DEVELOPMENT AND EVALUATION OF PEDIATRIC FORMULATION OF PRAZIQUANTEL

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On behalf of the Pediatric Praziquantel Consortium

15th MEETING OF THE INTEGRATED PROGRAM SCHISTOSOMIASIS (PIDE/FIOCRUZ)
Belo Horizonte - Minas Gerais / Brazil
4th to 6th April 2016
In July 2012, a Non-profit Public Private Partnership was Formed to Develop a Pediatric PZQ Formulation (< 6 yrs)

- International non-profit R&D consortium with a focus on extending 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)
- Experts in Praziquantel, in charge of the clinical development program and sponsor of the clinical trials
- Experts in innovative drug formulation strategies and provides expert advice on clinical development in children

- Consortium Board (chaired by Merck)
- Experts in pharmaceutical manufacturing in endemic countries

- Grants received in 2013, 2014 and 2015 from Bill & Melinda Gates Foundation and GHIT Fund (Japan)

- Lygature
- Experts in managing public-private partnerships in drug research and development

- Swiss TPH
- Experts in the field of clinical trials in endemic countries, epidemiology and antischistosomal drug discovery

- Consortium Team led by Merck
- Experts in pharmacokinetic modelling

- SimCYP
- Experts in pharmacokinetic modelling

- farmanguinhos
- Experts in pharmaceutical manufacturing in endemic countries
The 2 new oral dispersible tablet (ODT) formulations are being developed in parallel until end of phase II clinical trial

L-PZQ ODT Formulation 150 mg
- Removal of the biologically inactive D-PZQ
- Less number of tablets per treatment as compared to Rac-PZQ
- Expected to be Less Bitter than the racemate ODT formulation (also due to taste masking)

Racemate-PZQ ODT Formulation 150 mg
- Improvement vs. existing commercial PZQ tablets: Cesol® 600 mg and Cisticid® 500 mg (Less bitter due to taste masking, smaller size and suitable for use in very young children)
Two-Directional Technology Transfer for the New ODT Formulation

- Paper-based TT
- F2F Meeting Brazil
- Formulation changes done

Rac-PZQ ODTs (Tech transfer)

Rac-PZQ ODTs (GMP batch Ph I)

Synergies can be utilised as experts in both teams

L-PZQ ODTs (Tech transfer)

L-PZQ ODTs (GMP batch Ph I)

2012

Formulation Development

2014

On-site visit for TT

Limited stability of TT batches

Adaptions for GMP batch
Where Do We Want to Go?
Submission currently planned for e/o 2018

PhI API process & formulation

PhII API process & formulation

Robustness & QbD/Upscale

API
Tech Transfer/Process validation

DP
Clinical Program with ODTs is progressing to phase II with a target regulatory submission in 2018

**Completed**

Two Phase I Studies in South Africa (Rac-PZQ and L-PZQ)
Relative Bioavailability study in healthy male adults between the current PZQ formulation registered by Merck (Praziquantel 500mg) and the new 150mg tablet (n = 32 for each study)

**Completed**

Taste Study of the new ODTs in African children (Tanzania)
The taste study is a 5 groups cross-over randomized study in African children age 6-11 years *(primary school in Tanzania, n ≈ 48)*

**2016**

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* / Part 2a: children (3 months-2 years) infected with *S. mansoni*; Part 2b: Children 2-6 years infected with *S. haematobium*

Go/no go on Rac-PZQ ODTs vs L-PZQ ODTs

**2017**

Phase III study with either L-PZQ or Rac-PZQ ODTs *
To demonstrate efficacy /safety of PZQ ODTs in children age 3 month-6 years
Design TBC

* For L-PZQ ODTs, additional clinical studies will be conducted including drug interaction studies
The taste study is a 5 groups cross-over randomized study in African children age 6-11 years (primary school in Tanzania)

