each study)

Completed

Taste Study of the new ODTs in African children (Tanzania)

5 groups cross-over randomized study in African children age 6-11 years *(primary school in Tanzania, n* ≈ 48)

Started in June 2016-ongoing

Phase II PK/PD dose finding Study with L-PZQ and rac-PZQ ODTs + control commercial PZQ (in Ivory Coast)

Part 1: children age 2-6 years infected with *S. mansoni (n=420)*

Part 2: *children age 3 months-2 years infected with S. mansoni (n=40)*

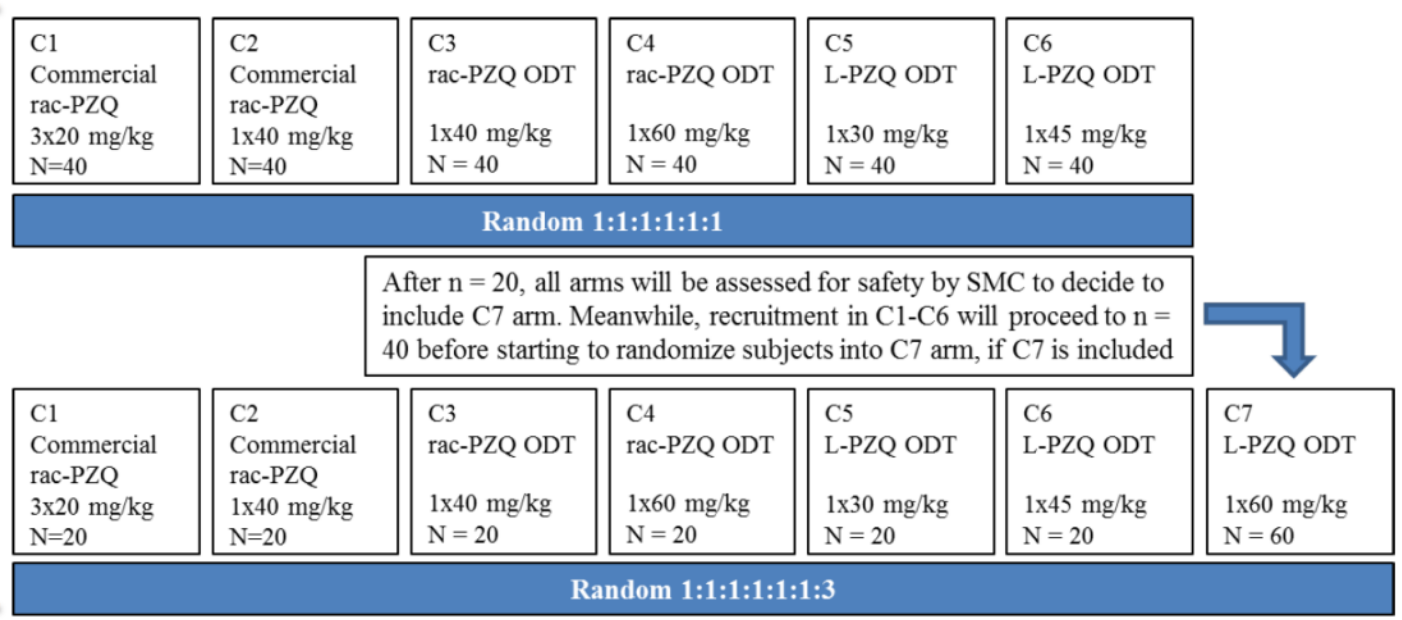
2018

Phase III studies with either L-PZQ or rac-PZQ ODTs (in Kenya and Ivory Coast)

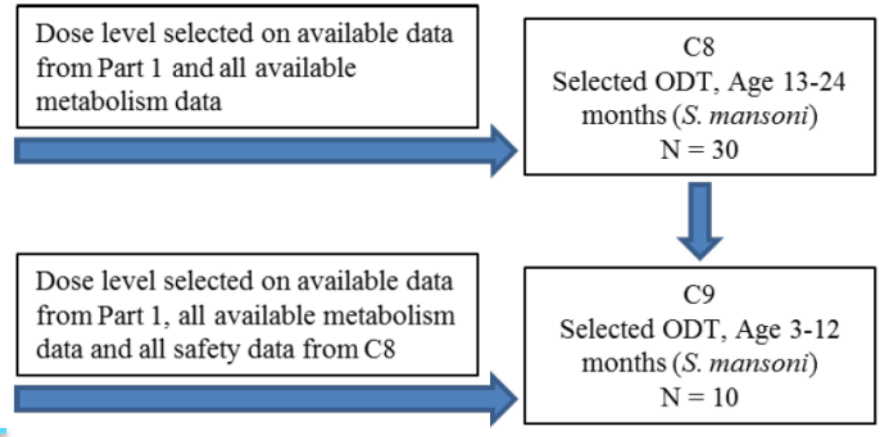
To demonstrate efficacy /safety of PZQ ODTs in pre-school age children infected with *S. mansoni* and *S. haematobium*

