PEDIATRIC PRAZIQUANTEL CONSORTIUM

PRESS RELEASE

The Pediatric Praziquantel Consortium Announces Positive Phase III Results for Arpraziquantel To Treat Schistosomiasis

- The Pediatric Praziquantel Consortium completes its pivotal clinical Phase III trial of *arpraziquantel* – a potential new treatment option for the estimated 50 million preschool-aged children with schistosomiasis
- Positive results of the Phase III trial confirm earlier promising Phase II trial results
- Founding Consortium partner Merck intends to submit regulatory file to the European Medicines Agency

16 November 2021, Utrecht, The Netherlands. Today, the Pediatric Praziquantel Consortium, a public-private partnership dedicated to the development of arpraziquantel, a potential new treatment option for schistosomiasis in preschool-aged children, announced the completion of its pivotal Phase III trial in Côte d'Ivoire and Kenya.

The results of the trial, co-funded by the Global Health Innovative Technology (GHIT) Fund and the European & Developing Countries Clinical Trials Partnership (EDCTP), confirm a favorable efficacy and safety profile for arpraziquantel in children 3 months to 6 years of age, affected by this neglected tropical disease.

Schistosomiasis is one of the most damaging parasitic diseases, affecting the lives of around 240 million people, and is highly prevalent in sub-Saharan Africa. The drug praziquantel – the current standard treatment developed in the 1970s – is safe, effective, and available for school-aged children and adults. At present, around 50 million preschool-aged children have been left untreated in public health programs primarily due to the lack of an appropriate child-friendly formulation of the drug.

Derived from praziquantel, arpraziquantel is an orally dispersible tablet (dissolves in the mouth). It was developed by Astellas Pharma Inc. in Japan, subsequently optimized by Merck in Germany and transferred for clinical manufacturing to Farmanguinhos in Brazil. The new tablet is small, has appropriate taste properties, can be taken with or without water, and withstands the hot and humid challenges presented by a tropical climate.

Kio Yamabe, Acting CEO of the GHIT Fund said: *"Having partnered with the Pediatric Praziquantel Consortium since 2013, we believe that international collaborations like this are key to addressing the burden of major infectious diseases in the developing world. The successful joint development of arpraziquantel by Consortium partners Astellas, Merck, and Farmanguinhos embodies our unwavering commitment to drive Japanese innovation and technology through global partnerships."*

The successful completion of the Phase III trial has been a consolidated effort of strong and experienced in-country partners – the Kenya Medical Research Institute and Université Félix Houphouet-Boigny – with the Swiss Tropical and Public Health Institute overseeing the trial management. Merck acted as trial sponsor, ensuring that the necessary quality standards and regulatory requirements from authorities such as EMA were addressed. Expert input, including from the World Health Organization (WHO), has supported the development of the program.

Dr Michael Makanga, Executive Director, EDCTP said: *"With the completion of the Phase III trial, the Pediatric Praziquantel Consortium demonstrates that balanced North-South collaboration with complementary expertise, bidirectional knowledge sharing, and mutual trust, is a key success factor to develop and deliver safe and affordable treatments for neglected tropical diseases, such as schistosomiasis."*

The rationale for the study was based on data gathered from the clinical Phase I study in adult volunteers, a taste study in children 6-11 years of age, and a Phase II dose-finding study in *Schistosoma mansoni*-infected children 3 months to 6 years of age, conducted in African countries.

In the completed Phase III trial, children aged 3 months to 6 years infected with *S. mansoni* or *S. haematobium* were enrolled in different age groups and treated with a single dose of arpraziquantel. High efficacy was observed with cure rates close to or above 90% for *S. mansoni* (at a dose of 50 mg/kg) and *S. haematobium* (at a dose of 60 mg/kg). The primary endpoint of clinical cure, defined as no parasite eggs in the stool (*S. mansoni*) 17 to 21 days after treatment or urine (*S. haematobium*) 17 to 21 days and additionally 35 to 40 days after treatment, met the pre-specified success criteria. Arpraziquantel treatment at both doses demonstrated favorable safety, tolerability and improved palatability among preschool-aged children. No new potential risks or safety concerns were identified.

With the full clinical development phase successfully completed, the program has entered the regulatory filing stage, while preparing for the potential delivery of arpraziquantel through the Consortium's dedicated access program, ADOPT.

On behalf of the Consortium, Merck intends to apply for a scientific opinion by EMA under the EU-M4all procedure for high-priority medicines for human use intended for markets outside the European Union. A positive opinion by EMA would facilitate the inclusion of arpraziquantel in the WHO list of prequalified medicinal products, as well as regulatory approvals in endemic countries.

Peter Guenter, Member of the Executive Board of Merck and CEO of Healthcare, said:
"With this milestone, we continue our commitment to eliminating schistosomiasis and ensuring all people affected by this neglected tropical disease have access to a life-saving therapy. Together with our Consortium partners, we are steadfast in our vision to bring new hope to the world's most vulnerable populations."