**DAY 1 (n=48)**
Children will receive the following treatments in a randomized order (put and disintegrated in the mouth without water)

- L-PZQ ODT 150 mg (A)
- Rac. PZQ ODT 150 mg (B)

**DAY 2 (n=48)**
The same children from Day 1 will receive the following 3 treatments in a randomized order (dispersed in water and administered to the mouth cavity)

- L-PZQ ODT 150 mg (C) Dispersed in water
- Rac. ODT 150 mg (D) Dispersed in water
- Current tablet 150 mg (E) Crushed, dispersed in water (2 ml)

**Visual analogue scale (VAS)**

Very poor taste
Poor taste
Neither good nor bad taste
Good taste
Very good taste
THE TASTE STUDY RESULTS (DAY 1)

• Over all age groups no statistically significant difference could be shown between L-PZQ ODT and Rac-PZQ ODT.

• For age group 9-11:
  – T = 0 min: Mean VAS score for L-PZQ ODT was higher than Rac-PZQ ODT but difference was borderline significant (p-value = 0.052).
  – T = 2-5 min: A significant difference can be seen (p-value = 0.042).
THE TASTE STUDY RESULTS (DAY 2)

- The overall palatability for all age groups and sexes was better for both new ODT formulations compared to Cesol® (p-values <0.002).
- From a questionnaire on the mouth feeling for Rac-PZQ ODT a trend revealing that it is less bitter than Cesol® could be seen.
- For L-PZQ ODT versus Cesol® the difference was statistically significant (p-value = 0.014).

CONCLUSION
The taste of the new L-PZQ ODT as well as the Rac-PZQ ODT tablets were much better than the current 600 mg PZQ commercial racemate tablets (Cesol®) tablets.
Phase I trial for L-PZQ ODT
Benefit/risk of L-PZQ and inform dose for phase II

A phase I, open-label, randomized, single dose, five period, crossover, single center trial to assess the relative bioavailability of the 150 mg ODT formulation of L-PZQ versus the current 500 mg PZQ commercial racemate tablet formulation in healthy male volunteers.

Population: Healthy male volunteers (n=36)

Region: South Africa; CRO: Parexel

Primary Objective:
Relative Bioavailability of L-PZQ 150 mg tablet vs Cysticide® 500 mg with food at 20 mg/kg L-PZQ dose.

Primary Endpoints
AUC\(_{0-\infty}\) of L-PZQ concentration in plasma (extensive PK sampling).

Secondary Objectives
Effect of food on Rel. BA of L-PZQ.
Assessment of dose proportionality of L-PZQ (10 and 30 mg/kg).
Assessment of ODT property of L-PZQ.

Safety, tolerability and palatability of L-PZQ
Phase I trial for L-PZQ ODT – RESULTS

• L-PZQ mean concentration time profile
  – L-PZQ levels when given as racemate (treatment B) are higher than given as equal amount of single enantiomer (treatment A).

![Graph showing concentration-time profiles of L-PZQ, D-PZQ and total racemate PZQ.](diagram)

Treatment A: L-PZQ ODTs dispersed in water
Treatment B: Commercial PZQ Tablets administered with water
Phase I trial for L-PZQ ODT – RESULTS (cont.)

- **Dose Response:**
  - L-PZQ after treatment with 10, 20 or 30 mg/mL L-PZQ ODT shows a supraproportional dose response.

- **Food effect:**
  - With food (treatment A) L-PZQ parameters are 69% higher than if given without food (Treatment D).

![Graph showing dose response and food effect](image-url)
Phase I trial for L-PZQ ODT – RESULTS (cont.)

• Safety
  – Few treatment emergent adverse events (TEAEs) reported after L-PZQ treatment. Some more TEAEs reported after treatment with commercial rac-PZQ (treatment B).
  – No new type of TEAEs was observed after L-PZQ administration, most TEAEs were of mild severity and transient.
  – L-PZQ was considered safe and tolerable.