Phase II study (Open-label, dose-finding, 2-parts)

PART 1
INFECTED CHILDREN
aged 2-6 years
(n = 420)



PART 2
INFECTED CHILDREN
Aged 3-24 months
(n = 40)



*Country: Ivory Coast

Phase II study update

- First patient included in June/2016
- **Last patient from Part 1 (subject 420) enrolled on Nov. 29th.**
- Decision of formulation and dose scheduled for April 2018
- Part 2 planned to start in Q2 2018

Dose decision for phase III trials based on safety & efficacy results form phase II (Part 1)

Weighted Scoring Algorithm for Choice of Phase III Dose: Efficacy and Safety Criteria with Weights

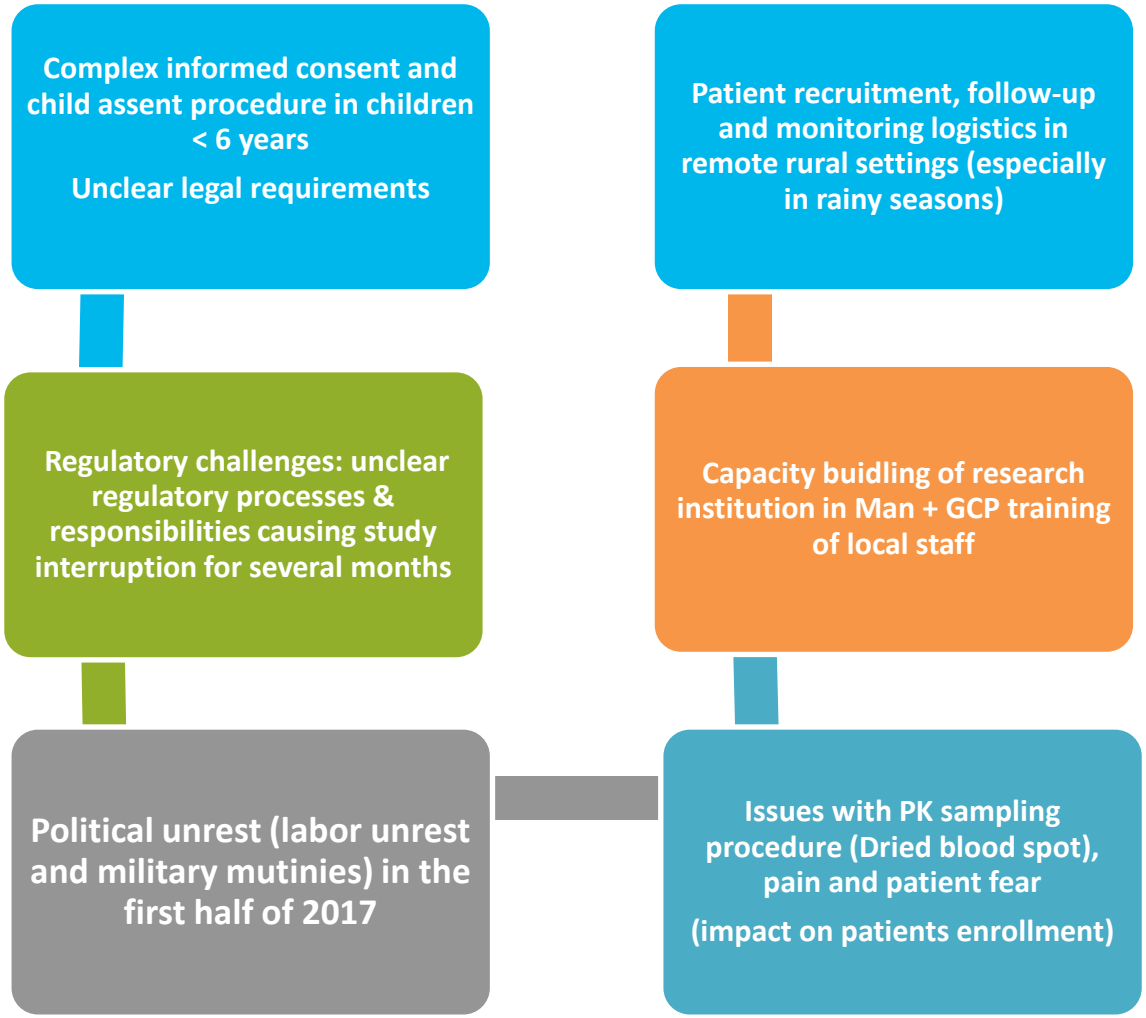
Order	Criteria	Weighting (% of Total)
1	Primary Efficacy – overall cure rate	*25%*
2	Cure rate in moderate/heavy infected	*7.5%*
3	Cure rate in light infected	*7.5%*
4	Secondary Efficacy – egg reduction rate	*20%*
5	Safety – type of AEs*	*13.3%*
6	Safety – severity of AEs*	*13.3%*
7	Safety – number of AEs*	*13.3%*
		100%

