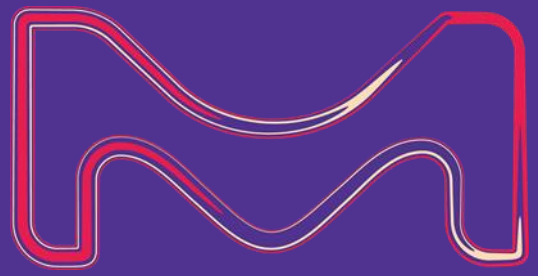
Merck's R&D Contributions towards schisto elimination

7th Symposium on Surveillance & Response

GSA&RNAS+ Meeting

17-18 June 2024, Shanghai



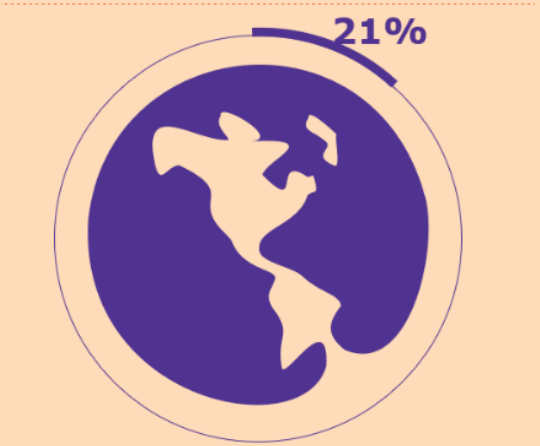
MERCK

R&D for Poverty-related diseases

Poverty-related and neglected tropical diseases represent

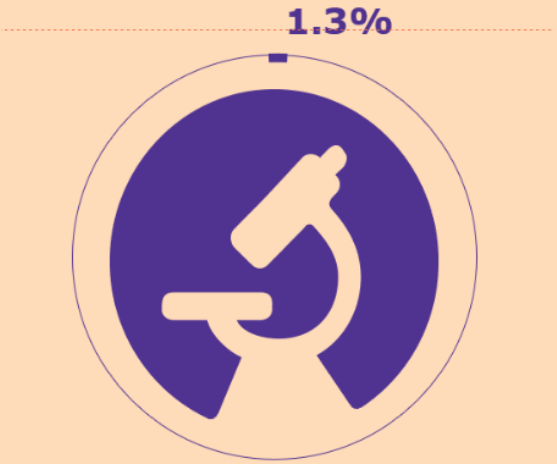
21% of the global burden

of diseases



But they attract only

1.3% of global R&D expenditure



Schistosomiasis goals according to WHO NTD Roadmap 2030

WHO Schistosomiasis Goals, Strategies and Critical actions - *New NTD road map 2021-2030*

GOALS

- Global Elimination of schistosomiasis as Public Health Problem: **<1% prevalence of heavy intensity of schistosomiasis infections measured by Kato-Katz/UF**
- Validation of absence of infection in human in selected countries

STRATEGY

- Mass Drug Administration
- Case management
- Veterinary public health
- WASH/health education
- Vector control

ACTIONS

- Define indicators for the measurement of the morbidity and the elimination of as public health problem
- Expand MDAs to all populations
- Implement targeted snail control
- Continue micro-mapping & Targeting interventions
- Develop diagnostics, develop new interventions including alternatives to Praziquantel and methods to snail control
- Create cross sectoral governance mechanisms to coordinate with WASH, vector control, animal heath, environment
- Ensure sufficient domestic funding for interventions, development of new tools, and strengthening of the healthcare capacity

Towards elimination of schistosomiasis

Our integrated Approach

Health Education

» **Health education & WASH** to enact behavior change

» **Scientific education & training** to health workers in Africa

Water, Sanitation & Hygiene Tailored Programs

» Development of w**ater technologies** to strengthen health systems and decrease exposure of populations to parasites

Diagnostic Tools

» Development of schistosomiasis circulating anodic antigens (CAA) **Rapid Diagnostic Test**

» Development of a soil transmitted helminth & schistosomiasis **Artificial Intelligence-based Kato Katz diagnostics**

Drug Discovery

» Bringing a **new drug candidate** to support breaking transmission goals

» **Generate real-world evidence** to support our clinical programs and contribute to building capacity for research and innovation in the field.

