14 December 2023
EMA/18898/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Arpraziquantel

International non-proprietary name: Arpraziquantel

Procedure No. EMEA/H/W/004252/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI	Acceptable intake
ALT	Alanine transferase
AST	Aspartate transferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CMC	Chemistry, Manufacturing and Controls
CNS	Central nervous system
CR	Cure rate
CrCL	Creatinine clearance
CSR	Clinical study report
CV%	Coefficient of variation
CVMP	Committee for Veterinary Medicinal Products
CYP	Cytochrome P450
D-PZQ	D-Praziquantel
DDI	Drug-drug interactions
DMON	2,2-dimethoxy ethylamine
DP	Drug product
DS	Drug substance
DS SM	Drug substance starting material
eGFR	Glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
ERR	Egg reduction rate
ERR_A	Egg reduction rate per arithmetic mean
ERR_G	Egg reduction rate per geometric mean
EU	European Union
FDA	Food and Drug Administration
FT-IR	Fourier-transform infrared
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HPLC	High-performance liquid chromatography
HR ESI MS	High resolution-electrospray ionization mass spectrometry
ICH	International Conference on Harmonization
ICPEMC	International Commission for Protection Against Environmental Mutagens and Carcinogens

IDMC	Independent Data Monitoring Committee
iERR	Individual egg reduction rate
INN	International non-proprietary name
L-PZQ	Levo-Praziquantel, L-Praziquantel
LD_{50}	Lethal dose 50% – the dose causing lethality in 50% of animals
LDPE	Low-density polyethylene
LTL	Less than lifetime
MDD	Maximum daily dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MSA	Methanesulfonic acid
NF	National Formulary
NMR	Nuclear magnetic resonance
NOAEL	No-observed-adverse-effect levels
ODT	Orodispersible tablet
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
POC-CCA	Point-of-care circulating cathodic antigen
popPK	Population PK
PP	Per-protocol
PPQ	Process performance qualification
PQ-A	2-chloro-N-(2-phenylethyl) acetamide
PQP	Prequalification of Medicines Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSAC	Preschool-aged children
PSD	Particle size distribution
PSUR	Periodic safety update report
PSUSA	PSUR single assessment
PT	Preferred term
PZQ	Praziquantel
R-(-)-PZQ	R-(-)-Praziquantel
R-PZQ	R-Praziquantel
rac-PZQ	Racemic praziquantel
RH	Relative humidity
S-(+)-PZQ,	S-(+)-Praziquantel
S-PZQ	S-Praziquantel
SAE	Serious adverse event
SD	Standard deviation
SM	Starting material
SmPC	Summary of Product Characteristics
SOC	System organ class
TDI	Time-dependent inhibitors
TEAE	Treatment-emergent adverse event
TPGS	d-α-tocopherol polyethylene glycol succinate
$TRPM_{PZQ}$	Transient receptor potential melastatin ion channel
USA	United States of America
USP	United States Pharmacopoeia
VAS	Visual analogue scale
Vc/F	Apparent volume of distribution
WHO	World Health Organization
XRPD	x-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Europe B.V. submitted on 11 November 2022 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Arpraziquantel.

The eligibility by the World Health Organisation (letter dated 22 September 2021) was agreed upon by the CHMP on 14 October 2021.

Arpraziquantel will exclusively be intended for markets outside the European Union.

The applicant initially applied for the following indication: *treatment of schistosomiasis (Schistosoma mansoni, Schistosoma haematobium) in children aged 3 months to 6 years and weighing at least 5 kg*.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Scientific advice

Scientific advice on the clinical development programme was obtained from EMA and the WHO. CHMP scientific advice was obtained on several occasions and covered quality, non-clinical, and clinical aspects. Clinical advice focused on the design of the planned (and later ongoing) pivotal Phase 3 study.

Phase 3 study (MS200661-0003) to demonstrate the efficacy and safety of arpraziquantel in Schistosoma-infected children 3 months to 6 years of age, including a 2:1 randomised, controlled cohort of *S. mansoni*-infected children 4 to 6 years of age treated with arpraziquantel (50 mg/kg) or commercial rac-PZQ (Biltricide). A separate, non-randomised cohort of children 3 months to 6 years of age infected with *S. haematobium* was treated with arpraziquantel 50 or 60 mg/kg.

There were four requests for CHMP scientific advice between 2017 and 2022.

In 2017, the questions covered aspects of quality, non-clinical and clinical development. At that time, Phase 2 was ongoing. This had a primary efficacy endpoint of eradication rate, which was considered acceptable.

The applicant proposed a Phase 3 study with no reference (licensed racemate) group. The CHMP considered it not possible to interpret an uncontrolled Phase 3 trial in children aged from 3 months to <6 years without including a parallel randomised control group. However, since there is no approved comparator for children aged <4 years, the CHMP recommended a randomised comparison vs. standard of care (i.e. best guess racemic PZQ dosing and using crushed tablets as needed) in children aged from 4-<6 years infected with *S. mansoni* for whom there are some dose recommendations

available. The applicant should compare the point estimates for eradication and the 95% confidence intervals around the estimates. If this randomised comparison in 4-6 year-olds with *S. mansoni* supports the test regimen, it could be acceptable that there is no control group for the younger children infected with *S. mansoni* or the *S. haematobium* cohort. The CHMP agreed with clinical cure (eradication) as the primary endpoint in Phase 3.

In 2018, the applicant proposed the 50 mg/kg dose for Phase 3 with a plan to explore 60 mg/kg for *S. haematobium*, depending on results. The CHMP commented on ensuring that the banded mg/kg dosing resulted in no less than 45 mg/kg in any individual when the target dose was 50 mg/kg. The Phase 3 study was revised to include a Biltricide 40 mg/kg dose group as a control in children aged 4-6 years. The CHMP preferred 3x20 mg/kg of racemate but accepted 40 mg/kg subject to justification that this was standard of care in the countries where the study was to be conducted.

In 2020, the difficulty in enrolling preschool-aged children (PSAC) <2 years of age was highlighted. The CHMP agreed that a lower bound of the 95% CI around the observed cure rate that was >70% could be accepted provided that the efficacy in Cohort 1 was deemed to be acceptable and there were no major safety concerns with the 50 mg/kg dose.

In 2021, the applicant proposed combined evaluation of cure rate (CR) and egg reduction rate (ERR) in the *S. haematobium* cohort. The CHMP did not agree and recommended setting a criterion based on a 70% lower bound of the 95% CI around the CR and/or adding a control arm for the *S. haematobium* cohort.

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
14 December 2017	EMEA/H/SA/3674/1/2017/PED/III	Dieter Deforce, Mair Powell
28 June 2018	EMEA/H/SA/3674/1/FU/1/2018/PED/II	Dieter Deforce, Mair Powell
17 September 2020	EMEA/H/SA/3674/1/FU/2/2020	Mair Powell, Ewa Balkowiec-Iskra
19 November 2020	EMEA/H/SA/3674/1/FU/2/2020 Clarification letter	Mair Powell, Ewa Balkowiec-Iskra
20 May 2021	EMA/SA/0000051359	Mair Powell, Sara Galluzzo

The applicant received scientific advice on the development of arpraziquantel for the treatment of schistosomiasis (due to *S. mansoni*, *S. haematobium*) in infants, toddlers and children aged from 3 months to 6 years from the CHMP on 14 December 2017 (EMEA/H/SA/3674/1/2017/PED/III). The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Designation of drug substance starting materials.
- Classification of L-praziquantel as a not new active substance.
- Chemistry, manufacturing, and controls (CMC) strategy to bridge between the current formulation of drug product for Phase 2 and considered formulation of drug product for Phase 3 and commercial supply.

- Adequacy of the non-clinical development programme.
- Design of a Phase 3, open-label, single-arm trial to demonstrate the efficacy and safety of a single dose of the new praziquantel oral dispersible tablet in children age 2 to 6 years and infants and toddlers age 3 to 24 months infected with *S. mansoni* (intestinal schistosomiasis), and in children age 3 months to 6 years infected with *S. haematobium* (urinary schistosomiasis) including single-arm design, primary and secondary efficacy, and PK endpoints, study population, dose selection across different age groups.
- Need for a drug-drug interaction study.
- Adequacy of the overall clinical development programme.

The applicant received scientific advice on the development of arpraziquantel for the treatment of schistosomiasis (due to *S. mansoni*, *S. haematobium*) in infants, toddlers and children aged from 3 months to 6 years from the CHMP on 28 June 2018 (EMEA/H/SA/3674/1/FU/1/2018/PED/II). The Scientific Advice pertained to the following Clinical aspects:

- Design of a Phase 3, open-label, efficacy and safety study of L-praziquantel oral dispersible tablets (L-PZQ DT) in Schistosoma-infected children 3 months to 6 years of age with a 2:1 randomized, controlled cohort of *Schistosoma mansoni*-infected children 4 to 6 years of age treated with L-PZQ DT or Biltricide including dose selection, primary efficacy endpoint and its statistical analysis.

The applicant received scientific advice on the development of arpraziquantel for the treatment of schistosomiasis (due to *S. mansoni*, *S. haematobium*) in infants, toddlers and children aged from 3 months to 6 years from the CHMP on 17 September 2020 (EMEA/H/SA/3674/1/FU/2/2020/PED/III). The scientific advice pertained to the following quality and clinical aspects:

- Synthesis process of arpraziquantel drug substance.
- Dissolution medium for routine quality control testing of the drug product.
- Qualification threshold for non-mutagenic organic impurities in arpraziquantel drug substance.
- Slow recruitment seen for *S. mansoni* infected children aged 3 to 24 months (Cohort 3 of the ongoing Phase 3 study) and proposal to adjust the sample size in this group.

The applicant received scientific advice on the development of arpraziquantel for the treatment of schistosomiasis (due to *S. mansoni*, *S. haematobium*) in infants, toddlers and children aged from 3 months to 6 years from the CHMP on 20 May 2021 (EMA/SA/0000051359). The scientific advice pertained to the following clinical aspects:

- Combined evaluation of cure rate (CR) and egg reduction rate (ERR) for the efficacy assessment of arpraziquantel in *S. haematobium* infected children in the ongoing pivotal Phase 3 study (MS200661-0003).
- Extension of the pivotal Phase 3 study (MS200661-0003) with an additional cohort that would include S*. haematobium* infected children aged from 3 months to 6 years in a double arm design randomized 1:1 to arpraziquantel and Biltricide.

1.4. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Jean-Michel Race

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	11 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	06 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 July 2023
The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two sites involved in the pivotal clinical trial in Kenya and Ivory Coast between 26 June and 07 July 2023. The outcome of the inspection was issued on 12 October 2023.	12 October 2023
– A GMP inspection at the manufacturer of the drug product in Brazil between 14 August and 18 August 2023. The outcome of the inspection was issued on 6 November 2023.	6 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 November 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Arpraziquantel on	14 December 2023

2. Scientific discussion

2.1. Problem statement

The applicant proposed that Arpraziquantel (L-PZQ) 150 mg dispersible tablets should be indicated for the treatment of schistosomiasis caused by *Schistosoma mansoni* or *Schistosoma haematobium* in children aged 3 months to 6 years (and weighing at least 5 kg).

2.1.1. Disease or condition

Schistosomiasis (bilharzia) results from infection by parasitic flatworms (blood flukes). The infection is prevalent in tropical and subtropical areas without potable water and adequate sanitation. More than 90% of affected areas are in Africa. The disease comprises an acute phase that progresses to a severe chronic inflammatory disease and is endemic in 78 developing countries, with moderate to high transmission kinetics in 51 of these countries. The WHO estimated that 779 million people are at risk of acquiring a Schistosoma infection and in 2019 more than 236 million people required preventative chemotherapy for schistosomiasis.

2.1.2. Epidemiology and screening tools/prevention

The prevalence of schistosomiasis in children < 14 years of age in endemic countries is high, accounting for approximately 50% of infections. A recent study published in 2020 found a pooled prevalence estimate of 19% for any Schistosoma species in pre-school aged children (PSAC) in sub-Saharan Africa (Kalinda 2020). Studies in Nigeria, Ghana and Uganda (Odogwu 2006) identified infection with *S. mansoni* and *S. haematobium* in very early childhood. In a study in Niger, the prevalence of schistosome infection among children < 5 years of age exceeded the recommended threshold for large-scale administration of racemic praziquantel (rac-PZQ) (Garba 2010).

Approximately 20 million people suffer severe consequences from the disease, with approximately 20,000 to 200,000 annual deaths. According to the WHO, this rate should have decreased considerably over the past decade with the increase in large-scale preventative chemotherapy campaigns. However, a major limitation to schistosomiasis control has been the limited availability of rac-PZQ and lack of a paediatric formulation suitable for young children. Data for 2020 show that only 31.9% of people requiring treatment were reached globally, with 44.9% of school-aged children requiring preventive chemotherapy for schistosomiasis being treated. The number of treatments and coverage was 27.1% lower in 2020 (76.9 million treated) than in 2019 (105.5 million treated), due mainly to control measures for the COVID-19 pandemic, which resulted in suspension of preventative chemotherapy in many countries and endemic areas.

2.1.3. Aetiology and pathogenesis

Schistosomiasis presents mainly in intestinal or urogenital forms and is caused by six main Schistosoma species. Intestinal schistosomiasis is caused by *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis* (and related *S. intercalatum*) while urogenital schistosomiasis is caused by *S. haematobium*. The most prevalent species in sub-Saharan Africa are *S. mansoni* and *S. haematobium*.

The life cycle of the species that infect humans involves a snail development phase and a human phase. The adult worms develop in humans and fertilised eggs are excreted into the environment.

After completion of development within snails, the cercariae enter water sources. Infection of humans occurs via skin penetration during water exposures (e.g. bathing, agricultural work, fishing work). The disease manifestations in humans depend on whether adult worms reside in the mesenteric veins (*S. mansoni* and *S. japonicum*) or in the bladder venous plexus (*S. haematobium*). Trapping of some eggs in the organs (e.g. bowel, liver, lung, bladder, CNS) produces local symptoms through formation of granulomas resulting from the host inflammatory response.

This application concerns only *S. mansoni* and *S. haematobium*.

2.1.4. Clinical presentation

The clinical manifestations of schistosomiasis can be acute (Katayama syndrome) or chronic.

The incubation period of Katayama syndrome is typically 14 to 84 days. Symptoms may include fever, headache, myalgia, rash and respiratory (asthma-like) symptoms.

For *S. mansoni*, clinical manifestations of chronic disease are blood in the stool, constipation, diarrhoea and chronic inflammation, which can cause bowel wall ulceration, fibrosis, hyperplasia, polyposis and portal hypertension accompanied by hepatosplenomegaly. Leukocytosis is frequent and eosinophilia occurs in almost 70% of infected patients.

For *S. haematobium*, clinical manifestations of chronic disease include dysuria and haematuria, as well as injury to the genital tract and susceptibility to other infections, which can lead to bladder cancer in the long term.

In children, schistosomiasis is associated with severe consequences, including impairment of growth, cognition, development and physical fitness. There is also morbidity related to anaemia, malabsorption and hepatosplenic dysfunction. For example, a study of Brazilian school children with mild- to moderate-intensity schistosome infections (< 400 *S. mansoni* eggs/g stool) found that those treated for schistosome infection with oxamniquine for 1 year had greater measurements for weight, triceps skinfold thickness, mid-arm circumference, arm muscle area and BMI vs. those who were untreated. A meta-analysis of 30 studies reporting on 38,992 children aged 5-19 years found that schistosoma infection or non-dewormed status was associated with educational, learning and memory deficits.

2.1.5. Management

Racemic praziquantel (rac-PZQ) was developed in the 1970s. It has been registered and marketed since 1980 as an anthelminthic drug (e.g. Biltricide or Cysticide) and is well established as the standard treatment for schistosomiasis. Preventive chemotherapy by mass drug administration with annual or biannual single doses of rac-PZQ is the cornerstone of the control of schistosomiasis since the WHO resolution in 2001, which urged endemic countries to treat at least 75% of all at-risk children of school age by 2010. Rac-PZQ 600 mg tablets are included in the WHO list of essential medicines for the treatment of schistosomiasis in adults and school-aged children at an annual or biannual single dose of 40 mg/kg according to the WHO Guideline for treatment and control of schistosomiasis. This strategy is recommended for all at-risk people aged ≥ 2 years of age. Praziquantel is also used to treat individual children < 2 years of age who have schistosomiasis. Currently, there is no acceptable paediatric formulation for pre-school age children (PSAC).