Total Efficacy 60%

Total Safety 40%

Notes: ***only treatment related AEs/SAEs**

Key challenges faced in conducting the phase II trial in Ivory Coast



Phase II trial in Ivory Coast (Man): Clinical research facility refurbished

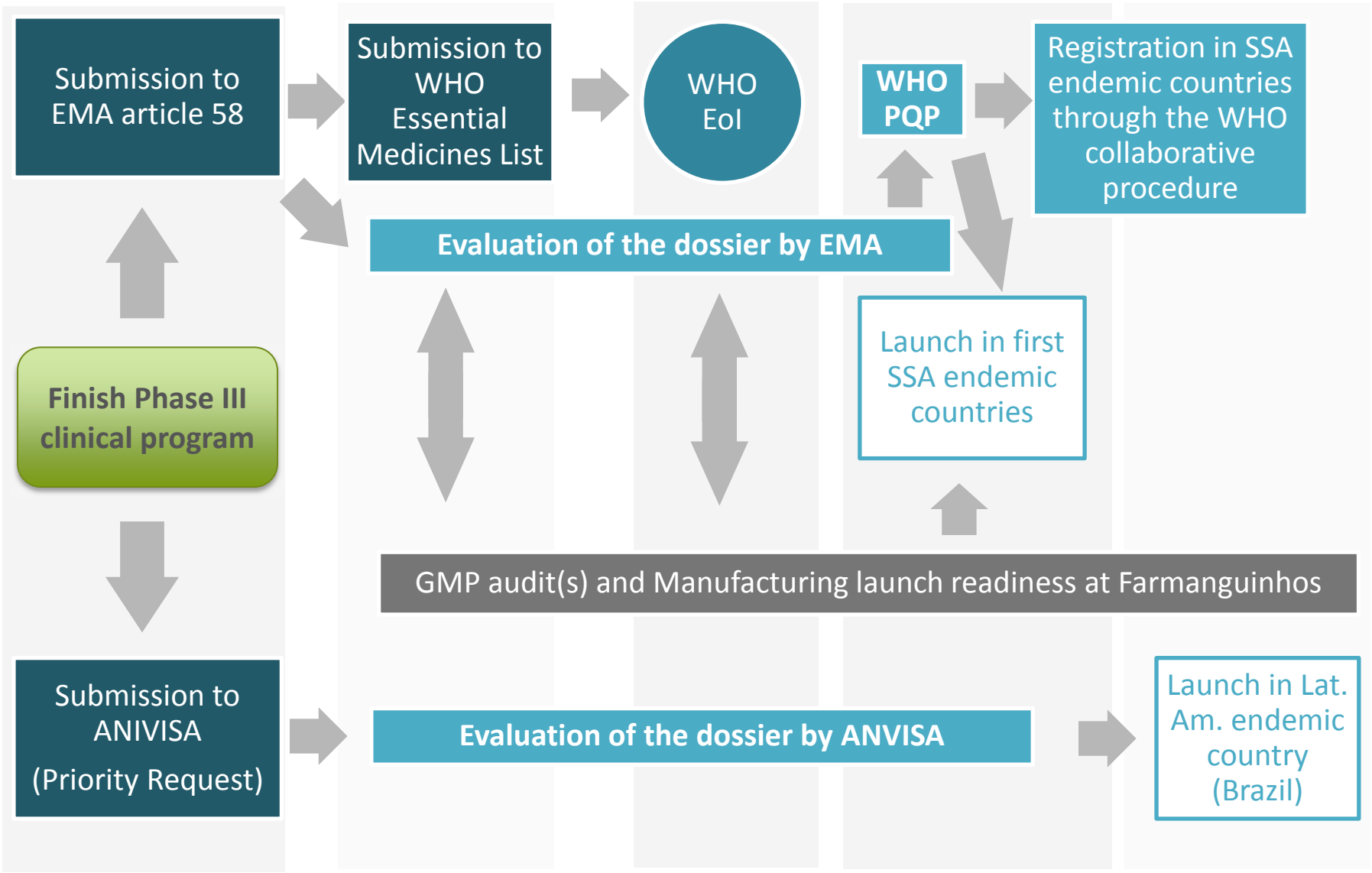
March 2016, pre-study visit

June 2016, initiation visit

Construction of a new refectory and data clerk / monitoring room (October 2017)

Phase II trial in Ivory Coast (Man): Training of local staff

Regulatory Pathway



Delivery and Access Plan

How can children 1-5 years of age be reached for SCH treatment?

- Access task force in place with members from the Consortium, GHIT, NGO experts and WHO as observer.
  - Access force will be expanded upon progress of the project

- The product will not be donated, but distributed on a not-for-profit basis (free cost for children).

- We will start in a fewer countries with well documented high endemicity of schistosomiasis

- Farmanguinhos will be responsible for manufacturing to supplying the endemic countries for the first years of launch until an alternative manufacturer has been identified & qualified to take over for local procurement

Delivery and Access Plan: Next Steps

- Continue discussions with the WHO departments for NTD, Child/Adolescent Health, and Essential/Safety of Medicines to insure incorporation of PSAC treatment in the relevant guidelines/documents towards a global consensus.