Praziquantel

» Provision of **250 million Cesol600 tablets per year** in partnership with World Health Organization (WHO)

» **Optimized formulation** with extended shelf-life and improved taste

» **Pediatric Arpraziquantel received EMA Art. 58 positive opinion & WHO prequalifiquation.**

» **ADOPT access programme**

Global Schistosomiasis Alliance

» Advocate and accelerate **progress** in elimination

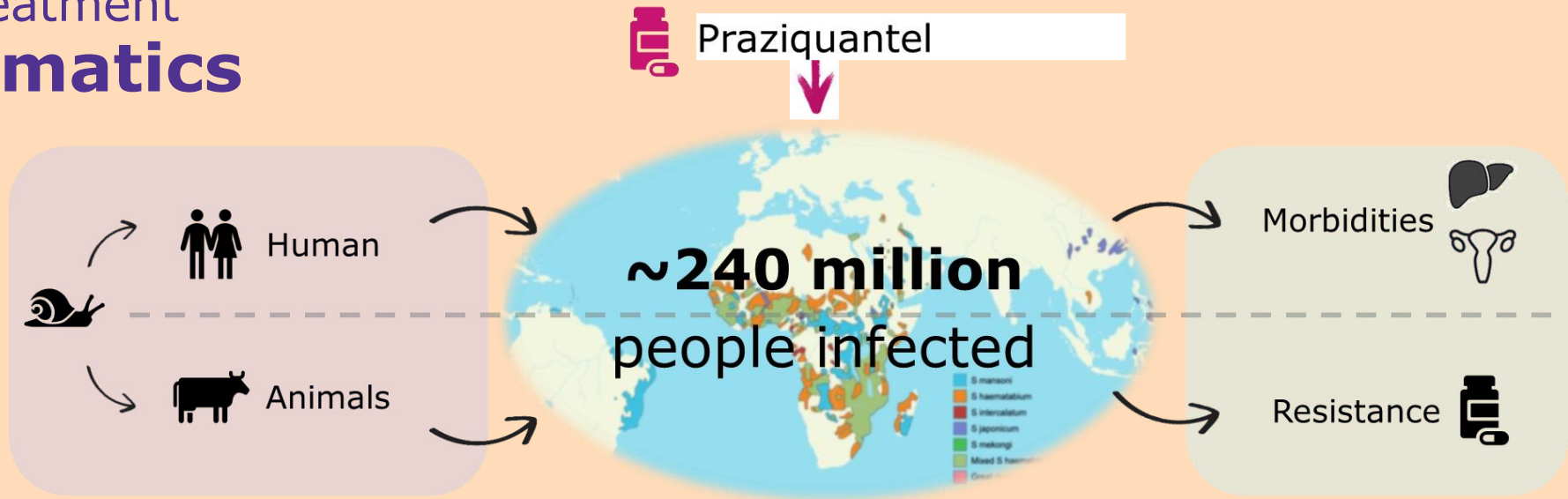
Female Genital Schistosomiasis (FGS)

» Creating awareness and improving **local skills**

» Identifying **optimal treatment** approaches

Schisto treatment

Problematics



- **Lack of adequate treatment portfolio**
  - 240 million people infected relying on one drug i.e. Praziquantel
  - Lack of effective prevention attributes

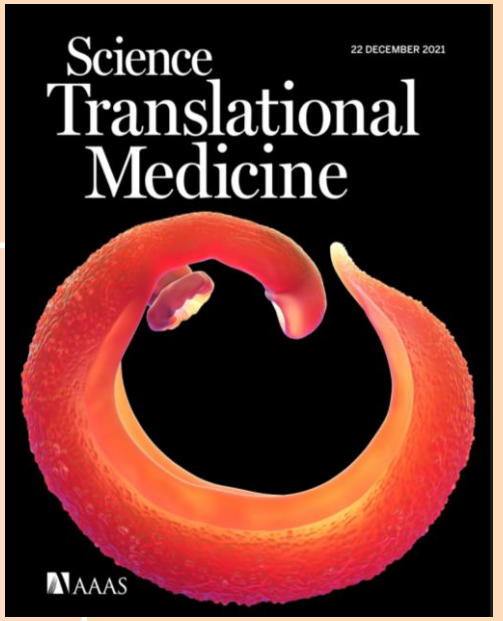
- **Lack of understanding of transmission dynamics**
  - Monitoring PZQ resistance
  - Understand the contribution of the animal reservoir (one Health approach)