• Palatability
  – Overall palatability of L-PZQ ODT formulation tended to be higher than for commercial rac-PZQ, with much higher scores for flavor and sweetness.

CONCLUSION

L-PZQ showed a good safety profile and good palatability. Due to the lower bioavailability of L-PZQ when given as a single enantiomer, higher doses of L-PZQ than 50% of the dose of rac-PZQ need to be administered to reach similar exposures. The reason for the lower bioavailability of L-PZQ needs further investigations.
Phase I trial for Rac-PZQ ODT
Benefit/risk new formulation & inform dose for phase II

A phase I, open-label, randomized, four-period, crossover, single center trial to assess the relative bioavailability of a single oral dose of the new 150 mg Oral Dispersible Tablet (ODT) formulation of Praziquantel (PZQ), MSC1028703A, at different dose levels vs the current commercial 500 mg tablet formulation of PZQ in healthy male volunteers

Population: Healthy male volunteers (n=32)
Region: South Africa; CRO: Parexel

Primary Objective:
Relative bioavailability of the Racemate ODT-PZQ tablet of 150 mg dispersed in water versus the current racemate Cysticide® tablet of 500 mg at a dose of 40 mg/kg in healthy subjects under fed conditions.

Primary Endpoints
AUC$_{0-\infty}$ of L-PZQ concentration in plasma.

Secondary Objectives
Assessment of dose proportionality of rac-PZQ (20 and 40 mg/kg).
Effect of food on Rel. BA of rac-PZQ.
Relative bioavailability of crushed 500 mg current PZQ tablets.
Safety, tolerability and palatability of rac-PZQ.
Phase I trial for Rac-PZQ ODT – RESULTS

- The results showed that the relative BA of L-PZQ when administered as Rac-PZQ ODT is similar to when given as an equal amount in the Rac-PZQ (Cysticide®) formulation, meeting the bioequivalence criteria for AUC.

![L-PZQ, D-PZQ and total racemate PZQ mean concentration-time profiles](image)

Treatment A: Rac-PZQ ODTs
Treatment B: Commercial PZQ Tablets
Phase I trial for Rac-PZQ ODT – RESULTS (cont.)

- The data indicated that L-PZQ in the Rac-PZQ ODT formulation after treatment with 20, 40 and 60 mg/kg showed a supraproportional dose-PK-relationship.
- The food effect was also confirmed (PK parameters are higher if given with food), whereas administration of crushed commercial tablets showed somewhat lower AUC levels than the non-crushed tablets.
- In terms of safety, few TEAEs were reported after Rac-PZQ ODT treatment or commercial rac-PZQ and number of TEAEs increased with increasing dose of rac-PZQ ODT.
- No new types of TEAEs were observed after Rac-PZQ ODT administration, most TEAEs were of mild severity and all were transient.
- Although some individual changes from baseline were observed, the laboratory parameters, blood pressure, pulse rate, ECG and body temperature showed no trends or clinically relevant changes.

CONCLUSION

Rac-PZQ ODT was considered safe and tolerable
Phase II study (Open-label, dose-finding, 2-parts)  
Overall Trial Design and Plan (Region: Ivory Coast)

### PART 1
**INFECTED CHILDREN**  
aged 2-6 years  
(n = 360 - 420)

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<tr>
<th>C1</th>
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</table>
| Commercial rac-PZQ 3x20 mg/kg  
N = 40 | Commercial rac-PZQ 1x40 mg/kg  
N = 40 | rac-PZQ ODT 1x40 mg/kg  
N = 40 | rac-PZQ ODT 1x60 mg/kg  
N = 40 | L-PZQ ODT 1x30 mg/kg  
N = 40 | L-PZQ ODT 1x45 mg/kg  
N = 40 |

Random 1:1:1:1:1

After n = 20, all arms will be assessed for safety by SMC to decide to include C7 arm. Meanwhile, recruitment in C1-C6 will proceed to n = 40 before starting to randomize subjects into C7 arm, if C7 is included.