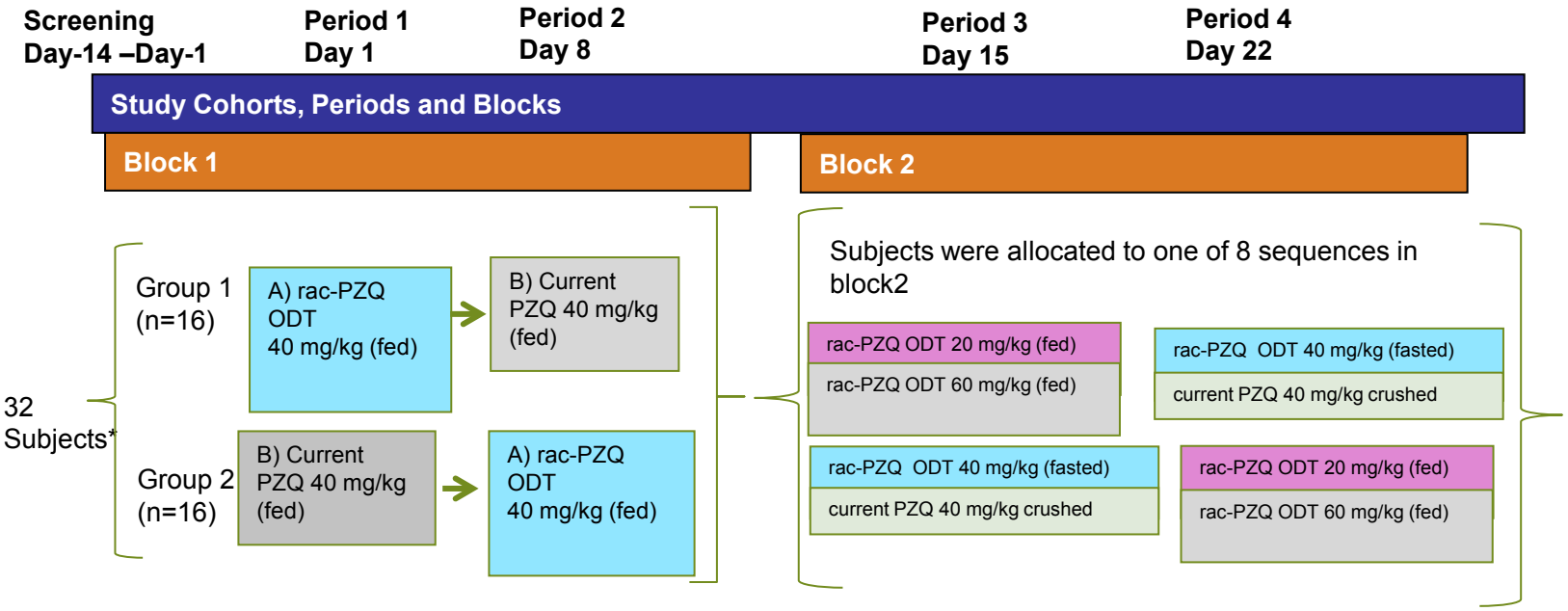
- Prepare an Access expert meeting in Q3/2018 with various global and local stakeholders to further define the access plan.

PZQ pediatric phase II in children ≤6 years in Côte d'Ivoire: Developing collaborative partnership

