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
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**!
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

International Expert Panel (World Health Organization) as observer

Consortium Board (chaired by Merck)

Consortium Team led by Merck

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

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

In kind or in cash contribution or both

Simcyp exited the Consortium in Oct. 2017

Swiss TPH

Global Health Innovative Technology Fund

Bill & Melinda Gates Foundation

GHIT Fund

Farmaninhos Instituto de Tecnologia em Fármacos

Schistosomiasis Control Initiative

lygature
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

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Cesol 600 mg
Cisticid 500 mg
New PZQ ODTs 150 mg
Non-clinical & clinical program designed based on consultations with health authorities & WHO PQP

**US FDA** (2013)
Type C Meeting to discuss the L-PZQ development

**ANVISA (Brazil)** (2013, 2014)
Scientific advice on the clinical development for L-PZQ & rac-PZQ ODTs

**BfArM (Germany)** (2016)
Scientific advice on the non-clinical & phase III program for L-PZQ & rac-PZQ ODTs

**EMA (article 58)** (2017)
Scientific advice on the non-clinical & phase III program for L-PZQ & rac-PZQ ODTs

**WHO pre-qualification Expert Committee** (2015)
Technical advice on the clinical program for L-PZQ & rac-PZQ ODTs
Clinical Program ongoing, targeting the 1st regulatory submission in 2019

- **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)

- **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*)

- **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)*

- **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

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

Total Efficacy 60%
Total Safety 40%

Notes: *only treatment related AEs/SAEs
Key challenges faced in conducting the phase II trial in Ivory Coast

Complex informed consent and child assent procedure in children < 6 years
Unclear legal requirements

Patient recruitment, follow-up and monitoring logistics in remote rural settings (especially in rainy seasons)

Regulatory challenges: unclear regulatory processes & responsibilities causing study interruption for several months

Capacity building of research institution in Man + GCP training of local staff

Political unrest (labor unrest and military mutinies) in the first half of 2017

Issues with PK sampling procedure (Dried blood spot), pain and patient fear (impact on patients enrollment)
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

Submission to EMA article 58

Submission to WHO Essential Medicines List

WHO EoI

WHO PQP

Registration in SSA endemic countries through the WHO collaborative procedure

Evaluation of the dossier by EMA

Launch in first SSA endemic countries

GMP audit(s) and Manufacturing launch readiness at Farmanguinhos

Evaluation of the dossier by ANVISA

Launch in Lat. Am. endemic country (Brazil)

Finish Phase III clinical program

Submission to ANIVISA (Priority Request)

Q4 2019

Q1 2020

Q3 2020

Q4 2020

Q3 2021
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
Thank you

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

Study Cohorts, Periods and Blocks

Block 1

<table>
<thead>
<tr>
<th>Screening</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Period 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-21 –Day-1</td>
<td>Day 1</td>
<td>Day 8</td>
<td>Day 15</td>
<td>Day 22</td>
<td>Day 29</td>
</tr>
</tbody>
</table>

Group 1
(n=18)

L-PZQ 20 mg/kg (fed)

L-PZQ 20 mg/kg (fed)

Current PZQ 40 mg/kg (fed)

Block 2

<table>
<thead>
<tr>
<th>L-PZQ 10 or 30 mg/kg (fed)</th>
<th>L-PZQ 20 mg/kg (fed)</th>
<th>L-PZQ 20 mg/kg in mouth (fed)</th>
</tr>
</thead>
</table>

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<th>L-PZQ 20 mg/kg (fed)</th>
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</thead>
</table>

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)

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

<table>
<thead>
<tr>
<th>Subject age</th>
<th>Light infection</th>
<th>Moderate infection</th>
<th>Severe infection</th>
<th>Sum</th>
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<tbody>
<tr>
<td>2</td>
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<td>8</td>
<td>4</td>
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<td>16</td>
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Total: 416