Table 1 Praziquantel Enantiomers and Metabolites

Generic Name	Abbreviations	Alternate Names	MSC# (refers only to drug substance synthesized by the Sponsor)	Terminology Used in this Document
Praziquantel	PZQ rac-PZQ	Racemic Praziquantel Tradename: Biltricide®, Cisticid®, Cysticide®, Cesol®	MSC1028703A	rac-PZQ
Enantiomers				
Levo-Praziquantel	L-PZQ R-PZQ	INN: Arpraziquantel R-(-)-Praziquantel R-Praziquantel, R-Enantiomer, L-Praziquantel, L-Enantiomer	MSC2499550A	Arpraziquantel, L-PZQ, R-(-)-PZQ
Dextro-Praziquantel	D-PZQ, S-PZQ	S-(+)-Praziquantel, D-Praziquantel, D-Enantiomer, S-Enantiomer	MSC2499551A	S-(+)-PZQ
Metabolites[a]				
Cis-4-Hydroxy-Levo-Praziquantel	Cis-4-OH-R-PZQ	Cis-4-OH-arpraziquantel	MSC2527113A	Cis-4-OH-arpraziquantel
Trans-4-Hydroxy-Levo-Praziquantel	Trans-4-OH-R-PZQ	Trans-4-OH-arpraziquantel	MSC2527114A	Trans-4-OH-arpraziquantel
Cis-4-Hydroxy-Dextro-Praziquantel	Cis-4-OH-S-PZQ	Cis-4-OH-arpraziquantel	MSC2527733A	Cis-4-OH-S-PZQ
Trans-4-Hydroxy-Dextro-Praziquantel	Trans-4-OH-S-PZQ	Trans-4-OH-arpraziquantel	MSC2527115A	Trans-4-OH-S-PZQ

a These main metabolites are identified for the racemic product and for the R- and S-enantiomers.

Commercially available rac-PZQ is composed of two enantiomers in a 1:1 ratio: R-(-)-PZQ (=L-PZQ) and S-(+)-PZQ. Arpraziquantel (R-[-]-PZQ) is the main biologically active form. The S-(+)-PZQ enantiomer has been reported to play an important role in the bitter taste of the drug and is not converted to R-(-)-PZQ *in vivo*. The marketed rac-PZQ tablets need to be divided, crushed and given with water for dosing in young children. The intense bitter taste risks under-dosing due to gagging or vomiting, with negative implications for treatment adherence. In 2010, the WHO recommended the development of a water dispersible PZQ formulation for appropriate treatment of PSAC.

2.2. About the product

In response to the issues noted above and the WHO recommendations, the Paediatric Praziquantel Consortium initially developed rac-PZQ and single active enantiomer (L-PZQ; arpraziquantel) paediatric formulations in the form of dispersible/orodispersible tablets (DT/ODTs). After Phase 1 and 2 results became available, the arpraziquantel 150 mg paediatric formulation was selected for Phase 3. The final product consists of Arpraziquantel 150 mg dispersible tablets (DTs).

The arpraziquantel DT formulation is approximately ¼ the size of current commercially available rac-PZQ tablets and is less bitter than rac-PZQ, resulting in improved palatability in PSAC. The 150 mg DTs are not to be divided and the recommended mg/kg doses (50 mg/kg for *S. mansoni* and 60 mg/kg for *S. haematobium*) are achieved by rounding of doses to approximate to the target mg/kg dose (see tables below from section 4.2 of the SmPC). Reflecting dosing in Phase 3, the SmPC instructs that the tablets are to be dispersed in water before ingestion (rather than being dispersed in the mouth) and are to be taken after a meal.

Table 2 Dosing for S. mansoni infection (target dose 50mg/kg)

***S. mansoni* infection, target dose 50 mg/kg**	
Body weight in kg	**Number of tablets**
5.0 - 6.9	2
7.0 - 9.9	3
10.0 - 12.9	4
13.0 - 16.9	5
17.0 - 22.9	7
23.0 - 30.0	9

Table 3 Dosing for S. haematobium infection (target dose 60mg/kg)

***S. haematobium* infection, target dose 60 mg/kg**	
Body weight in kg	**Number of tablets**
5.0 - 5.9	2
6.0 - 7.9	3
8.0 - 10.9	4
11.0 - 13.9	5
14.0 - 18.9	7
19.0 - 23.9	9
24.0 - 30.0	11

2.3. Type of application and aspects on development

Legal basis

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Specifically, the applicant seeks a scientific opinion under the EU-M4all procedure (based on Article 58 of Regulation (EC) No 726/2004), submitted in accordance with Article 8(3) of Directive 2001/83/EC, full-mixed application, known active substance.

New active substance status

Not applicable.

Orphan designation

Not applicable.

Information on paediatric requirements

Due to the legal basis for this application, no PIP was required.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as dispersible tablet containing 150 mg of arpraziquantel as active substance.

Other ingredients are: mannitol, starch pregelatinized, sodium starch glycolate type A, maize starch, sucralose, sodium stearyl fumarate, silica colloidal anhydrous, and vitamin E polyethylene glycol succinate.

The product is available in a high-density polyethylene (HDPE) bottle with polyethylene (PE) closure as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of the active substance is (11b*R*)-2-cyclohexanecarbonyl-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrazino[2,1-a]isoquinolin-4-one or(11b*R*)-2-(cyclohexanecarbonyl)-3,6,7,11b-tetrahydro-*1H*-pyrazino[2,1-a]isoquinolin-4-one corresponding to the molecular formula $C_{19}H_{24}N_2O_2$ It has a relative molecular mass of 312.42 g/mol and the following structure:

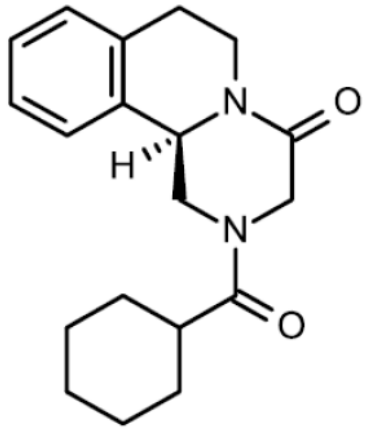


Figure 1 Active Substance Structure

The chemical structure was elucidated by a combination of nuclear magnetic resonance (NMR) spectroscopy, high resolution-electrospray ionization mass spectrometry (HR-ESI-MS) analysis, Fourier transform infrared (FT-IR) spectroscopy, UV-VIS spectroscopy, single crystal x-ray diffraction, x-ray powder diffraction (XRPD) and elemental analysis.

The active substance is a white to off-white slightly hygroscopic powder that is very slightly soluble in water.

The active substance is the *R* enantiomer of the Ph. Eur. monographed substance racemic praziquantel. Enantiopurity is routinely control in the specifications of the active substance.

A comprehensive polymorph screen has been carried out, confirming the hydrate form H2 as the only crystalline and thermodynamically stable morphic form.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

The active substance is synthesized in 7 main steps using well defined starting materials with acceptable specifications.

The process development and process validation completed by the active substance manufacturer supports their understanding and control of the synthesis. A systematic approach was used to evaluate, understand, and refine the process to identify critical material attributes (CMAs) of all used raw materials (active substance starting materials, reagents, solvents, and process aids) as well as of all process intermediates. Furthermore, the critical process parameters (CPPs) with potential effect on active substance CQAs were identified based on risk assessment.

The known and potential impurities have been discussed with respect to their fate and control. Any mutagenic impurities that may occur in the active substance have been demonstrated to be absent below 1 ppm.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Specification

The active substance specification includes tests for identification (FT-IR, HPLC), assay (HPLC), purity (HPLC), organic impurities (HPLC), *N*-Nitrosamine impurity (LC-MS), enantiomeric impurity (HPLC), residual solvents (HS-GC), water content (KF) and particle size distribution (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurities and assay testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (30 °C ± 2 °C/75% ± 5% RH) and for up to 6 months under accelerated conditions (40 °C ± 2 °C/75% ± 5% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* assay, purity, organic impurities, *N*-Nitrosamine impurity, enantiomeric impurity, and water content.

Each tested parameter complied with specification at all time points. No trends were observed under long term or accelerated conditions.

Stress stability studies were performed in two commercial scale batches. The photostability study was performed according to ICH guideline Q1B Stability Testing Photostability Testing of New Drug Substances and Product. Considering the results, the active substance is not considered as sensitive to light.

The results collected from the stress stability studies revealed the high sensitivity of the active substance towards dry heat, peroxidic oxidation, as well as hydrolysis under acidic and basic conditions. Humid heat turned out to have only slight impact on the stability of the active substance whereas no sensitivity to oxidative Cu(II) ions, hydrolysis under neutral conditions, and freezing and thawing could be seen. None of the tested conditions revealed an effect on the polymorphic form of the active substance. The water content and the enantiomeric purity underwent only slight changes when applying dry heat. Storage under humid heat only had an impact on the water content.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 month when stored below 30°C in the container closure system described.

2.4.3. Finished Medicinal Product

The finished product is presented as white to off-white, round, biconvex dispersible tablets.

The overall formulation development was guided by the EMA Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012). The strategy was to obtain a ready-to-use tablet formulation that can be administered as a dispersible tablet with an acceptable palatability (taste, smell, volume/size and texture) and safety for use in paediatric population.

The intended quality of the finished product was defined in the quality target product profile (QTPP), describing the design criteria and forming the basis for development, considering the route of administration, dose strength, dosage form, and stability.

The following key physicochemical properties of the active substance that could influence the performance of the finished product, its manufacturability, and stability were considered during development: solubility, water content, polymorphic form, crystal habit, and particle size distribution.

The QTPP was used to identify potential CQAs of arpraziquantel having an impact on the quality of the finished product. The impact of each active substance quality attribute on the manufacturability, safety, and efficacy of the finished product as well as on the finished product CQAs was evaluated. The criticality of the quality attributes was assessed and scored based on their severity (low, moderate, or high). A quality attribute was designated critical when it had at least a high severity score in one category or a moderate severity score in two categories.

As part of the process control strategy, normal operating ranges (NORs) and proven acceptable ranges (PARs) were established and are monitored or controlled during the manufacturing process.

The compatibility of the active substance with several commonly used excipients was studied during pharmaceutical development. Two compatibility tests were performed over the course of development using an accelerated stressing program with binary 1:1 mixtures of the active substance and each excipient. Based on the data provided, no negative influence of the selected excipients on the

performance of the finished product was observed. Therefore, the active substance is regarded as compatible with the excipients employed in the finished product.

Several types of excipients were evaluated by manufacturing small-scale batches: fillers for the inner and outer phase as well as different wet binders, disintegrants, lubricants and sweeteners. On the basis of the previously conducted excipient compatibility studies, excipients with high compatibility were preferably chosen. Since the finished product was known to be moderately sensitive towards oxidation, the commonly used antioxidants were included in the study as well. The applied concentrations of antioxidants were based on scientific literature and on concentrations used in other marketed formulations.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except vitamin E which is compliant with National Formulary standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The quality control (QC) dissolution method was developed taking into account the conditions recommended by the USP monograph for praziquantel tablets and also the physiochemical characteristics of the active substance in order to achieve sink conditions. All other parameters of the dissolution method are considered standard. The discriminatory power of the dissolution method was assessed and concluded that it is capable of detecting differences in tablets manufactured using active substance with an unacceptable particle size and in tablets exposed to conditions of high heat and humidity. Correlations with disintegration data and resistance to crushing are also made.

Manufacturing process development is described in sufficient detail. Manufacturing process development paralleled the formulation development which was modified to improve stability and processability and to accommodate process scale up. During process development trials, the process parameters were varied, and PARs were evaluated for most of the unit operations, however set-up points are defined. Furthermore, the process was transferred to the commercial manufacturing site and successfully scaled-up to commercial scale, showing suitable manufacturability, stability and process robustness as well as consistently delivering finished product of the desired quality.

Disintegration time is considered a CQA of the finished product and is tested as a release and stability parameter for compliance with the Ph. Eur. requirement of 3 minutes. The finished product is dispersed within 3 minutes in water, and is therefore suitable for dispersion in water before administration.

The primary packaging is a high-density polyethylene (HDPE) bottle with polyethylene (PE) closure. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site.

Further to a CHMP request, an inspection of the finished product manufacturer was completed. A GMP certificate has been issued, confirming that the site was considered to operate in general compliance with the principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572. Therefore, the issue was considered resolved.

The GMP status of the drug substance manufacturing site is supported by a declaration of GMP compliance from a designated quality representative of the site of drug product manufacture and local release (non-EEA) in Brazil.

The manufacturing process consists of 7 main steps. The process is considered to be a standard manufacturing process.

Arpraziquantel 150 mg dispersible tablets are manufactured using a standard wet granulation and tabletting process. Process validation will be performed on three consecutive batches at production scale. A process validation scheme has been provided. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), identification (IR, HPLC), assay (HPLC), degradation products (HPLC), *N*-nitrosamine impurity (LC-MS), dissolution (Ph. Eur.), disintegration (Ph. Eur.), identification of vitamin E (HPLC), content of vitamin E (HPLC), uniformity of dosage units (Ph. Eur.), uniformity of mass (Ph. Eur.), fineness of dispersion (Ph. Eur.), loss on drying (TGA), and microbial limits (Ph. Eur.) .

The following parameters have been omitted in the specifications of the finished product: dimensions, resistance to crushing, friability, enantiomeric purity, polymorphic form, and residual solvents. All the omissions have been justified and they were considered acceptable.

The specifications of the finished product were established based on the relevant ICH guidelines, pharmacopeial standards, results obtained from batch release, accelerated and long-term stability studies including primary stability batches, analytical variability as well as manufacturing variability and considering the critical quality attributes of the finished product.

There are no impurities specified with all impurities controlled according to the ICH Q3B Identification threshold.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

However, the AI initially proposed for nitroso-praziquanamine was not agreed and the applicant was asked to apply the AI of 1500 ng/day as per Appendix 1, of the EMA Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products, to set the appropriate limits in the finished product as a MO. The applicant agreed to update the proposed specification limits for the active substance and finished product in accordance with the published AI for nitroso-praziquanamine of 1500 ng/day. Therefore, this issue was considered resolved.

The applicant also proposed to use two batches manufactured with active substance containing a higher nitroso-praziquanamine AI temporarily to supply the market for up to 2 years. This proposal was not agreed. The limits were revised by the applicant accordingly. Therefore, this MO was considered resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurity and assay testing has been presented.

Batch analysis results are provided from 10 production and pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 48 months under long term conditions (30°C ± 2°C / 75% ± 5% RH) and for up to 6 months under accelerated conditions (40°C ± 2°C / 75% ± 5% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, dissolution, disintegration, content of vitamin E polyethylene glycol succinate, fineness of dispersion, loss on drying, and microbial limits. The analytical procedures used are stability indicating.

Test parameters under long term and accelerated conditions comply with the specification at all time points available. No trends were observed.

Stress stability studies were performed to deliver insights into the chemical and physical stability of the finished product. The studies included testing.

The photostability study was performed according to ICH guideline Q1B Stability Testing Photostability Testing of New Drug Substances and Product. Based on the results, the finished product is not considered as sensitive to light.

The results collected from the stress stability studies revealed the high sensitivity of the finished product towards peroxidic oxidation, dry heat, as well as hydrolysis under acidic and basic conditions. Humid heat turned out to have only slight impact on the stability of the finished product. None of the tested conditions revealed an effect on the polymorphic form. The water content and the enantiomeric purity underwent only slight changes when applying dry heat. Storage under humid heat did only have an impact on the water content. It can be concluded that no specific storage declaration is required for the DP based on the obtained results and in accordance with the EMA *Guideline on Declaration of Storage Conditions* (CPMP/QWP/609/96/ Rev 2). However, considering the climatic zone of the locations of the intended target population, the storage advice 'Do not store above 30 °C' is applied.