http://www.pediatricpraziquantelconsortium.org
http://www.merckgroup.com/mghi

Back up slides

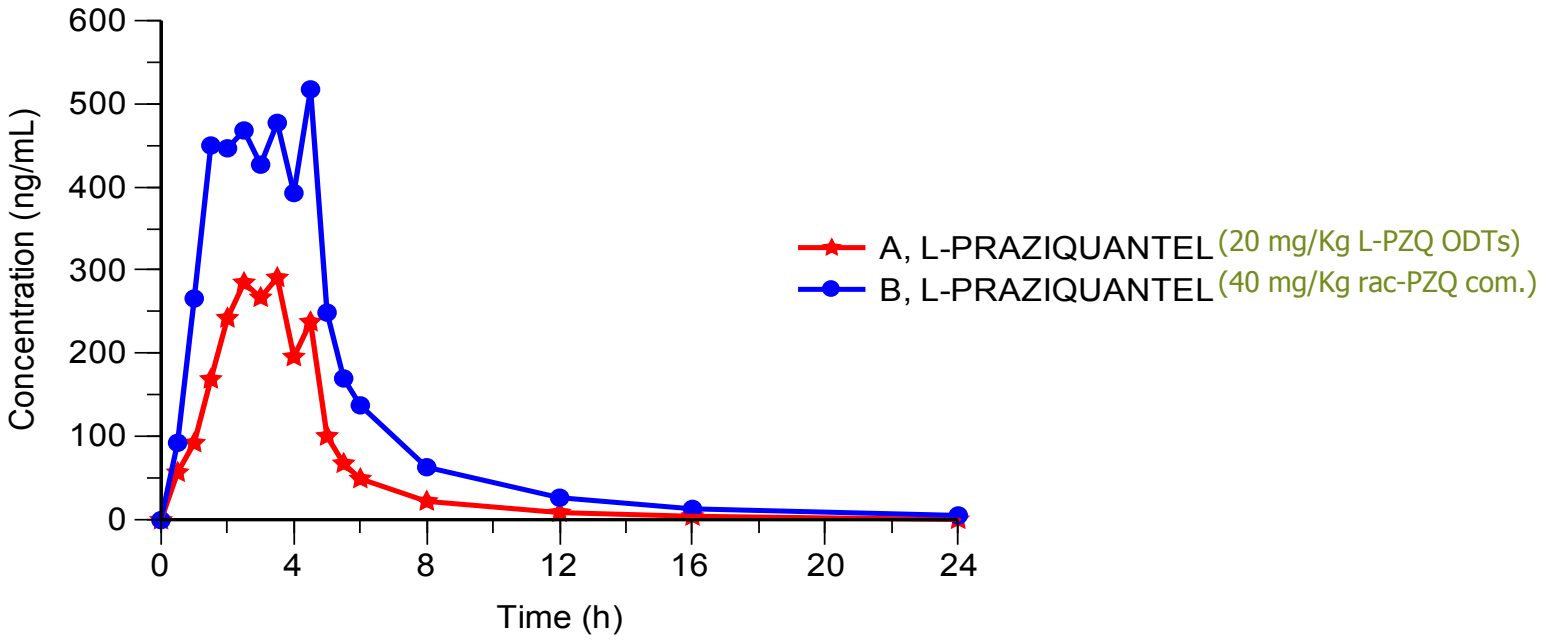
Rac-PZQ ODTs phase I Design: A Randomized, Open-Label, Single-dose, 4-Period Crossover, relative Bioavailability Study in Healthy Male Adults



Block 1: Relative bioavailability of the ODT formulation of rac-PZQ at 40 mg/kg versus the current rac-PZQ formulation at 40 mg/kg.

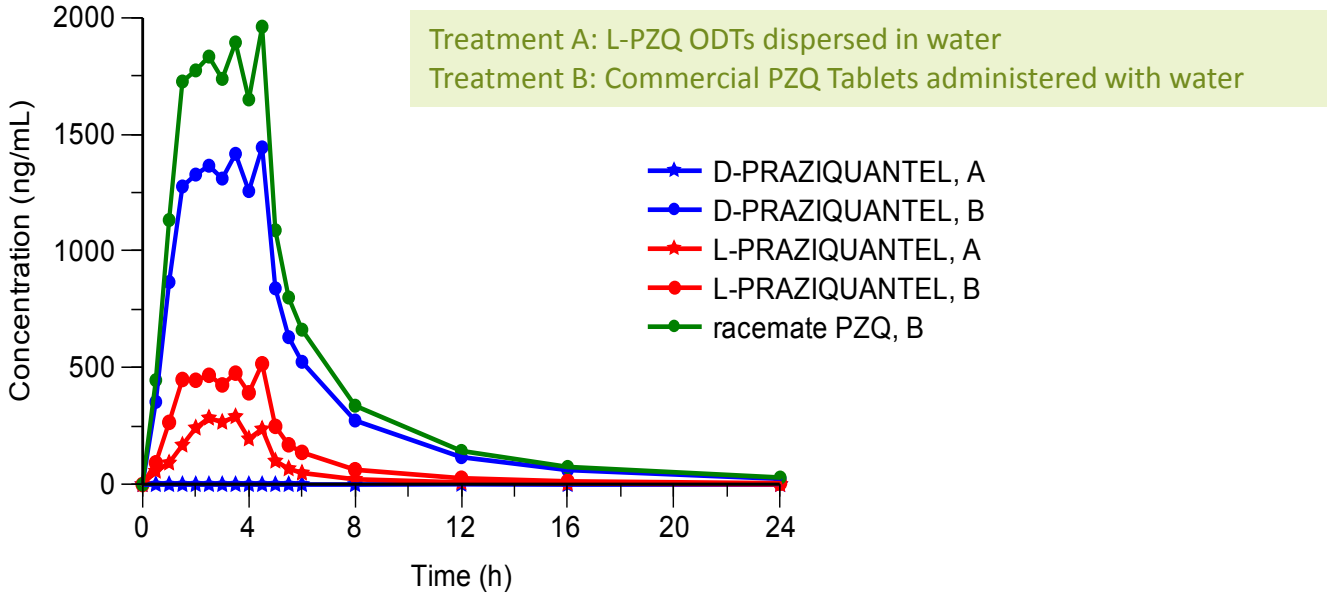
Block 2: Dose-dependency and food effect of rac-PZQ ODT and crushed current formulation of rac-PZQ.