- **Lack of morbidity management** e.g. Female Genital Schistosomiasis

Schisto treatment

Praziquantel

- Composition: 1(***R***): 1(*S*)-PZQ
- Dose: 40 mg/kg
- Active on all schistosome species
- Effective on adult worm only
- Parasitological cure rate: 70-75%
- Eggs reduction rate: 90%
- Mode of Action: transient receptor potential melastatin ion channel ($TRPM_{PZQ}$)



https://www.who.int/en/news-room/fact-sheets/detail/schistosomiasis
Zwang, J. et al. Parasit. Vectors 10, 47 (2017)
Utzinger J et al. Trop Med Int Health. 2000 Nov;5(11):771-8
Park SK et al. Sci Transl Med. 2021 Dec 22;13(625):eabj5832
Le Clec'h et al. Sci Transl Med. 2021 Dec 22;13(625):eabj9114

An alternative to Praziquantel for the prevention and elimination of schisto

A New Chemical Entity that has …

Fast acting mode of action

(Same as PZQ)

Activity on juvenile and adult worms i.e. potential to interrupt transmission

(Different to PZQ)

A low projected single oral dose

(Potentially better than PZQ)

KOL meeting: "Perspective on Schistosomiasis Drug Discovery: Highlights from a Schistosomiasis Drug Discovery Workshop at Wellcome Collection, London, September 2022". ACS Inf. Dis. 2023

New anthelmintic high-level status

- **Meets outlined Target Product Profile**
  - **Fast acting**
  - **Active on mature and immature worms**
  - **Highly potent with low projected human dose**

- **Early safety studies have been completed.**

- **Merck is now preparing for GLP safety studies in view of reaching Phase 1 human trials**

Generate real-world evidence to support decision-making

Transmission

SCREENING

Transmission dynamics and hybridization of human and animal schistosoma (One Health: integrated health approaches)
USTTB, Mali

Detect evidence of praziquantel resistance and map it to elucidate thethreat of drug resistance to control programs
National History Museum, UK


Agniwo et al. Parasites & Vectors (2023) 16:263
https://doi.org/10.1186/s13071-023-05860-8

Parasites & Vectors

RESEARCH Open Access

Genetic profiles of *Schistosoma haematobium* parasites from Malian transmission hotspot areas

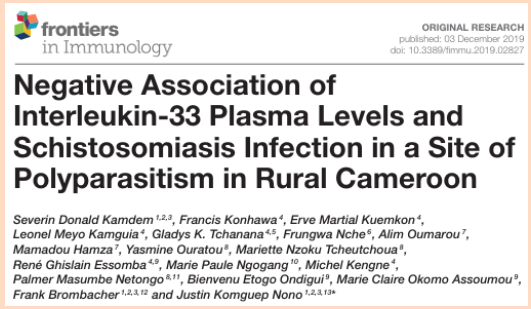
Privat Agniwo[1,2,3], Jérôme Boissier[2], Bakary Sidibé[1], Laurent Dembélé[1], Assitan Diakité[1], Doumbo Safiatou Niaré[2], Ahristode Akplogan[1], Hassim Guindo[1], Manon Blin[2], Sarah Dametto[2], Moudachirou Ibikounlé[3], Thomas Spangenberg[4] and Abdoulaye Dabo[1*]

Morbidities

LEAD IDENTIFICATION

Identification of specific factors influencing host-parasite associations and pathology outcomes
IMPM, Cameroon

Female Genital Schistosomiasis (FGS) – infertility mechanisms
IMPM, Cameroon


frontiers in Immunology

ORIGINAL RESEARCH
published: 03 December 2019
doi: 10.3389/fimmu.2019.02827

Negative Association of Interleukin-33 Plasma Levels and Schistosomiasis Infection in a Site of Polyparasitism in Rural Cameroon

Severin Donald Kamdem[1,2,3], Francis Konhawa[4], Erve Martial Kuemkon[4], Leonel Meyo Kamguia[4], Gladys K. Tchanana[4,5], Frungwa Nche[6], Alim Oumarou[7], Mamadou Hamza[7], Yasmine Ouratou[8], Mariette Nzoku Tcheutchoua[8], René Ghislain Essomba[4,9], Marie Paule Ngogang[10], Michel Kengne[4], Palmer Masumbe Netongo[8,11], Bienvenu Etogo Ondigui[9], Marie Claire Okomo Assoumou[9], Frank Brombacher[1,2,3,12] and Justin Komguep Nono[1,2,3,13]


PLOS PATHOGENS

RESEARCH ARTICLE

Schistosoma mansoni infection induces plasmablast and plasma cell death in the bone marrow and accelerates the decline of host vaccine responses

Fungai Musaigwa[1,2,3], Severin Donald Kamdem[1,2,3,4,5], Thabo Mpotje[1,2,3], Paballo Mosala[1,2,3¤], Nada Abdel Aziz[1,2,3,6¤], De'Broski R. Herbert[7], Frank Brombacher[1,2,3,5], Justin Komguep Nono[1,2,8¤]

First international public-private partnership on schistosomiasis

- The Consortium was established in July 2012 as the **first international, non-profit, public-private partnership working on schistosomiasis**
- It operates through an innovative approach that engages new partners and collaborators as needed
- The model is built on a **solid governance** structure with:
  - A Consortium Board (led by Merck)
  - A Development Team and Access Team & other Sub-teams
- Supported by international experts and funders, including the World Health Organization (observer).