In-use stability studies are performed to establish a period of time during which the finished product can be used whilst retaining quality within an acceptable specification once the container is opened. The studies were designed taking into account the foreseen use of the finished product during mass drug administrations to treat affected populations. Results of the 60 days in-use stability are available for samples stored for 36 months of long-term storage. All results met the acceptance criteria and

were well within specification. No trends or influence of the applied storage conditions on the stability-indicating parameters were observed.

Based on available stability data, the proposed shelf-life of 4 years and 'do not store above 30°C' as stated in the SmPC (section 6.3) are acceptable. In-use shelf life after first opening is 60 days.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During evaluation, two major objections were raised by the CHMP in relation to GMP issues on the manufacturing site of the finished product, and risk assessment and control of nitrosamines. The applicant's responses to the MOs were considered satisfactory and these issues were considered to be resolved, as explained above.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Pharmacology

The applicant presented a literature review of the known pharmacology of racemic praziquantel (rac-PZQ) in support of this scientific opinion for arpraziquantel. The mechanism of action of rac-PZQ (and thus arpraziquantel) is tegumental disruption on schistosoma and subsequent induction of muscular paralysis. Activation of a transient potential melastatin ion channel in schistosomes leads to intracellular calcium entry and paralysis. This leads to migration of the worms from the mesenteric vein to the liver.

Arpraziquantel has significantly greater potency over S-(+)-PZQ and the major metabolite trans-4-OH-arpraziquantel. Following paralysis, which is reversible, hepatic shift occurs. In mice, arpraziquantel was significantly more potent at reducing worm burden compared to its enantiomer, and metabolites, suggesting arpraziquantel is the main effector in the anti-parasitic activity of rac-PZQ. However, there

is evidence that trans-4-OH-arpraziquantel may also contribute to arpraziquantel activity, as observed in clinical trials (discussed in relevant sections).

No secondary pharmacodynamic studies were conducted for arpraziquantel. Formal safety pharmacology studies were conducted with rac-PZQ. Original study reports were not available. High IV doses of rac-PZQ were associated with central nervous system observations (e.g. convulsions) were not considered relevant for humans, which is agreed. The arrhythmogenic effects of rac-PZQ appear to be related to S- (+)-PZQ activity and thus not relevant for this application. There were no observations in the repeat dose toxicity studies (including the GLP-bridging study) that suggest any clinically relevant effects on cardiovascular, respiratory, CNS or other system effects, nor has there been any signal in clinical trials thus far.

The pharmacology package was considered sufficient to support the application for arpraziquantel in the proposed indication.

2.5.2. Pharmacokinetics

The pharmacokinetic (PK) evaluation of arpraziquantel is primarily supported with data on the PK data available for rac-PZQ. Studies were performed in a number of nonclinical species including mouse, rat and dog and supported by clinical PK for rac-PZQ. The measurement of arpraziquantel was appropriately validated and employed in the bridging toxicity studies (2-week non-GLP and 4-week GLP). The method developed for measuring the main metabolite, trans-4-OH-arpraziquantel, did not meet the 'selectivity' criteria at the lower range of concentrations due to interference from cis-4-hydroxy-praziquantel and s-trans-4-hydroxy-praziquantel enantiomers. However, only interference from cis-4-OH-arpraziquantel may be relevant for quantification of trans-4-OH-arpraziquantel concentrations since chiral inversion is not observed with arpraziquantel. The interference from cis-4-OH-arpraziquantel was only observed at the QC-L level (15.0 ng/mL) of trans-4-OH-arpraziquantel. For the toxicokinetics measured during the 4-week pivotal GLP rat study the trans-4-OH-arpraziquantel levels were substantially higher at all time points with the exception of 24 h suggesting that only the values around this time point are likely to have been affected by the issue. Although the selectivity criteria was not met, the impact of the interference in the measured concentrations and toxicokinetic evaluation is likely minimal.

In terms of ADME in nonclinical species, rac-PZQ is highly absorbed (ranging 75-90%) and similar is expected for arpraziquantel. Clearance and volume of distribution data for rac-PZQ (in mice) indicate high clearance and low bioavailability after oral dosing. In repeat dose toxicology studies (see Toxicology section for detail), arpraziquantel exposure was higher in males and dose-proportional (in both sexes).

Arpraziquantel is moderately plasma protein bound, with an estimated free fraction of approximately 20% in nonclinical species and humans. Tissue distribution studies with rac-PZQ indicated target organs include the liver, kidney and intestine and brain exposure was reported to be 5-10% of plasma levels. Metabolism of arpraziquantel has been investigated in vitro and supplemented by in vivo studies with rac-PZQ. It is metabolised to mono-hydroxylated products with trans-4-OH-arpraziquantel being the predominant metabolite in humans, via the majority of CYP enzymes. While the IC50 is significantly lower (approximately 200-fold), trans-4-OH-arpraziquantel has lower plasma protein binding versus arpraziquantel and may contribute to clinical activity (based on higher unbound exposure) and formed from the metabolism of cis-4-OH-arpraziquantel, presumably via cytosolic enzymes (as transformation is observed in human hepatocytes and not human liver microsomes). Trans-4-OH-arpraziquantel is itself metabolized by CYP 1A1, 1A2, 2A6, 2C8 and 3A4 isoforms in recombinant systems. However, as trans-4-OH-arpraziquantel is stable in human hepatocytes the

fraction metabolized through each isoform is not known. Trans-4-OH-arpraziquantel has also been investigated in repeat dose toxicology studies (see relevant section for discussion) and is present at significantly higher levels than arpraziquantel in nonclinical species (72-fold mouse, 4-183-fold in rat) and humans 159-fold in PSAC in a clinical study. Trans-4-OH-arpraziquantel levels observed in clinical studies exposure measured in the pivotal toxicology study was similar to that observed following 50 mg/kg or 60 mg/kg dose in PSAC.

The metabolism of arpraziquantel has been investigated in dedicated *in vitro* studies and also previously assessed with rac-PZQ studies. The biotransformation of arpraziquantel or rac-PZQ has been extensively studied in vitro and in vivo with consistent results observed across species. The primary metabolites observed are hydroxylated (mono- and poly-hydroxylation) with subsequent glucuronidation and/or sulfation. However, the exact identification of most of these metabolites is unknown. Metabolism is the major elimination pathway in humans with > 80% of an oral dose of rac-[14C]-PZQ recovered as metabolites in urine. Unchanged rac-PZQ was observed at trace levels in urine. The primary mediators of arpraziquantel include CYP 1A2, 2C9, 2C19 and 3A4/5 isoforms contributing approximately equally to clearance. Arpraziquantel can also be metabolised by CYP3A7 to a limited extent; this enzyme is present in the foetal liver and expression gradually declines in the postnatal period with concomitant increases in CYP3A4 expression thus CYP3A7 is not anticipated to contribute significantly to arpraziquantel metabolism in children under the age of 1.

Additional studies were conducted to assess any potential effect of the S- (+)-PZQ enantiomer on arpraziquantel bioavailability when administered as rac-PZQ dispersible tablet (DT), as a result of lower than expected arpraziquantel bioavailability (based on physiologically based pharmacokinetics model predictions) when administered as arpraziquantel paediatric formulation and more than dose proportional increases in exposure in adults. There was no evidence of a significant effect on any CYP-mediated effects on clearance with or without the presence of S-(+)-PZQ. Thus, the mechanism underlying this observation is unclear. Studies on the excretion of rac-PZQ found that the main route of clearance is renal, ranging from 59-74% in nonclinical species and 80-84% in human urine.

Drug interaction potential was investigated for arpraziquantel and trans-4-OH-arpraziquantel. No induction of CYP 1A1/2 was observed at clinically relevant concentrations of rac-PZQ and arpraziquantel was observed to induce CYP3A4 mRNA and protein expression in transfected HepG2 cells. The potential for arpraziquantel to induce other CYP enzymes has not been tested and trans-4-OH-arpraziquantel has not been investigated for induction potential.

The potential for arpraziquantel and trans-4-OH-arpraziquantel to act as perpetrators of a drug-drug interaction has been evaluated in vitro against CYP isoforms, efflux transporter P-gp and hepatic uptake transporters OATP1B1, OATP1B3 and OCT1 and for rac-PZQ against hepatic or renal transporters OCT1, OCT2, OCT3, MATE1 and MATE2K. From this evaluation, the potential for arpraziquantel to be a clinically relevant reversible inhibitor of CYP isoforms can be excluded. A clinically relevant TDI with CYP 2D6 or 3A4 substrates cannot be excluded but is considered unlikely due to the weak effects observed. However, the potential for a clinically relevant DDI with drug transporters P-gp, OATP1B1, OATP1B3 and OCT1 could not be excluded at a theoretical maximum dose of 1800 mg to PSAC. Trans-4-OH-arpraziquantel is a weak in vitro inhibitor of efflux transporters P-gp and BCRP and hepatic uptake transporters OATP1B3 and OCT1 but does not inhibit OATP1B1. A study in dogs on the effect of grapefruit juice (CYP3A4 inhibitor) indicated an increase in rac-PZQ may be due to heightened metabolism at the levels of the small intestine. Clinical studies with rac-PZQ have also demonstrated concomitant administration of strong and moderate CYP inhibitors ketoconazole, grapefruit juice, cimetidine, and albendazole lead to AUC ratio increases up to 2-fold.

In summary, the pharmacokinetic evaluation of arpraziquantel indicate a similar profile for rac-PZQ and potential clinically relevant features of arpraziquantel and trans-4-OH-arpraziquantel have been identified.

2.5.3. Toxicology

The toxicology package submitted for arpraziquantel consists of a battery of studies conducted with rac-PZQ (non-GLP) supplemented by a 2-week non-GLP and a 4-week pivotal repeat-dose toxicity study bridging the toxicity assessment of rac-PZQ to arpraziquantel. The pivotal 4-week "bridging" repeat-dose toxicity study was conducted in compliance with GLP.

Single dose studies with rac-PZQ were performed in mice, rats, rabbits and dogs. An emetic effect prevented identification of the lethal dose in dogs but was greater than 2000 mg/kg in all other species thus the acute toxicity of arpraziquantel is limited. Repeat dose toxicity studies of up to 4 and 13 weeks in rats and dogs, respectively, were performed with rac-PZQ. Effects observed included transient signs of vomiting and depressed appetite in dogs and increased organ weights at high doses (rat: liver, kidney, spleen, heart, thyroid, and adrenals; dog: liver) which were without histological correlate and not considered to be adverse. In the pivotal bridging study the toxicological profile of rac-PZQ and arpraziquantel were comparable, however increases in serum and urinary calcium and serum inorganic phosphorus persisted in the recovery phase of arpraziquantel-treated animals.

Toxicokinetic evaluation revealed higher arpraziquantel levels in male rats and higher trans-4-OH-arpraziquantel exposure in female rats. The arpraziquantel exposure levels at the proposed NOAEL of 300 mg/kg was 5-9-fold greater than that observed clinically. The measured exposure on Day 1 of dosing to the trans-4-OH-arpraziquantel metabolite were in excess of those seen in the paediatric population for both C_{max} and AUC. There was no correlation between the exposure levels of trans-4-OH-arpraziquantel and the measured serum calcium, serum IP or urinary calcium levels. Furthermore, the increases in serum calcium and inorganic phosphorus levels were seen in the absence of any histopathological correlates.

No genotoxicity studies have been conducted with arpraziquantel. A number of non-GLP genotoxicity studies conducted with rac-PZQ at the time of that approval were submitted in support of this application. Some of them, while not conducted to GLP standards (as these were not in effect at the time of rac-PZQ registration), appear to be scientifically sound and the totality of the data do not indicate any potential mutagenicity or clastogenicity with rac-PZQ and by extension, arpraziquantel.

While a direct assessment of arpraziquantel in GLP-compliant studies would have been preferable, it was accepted that the genotoxic potential had been reliably evaluated at the time of registration of the racemic mixture. No carcinogenicity studies were conducted with arpraziquantel. However, long-term studies with weekly administration of up to 250 mg/kg in rats and hamsters did not show a carcinogenic potential of rac-PZQ.

Reproductive and developmental toxicity studies were conducted in rats and rabbits at doses up to 300 mg/kg/day rac-PZQ. There was no evidence of significant effects on maternal or embryofoetal toxicity. A prenatal and postnatal toxicity study in rats and a single-dose toxicity study in juvenile rats, showed no differences in the sensitivity and target organ toxicity relevant for the paediatric population. Although the evaluation of rac-PZQ data indicates no significant concerns, an evaluation of toxicokinetic data was not presented/available and thus the level of exposure to arpraziquantel (and trans-4-OH-arpraziquantel) cannot be commented on. No effects on the reproductive organs were noted in the pivotal 4-week GLP rat toxicity study where exposure to arpraziquantel and trans-4-OH-arpraziquantel was in excess of that seen clinically.

Additional toxicity studies included dermal toxicity, skin sensitisation study (in humans) and photosafety evaluation – none of which identified any relevant clinical risk for arpraziquantel treatment as indicated in this application. No dedicated local tolerance study was performed with arpraziquantel. However, the excipients in the formulation are not of toxicological concern regarding local tolerance and therefore a dedicated study was not performed in accordance with the "Guideline on non-clinical local tolerance testing of medicinal products" (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1). No treatment-related histopathological findings were detected in the mucous membranes of oesophagus, stomach, or intestine in the pivotal GLP 4-week toxicity rat study.

An evaluation of non-mutagenic impurities was performed and appropriately controlled and/or validated. A risk assessment for the presence of n-nitrosamine impurities identified a new nitrosamine, nitroso-praziquanamine in the drug substance and which tested positive in a GLP-compliant Ames test. Using the Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines nitroso-praziquanamine was categorised as CPCA Category 4 with an associated AI of 1500 ng/day (Appendix 1 of "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products"). Specification limits for nitroso-praziquanamine in the drug substance and drug product have been included to reflect the AI of 1500 ng/day.

2.5.4. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) has been performed utilising internal data and publicly available data for arpraziquantel and racemic praziquantel. No study reports have been provided to support the conclusion of several endpoints including logKow. This ERA follows the principles of the 'Guideline on Environmental Risk Assessment of Medicinal Products for Human Use' (EMEA, 2006) and the 'Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use' (EMA, 2016).

This scientific opinion for arpraziquantel is being sought under Article 58 of Regulation (EC) No 726/2004 and as such will be marketed outside the European Union. As per 'EMA procedural advice for medicinal products intended exclusively for markets outside the European Union in the context of co-operation with the World Health Organisation (WHO)' (MA/534107/2008 Rev.2), the submission of an ERA is recommended, however ultimately the documentation should comply with acceptable national legislation in the countries where the product will be authorised. The applicant indicated that there are no specific requirements on ERA in the African countries where it will be marketed. Any relevant practical instructions for disposal of the medicinal product and waste materials derived from the use of the medicinal product to minimise environmental exposure are to be included in the product information, as appropriate.

2.5.5. Discussion on non-clinical aspects

The non-clinical package submitted in support of this scientific opinion for Arpraziquantel is broadly based on the known nonclinical and clinical profile of racemic praziquantel with a pivotal bridging repeat dose toxicity study. This is generally acceptable given the clinical experience with rac-PZQ. An AI of 1500 ng/day for the identified nitrosamine impurity, nitroso-praziquanamine, has been established on the basis of its categorisation as a CPCA Category 4 nitrosamine as published in Appendix 1 of the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products)". Appropriate limits for the drug substance and drug product have been set to ensure that the 1500 ng/day AI is not exceeded.

2.5.6. Conclusion on the non-clinical aspects

Overall, the non-clinical package provided by the applicant provides adequate evidence supporting the clinical use of arpraziquantel in the applied therapeutic indication, and the SmPC in general reflects the findings.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The applicant provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC. However, considering the lack of recent regulatory experience in the countries where the study was conducted, a GCP inspection of the sites involved in the pivotal clinical trial MS200661-0003 was conducted. The outcome of this inspection was overall satisfactory.