L-PZQ BA key results: Lower L-PZQ levels after administration of L-PZQ ODTs vs rac. PZQ commercial tablets (Cisticid 500 mg)



Lower levels (about 50%) of L-PZQ when given as single enantiomer (L-PZQ ODTs) could be hypothesized to be due to non dose linear PK or to L/D metabolic interaction when given as racemic mixture.

L-PZQ ODTs Phase I rel. BA study show lower exposure of L-PZQ when given as a pure enantiomer

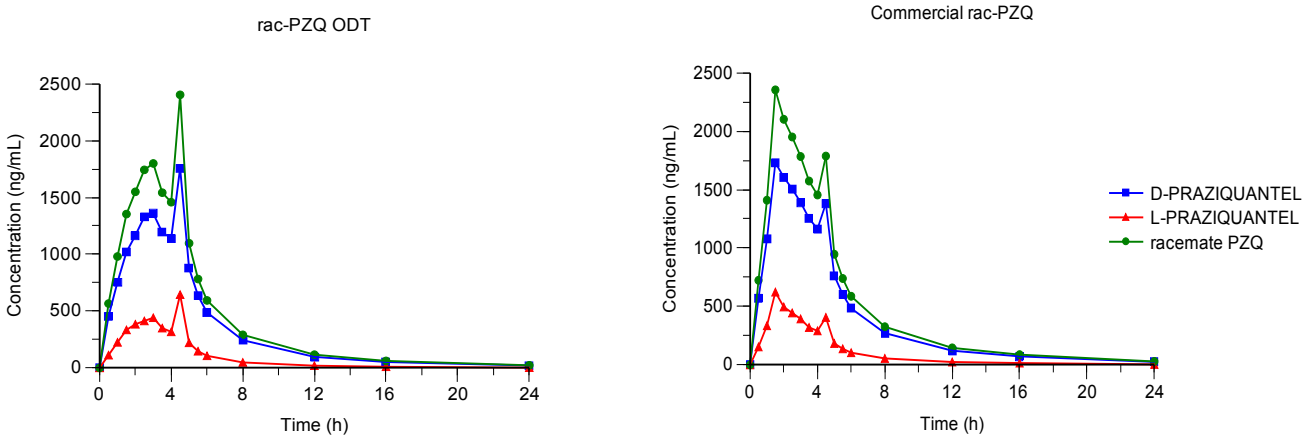


- L-PZQ and D-PZQ levels not evenly distributed after racemate PZQ administration (in line with the literature)
- L-PZQ levels when given as single enantiomer lower than L-PZQ levels after racemate PZQ administration

L-PZQ , D-PZQ and total racemate PZQ mean concentration-time profiles:

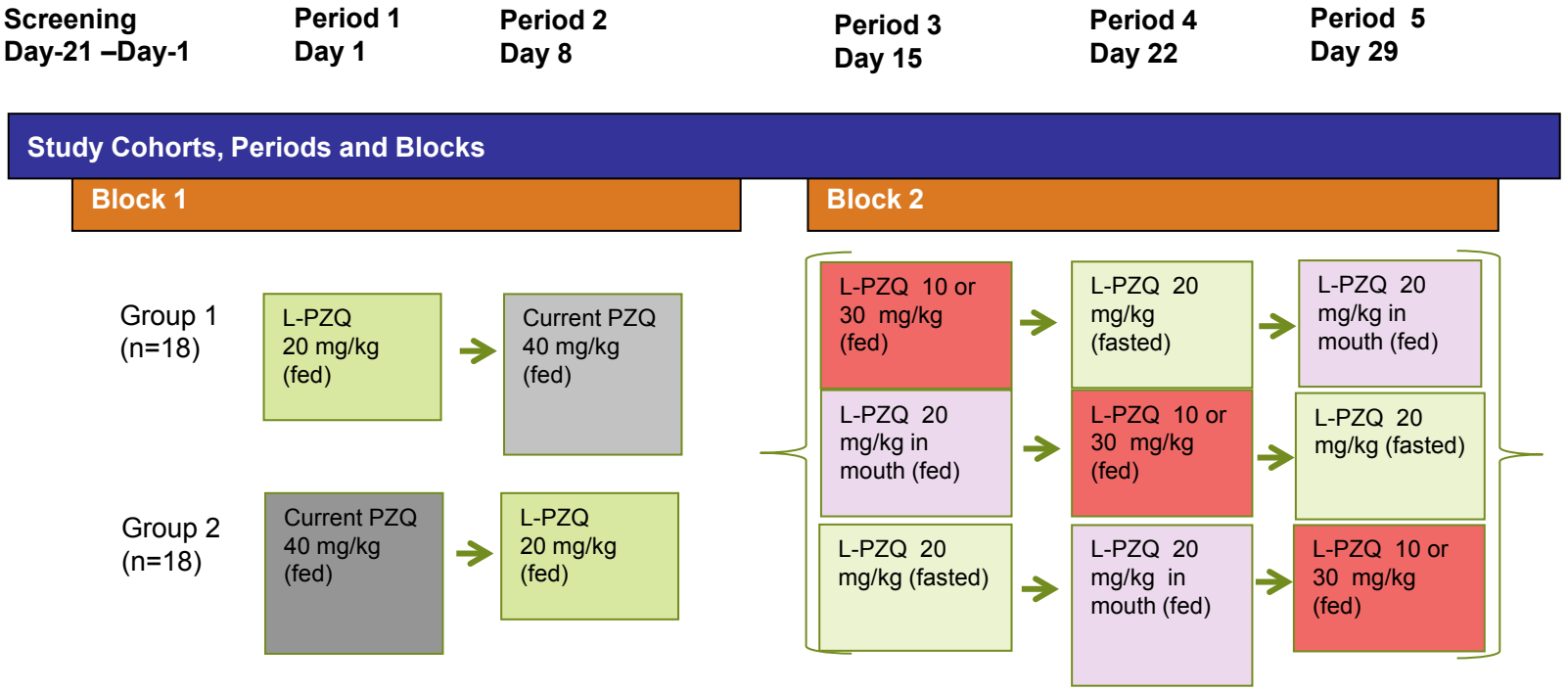
L-PZQ levels lower than D-PZQ levels both after rac-PZQ ODT (left figure) & rac-PZQ commercial formulation (right figure) administration.