Consortium partners: Merck (Germany); Astellas Pharma Inc. (Japan); the Swiss Tropical and Public Health Institute (Switzerland); Lygature (The Netherlands); Farmanguinhos (Brazil); Unlimit Health (United Kingdom); Kenya Medical Research Institute (Kenya); Université Félix Houphouët-Boigny (Côte d'Ivoire); Klinikum rechts der Isar der Technischen Universität München (TUM) (Germany); Ministry of Health, Côte d'Ivoire; African Institute for Health and Development (AIHD), Kenya.
Consortium collaborators: Ministry of Health, Kenya; Ministry of Health, Uganda; Makerere University, Uganda.

The Consortium is financially supported by Merck; in-kind contributions from the Consortium's partners; and grants by the **Global Health Innovative Technology (GHIT) Fund**, and **the European & Developing Countries Clinical Trials Partnership (EDCTP).**

The Development Candidate

New Innovative Pediatric Dispersible Tablets (DTs)

The development candidate **arpraziquantel** is based on praziquantel (racemic mixture of L and D enantiomers) but contains only the active L enantiomer (L-PZQ)

Ease of use/improved palatability

- Small size (¼ size of the current standard of care)
- More precise dosing
- Dispersible
- Reduced bitterness

Stability

- Ensuring stability in the hot and humid conditions of tropical regions

Manufacturing process

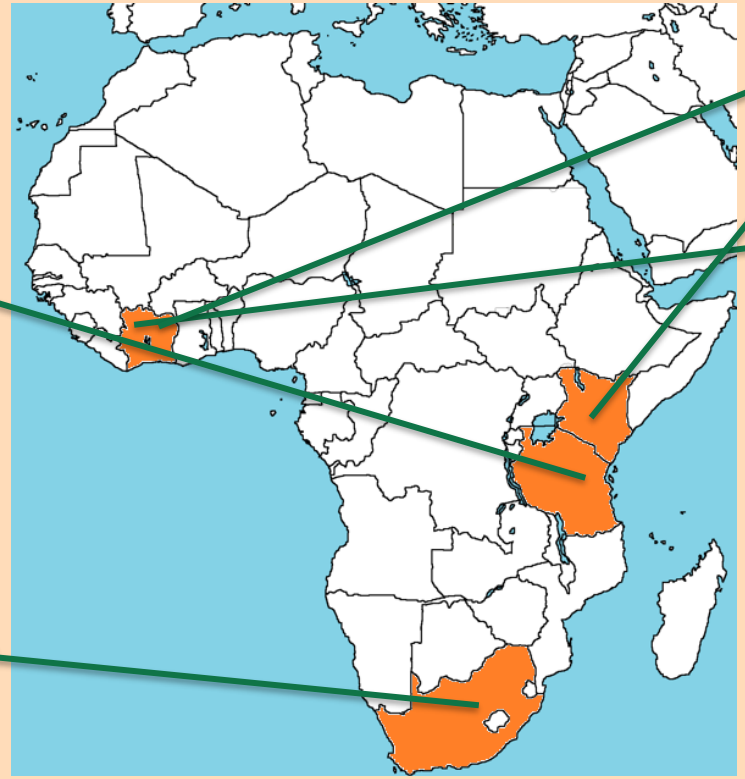
- Transfer for local production at large-scale

Successfully completed comprehensive Clinical development Program conducted with endemic countries

Completed (2019)

Phase II PK/PD dose finding Study (Côte d'Ivoire)

S. mansoni infected children aged 3 months-6 years



Completed (2021)

Phase III confirmatory trial (Kenya/Côte d'Ivoire)

S. mansoni and *S. haematobium* infected children aged 3 months-6 years

Completed (2015)

Two Phase I Bioavailability studies (South Africa)

Completed (2015)