In the final GCP Inspection Report (dated 12 October 2023), the inspectors indicated that after inspection of the sites in Kenya and Ivory Coast there were no issues found that would affect the acceptability of the data for this application. Overall, the trial was conducted in accordance with GCP, was well documented and was of sufficient quality at both investigator sites.

The final recommendation was that the findings of the inspections did not affect the use of the clinical data to support the scientific opinion.

- ***Tabular overview of clinical studies***

The dossier in support of this application comprises three clinical studies. The Phase 1 study was conducted in healthy adults. The Phase 2 and Phase 3 studies were conducted in children infected with *S. mansoni* or *S. haematobium* and resident in endemic areas of Africa.

Table 4 Tabular overview of clinical studies

Study No.	Study Design	Population	No. of Participants and Treatment Exposure
Adult Phase 1 Study			
EMR200661-001 Conducted in South Africa Completed on 03 December 2014	Phase 1, open-label, randomized, single-dose, 5 period, crossover, single center trial to assess the relative bioavailability of the 150 mg pediatric formulation of arpraziquantel (MSC2499550A) versus the 500 mg rac-PZQ commercial tablet formulation Objectives: to assess relative bioavailability, PK, safety/tolerability	Healthy male participants 18 to 55 years of age	Total: N = 36 (3 participants in each of 12 sequences) Treatment A: n = 36 L-PZQ ODT at 20 mg/kg dispersed in water, after a meal Treatment B: n = 36 rac-PZQ formulation (Cysticide) at 40 mg/kg given with water, after a meal Treatment C: n = 35 L-PZQ ODT formulation at 10 (C1) or 30 (C2) mg/kg (randomized 1:1; n = 18 and n = 17, respectively) given dispersed in water, after a meal Treatment D: n = 35 L-PZQ ODT formulation at 20 mg/kg given dispersed in water without a meal Treatment E: n = 36 L-PZQ ODT formulation at 20 mg/kg directly disintegrated in the mouth without water after a meal

Study No.	Study Design	Population	No. of Participants and Treatment Exposure
		Pediatric Phase 2 and 3 Studies	
MS200661-0005 Conducted in the Ivory Coast Completed on 17 November 2018	Phase 2, open-label, dose finding, 2-part efficacy study Part 1: randomized, controlled, exploratory dose finding study to evaluate 3 formulations (commercial rac-PZQ oral tablets and pediatric formulations of rac-PZQ and arpraziquantel) to identify the optimal dose and formulation based on efficacy and safety Part 2: to assess efficacy and safety with the Part 1 selected formulation and dosage Objectives: to identify the optimal dose and formulation based on efficacy and safety; evaluate efficacy, safety, acceptability, and PK	Part 1 (Cohorts 1-7): S. mansoni-infected children 2 to 6 years of age Part 2 (Cohorts 8 and 9): S. mansoni-infected children 3 to 24 months of age	Total: N = 444 Part 1: n = 420 S. mansoni-infected children 2 to 6 years of age, treated with: Cohort 1: n = 60 Commercial rac-PZQ oral tablets (Biltricide 600 mg; 20 mg/kg, tid every 4 hours; reference therapy) Cohort 2: n = 60 Commercial rac-PZQ oral tablets (Biltricide 600 mg; 40 mg/kg, single dose; reference therapy) Cohort 3: n = 60 rac-PZQ ODT 40 mg/kg, single dose Cohort 4: n = 60 rac-PZQ ODT 60 mg/kg, single dose Cohort 5: n = 60 L-PZQ ODT 30 mg/kg, single dose Cohort 6: n = 60 L-PZQ ODT 45 mg/kg, single dose Cohort 7: n = 60 L-PZQ ODT 60 mg/kg, single dose Part 2: n = 24 Cohort 8: n = 20 S. mansoni-infected children 13 to 24 months of age, treated with L-PZQ ODT 50 mg/kg, single dose Cohort 9: n = 4 S. mansoni-infected children 3 to 12 months of age, treated with L-PZQ ODT 50 mg/kg, single dose

Study No.	Study Design	Population	No. of Participants and Treatment Exposure
MS200661-0003 Conducted in the Ivory Coast and Kenya Completed on 07 August 2021	Phase 3, open-label, efficacy and safety study of arpraziquantel in Schistosoma-infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of S. mansoni-infected children 4 to 6 years of age treated with arpraziquantel pediatric formulation or commercial rac-PZQ (Biltricide) Objectives: Efficacy, safety/acceptability, PK	S. mansoni- and S. haematobium-infected children 3 months to 6 years of age	Total: N = 288 Cohort 1: n = 150 S. mansoni-infected children 4 to 6 years of age, randomized 2:1 into Treatment 1a (L-PZQ ODT 50 mg/kg, single dose; n = 100) or Treatment 1b (40 mg/kg rac-PZQ [Biltricide] crushed tablets, single dose; reference therapy; n = 50) Cohort 2: n = 30 S. mansoni-infected children 2 to 3 years of age, treated with L-PZQ ODT 50 mg/kg, single dose Cohort 3: n = 18 [b] S. mansoni-infected children 3 to 24 months of age, treated with L-PZQ ODT 50 mg/kg, single dose Cohort 4: n = 90 [a] S. haematobium-infected children 3 months to 6 years of age, treated with L-PZQ ODT 50 mg/kg, single dose (Cohort 4a, n = 30) or L-PZQ ODT 60 mg/kg, single dose (Cohort 4b, n = 60)

CSR= clinical study report; IDMC= Independent Data Monitoring Committee; L-PZQ= levo-praziquantel; L-PZQ ODT= arpraziquantel pediatric formulation; PK= pharmacokinetic(s); rac-PZQ= racemic praziquantel; tid= three times a day; rac-PZQ ODT= racemic praziquantel pediatric formulation.

[a] After 30 participants in Study MS200661-0003 Cohort 4 were treated with 50 mg/kg arpraziquantel, the efficacy data were evaluated by the IDMC, and it was determined that an increase of the dose to 60 mg/kg was needed. Therefore, 30 additional participants were added to this cohort and 60 participants were treated with the 60 mg/kg dose.

[b] n=41 was initially planned in order to have 65 participants in this age group in the pooled analysis with the Phase 2 Study MS200661-0005 Cohorts 8 and 9 (n=24). However, due to enrollment challenges and based on feedback received during scientific advice with EMA (EMEA/H/SA/3674/1/FU/2/2020), n ≥10 in Cohort 3 was considered appropriate by the Sponsor.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetic data come from two of the three clinical studies:

-EMR200661-001 – the Phase 1 study in healthy male adults, which compared the relative bioavailability of levo-praziquantel (L-PZQ) from 150 mg L-PZQ paediatric formulation (DT/OTD; see further below re formulations) and from 500 mg Praziquantel racemate tablets (using the commercial Cysticide tablets). The 150 mg tablets were used to deliver L-PZQ doses of ~10, 20 and 30 mg/kg while the Cysticide tablets were used to deliver racemate doses of 40 mg/kg.

-MS200661-0003 – the Phase 3 efficacy study in children infected with *S. mansoni* or *S. haematobium*. The table below summarises the doses of the L-PZQ and the commercial Biltricide tablets administered by cohort.

Table 5 the Phase 3 efficacy study in children infected with S. mansoni or S. haematobium

	L-PZQ ODT	Commercial PZQ (Biltricide®)
Study intervention names:	Arpraziquantel (INN)	Praziquantel (INN)
Compounds:	Levorotatory enantiomer of praziquantel (L-PZQ), dextrorotatory enantiomer of praziquantel (R-[-]-praziquantel)	Racemic (dextrorotatory and levorotatory) praziquantel (rac-PZQ)
Drug product name used in this document:	L-praziquantel orodispersible tablets / New oral disintegrating tablets of L-praziquantel Abbreviated: L-PZQ ODT	Racemate praziquantel commercial oral tablets *Related trade name: Biltricide®* Abbreviated: Commercial rac-PZQ or Commercial PZQ
Dose formulation:	ODT containing 150 mg of arpraziquantel drug substance	Tablet containing 600 mg of PZQ
Unit dose strength(s)/ dosage level(s):	Cohorts 1a, 2, 3 and 4a: 50 mg/kg; Cohort 4b: 60 mg/kg	Cohort 1b: 40 mg/kg
Route of administration:	Oral	Oral
Dosing instructions:	Single dose of L-PZQ ODT, dispersed in water, after food intake	Single dose of commercial PZQ (Biltricide) The Biltricide tablets were divided into 150 mg parts, crushed, suspended in water, and administered after food intake
Batch numbers:	Ivory Coast: 20070999 Kenya: 20071000	Ivory Coast: CT3388/1 Kenya: CT3388/2

Although samples for PK were collected in **MS200661-0005**, no blood concentrations were reportable due to inadequate performance of the assay.
In the two clinical studies that reported PK data, concentrations of R-(−)-PZQ (i.e. L-PZQ; arpraziquantel), S-(+)-PZQ and the metabolites trans-4-OH-arpraziquantel and trans-4-OH-S-PZQ were determined with validated bioanalytical methods.

- The Phase 1 tablet formulation 1 (TF1) was used only for EMR200661-001 in adults.
- The Phase 2 tablet formulation 2 (TF2) used in MS200661-0005 had minor differences from TF1 (e.g. small decrease in mannitol and maize starch, introduction of pre-gelatinized starch and vitamin E polyethylene glycol succinate).
- The Phase 3 tablet formulation 3 (TF3) used in MS200661-0003 differed from TF2 in that the maize starch content in the inner phase was reduced and substituted with sodium starch glycolate type A. Maize starch was completely removed from the outer phase and pre-gelatinized starch was added instead. The overall change in mannitol was below 5%.
- TF3 is identical to the proposed commercial formulation.

Table 6 Summary of Information on Arpraziquantel Formulations Used in the Clinical Studies

DP Batch Number	Strength	Formulation	DS Batch Number	Dose
0159838	150 mg	TF1 (Phase 1)	EE13002228	10, 20 and 30 mg/kg
016213 016360 016392	150 mg	TF2 (Phase 2)	EE15002517	30, 45 and 60 mg/kg
18100429	150 mg	TF3 (Phase 3/ commercial)	EE16002517	50 and 60 mg/kg
19100978	150 mg	TF3 (Phase 3/ commercial)	PBR-PZQ18005	50 and 60 mg/kg

Source: refer to CSR EMR200661-001, CSR MS200661-0005, CSR MS200661-0003.
CSR = clinical study report; DP = drug product; DS = drug substance.

Bioavailability

The Phase 1 study **EMR200661-001** was conducted in 2014 in 36 healthy male subjects at a single study site in S. Africa. The primary objective was to assess the relative bioavailability of L-PZQ after administration of TF1 150 mg formulation (denoted MSC2499550A) to provide a dose of 20 mg/kg L-PZQ and after administration of the licensed racemate PZQ 500 mg tablet (Cysticide) to provide a dose of 40 mg/kg PZQ. The primary comparison was made when each was dosed under fed conditions.

Subjects were randomised to receive single oral doses in a 5-period open label cross-over design with randomisation in 12 sequences (3 subjects per sequence). There was a washout period of at least 7 days in between treatments. The five single dose treatments were:
A) MSC2499550A at 20 mg/kg dispersed in water after a standard meal
B) Cysticide at 40 mg/kg with water after a standard meal
C) MSC2499550A at 10 (C1) or 30 (C2) mg/kg dispersed in water after a standard meal
D) MSC2499550A at 20 mg/kg dispersed in water without a meal
E) MSC2499550A at 20 mg/kg disintegrated in the mouth without water after a standard meal

The number of tablets used for each period was calculated based on the body weight (BW) of the subject at screening *Number of tablets = round {(BW x 20 mg/kg)/strength}. The table shows the number of tablets given by body weight group for treatments A, B, D and E.

Table 7 Number of tablets of MSC2499550A and PZQ administered to achieve a dose of 20 mg/kg L-PZQ

Bodyweight in kg	Number of 150 mg MSC2499550A tablets	Total dose of L-PZQ	Actual mg/kg range	Number of 500 (= 250 mg L-PZQ) mg PZQ tablets	Total dose of L-PZQ	Actual mg/kg range
55 - 56.2	7	1050	19.09 -18.7	4	1000	18.2- 17.8
56.3 - 63.7	8	1200	21.3 -18.8	5	1250	22.2 - 19.6
63.8 - 68.7	9	1350	21.2 -19.6	5	1250	19.6-18.2
68.8 - 71.2	9	1350	19.6 -18.96	6	1500	21.8 - 21.1
71.3 - 78.7	10	1500	21.0 -19.1	6	1500	21.8 - 21.1
78.8 - 81.2	11	1650	20.9 -20.3	6	1500	19.0 - 18.5
81.3 - 86.2	11	1650	20.3 -19.1	7	1750	21.5 - 20.3
86.3 - 93.7	12	1800	20.9 – 19.2	7	1750	20.3 - 18.6
93.8 - <95.0	13	1950	20.8 -20.5	8	2000	21.3 - 21.1

The L-PZQ tablets (7-13) were dispersed in 50 mL water. For Treatment E, the L-PZQ tablet dose disintegrated in the mouth. Racemate PZQ tablets (Cysticide) were administered one by one (total 4-8) and as quickly after one another as possible.

All dose dependent PK parameters were adjusted to the planned dose and statistical analyses were performed on the adjusted parameter values. The adjustment was necessary due to the dose differences between test and reference treatments and deviation from the nominal dose (see above).

As planned, there were 36 subjects randomised and 34 subjects completed. There were 3026 blood samples processed for PK analysis and 178 profiles with 17 samples each were analysed for L-PZQ and D-PZQ with a validated enantioselective bioanalytical assay. Levels of racemate-PZQ were calculated by adding the individual levels of L- and D-PZQ for a given sample. In addition, 72 profiles with 17 samples each were analysed for 4-OH-L-PZQ with a validated enantioselective assay.

L-PZQ

For Treatments A and B, the CSR states that individual relative bioavailability (Rel BA) of L-PZQ ranged from 17.11% to 105.69% with a geometric mean of 39.942% (i.e. ~40%). Four subjects had a value below 20 and two had a value above 100.

In the primary comparison, as shown below, the overall calculated relative bioavailability of L-PZQ when given as a single enantiomer (Treatment A) was ~40% of that when it was given as racemate (Treatment B). Correspondingly, C_{max} was lower with Treatment A and some other parameters differed as shown below, including longer $t_{1/2}$ and slower clearance of L-PZQ when it was given with D-PZQ.

L-PZQ exposure after dose normalisation showed supra-proportionality (quadratic) for adjusted C_{max} and AUC parameters across the 10, 20 and 30 mg/kg doses.

Table 8 Statistical analysis for PK parameter of L-PZQ $AUC_{0-\infty,adj}$

Parameter (h*ng/mL)	Treatment	N	Geo-LSMean	Ratio(Test/Ref) (%)	90% CI of Ratio	CV(%)
$AUC_{0-\infty,adj}$	A	36	825.2068	39.9	34.7-46.0	36.8
	B	36	2066.002			
$AUC_{0-\infty,adj}$	C1	17	225.5903	27.3	22.5-33.2	39.2
	A	36	825.2068			
$AUC_{0-\infty,adj}$	C2	17	2147.473	260.2	214.0-316.4	39.2
	A	36	825.2068			
$AUC_{0-\infty,adj}$	A	36	825.2068	167.1	143.9-194.0	39.2
	D	35	493.9041			
$AUC_{0-\infty,adj}$	E	36	954.5461	115.7	99.8-134.1	39.2
	A	36	825.2068			

AUC = area under the plasma concentration time curve, CI = confidence interval, CV% = coefficient of variability percentage, N = number included in the analysis

Table 9 Overview of PK Parameters for L-Praziquantel in Plasma: Treatments A and B

L-PZQ:	A	B
C_{max} (ng/mL)	389.37 (113.3) 67.8 – 2010.0	755.71 (61.6) 213.0 – 2460.0
t_{max} (h)	2.500 0.50 – 4.50	2.500 1.00 – 4.50
t_{lag} (h)	0 0 – 0	0 0 – 1
AUC_{0-t} (h*ng/mL)	813.0 (103.0) 210 – 3894	2089.3 (65.0) 606 – 6613
$AUC_{0-\infty}$ (h*ng/mL)	848.2 (100.4) 220 – 3936	2146.8 (63.6) 659 – 6732
$t_{1/2}$ (h)	2.777 (53.9) 1.01 – 6.49	3.827 (46.3) 1.44 – 10.1
$CL_{/f}$ (L/h)	1665 (94.3) 419 – 7100	667.3 (60.1) 194 – 1900
$Vz_{/f}$ (L)	6671 (62.9) 1620 – 19800	3685 (62.8) 846 – 20100
λ_z (1/h)	0.250 (53.9) 0.11 - 0.69	0.181(46.3) 0.07-0.48

Geomean (GeoCV%) and Range (Min-Max), for t_{max} and t_{lag} Median and Range are listed, (N=36, each treatment)

D-PZQ

There was effectively no conversion of the L-PZQ enantiomer to the D-PZQ enantiomer in that no D-PZQ was detectable in those given L-PZQ alone except for one subject with 44.5 ng/mL at 12 h after Treatment A where bioanalytical carry over was excluded and this finding remains unexplained. In contrast, D-PZQ was detected in all subjects at 0.5 h after dosing with the racemate (Treatment B).