Enantiomeric ratio in tablets is 1:1



It was not possible to build a model describing the individual PK profiles in adults.

L-PZQ ODTs study Design: A Randomized, Open-Label, Single-dose, Crossover Relative Bioavailability Study in Healthy Male Adults

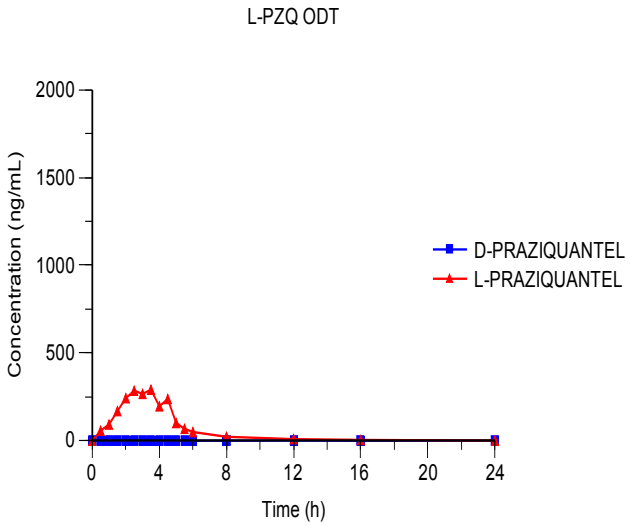


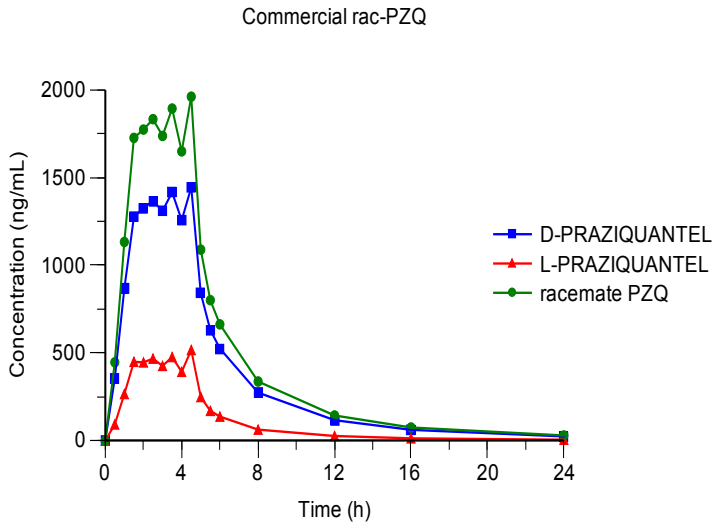
Block 1: Relative bioavailability of the new formulation of L-PZQ at 20 mg/kg versus the current rac-PZQ formulation at 40 mg/kg.

Block 2: Dose-dependency; food effect and given in mouth without water L-PZQ.

PK sampling over 24 hours (17 samples)

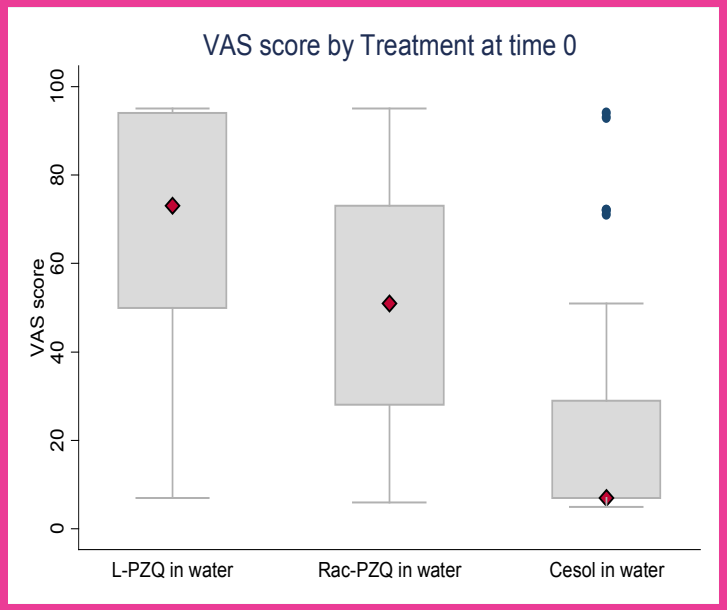
L-PZQ , D-PZQ and total racemate PZQ mean concentration-time profiles: L-PZQ levels when given as single enantiomer lower than L-PZQ levels after commercial racemate PZQ administration