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

Key conclusions from the Clinical Phase III Trial

- **Efficacy and safety data** (50 mg/kg for *S. mansoni* and 60 mg/kg for *S. haematobium*) shows a **favorable profile**
- The **study met its primary endpoint**
  - Cure rates in all age groups for all arpraziquantel 50 mg/kg treated *S. mansoni* infections have point estimates ≥88% with lower limit of the 95% CI >70%
  - Cure rates for arpraziquantel 60 mg/kg treated *S. haematobium* infection have point estimates ≥ 86% with lower limit of 95% CI >70% (Cohort 4b, weeks 3 and 5)
- **High ERR** in all dose groups and across both species (≈99%)
- **No new risks or safety concerns** were identified
- Arpraziquantel 50 mg/kg and 60 mg/kg demonstrated **favorable safety, tolerability, and improved palatability** among preschool-aged children

Assuring quality product provision through tailored regulatory approaches and addressing additional international requirements

EMA Approval 2023

EMA Scientific Opinion achieved in December 2023 will facilitate access to endemic countries

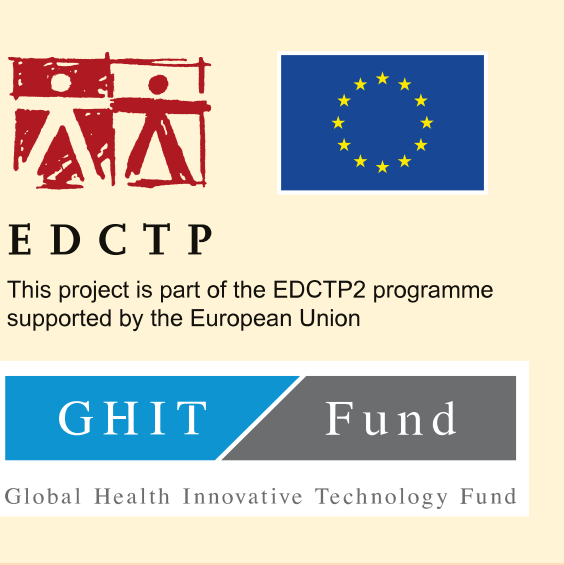
WHO Prequalification 2024

arPZQ in included in WHO Prequalified Produtcs

WHO Essential Medicine Listing 2025

Funding statement

The Consortium is financially supported by Merck, with in-kind contributions from partners and grants from the Bill & Melinda Gates Foundation (2012), the Global Health Innovative Technology Fund (GHIT) (2014, 2015, 2016, 2019 & 2020), and the European & Developing Countries Clinical Trials Partnership (EDCTP) (2018 & 2021).



Disclaimer

The content of this presentation reflects the views of the Pediatric Praziquantel Consortium.

www.pediatricpraziquantelconsortium.org

Consortium partners

MERCK

farmanguinhos
Instituto de Tecnologia em Fármacos

astellas

Swiss TPH

MINISTÈRE DE LA SANTÉ ET DE L'HYGIÈNE PUBLIQUE

lygature

KENYA MEDICAL RESEARCH INSTITUTE
KEMRI
In Search of Better Health

UNIVERSITÉ
Félix HOUPHOUËT-BOIGNY

Unlimit Health.
ENDING PARASITIC DISEASE

AFRICAN INSTITUTE FOR HEALTH & DEVELOPMENT
"Working with communities for better lives through evidence-based programming"

MRI TUM
Klinikum rechts der Isar
Technische Universität München

Supported by

REPUBLIC OF KENYA
MINISTRY OF HEALTH

MAKERERE UNIVERSITY

PEDIATRIC PRAZIQUANTEL CONSORTIUM

Schisto treatment options

Merck PZQ portfolio to treat schistosomiasis across all age groups

	Preschool-aged Children (PSAC)	School-aged Children (SAC)	Adults
Adult worms	Pediatric Praziquantel arPZQ-150 mg (in 2024)	Praziquantel (New formulation in 2026) Cesol 600mg	Praziquantel (New formulation in 2026) Cesol 600mg

Addressing transmission blocking & Resistance

Adult & Juvenile worms: DP0 in Q2 24: M4339 (preclin)

Summary

- **As a Science & Technology company dedicated to human progress, Merck is committed to combat schistosomiasis and provide impact to patients in need.**

- **From a Healthcare R&D perspective, investments are primarily focused on discovering and developing alternatives to praziquantel.**
  - **Most advanced asset is gearing toward Ph1**
  - **In-kind support for external partners**

- **When possible, we support the generation of real-world evidence by collaborating with organization from the global South, with focus on**
  - **Monitoring PZQ resistance**
  - **Understanding transmission dynamics**
  - **Develop innovative approaches to manage morbidities (e.g. FGS).**

- **Encourage collaboration and alignment on strategic investments are key in resources limited environment**