Table 10 Overview of PK Parameters for Treatment B

B:	L-PZQ	D-PZQ	Racemate PZQ
C_{max} (ng/mL)	755.71 (61.6) 213.0 – 2460.0	2010.30 (40.3) 814.0 – 4410.0	2782.41 (44.6) 1136.0 – 6440.0
t_{max} (h)	2.500 1.00 – 4.50	2.750 1.00 – 4.50	2.750 1.00 – 4.50
t_{lag} (h)	0 0 – 1	0 0 – 0	0 0 – 0
AUC_{0-t} (h*ng/mL)	2089.3 (65.0) 606 – 6613	7427.0 (49.8) 3194 – 23945	9606.6 (51.3) 3837 – 30577
$AUC_{0-\infty}$ (h*ng/mL)	2146.8 (63.6) 659 – 6732	7564.7 (50.1) 3238 – 24467	9765.7 (51.9) 3872 – 31500
$t_{1/2}$ (h)	3.827 (46.3) 1.44 – 10.1	4.245 (33.0) 2.07 – 8.39	4.042 (35.5) 1.89 – 8.70
$CL_{/f}$ (L/h)	667.3 (60.1) 194 – 1900	189.4 (46.0) 71.5 – 448	293.4 (47.8) 111 – 656
$Vz_{/f}$ (L)	3685 (62.8) 846 – 20100	1160 (51.8) 428 – 4180	1711 (48.5) 671 – 4570
λ_z (1/h)	0.181(46.3) 0.07-0.48	0.163 (33.0) 0.08 - 0.33	0.171 (35.5) 0.08 - 0.37

Geomean (GeoCV%) and Range (Min-Max), for t_{max} and t_{lag} Median and Range are listed, (N=36, all analytes)

(L)-Trans-OH-PZQ

Exposure to the metabolite was much greater than that to the parent compound L-PZQ. The C_{max} and the t_{max} were not different for Treatments A and B but t_{max} for the metabolite (4.5 h) was later than for

parent compound (2.5 h) as expected. There was a somewhat lower $AUC_{0-\infty}$ of the metabolite after Treatment A (116298.3 h*ng/mL) vs. B (148768.7 h*ng/mL). The variability in $AUC_{0-\infty}$ was much less than observed for the parent compound.

Table 11 Overview of PK Parameters for (L)-Trans-4`-OH-PZQ in Plasma: Treatments A and B

(L) trans-4'-OH-PZQ:	A	B
C_{max} (ng/mL)	14008.24 (18.5) 9930.0 – 19700.0	14843.32 (13.9) 11200.0 – 18600.0
t_{max} (h)	4.500 2.00 – 5.00	4.500 2.50 – 8.00
t_{lag} (h)	0 0 – 0	0 0 – 0
AUC_{0-t} (h*ng/mL)	112080.1 (25.9) 65763 – 178913	140499.2 (21.6) 89104 – 208785
$AUC_{0-\infty}$ (h*ng/mL)	116298.3 (28.0) 66993 – 192986	148768.7 (25.0) 92820 – 232885
$t_{1/2}$ (h)	4.289 (21.4) 2.92 – 7.49	4.748 (24.4) 3.32 – 8.93
λ_z (1/h)	0.162 (21.4) 0.09 - 0.24	0.146 (24.4) 0.08 - 0.21

Geomean (GeoCV%) and Range (Min-Max), for t_{max} and t_{lag} Median and Range are listed, (N=36, both treatments)

Food effect

A food effect for DTs was confirmed with C_{max} and AUC 197% and 69% higher, respectively, compared to fasting. Furthermore, the table below summarises the PK data across the fed and fasted groups.

Table 12 Overview of PK Parameters for Arpraziquantel in Plasma: All Treatments

Treatment	A L-PZQ ODT 20 mg/kg Fed N=36	B rac-PZQ (Cysticide) 40 mg/kg Fed N=36	C1 L-PZQ ODT 10 mg/kg Fed N=18	C2 L-PZQ ODT 30 mg/kg Fed N=17	D L-PZQ ODT 20 mg/kg Fasted N=35	E L-PZQ ODT 20 mg/kg Fed N=36
C_{max} (ng/mL)	389.37 (113.3) 67.8 – 2010.0	755.71 (61.6) 213.0 – 2460.0	90.85 (93.4) 27.3 – 402.0	1067.35 (83.5) 325.0 – 3860.0	134.62 (110.3) 15.5 – 643.0	484.19 (99.0) 70.6 – 1760.0
t_{max} (h)	2.500 0.50 – 4.50	2.500 1.00 – 4.50	2.250 1.00 – 4.50	3.000 1.00 – 4.50	2.000 0.50 – 4.50	4.000 0.50 – 5.00
t_{lag} (h)	0 0 – 0	0 0 – 1	0 0 – 0	0 0 – 0	0 0 – 0	0 0 – 0
AUC_{0-t} (h*ng/mL)	813.0 (103.0) 210 – 3894	2089.3 (65.0) 606 – 6613	188.1 (108.9) 61 – 1121	2307.2 (78.1) 815 – 9836	477.3 (102.0) 52 – 1966	943.3 (98.2) 154 – 4658
$AUC_{0-\infty}$ (h*ng/mL)	848.2 (100.4) 220 – 3936	2146.8 (63.6) 659 – 6732	217.9 (105.2) 67 – 1169	2359.3 (76.6) 870 – 10030	520.0 (99.0) 62 – 1997	980.9 (96.0) 158 – 4709
$t_{1/2}$ (h)	2.777 (53.9) 1.01 – 6.49	3.827 (46.3) 1.44 – 10.1	1.604 (88.6) 0.623 – 7.58	3.361 (31.9) 1.82 – 5.46	2.837 (62.3) 0.869 – 24.9	2.625 (65.2) 0.452 – 6.65
$CL_{/f}$ (L/h)	1665 (94.3) 419 – 7100	667.3 (60.1) 194 – 1900	3091 (92.9) 770 – 8940	923.5 (71.4) 254 – 2760	2729 (95.4) 826 – 29200	1440 (89.3) 255 – 8530
$Vz_{/f}$ (L)	6671 (62.9) 1620 – 19800	3685 (62.8) 846 – 20100	7155 (72.4) 3030 – 34800	4478 (62.8) 1960 – 13100	11170 (81.1) 3370 – 54900	5452 (62.4) 970 – 26200
λ_z (1/h)	0.250 (53.9) 0.11 – 0.69	0.181(46.3) 0.07 – 0.48	0.432 (88.6) 0.09 – 1.11	0.206 (31.9) 0.13 – 0.38	0.244 (62.3) 0.03 – 0.80	0.264 (65.2) 0.10 – 1.53

Source: refer to CSR EMR200661-001, Table 11-4.

AUC_{0-t} = Area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $CL_{/f}$ = apparent total body clearance of drug from plasma; C_{max} = maximum concentration; λ_z = apparent terminal elimination constant; L-PZQ ODT= arpraziquantel pediatric formulation; PK = pharmacokinetic; $t_{1/2}$ = half-life; t_{lag} = time prior to the first measurable (nonzero) concentration; t_{max} = time to reach the maximum plasma concentration; $V_{z/f}$ = apparent volume of distribution during the terminal phase.

Parameters are presented as the geometric mean (Geomean) (geometric mean coefficient of variability [GeoCV%]) and range (min-max). In the case of t_{max} and t_{lag}, the median and range are presented.

A: arpraziquantel at 20 mg/kg dispersed in water, after a meal.

B: Rac-PZQ (Cysticide) at 40 mg/kg given with water, after a meal.

C: arpraziquantel at 10 mg/kg (C1) or 30 mg/kg (C2) dispersed in water, after a meal.

D: arpraziquantel at 20 mg/kg dispersed in water, without a meal.

E: arpraziquantel at 20 mg/kg directly disintegrated in the mouth without water, after a meal.

Palatability

VAS scores were used to assess palatability. Overall, results indicated that it was preferable to disperse the L-PZQ 150 mg tablets in water rather than use direct disintegration in the mouth without water and to administer after a meal rather than without a meal. Generally, the L-PZQ formulation was preferred over the licensed racemate tablet for palatability.

Distribution

According to the literature, it is not known to what extent praziquantel crosses the placenta, but only a small amount (<0.001%) is excreted in breast milk.

In *in-vitro* nonclinical studies the plasma protein binding of arpraziquantel was approximately 80% in human plasma and that of the circulating major metabolite trans-4-OH-arpraziquantel was 36.2%. The arpraziquantel blood-to-plasma distribution ratios at concentrations of 0.156, 1.56 and 15.6 µg/mL were 0.66, 0.68 and 0.92, respectively, suggesting it is predominantly distributed in plasma at lower concentrations. The estimated apparent volume of distribution (Vc/F) for arpraziquantel was 28.2 L (IIV CV% of 2,099) in the POPPK analysis. The weight adjusted geometric mean values (geoCV%) for

arpraziquantel apparent volume of distribution for the 50 and 60 mg/kg doses were 1.73 (1,620) and 2.6 (3,240) L/kg, respectively.

Elimination

A published human mass balance study evaluated ^{14}C-labeled rac-PZQ administration to healthy volunteers at 14 and 46 mg/kg. Results indicated that 84% and 80% of the total administered radioactivity was recovered in urine after 4 days following oral doses of 14 and 46 mg/kg, respectively, and most of this (>90%) was recovered within the first 24 hours. Only trace levels of rac-PZQ were found in urine (< 0.02% of administered dose), indicating that elimination of rac-PZQ is almost completely via metabolism. The major excretory components were hydroxylation products of rac-PZQ and 7.1% of rac-PZQ was excreted as 4-OH-PZQ (exact stereochemistry is unknown) in urine.

The elimination half-life from serum was 4 hours for ^{14}C-radioactivity and 1.5 hours for intact rac-PZQ. In EMR200661-001, the geometric mean elimination half-life of arpraziquantel after administration of 40 mg/kg rac-PZQ to healthy adults was 3.8 hours (GeoCV 46.3%). The geometric mean half-lives for arpraziquantel in children included in the POPPK analysis were 2.65 and 2.81 hours for the 50 and 60 mg/kg arpraziquantel doses, respectively. The corresponding values for trans-4-OH-arpraziquantel were 2.77 and 2.94 hours.

The estimated value for CL/F for arpraziquantel estimated in the POPPK analysis was 574 L/h (90% CI: 429, 719 L/h). The geometric mean (%CV) weight adjusted clearance value was 33.8 L/h/kg (126%). The estimated CL/F value (in L/h) compares well with the value estimated for arpraziquantel by Falcoz *et al*. (2022) for a combined child and adult population of 657 L/h (95% CI: 592, 869 L/h) and where CL/F values could be expected to be higher due to the use of the dried blood spot assay.

Metabolism

Metabolism of racemic praziquantel and L-PZQ

According to the literature, although the estimated bioavailability of praziquantel is 80% to 100%, it undergoes extensive first-pass hepatic metabolism to inactive metabolites so that most of the active drug does not reach the systemic circulation. Subsequently, it is completely metabolised, with 80% of the dose recovered as metabolites in urine within 4 days (see above). In a human radiolabel study with rac-PZQ, metabolism after oral administration of approximately 44 mg/kg rac-PZQ to healthy adult participants in the fed state was rapid, with unchanged parent compound representing less than 0.1% of the total plasma radioactivity after 4 hours. The 4-hydroxypraziquantel (4-OH-rac-PZQ) metabolite was the main circulating metabolite, accounting for 40% to 50% of the radioactivity in serum.

Biotransformation of praziquantel was investigated in both human liver microsomes and hepatocytes where incubations with rac-PZQ resulted in up to 11 phase 1 metabolites. Similar to the racemate, L-PZQ (arpraziquantel) is mainly cleared through metabolism.

The fractional contribution of CYP isoforms to metabolism in human hepatocytes ranged between:
- 0.22 to 0.31 for CYP1A2
- 0.24 to 0.34 for CYP2C9
- 0.36 to 0.52 for CYP2C19
- 0.19 to 0.27 for CYP3A4/5

Only minimal contribution from CYP2D6 and no turnover with CYP 2B6 or 2C8 isoforms was observed in recombinant systems. CYP 1A1 was not considered for testing in human hepatocytes as protein expression levels in the liver are relatively low.

In a clinical study, rac-PZQ and trans-4-OH-arpraziquantel exposures increased by 75% and 67%, respectively, when rac-PZQ was co-administered with ketoconazole. In contrast, an undefined hydroxy metabolite (X-OH-PZQ) decreased by about 57%. These data suggest that CYP3A4 is not responsible for the formation of trans-4-OH-arpraziquantel.

The adult and paediatric PK data generated by the applicant showed that the exposure in plasma to (L)-trans-OH-PZQ (=R-4-OH-PZQ) was much higher than that to the parent drug after oral dosing with L-PZQ or with the licensed racemate. Trans-4-OH-arpraziquantel is mainly formed via conversion from cis-4-OH-arpraziquantel, which itself is formed predominantly via metabolism of arpraziquantel by CYP 1A1, 1A2, 2C9, 2C19 and 2D6 isoforms. While the enzyme/s responsible for the cis- to trans-conversion are unknown, it is most likely due to cytosolic enzymes as the transformation is observed in human hepatocytes and not in human liver microsomes.

Interaction between L-PZQ and D-PZQ

In EMR200661-001, with a target L-PZQ dose of 20 mg/kg, the actual doses of L-PZQ administered using the 150 mg L-PZQ paediatric formulation ranged from 18.7 to 21.3 mg/kg whereas the actual mg/kg dose of L-PZQ administered using the 500 mg licensed racemate tablets ranged from 17.8 to 22.2 mg/kg. Despite very similar actual mg/kg doses administered, the mean concentration time profile of L-PZQ when given alone (L-PZQ paediatric formulation; Treatment A) was quite different to that after administration as a racemic mixture (Racemate 500 mg tablets; Treatment B). Mean levels of L-PZQ were much lower when it was administered alone with individual relative bioavailability that ranged from ~17% to 106% and a geometric mean of ~40%. Of the 36 subjects, four had a Rel BA value below 20 although two had a value above 100. A similar trend was observed for the main metabolite, trans-4-OH-arpraziquantel for which systemic exposure was approximately 79% after administration of arpraziquantel relative to administration of rac-PZQ.

Published studies have investigated the possible reasons for the lower than expected plasma levels of L-PZQ when it was given alone at ~20 mg/kg compared to administration of a similar amount of L-PZQ (~20 mg/kg) administered as 40 mg/kg of the 1:1 racemate. When turnover was determined in selected recombinant human CYP P450 isoenzymes (rhP450s) for R-PZQ, S-PZQ and rac-PZQ it was found that R-PZQ was a preferred substrate over S-PZQ for CYP1A1, 1A2, 2C9 and 2D6. S-PZQ was preferred over R-PZQ for CYP3A7. The P450 isoforms 3A4, 3A5 and 2C19 presented similar efficiency in metabolizing both PZQ enantiomers. Comparison of kinetic parameters of PZQ enantiomers, whether tested individually or as racemate, were the basis to select which rhP450s might be subject to enantiomer-enantiomer interactions.