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For the media
For more information and interview requests, please send an email to
info@pediatricpraziquantelconsortium.org

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Notes to Editors

1. About schistosomiasis

   Schistosomiasis (also known as bilharzia) is one of the most prevalent parasitic diseases in sub-Saharan Africa, caused by parasitic flatworms called schistosomes, of which *Schistosoma mansoni and S. haematobium* are the two major species. The disease affects almost 240 million people[1], mainly in communities without access to safe drinking water and with poor sanitation, with an estimated number of deaths of about 200,000[2] per year. The parasites live within freshwater snails and infect humans by penetrating the skin. The disease can lead to chronic inflammation of the organs, which can be fatal but also to anemia, stunted growth, and impaired learning ability with devastating consequences for the lives of the young children.

2. About arpraziquantel and preceding clinical trials

   Praziquantel, the current standard treatment against schistosomiasis, is a racemic mixture composed of the R-praziquantel and S-praziquantel enantiomers in a 1:1 ratio. The cidal activity resides in the R-praziquantel enantiomer (as shown *in vitro* and in animal experiments[3]) whereas the S-praziquantel enantiomer was suggested to be largely responsible for the bitterness of the commercial formulation. Arpraziquantel, the new pediatric enantiopure R-praziquantel solid dosage form under investigation has been designed to be smaller, exhibit an improved palatability and be orally dispersible compared with the current commercial formulation to ensure acceptability by preschool-aged children.[4] It also withstands the challenges presented by a tropical climate.

   The clinical program was set up in line with EMA recommendations for pediatric development. It was designed with the support of regulatory authorities and a panel of international experts, including clinicians from endemic countries. The R-praziquantel formulation and the target age group were new and required a full clinical development program:

   - Two **phase I** bioavailability studies in healthy adult volunteers were performed in South Africa with the aim of determining the pharmacokinetic properties of the Racemate (Rac)-PZQ and arpraziquantel formulation candidates in comparison to the current Cesol 600 mg PZQ commercial racemate tablet formulation. The pharmacokinetics of the two formulation candidates was characterized and both formulations showed a good safety profile and acceptable palatability. The studies were completed in 2015.
   - A **swill-and-spit taste study** was performed in 2015 in Tanzanian children (age 6-11 years) to compare the "overall palatability" of the arpraziquantel and Racemate PZQ ODT formulations with the current Cesol 600 mg PZQ commercial racemate tablet formulation.
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[1] http://www.who.int/schistosomiasis/disease/en/
[2] https://www.who.int/en/news-room/fact-sheets/detail/schistosomiasis
[3] Wu MH, et al. (1991) Comparative efficacy of levo-praziquantel and praziquantel in treatment of schistoso miasis japonica at a single dose. Chin Med J (Engl) 104(9):732-5
[4] Mahende MK, et al. (2021) Comparative palatability of orally disintegrating tablets (ODTs) of Praziquantel (L-PZQ and Rac-PZQ) versus current PZQ tablet in African children: A randomized, single-blind, crossover study. PLoS Negl Trop Dis 15(6): e0007370. https://doi.org/10.1371/journal.pntd.0007370

The study demonstrated that the tastes of the arpraziquantel and the Rac-PZQ ODT tablets were improved compared to the bitter taste of Cesol tablets.

- A **phase II** dose-finding study was performed in Côte d'Ivoire in *S. mansoni*-infected children of different ages (range 3 months to 6 years) from 2016-2018. The study confirmed the formulation (arpraziquantel) and the dose to be pursued by the Consortium until registration.

3. About the confirmatory multicenter open-label Phase III study in Côte d'Ivoire and Kenya

This was a multicenter open-label **Phase III** study of arpraziquantel that took place in Côte d'Ivoire and Kenya between 2018 and 2021. Study participants were assigned to 1 of 4 cohorts based on age (infants and children 3 months to 6 years of age) and *Schistosoma* species of infection. On Day 1, the participants received a single treatment dose of arpraziquantel 50 mg/kg. The study included 2:1 randomization of children 4 to 6 years of age infected with *S. mansoni* (Cohort 1, n= 150) to the arpraziquantel treatment (Treatment group 1a) or the control treatment (40 mg/kg commercial praziquantel crushed tablets, Treatment group 1b). *S. mansoni*-infected children 2 to 3 years of age (Cohort 2, n= 30), *S. mansoni*-infected children 3 to < 24 months of age (Cohort 3, n= 18) and *S. haematobium*-infected children 3 months to 6 years of age (Cohort 4, n= 90).

The primary efficacy outcome measure was clinical cure defined as no parasite eggs in the stool 17 to 21 days after treatment for *S. mansoni* and in urine for *S. haematobium*. Egg reduction rate (ERR) from pre-treatment to 17 to 21 days after treatment, using parasite egg counts was included as the secondary efficacy outcome measure. Safety and tolerability assessments consisted of occurrence, nature, severity and outcome of adverse events, occurrence of treatment-related adverse events and changes in laboratory safety parameters and vital signs.