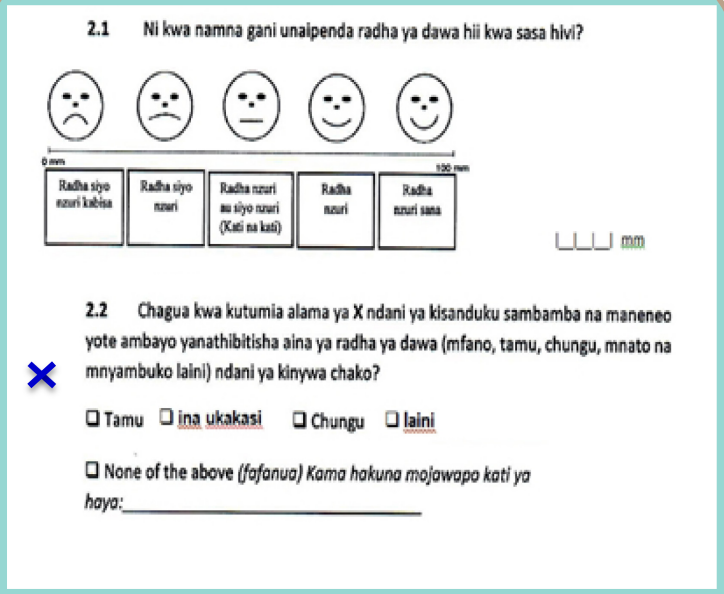


- When L-PZQ (left) is administered as a single enantiomer there is no conversion to the D-PZQ enantiomer

Taste Study in Tanzanian children (6-11 years): rac-PZQ ODTs & L-PZQ ODTs more palatable than Cesol 600 mg



For all age groups & genders, the overall palatability was better for both new ODTs dispersed in water vs Cesol 600 mg tablets crushed & dispersed in water (p-values <0.002)



2.1 Ni kwa namna gani unaipenda radha ya dawa hii kwa sasa hivi?

0 mm 100 mm

Radha siyo nzuri kabisa	Radha siyo nzuri	Radha nzuri au siyo nzuri (Kati na kati)	Radha nzuri	Radha nzuri sana

⌊_⌊_⌊ mm

2.2 Chagua kwa kutumia alama ya X ndani ya kisanduku sambamba na maneneo yote ambayo yanathibitisha aina ya radha ya dawa (mfano, tamu, chungu, mnato na mnyambuko laini) ndani ya kinywa chako?

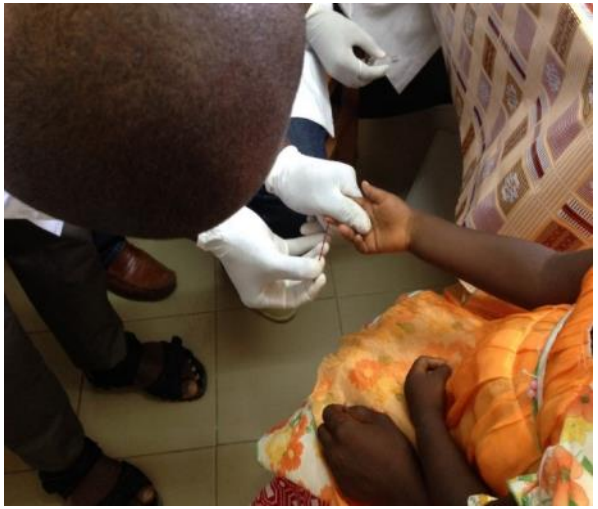
☐ Tamu ☐ ina ukakasi ☐ Chungu ☐ laini

☐ None of the above *(fafanua) Kama hakuna mojawapo kati ya haya:*_____

Trend revealing that rac-PZQ ODTs are less bitter than Cesol 600 mg.
For L-PZQ ODTs versus Cesol, this difference was statistically significant (p-value=0.014)

Pediatric phase II in children ≤6 years in Côte d'Yvoire: First patient dosed in June 2016- Study ongoing

Study team supervised by the PI (Prof. N'Goran), members of the Merck team and the Swiss TPH team



Back up slides

- **Subjects enrolled in the phase II**

Subject age	Light infection	Moderate infection	Severe infection	Sum
2	26	8	4	38
3	47	23	9	79
4	57	30	21	108
5	65	32	27	124
6	33	18	16	67
				416