It was concluded that the data from incubations of PZQ enantiomer mixtures with CYP2C9, 2C19, 3A4 and 3A5 were best fitted using models of competitive inhibition between the enantiomers. Comparison of Ki values between PZQ enantiomers generally resulted in differences below twofold, except for CYP2C19, for which Ki was lower for S-PZQ, potentially indicating that S-PZQ is prevalently playing an inhibitor role. Also, S-PZQ seems to act as perpetrator of CYP1A1-mediated metabolism of R-PZQ.

Dose proportionality

The study in healthy adults showed supra-proportional increases in the geometric mean AUC_{0-t} between 10 mg/kg and 30 mg/kg doses. However, variability of the PK parameters was high, particularly for the 10, 20 and 30 mg/kg dose groups. Phase 3 PK data from children aged 3 months to 6 years infected with *S. haematobium* who received 50 mg/kg (n=14) and 60 mg/kg (n=15) of L-PZQ

in the fed state showed high variability for AUC_{0-t} and a small (20%) difference between the 2 dose levels.

Intra- and inter-individual variability

The inter-individual variability (IIV) in arpraziquantel PK parameters is high, as expected from the observed high variability in concentration vs. time profiles. The trans-4-OH-arpraziquantel concentration vs. time profiles are much less variable. When the proposed commercial formulation of arpraziquantel was administered orally as a single dose after a meal to infected children, the IIV based on geometric means CV% was:

- 94.9% for C_{max} and 101.2% for AUC_{0-t} for 50 mg/kg in 17 PSAC (4 to 6 years) infected with *S. mansoni*
- 97.7% for C_{max} and 84.1% for AUC_{0-t} for 50 mg/kg in 9 PSAC (2 to 3 years) infected with *S. mansoni*
- 195.7% for C_{max} and 236.5% for AUC_{0-t} for 60 mg/kg in 15 PSAC (3 months to 6 years) infected with *S. haematobium*

The final POPPK model included the effects of body weight on CL and V parameters as part of the structural model. The magnitude of IIV in CL/F was estimated to be 135% in the final model while that for trans-4-OH-arpraziquantel CLM/F/fm was lower (53.1%). The geometric CV% values for arpraziquantel AUC values for the 50 and 60 mg/kg doses were 129% and 86.4%, respectively, whereas those for trans-4-OH-arpraziquantel were 44.3% and 38.1%, respectively. Since most of the compound is metabolised and only low amounts of unchanged compound are observed in the systemic circulation, small differences in first pass metabolism between individuals could result in substantially different arpraziquantel exposure and explain the high observed IIV. The applicant considers that the low bioavailability and the resulting high IIV in arpraziquantel exposures are not clinically relevant due to the high cure rates obtained despite the high IIV for exposures.

Pharmacokinetics in target population

MS200661-0003 - Observed data

Of the 86 subjects who received study drug and had ≥ 1 measurable post-dose concentration there were 19 excluded from the analysis of PK. The PK population included 67 subjects: 17 from Cohort 1a, 10 from Cohort 1b, 9 from Cohort 2, 2 from Cohort 3, 14 from Cohort 4a and 15 from Cohort 4b.

R-PZQ (=L-PZQ)

Individual PK profiles in all treatment cohorts were erratic with strong fluctuations between sampling time points and high inter-individual variability. There was no consistent time to maximal concentration across the profiles and many profiles showed multiple peaks. The mean profiles per cohort did not suggest strong differences between Cohorts 1a, 2, 3 and 4, which received L-PZQ paediatric formulation. In contrast, Cohort 1b, which received the licensed racemate as Biltricide tablets, clearly had lower mean R-PZQ plasma concentrations. The CV% values for AUC_{0-t} and C_{max} were high and the erratic nature of the PK profiles with multiple peaks also resulted in a large range for t_{max}.

Table 13 Pharmacokinetic Parameters – PK Population

Analyte PK Parameter Statistic	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=17	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=10	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=9	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=2	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=14	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=15
R-PZQ						
AUC_{0-t} (h·ng/mL)						
n	17	9	9	NC	14	15
Mean	1080	184	2720	NC	1190	907
GeoMean	778	135	2220	NC	700	523
Median	725	116	2370	NC	799	727
CV%	95.5	81.7	63.1	NC	92.9	85.6
Min; Max	150; 4500	49.9; 434	597; 6460	NC	55.1; 3540	16.2; 2700
C_{max} (ng/mL)						
n	17	10	9	NC	14	15
Mean	347	59.3	1470	NC	523	300
GeoMean	259	50.1	1090	NC	212	182
Median	254	42.5	1250	NC	285	275
CV%	81.0	101.9	90.0	NC	127.6	79.8
Min; Max	65.3; 1110	0.00; 214	355; 4690	NC	19.3; 2230	13.3; 854
T_{max} (h)						
n	17	10	9	NC	14	15
Median	02.00	01.00	03.00	NC	1.50	03.00
Min; Max	0.500; 8.00	0.00; 12.0	01.00; 12.0	NC	0.500; 6.02	0.500; 8.02

The geometric mean AUC_{0-t} and C_{max} values after administration of 40 mg/kg Biltricide in Cohort 1b were around 17% and 19% of those in Cohort 1a, which was lower than the anticipated ratio of 40% (since Biltricide delivers 20 mg/kg of R-PZQ vs. 50 mg/kg with the L-PZQ paediatric formulation). The geometric mean AUC_{0-t} and C_{max} after administration of 50 mg/kg R-PZQ in Cohort 2 (2-3 years) were higher than those in Cohort 1a (age group 4-6 years). However, variability was large and the range of systemic exposure overlapped between the cohorts. From Cohorts 1a and 2 the applicant concluded that an effect age on R-PZQ exposure could not be excluded. There were only two subjects sampled in Cohort 3 (3-24 months) so values were not calculated.

There was no major difference in PK parameters in the 4-6 years children infected with *S. mansoni* (Cohort 1a) and *S. haematobium* (Cohort 4a) who received 50 mg/kg R-PZQ. The applicant also concluded that, after accounting for the high CV%, there was no important difference in AUC_{0-t} and C_{max} between Cohorts 4a (50 mg/kg) and 4b (60 mg/kg) who were infected with *S. haematobium*.

R-4-OH-PZQ Plasma Concentrations

Individual and mean R-4-OH-PZQ profiles had a more typical shape with a single peak, consistent time to maximal concentration and steady decline in concentration. Although the sample size was low, particularly in Cohorts 2 and 3 (n=9 and n=2, respectively), the intra-individual variability was less than for the parent compound.

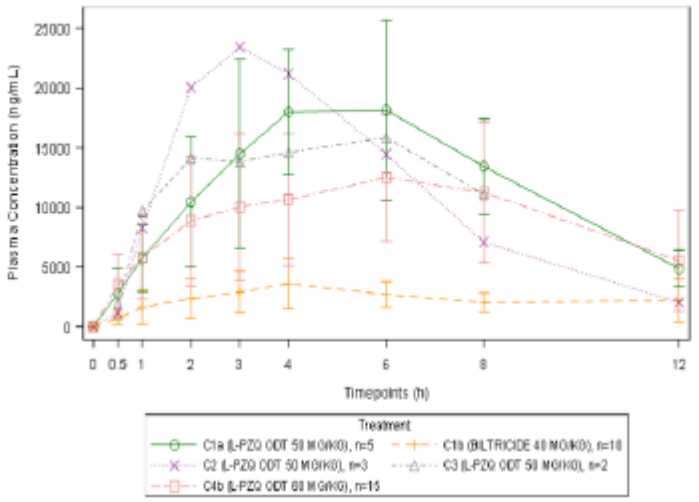


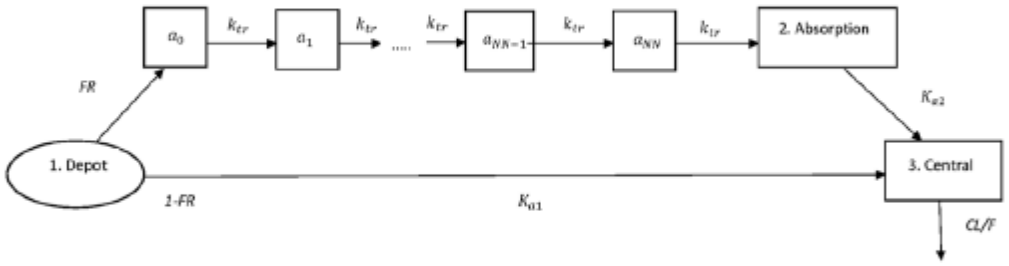
Figure 2 Mean (SD) R-4-OH-PZQ Concentration-Time Curve by Treatment Cohort (PK Population)

The geometric mean AUC_{0-t} was approximately 177-fold (Cohort 1a), 196-fold (Cohort 1b) and 159-fold (Cohort 4b) higher for 4-OH-R-PZQ than for R-PZQ. The geometric mean C_{max} was 76-fold (Cohort 1a), 84-fold (Cohort 1b) and 77-fold (Cohort 4b) higher for 4-OH-R-PZQ than for R-PZQ. The lowest plasma levels occurred after dosing with Biltricide, reflecting reduced metabolism of parent R-PZQ in the presence of the S-PZQ enantiomer.

MS200661-0003 - POPPK analysis

A POPPK analysis was conducted using data from 74 children with median age 5.0 years (range 10 months to 6.9 years) who received arpraziquantel 50 mg/kg or 60 mg/kg and provided arpraziquantel and/or trans-4-OH-arpraziquantel concentration data. The POPPK models for arpraziquantel and trans-4-OH-arpraziquantel were built using NONMEM (v 7.5) with Monte Carlo Importance Sampling (IMP) Expectation Maximization as the estimation method. Goodness-of-fit of the structural model was assessed by diagnostic plots and visual predictive checks. The arpraziquantel population PK model was built first and then extended to incorporate the data for trans-4-OH-arpraziquantel, under the assumption that all arpraziquantel is converted to trans-4-OH-arpraziquantel. The final model was simultaneously fit to both arpraziquantel and trans-4-OH-arpraziquantel data.

Different models were evaluated to describe the absorption of arpraziquantel. A joint first-order and transit compartment absorption was selected as it provided a stable model with the lowest Akaike Information Criterion. The figure below is a schematic representation of the PK model for arpraziquantel including a joint first-order and transit compartment model for describing absorption.



Source: refer to Population PK Report, Figure 3.
a_n = the drug amount in the nth compartment; CL/F = apparent clearance; FR = fraction of the dose absorbed through the absorption compartment; K_{a1} = absorption rate constant from the depot; K_{a2} = absorption rate constant from the final transit compartment to the central compartment; k_{tr} = identical transfer rate constant of the transit compartment model; NN = number of transit compartments placed before the central compartment.

Figure 3 Schematic Representation of Arpraziquantel Joint First Order and Transit Model Absorption

One-compartment models were selected to describe disposition for both arpraziquantel and trans-4-OH-arpraziquantel. The IIV was included on all model parameters and all covariance between the IIV parameters was also estimated. The residual error model included proportional terms for both arpraziquantel and trans-4-OH-arpraziquantel, and a single additive residual error term for arpraziquantel only. The covariates evaluated were:

- Age (in years)
- Body size metric (body weight [in kg], body surface area [in m^2])
- Sex (male vs female)
- Country (Kenya vs. Ivory Coast)
- Intensity of infection at baseline (light vs moderate/heavy)
- Type of infection (*S. mansoni* vs. *S. haematobium*)
- Laboratory parameters (ALT, AST, CrCL, Schwarz formula and eGFR-MDRD)

The influence of body weight as body size metric was accounted for on both arpraziquantel and trans-4-OH-arpraziquantel clearance and volume parameters. Body weight effects were included in the model by fixing the allometric exponents to 0.75 for clearance terms and 1.0 for volume terms. During model development, the body weight exponents on arpraziquantel CL/F and Vc/F were estimated to be higher than the allometric values and had wide 95% CIs. Consequently, the fixed exponents were used in the final combined model for arpraziquantel and trans-4-OH-arpraziquantel. Eta vs covariate plots were used to screen for additional covariates (eta shrinkage was acceptable [< 20%]), but no covariate effects were indicated.

The single covariate included in the final model was body weight, with effects on arpraziquantel and trans-4-OH-arpraziquantel apparent clearance and volume parameters fixed at the allometric scaling exponents, 0.75 and 1, respectively.

The table below presents the estimated structural model, IIV and residual error model parameter values for the final arpraziquantel and trans-4-OH-arpraziquantel POPPK model.

Table 14 Parameter Estimates of the Final Arpraziquantel and Trans-4-OH-arpraziquantel Population PK Model (Run pki0066)

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	IIV% [Shr]
CL/F [L/hr] [a]	574	12.9	429-719	135 [2.91]
Vc/F [L] [b]	28.2	29.8	11.8-44.7	2099 [2.48]
Ka1 (h^{-1})	0.324	12.0	0.248-0.400	61.6 [12.9]
Ka2 (h^{-1})	0.608	19.3	0.377-0.838	130 [15.4]
MTT (h)	3.48	9.74	2.81-4.14	81.5 [1.90]
NN	54.0	21.5	31.3-76.8	267 [21.5]
FR	0.684	3.15	0.642-0.727	15 FIX
CLM/F/fm[L/hr] [a]	4.71	7.74	4.00-5.42	53.1 [14.6]
VcM/F/fm [L] [b]	11.7	6.79	10.2-13.3	40.3 [21.8]
Residual variability	**Point Estimate**	**%RSE**	**95% CI**	**CV%**
Proportional Error R-PZQ	0.166	10.3	0.132-0.199	40.7
Additive Error R-PZQ (ng/mL)	28.0	28.2	12.5-43.5	5.29[c]
Proportional Error R-4-OH-PZQ	0.0277	18.4	0.0177-0.0377	16.6

Source: refer to Population PK Report, Table 10.
%CV = % coefficient of variation; %RSE = percent relative standard error; CL/F = apparent clearance; CLM/F/fm = metabolite clearance expressed as fraction metabolized; FR = fraction of dose which goes down transit compartment route; Ka1 = first-order absorption rate constant; Ka2 = first-order absorption rate constant from transit depot; MTT = mean transit time; NN = number of transit compartments; Shr = shrinkage; Vc/F = apparent volume of central compartment; VcM/F/fm = apparent volume of central compartment of metabolite expressed as fraction metabolized.
CV%= 100* $\sqrt{\omega^2}$ for log-normally distributed variability terms. If $\omega^2 > 0.15$, CV% = 100 * $\sqrt{e^{\omega^2}-1}$
RSE calculated as SE/parameter estimate * 100
Shrinkage (standard deviation based = 1-(sd(η)/sqrt(η))*100)
a Includes body weight effect fixed at 0.75.
b Includes body weight effect fixed at 1.
c SD.

The final POPPK model was used to generate individual exposure parameters for arpraziquantel and trans-4-OH-arpraziquantel (see tables below) to examine:

- Exposure-efficacy relationships in terms of egg reduction rate and cure/non-cure
- Exposure-safety relationships in terms of TEAEs, treatment-related TEAEs, gastrointestinal TEAEs and somnolence TEAEs

Arpraziquantel geometric mean AUC_{0-24} (CV%) values were 1.84 (129) µg.h/mL and 0.965 (86.4) µg.h/mL after 50 mg/kg and 60 mg/kg doses, respectively. Corresponding trans-4-OH-arpraziquantel geometric mean (CV%) AUC_{0-24} values were 195 (44.3) µg.h/mL and 175 (38.1) µg.h/mL. The trans-4-OH-arpraziquantel to arpraziquantel AUC ratio ranged between 37.5 and 512.