To conform with the clinical protocol, an interim analysis of the first 30 patients included in cohort 4 was performed. The analysis revealed a sub-optimal cure rate of arpraziquantel in *S. haematobium*-infected children, but a strong egg reduction rate. Upon recommendation of the independent Data Monitoring Committee (IDMC), the dose administered to the remaining 60 participants in Cohort 4 was increased to 60 mg/kg and an additional and later urine sampling point was included.

4. EU-M4all[5]

Through the EU-M4all procedure, the European Medicines Agency (EMA), in cooperation with the World Health Organization (WHO), can provide scientific opinions on high priority human medicines, including vaccines, that are intended for markets outside of the European Union (EU). The procedure was previously known as the Article 58 procedure, as the legal basis is Article 58 of Regulation (EC) No 726/2004.

[5] EU-M4all (europa.eu)

5. About the Pediatric Praziquantel Consortium

The Pediatric Praziquantel Consortium is an international not-for-profit partnership that aims to reduce the global disease burden of schistosomiasis by addressing the medical needs of infected preschool-aged children. Its mission is to develop, register and provide access to a suitable pediatric praziquantel formulation for treating schistosomiasis in this age group. For more information, visit the Consortium website: www.pediatricpraziquantelconsortium.org

6. Consortium Partners

- **Merck** (Germany) leads the clinical development program and provides expertise and support from different areas: preclinical, clinical, drug substance/drug product development and manufacturing, regulatory and access. Merck is the sponsor of the clinical trials. www.merckgroup.com
- **Astellas Pharma Inc.** (Japan) has developed the new pediatric PZQ formulations, and provides expert advice on clinical development in children, and pharmacokinetic modeling. www.astellas.com
- **The Swiss Tropical and Public Health Institute (Swiss TPH)** (Switzerland) is a world-leading institute in global health with a particular focus on low- and middle-income countries. Swiss TPH uniquely combines research, education and services at local, national and international level, and has extensive experience in helminths biological and pharmacological research; epidemiology; and clinical research in endemic regions. Besides its role in the clinical development program, Swiss TPH is co-leading the Consortium ADOPT program. www.swisstph.ch/en
- **Lygature** (The Netherlands), a not-for-profit foundation, acts as the independent coordinator of the Consortium, providing governance in terms of progress, finance and collaboration. Since 2006, Lygature has supported close to 100 public-private partnerships in the field of life sciences & health, including poverty-related diseases. www.lygature.org
- **Farmanguinhos** (Brazil), the federal governmental pharmaceutical laboratory of the Fiocruz Foundation in Brazil, brings unique expertise to producing and distributing the new pediatric formulation product in endemic countries. www.far.fiocruz.br
- **The SCI Foundation** (United Kingdom) is a non-profit organisation that works in partnership with Ministries of Health in sub-Saharan African countries supporting and facilitating sustainable public health programmes that reduce the impact of preventable diseases like schistosomiasis and soil-transmitted helminthiasis. SCI Foundation is co-leading the Consortium ADOPT program. www.schistosomiasiscontrolinitiative.org
- **Kenya Medical Research Institute** (Kenya) provides expertise on local disease epidemiology, clinical trials and clinical care and was responsible for conducting the clinical phase III trial in Kenya according to Good Clinical Practice and national and local regulatory and ethics standards. www.kemri.org
- **Université Félix Houphouët-Boigny** (Côte d'Ivoire) was involved in the clinical phase II trial of the pediatric praziquantel formulation. It provides expertise on local disease epidemiology, clinical trials and clinical care and was responsible for the clinical phase III trial in Côte d'Ivoire according to Good Clinical Practice and national and local regulatory and ethics standards. www.univ-fhb.edu.ci

- **Klinikum rechts der Isar der Technischen Universität München (TUM)** (Germany) represented by the Center for Global Health provides multidisciplinary expertise and partnership in the field of Neglected Tropical Diseases in several countries of the global South. www.tum.de
- **Ministry of Health Côte d'Ivoire** has specific expertise regarding the design and implementation of the access strategy and will ensure a smooth future roll-out of arpraziquantel in Côte d'Ivoire. www.sante.gouv.ci
- **African Institute for Health and Development (AIHD)** has specific expertise regarding implementing evidence-based programming, conducting research, training and advocacy on development issues with contextual relevance to the African continent. www.aihdint.org

Other collaborators that contribute to the mission of the Pediatric Praziquantel Consortium:

- **Makerere University School of Public Health** (Uganda) provides the expertise for the social science research conducted in Uganda. https://sph.mak.ac.ug/
- **Ministry of Health Kenya, Division of Vector Borne and NTDs** has specific expertise regarding the design and implementation of the access strategy and will ensure a smooth future roll-out of arpraziquantel in Kenya. www.health.go.ke
- **Ministry of Health Uganda, Vector Borne and NTDs Control Division** has specific expertise regarding the design and implementation of the access strategy and will ensure a smooth future roll-out of arpraziquantel in Uganda. www.health.go.ug

7. Acknowledgement of support

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