### PART 2
**INFECTED CHILDREN**  
(n = 100)

Dose level selected on available data from Part 1 and all available metabolism data

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<th>C8</th>
<th>C9</th>
<th>C10</th>
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| Selected ODT, Age 13-24 months (S. mansoni)  
N = 30 | Selected ODT, Age 3-12 months (S. mansoni)  
N = 10 | L-PZQ ODT, Age 2-6 years (S. haematobium)  
N = 60 |

Dose level selected on available data from Part 1, all available metabolism data and all safety data from C8

Optimal dose from Part 1 and only if L-PZQ ODT is selected

**PART 2a**

**PART 2b**
• Primary Objective:
  • **Part 1:** To identify the optimal single dose of rac-PZQ ODT or L-PZQ ODT formulation which has a clinically meaningful cure rate (as assessed by Kato-Katz method) and an acceptable safety profile in 2- to 6-year-old children infected with *S. mansoni*.
  • **Part 2:** To evaluate the efficacy and safety of the selected ODT formulation (L-PZQ or rac-PZQ) from Part 1 at the appropriate adjusted dose(s) in infants aged 3 to 24 months infected with *S. mansoni*.

• Primary Endpoints
  • Clinical cure defined as no parasite eggs in the stools (*S. mansoni* infections) or urine (*S. haematobium* infections) 14-21 days after treatment. Egg counts will be determined by the Kato-Katz method.

• Secondary Endpoints
  • Egg Reduction Rate (ERR, %) calculated based on the arithmetic (and geometric) mean egg count per gram of stool (epg) before and 14-21 days after treatment (as determined by Kato-Katz method).
  • Cure defined as no parasite eggs in the stools as assessed by the commercially available POC-CCA test for *S. mansoni*
ACTUAL PLAN - MAIN ACTIVITIES

2016
- Rac-PZQ ODT: QbD Studies
- L-PZQ ODT: QbD and TT Merck to FAR
- Clinical Trials: Ph II CT Part 1 + Part 2

2017
- Ph III and Validation Batches (QbD and Ph III)
- Ph III CT

2018
- After Registration Approval
  - DP Manufacture in FAR: Supply Brazil/LatAm & Africa (Early years)
  - TT to 2nd site selected in Africa
  - Supply Africa (ROW)

Decision ODT Formulation L-PZQ or Rac-PZQ
Submission File (ANVISA + WHO)
CONSORTIUM IS WORKING ON THE REGULATORY AND PRODUCT ACCESS STRATEGY

The Access & Delivery Plan will incorporate the following:

• Plan & timelines for obtaining WHO prequalification & regulatory authorisation for – and subsequently launch of the new formulation in key Endemic Countries in Sub-Saharan Africa (SSA) & Brazil
• A commitment to sell the product on a not-for-profit basis for distribution in the Public Sector.
• A plan to make the product available to meet Public-Sector needs in endemic countries following marketing authorisation.
• A plan to support uptake of the product in key endemic SSA Countries, including consideration of inclusion of the new PZQ ODTs in WHO treatment guidelines.
• A commitment to make the new PZQ ODTs available & affordable

*How to involve Brazil in the Access Plan Taskforce?*
THANK YOU!!

http://www.pediatricpraziquantelconsortium.org
Backup slides
Example Taste Study design on Day 1

Morning breakfast (standardized)

Period 1: Treatment A or B put on the tongue and spitting

VAS assessment and question on taste

Period 2: Other treatment (A or B) and spitting

VAS assessment and question on taste

Overall palatability

1 hr fasting
Rinsing + Cracker prior to tasting

0 and ≈5 min

Washout 1h
Rinsing + Cracker

0 and ≈5 min

Visual analogue scale (VAS)

- Recording of any discomfort or other observation will be done throughout the study