Table 15 Summary Arpraziquantel AUC and C_{max} Derived from Final Parent and Metabolite Mode (run pki0066/pki0040)

Parameter	AUC (µg.h/mL)		C_{max} (µg/mL)	
Dose arpraziquantel (mg/kg)	50	60	50	60
N	59	15	59	15
Geomean	1.84	0.965	0.460	0.204
Geomean CV%	129	86.4	169	80.1
Mean	2.91	1.23	0.802	0.253
SD	3.16	0.846	0.904	0.169
Median	1.81	1.04	0.518	0.232
Min	0.164	0.299	0.033	0.067
Max	19.65	2.89	4.85	0.662
Lower 90% CI	0.341	0.310	0.047	0.077
Upper 90% CI	7.19	2.58	1.908	0.499

Source: refer to Population PK Report, Table 14.

AUC = area under the time concentration curve; CI = confidence interval; C_{max} = maximum observed concentration; CV% = coefficient of variance; Geomean = geometric mean; Max = maximum; Min = minimum.

Table 16 Summary Trans-4-OH-arpraziquantel AUC and C_{max} Derived from Final Parent and Metabolite Model (run pki0066)

Parameter	AUC (µg.h/mL)		C_{max} (µg/mL)	
Dose arpraziquantel (mg/kg)	50	60	50	60
N	15	15	15	15
Geomean	195	175	27.0	20.8
Geomean CV%	44.3	38.1	51.7	42.4
Mean	210	187	30.0	22.4
SD	79.3	70.7	13.8	8.46
Median	203	173	28.5	23.5
Min	68.7	87.6	11.6	11.1
Max	376	371	59.6	37.6
Lower 90% CI	101	106	12.8	11.7
Upper 90% CI	353	286	49.3	35.9

Source: refer to Population PK Report, Table 15.

AUC = area under the time concentration curve; CI = confidence interval; C_{max} = maximum observed concentration; CV% = coefficient of variance; Geomean = geometric mean; Max = maximum; Min = minimum.

The final population PK model was used to simulate single dose concentration-time profiles of arpraziquantel and trans-4-OH-arpraziquantel for the intended 50 and 60 mg/kg dose levels of arpraziquantel and in the intended (PSAC) population. The applicant concluded that there was no relevant difference between AUC and C_{max} after administration of 50 mg/kg and 60 mg/kg arpraziquantel. This was considered to be consistent with the relative dose difference of 20% being substantially below the IIV in apparent clearance (%CV of 135%).

The applicant also mentioned a publication (Falcoz *et al*., 2022) which described the development of a POPPK model for arpraziquantel in 493 children from Africa (220 PSAC, 273 SAC, age range 2 to 15 years) with *S. mansoni* and *S. haematobium* and 171 adults from Lao (15 to 78 years) infected with *Opisthorchis viverrine*. The data came from 3 Phase 2a studies in which single (children and adults) or multiple (adults only) rac-PZQ doses ranged from 20 to 75 mg/kg/day in the presence of food. Blood samples were taken up to 24 hours post-dose using a dried blood spot technique, which is reported to lead to 10% underestimation vs. venous sampling.

A two-compartment disposition model, with allometric scaling and dual first-order and transit absorption, was developed to describe the arpraziquantel concentration-time profile.

Inversely, parallel functions of age described the apparent oral bioavailability and clearance maturation in children and aging in adults. Bioavailability decreased slightly in children with dose increases (dose

range 20 to 60 mg/kg) and by 35% in adults with multiple dosing (3 doses of 25 mg/kg). Arpraziquantel clearance for the combined children and adult population was estimated to be 657 L/h.

Special populations

Impaired renal function

This was not studied due to understanding of the elimination of L-PZQ after oral administration. The CrCL (Schwartz formula) in PSAC included in the POPPK analysis ranged from 67.0 to 335 mL/min/1.73 m^2. While 67 (91%) had CRCL ≥ 90 mL/min/1.73 m^2, 7 (9%) had mild renal impairment (CrCL 60 to 90 mL/min/1.73 m^2). The plots did not suggest an effect of CrCL on final model parameters.

Impaired hepatic function

No patients with hepatic impairment were included in arpraziquantel clinical studies.

A published study in patients with hepatic dysfunction showed higher rac-PZQ serum concentrations in Schistosomiasis patients with moderate liver dysfunction (Child-Pugh B) and severe liver dysfunction (Child-Pugh C) compared with patients without/mild (Child-Pugh A) hepatic dysfunction. The table shows 3.5- and 15-fold increases in mean AUC for the moderate and severe hepatic dysfunction groups, respectively, when compared to the normal hepatic function group.

Table 17 PK of Praziquantel in Four Groups of Patients with Varying Degrees of Liver Function Following Administration of 40mg/kg of rac-PZQ Under Fasting Conditions

Patient Group	AUC (µg/mL*h)	Cmax (µg/mL)	Tmax (h)	Half-life (h)
Normal hepatic function (Group 1)	3.02 ± 0.59	0.83 ± 0.52	1.48 ± 0.74	2.99 ± 1.28
Child-Pugh A (Group 2)	3.87 ± 2.44	0.93 ± 0.58	1.37 ± 0.61	4.66 ± 2.77
Child-Pugh B (Group 3)	10.72 ± 5.53	1.47 ± 0.74 [a,b]	2.21 ± 0.78 [a,b]	4.74 ± 2.16 [a]
Child-Pugh C (Group 4)	45.36 ± 17.51 [a,b,c]	3.57 ± 1.30 [a,b,c]	3.2 ± 1.05 [a,b,c]	8.45 ± 2.62 [a,b,c]

Source: refer to El Guiniady 1994.
Values are the mean ± standard deviation.
a p > 0.05 compared to Group 1
b p > 0.05 compared to Group 2
c p > 0.05 compared to Group 3

Watt *et al*. (1988) reported on PZQ PK in patients with *S. japonicum* and severe or moderate liver disease or no hepatic disease who received 60 mg/kg of rac-PZQ. There were 2.6- and 4.2-fold increases in mean AUC_{0-24} for the moderate and severe liver disease groups, respectively, compared to the group with no liver disease.

Table 18 PK of Praziquantel in Three Groups of Patients with Varying Degrees of Liver Function Following Administration of 60 mg/kg of rac-PZQ

Severity of Liver Disease	Half-life (h)	Tmax (h)	Cmax (µg/mL)	AUC_{0-24} (µg/mL*h)
No apparent liver disease	1.7 ± 0.8	2.5 ± 1.7	2.2 ± 1.1	8.9 ± 4.3
Moderate	2.2 ± 0.6	1.9 ± 1.3	5.0 ± 2.5	22.9 ± 15.8
Severe	2.3 ± 1.0	2.6 ± 2.0	8.2 ± 4.9	37.8 ± 24.5

Source: refer to Watt 1988.
Rac-PZQ was administered orally in 3 doses of 20 mg/kg each over 1 h.
Values are the mean ± standard deviation.

A study in nine patients with hepatosplenic schistosomiasis and different grades of periportal fibrosis also indicated higher rac-PZQ plasma concentrations (Mandour 1990) compared with healthy volunteers (n=6). There was a prolonged mean (± SD) half-life in those with hepatosplenic schistosomiasis compared to healthy volunteers (11.9 ± 5.4 and 2.3 ± 0.4 hours, respectively).

Weight

Additional analyses of L-PZQ concentrations in EMR200661-001
The study was confined to adult male subjects from 55-95 kg with mean BMI was 24.20 kg/m^2. The expanded model for the primary analysis, which included body weight and race/ethnicity ("White" and "Non-White") as covariates and the interactions weight*treatment and treatment*race, led to a Test/Reference ratio of 32.7% (i.e. lower than the 39.9% reported in the primary analysis). In the adjusted model (weight, treatment, period, sequence and race), body weight and race were significant factors on AUC at a significance level of 0.05.

POPPK model

Body weight in PSAC included in the POPPK analysis ranged from 8.3 kg to 24.5 kg. Body weight was the body size covariate and effects were included in the model by fixing the allometric exponents to 0.75 for CL/F and 1.0 for apparent volume of distribution (Vc/F) for both arpraziquantel and trans-4-OH-arpraziquantel. Scatterplots of model derived individual arpraziquantel AUC and dose-normalized AUC vs. weight did not show a consistent trend for arpraziquantel AUC across the weight range. The distribution of body weight adjusted apparent clearance (this being the parameter that determines the AUC following weight-based dosing) vs. age and body weight categories showed considerable overlap across the weight categories with no clinically relevant PK differences across the body weight range.

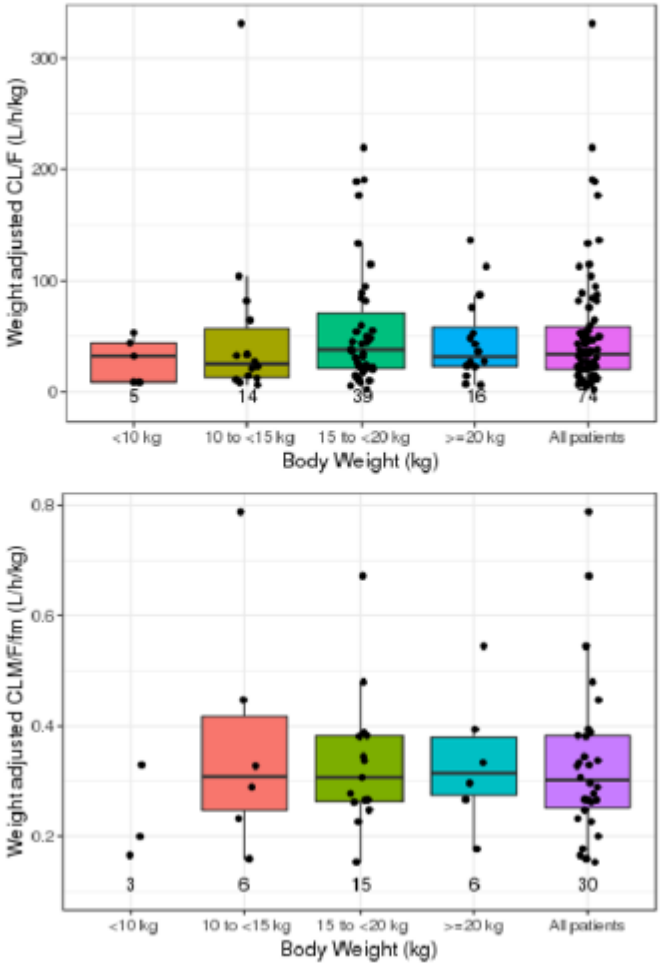


Figure 4 Box Plots Bodyweight Adjusted Arpraziquantel (upper) and Trans-4-OH-apraziquatel (lower) Apparent Clearance vs Weight Categories

Age

The plots of the ETAs for all parameters in the final population PK model vs age, which represent the unexplained variability in the model parameters as a function of age showed that there is no influence of age on the parameters in the final population PK model across the 10 months to 6.9 years age range. Scatterplots of the POPPK model derived individual arpraziquantel AUC and dose-normalized AUC data vs. age showed no consistent trend for arpraziquantel AUC by age.

Infection type and intensity

In MS200661-0003, arpraziquantel PK parameters (C_{max}, t_{max}, AUC_{0-t}) were similar in participants infected with *S. mansoni* or *S. haematobium*. In the POPPK analysis, 44/74 (59%) were infected with *S. mansoni* and 30 (41%) with *S. haematobium*. The majority of infections was light (58%). Of the 31 with moderate/heavy infection, 23 (74%) were infected with *S. mansoni*. Neither species of worm nor infection intensity influenced the parameters of the POPPK PK model.

Kovac *et al.* (2018) studied rac-PZQ PK in both PSAC (< 6 years) and SAC (6 to 15 years) infected with *S. mansoni* or *S. haematobium* in Ivory Coast. PK parameters differed statistically significantly ($p < 0.05$) between the PSAC and SAC age groups for *S. mansoni* infection but this trend was not observed with *S. haematobium*. Statistically significantly higher exposure was observed for the two rac-PZQ enantiomers in PSAC compared with SAC infected with *S. mansoni* ($p < 0.05$) while exposure for trans-4-OH-praziquantel was statistically significantly lower ($p < 0.05$).

With respect to disease intensity, Utzinger *et al*. (2000) reported on 253 school children in Ivory Coast who received 60 mg/kg rac-PZQ. There was a significant association between cure rate and intensity of infection (*S. mansoni*) with highest cure rates observed in light infections ($p < 0.01$).

Pharmacokinetic interaction studies

Transporters

Victim
Arpraziquantel is not a substrate for P-gp, BCRP, OATP 1B1, OATP1B3 and OCT 1. Trans-4-OH-arpraziquantel is not a substrate of OATP1B1, OATP1B3 and OCT1.

Perpetrator
Arpraziquantel was a weak inhibitor of P-gp with an IC50 value of 73.1 µM. Trans-4-OH-arpraziquantel was also an inhibitor of P-gp with an IC50 value of 247 µM. Arpraziquantel was a weak inhibitor of BCRP with an IC50 value of 12.1 µM. Trans-4-OH-arpraziquantel was also an inhibitor of BCRP with an IC50 value of 291 µM. Arpraziquantel was a weak inhibitor of OATP1B1, OATP1B3 and OCT1 with IC50 values of 654, 678 and 91 µM, respectively. Trans-4-OH-arpraziquantel did not inhibit OATP1B1 but weakly inhibited OATP1B3 and OCT1 with <50% inhibition observed at 1000 µM. The IC50 values for OATP1B3 and OCT1 were 1206 and 1003 µM, respectively. The potential of rac-PZQ to inhibit OCT1, OCT2, OCT3, MATE1 and MATE2K was investigated in transfected HEK293 cells. Results indicated that rac-PZQ is an inhibitor of OCT1, 2 and 3. The applicant concluded that the risk of a clinically relevant DDI via transporter inhibition by arpraziquantel cannot be excluded for sensitive substrates of P-gp, OATP1B1, OATP1B3 and OCT1.

CYP isoenzymes

Victim
1. Arpraziquantel is metabolised by various CYP enzymes, with substantial contributions from CYP 1A2, 2C9, 2C19, and 3A4/5 isoforms.
2. Clinical DDI studies for rac-PZQ show that the concomitant administration of strong and moderate CYP inhibitors ketoconazole, grapefruit juice, cimetidine and albendazole lead to AUC ratio increases up to 2-fold, i.e. weak to moderate effects.
3. Induction of multiple CYP enzymes led to clear decreases in exposure, with arpraziquantel AUC decreased 4-fold by efavirenz, and rac-PZQ exposure strongly (> 5-fold) reduced by rifampicin.

Perpetrator

- Arpraziquantel is a weak, reversible inhibitor of all CYP isoforms *in vitro*, especially CYP2C19 where an IC_{50} of 140 µM was determined.
- Trans-4-OH-arpraziquantel is a weaker reversible CYP inhibitor than arpraziquantel, with only inhibition of CYP 2B6 and 3A4/5 isoforms (testosterone) with measured IC_{50} values of 760 and 910 µM, respectively, and an estimated IC_{50} value of 1310 µM for CYP2C8.
- Arpraziquantel and trans-4-OH-apraziquantel were shown to have potential weak in vitro TDI of CYP3A4/5 with both midazolam and testosterone substrates. A clinically relevant time dependent inhibition by arpraziquantel or trans-4-OH-arpraziquantel is considered unlikely for CYP isoforms 2D6 and 3A4/5 but cannot be excluded.

Arpraziquantel activated PXRwt in a concentration-dependent manner with fold activation similar to rifampicin at 10 and 100 µM. At 1 µM arpraziquantel there was no apparent induction of CYP3A4 mRNA or protein expression. However, at 10 µM arpraziquantel, CYP3A4 mRNA and protein expression were similar to the 5.76- and 2.04-fold induction, respectively, observed for rifampicin. There was only a slight further increase in arpraziquantel CYP3A4 mRNA and protein expression at 100 µM. Overall, these results indicate that arpraziquantel is an in-vitro activator of PXRwt and can induce CYP3A4 mRNA and protein expression. However, as it is a single dose treatment with a short half-life, it is not anticipated for these in vitro effects to be clinically relevant. The applicant has not evaluated the CYP induction potential of trans-4-OH-arpraziquantel. The applicant concluded that no clinically relevant CYP-mediated drug interaction for arpraziquantel and trans-4-OH-arpraziquantel as perpetrators is expected.

In vivo

The applicant provided a table of published clinical DDI studies with rac-PZQ (see below).

Inducers of CYP isoenzymes (especially 2C9, 2C19 and 3A4/5), such as phenytoin and carbamazepine, may substantially reduce praziquantel levels by induction of first-pass hepatic metabolism. The applicant has proposed a contraindication for use of arpraziquantel with strong CYP inducers.

The applicant has placed a statement in section 4.5 of the SmPC to the effect that dexamethasone and efavirenz (termed moderate inducers) may reduce plasma levels of arpraziquantel.

Praziquantel plasma levels are reduced by chloroquine and glucose and increased during co-administration with CYP inhibitors (e.g. cimetidine, grapefruit juice and ketoconazole). The SmPC includes a statement not recommending co-administration with medicinal products that are inhibitors and grapefruit juice.

Table 19 Clinical DDI Studies Conducted for Rac-PZQ as Victim – Literature Overview

Comedication	Enzymes involved	Interaction	Population (n)	Rac-PZQ Dose	Rac-PZQ PK effect	Reference
Cimetidine	CYP 1A2, 2C9, 2C19, 2D6, 2E1, 3A4	Inhibition	HV (8)	3 x 25 mg/kg	~100% AUC increase	Jung 1997
Grapefruit juice	CYP 3A4 (small intestine)	Inhibition	HV (18)	1800 mg	90% AUC increase	Castro 2002
Ketoconazole	CYP 3A4	Inhibition	HV (10)	20 mg/kg	93% AUC increase	Ridtitid 2007
Ketoconazole	CYP 3A4	inhibition	HV (30)	20 mg/kg	75% AUC increase (rac-PZQ) 67% AUC increase (trans-4-OH-PZQ)	Nleya 2019
Efavirenz (multiple dose)	CYP2B6, 3A4	Inducer	HV (26)	40 mg/kg	R-PZQ, S-PZQ 4-fold decrease in AUC	Mutiti 2021
Ritonavir (multiple dose)	CYP1A2, 2B6, 2C, 3A (induction) CYP2D6, 3A4 (inhibition)	Inhibitor and Inducer	HV (26)	40 mg/kg	R-PZQ no change, S-PZQ 2-fold increase in AUC	Mutiti 2021
Rifampicin	CYP 2C9, 2C19, 3A4, P-gp	Inducer	HV (10)	40 mg/kg	PZQ undetectable in 7/10 HV, 85% decrease in AUC for 3/10 HV	Ridtitid 2002
Phenytoin	CYP 2B6, 2C8, 2C9, 2C19, 3A4	Inducer	HV (10)	25 mg/kg	PZQ AUC 74% decrease	Bittencourt 1992
Carbamazepine	CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4	Inducer	HV (10)	25 mg/kg	PZQ AUC 90% decrease	Bittencourt 1992
Dexamethasone	CYP 2B6, 2C8, 2C9, 3A4	Inducer	Patients (8)	50 mg/kg	PZQ AUC ~50% decrease	Vazquez 1987
Chloroquine	Unknown	Unknown	HV (8)	40 mg/kg	PZQ AUC reduction	Masimirembwa 1994

CYP = cytochrome p450; HV = human volunteers; n = number of volunteers; PK = pharmacokinetic; PZQ = praziquantel.

Furthermore, on request, the applicant considered the medicinal products most likely to be given with arpraziquantel and assessed their potential for clinically important interaction as shown below.

Table 20 Relevant co-medications for PSAC, metabolic pathway and possible clinically important effects

Comedication	Main Metabolic, Transporter or Clearance Pathway of Comedication	Potential Impact on Efficacy/Safety of Arpraziquantel	Potential Impact on Efficacy/Safety of the Coadministered Drug	References
Anticonvulsant drug: Carbamazepine	CYP2B6, 3A4	Rac-PZQ AUC decrease by 90%	No expected change in carbamazepine exposure	Bittencourt 1992, Kerr 1994
Anticonvulsant drug: Phenobarbital	CYP2C9, renal clearance	Arpraziquantel exposure may be decreased through induction of CYP enzymes	No expected change in phenobarbital exposure	Phenobarbital IE product information, Pacifici 2016
Anticonvulsant drug: Phenytoin	CYP2C9, 2C19	Rac-PZQ AUC decrease by 74%	No expected change in phenytoin exposure	Bittencourt 1992, Franco 2015

Comedication	Main Metabolic, Transporter or Clearance Pathway of Comedication	Potential Impact on Efficacy/Safety of Arpraziquantel	Potential Impact on Efficacy/Safety of the Coadministered Drug	References
Antifungal drug: Ketoconazole	CYP3A4	Rac-PZQ AUC increase by 75% (trans-4-OH-PZQ AUC increase by 67%)	No expected changes in ketoconazole exposure	Nleya 2019 Ketoconazole EMA product information
Anthelmintic drug: Albendazole	FMO3, CYP1A2, Pgp a	Arpraziquantel AUC increase by 65%	Albendazole active metabolites (ASOX) AUC increases ≥264%	Lima 2011
Antihistamine (H2 receptor antagoinist): Cimetidine	CYP 1A2, 2C9, 2C19, 2D6, 2E1, 3A4	Arpraziquantel AUC increase by 100%	No expected changes in cimetidine exposure	Jung 1997
Antimalaria, anthelmintic drug: Artemisin	CYP2A6; UGT 1A9, (DHA active metabolite)	Arpraziquantel AUC no change expected	Artemisin or metabolites no change expected	Artesunate Amivas EMA assessment report
Antimalaria drug: Chloroquine	CYP 2C8, 2D6 (hydroxychloroquine), 3A4, excretion unchanged	Rac-PZQ AUC decreased (4.17 vs 11.75 µg.h/mL)	No expected change in chloroquine exposure	Masimirembwa 1994, Rendic 2020
Antiretroviral drug: Efavirenz	CYP2B6, 3A4	Arpraziquantel AUC 4-fold decrease	No expected changed in efavirenz exposure	Mutiti 2021, Sustiva EMA product information
Antituberculosis drug: Rifampicin	Deacetylation by microsomal enzymes (possible esterase)	Rac-PZQ undetectable in 7/10 HV, AUC decrease by 85% and shorter half-life in 3/10 HV	No expected change in rifampicin exposure	Ridtitid 2002, Sarker 2016
Corticosteroid: Dexamethasone	CYP 2B6, 2C8, 2C9, 3A4	Rac-PZQ AUC decreases by 50%	No expected changed in dexamethasone exposure	Vazquez 1987
Nitroimidazole: Metronidazole	Hepatic metabolism	Increase in arpraziquantel exposure through inhibition of CYP 2C9 and 3A4 metabolism possible.	No change in metronidazole exposure expected	Miljkovic 2014
Macrolide: Erythromycin	CYP3A4, P-gp	Increase in arpraziquantel exposure through inhibition of CYP3A4 metabolism possible.	Erythromycin exposure may be increased through P-gp inhibition	Kanazawa 2001
Penicillin: Amoxicillin	Renal clearance	No change in arpraziquantel exposure expected	No change in amoxicillin exposure expected	Amoxil EMA product information

Comedication	Main Metabolic, Transporter or Clearance Pathway of Comedication	Potential Impact on Efficacy/Safety of Arpraziquantel	Potential Impact on Efficacy/Safety of the Coadministered Drug	References
Protease inhibitor: Ritonavir	CYP3A4	Arpraziquantel AUC no change	No expected change in ritonavir exposure	Mutiti 2021, Norvir EMA Prescribing Information
Sulfonamide: sulfamethoxazole	Renal clearance, NAT2, CYP2C9	No change in arpraziquantel exposure expected	No change in sulfamethoxazole exposure expected	Bactrim US product information, Huang 2021
Sulfonamide: Sulfasalazine	Intestinal bacterial metabolism, NAT2, BCRP	No change in arpraziquantel exposure expected	Arpraziquantel may increase sulfasalazine exposure through BCRP inhibition	Salazopyrin IE product information, Yamasaki 2008
Sulfonamide: Sulfadiazine	Excreted unchanged, NAT2, CYP2C9	No change in arpraziquantel exposure expected	No change in sulfadiazine exposure expected	Winter 2005, Polasek 2011

[a]Main metabolic enzyme or transporter protein liability known or hypothesized to be responsible for drug interaction with arpraziquantel or rac-PZQ.US

ASOX = albendazole sulfoxide; DHA = dihydroartemisinin; HV = Healthy Volunteers

2.6.2.2. Pharmacodynamics

Mechanism of action

The most obvious effects of rac-PZQ on schistosomes are tegumental disruption and the induction of muscular paralysis. These effects cause *Schistosoma mansoni* to loosen grip on the wall of mesenteric veins and migrate to the liver. There is some evidence that the anti-schistosomal effects are mediated by an alteration of intracellular calcium concentrations. Praziquantel also induces changes in the antigenicity of the parasite with the exposure or release of concealed antigens and causes alterations in schistosomal glucose metabolism, including decreases in glucose uptake, lactate release, glycogen content and ATP levels. Arpraziquantel has been determined to be the biologically active enantiomer against schistosome worms in non-clinical and in human clinical studies.

Primary and Secondary pharmacology

Primary pharmacology

Racemic praziquantel has been shown to be effective against adult trematodes (e.g. *Schistosoma, Paragonimus, Clonorchis, Opisthorchis, Metagonimus, Heterophyes*) independent of their location within the host body with exception of *Fasciola hepatica/gigantica*. Parasites living in the blood are almost equally susceptible to the drug as those in the intestine, lung, bladder and liver. Also, adult cestodes (e.g. *Taenia, Hymenolepis, Diphyllobothriurn, Mesocestoides*) and many larval cestodes can be successfully treated with rac-PZQ; however, rac-PZQ is not effective against nematodes.

The efficacy and pharmacokinetics of rac-PZQ were investigated in a mouse model of *Schistosoma mansoni* infection to determine the factors that drive its efficacy. Dose-response studies were performed with rac-PZQ with or without addition of an irreversible pan-cytochrome P450 (CYP)

inhibitor, 1-aminobenzotriazole. In addition, the efficacy of rac-PZQ in the presence of the CYP inducer dexamethasone was determined. The use of 1-aminobenzotriazole increased arpraziquantel plasma exposures in the systemic circulation by ~10- to 20-fold but the latter exposures were not predictive for efficacy against adult *Schistosoma mansoni*. The use of dexamethasone decreased plasma exposures of arpraziquantel in the systemic circulation by ~10-fold without reducing efficacy. It is suggested that the high arpraziquantel concentrations available before the hepatic first-pass metabolism in the liver drive the efficacy against *Schistosoma mansoni* adult worms residing in the mesenteric veins (Abla *et al*., 2017).

The *in-vitro* activities of rac-PZQ, R-cis- and S-cis- and R-trans- and S-trans-4-OH-arpraziquantel were investigated against adult worms and newly transformed schistosomula (Meister *et al*., 2014). For arpraziquantel, S-(+)-PZQ and trans- and cis-4-OH-arpraziquantel the IC_{50} concentrations at 72 h for adult *Schistosoma mansoni* were 0.02, 5.9, 4.1 and 2.4 µg/mL, respectively. In contrast, trans- and cis-4-OH-S-(+)-PZQ were not active at 100 µg/mL.

Additionally, the *in-vivo* activity and hepatic shift (i.e. the migration of the worms to the liver) produced by each PZQ enantiomer was explored in mice. Single oral doses of 400 mg/kg arpraziquantel and S-(+)-PZQ achieved worm burden reductions of 100% and 19%, respectively. Moreover, worms treated with S-(+)-PZQ displayed only a transient hepatic shift and returned to the mesenteric veins within 24 h. The authors concluded that arpraziquantel is the main effector molecule while S-(+)-PZQ and the metabolites do not play a significant role in the anti-schistosomal properties of rac-PZQ (Meister *et al*., 2014).

Table 21 In Vitro Activity of rac-PZQ, its Enantiomers, and 4-OH-Metabolites against Adult Schistosoma mansoni at 4 and 72 h Post-Incubation

	IC_{50} at 4 h (µg/mL)	IC_{50} at 72 h (µg/mL)	IC_{90} at 72 h (µg/mL)
rac-PZQ	0.1	0.05	0.4
Arpraziquantel	0.04	0.02	0.04
S-(+)-PZQ	5.7	5.9	17.9
trans-4-OH-rac-PZQ	16.7	7.9	3,694
trans-4-OH-arpraziquantel	13.4	4.1	58.4
trans-4-OH-S-(+)-PZQ	Not active at 100 µg/mL	Not active at 100 µg/mL	Not active at 100 µg/mL
cis-4-OH-Rac-PZQ	15.8	4.8	81.4
cis-4-OH-arpraziquantel	4.5	2.4	48.7
cis-4-OH-S-(+)-PZQ	Not active at 100 µg/mL	Not active at 100 µg/mL	Not active at 100 µg/mL

Source: (Meister et al., 2014).

S-(+)-PZQ: Dextro-praziquantel; IC_{50}: Concentration causing 50% inhibition; IC_{90}: Concentration causing 90% inhibition; PZQ: Praziquantel; rac-PZQ: Racemic praziquantel.

In-vitro and *in-vivo* studies were conducted to evaluate the activity of arpraziquantel, S-(+)-PZQ, rac-PZQ and the main human metabolite trans-4-OH-arpraziquantel against *Schistosoma haematobium* (Kovac *et al*., 2017). The IC_{50} values were determined for adult *Schistosoma haematobium*.

Arpraziquantel displayed the highest activity with an IC_{50} of 0.007 µg/mL at 4 h and 0.01 µg/mL at 72 h. The S-(+)-PZQ enantiomer was 501-fold less active (eudysmic ratio at 4 h), with IC_{50} values of 3.51 and 3.40 µg/mL at 4 and 72 h, respectively. Rac-PZQ and trans-4-OH-PZQ resulted in an IC_{50} of 0.03 µg/mL and 1.47 µg/mL, respectively, both at 4 and 72 h.

Table 22 In Vitro Activity of Arpraziquantel, rac-PZQ, S-(+)-PZQ and trans-4-OH-PZQ against Adult Worms of Schistosoma haematobium

	IC_{50} at 4 h [µg/mL]	IC_{50} at 72 h [µg/mL]	IC_{90} at 72 h [µg/mL]
Arpraziquantel	0.007	0.01	0.03
rac-PZQ	0.03	0.03	0.09
S-(+)-PZQ	3.51	3.40	5.98
Trans-4-OH-PZQ	1.47	1.47	3.31

Dose-response relationship studies were performed in golden Syrian hamsters harbouring a chronic *S. haematobium* infection. Arpraziquantel gave the highest worm burden reductions (WBRs) with 98.5%, 75.6% and 73.3% at doses of 125.0, 62.5 and 31.0 mg/kg, respectively. A single oral dose of 250 mg/kg rac-PZQ resulted in a WBR of 99.3%.

S-(+)-PZQ was highly active *in vivo* at 250 and 500 mg/kg with WBRs of 83.0 and 94.1%, respectively, whereas 125 mg/kg showed only moderate activity (WBR of 46.7%). The calculated ED_{50} for arpraziquantel and S-(+)-PZQ were 24.7 and 127.6 mg/kg, respectively, with a corresponding eudysmic ratio (the difference in pharmacologic activity between the two enantiomers) of 5.17.

Table 23 In Vivo Worm Burden Reduction in Golden Syrian Hamsters Following Different Single Oral Doses of Arpraziquantel, rac-PZQ and S-(+)-PZQ against Schistosoma haematobium

Compound/dose [mg/kg]	WBR [%]	ED_{50} [mg/kg]
Control		
Arpraziquantel		
125	98.5	24.7
62.5	75.6	
31	73.3	
rac-PZQ		
250	99.3	118.1
200	77.2	
150	66.1	
100	39.2	
S-(+)-PZQ		
500	94.1	127.6
250	83.0	
125	46.7	

Contribution of the major metabolite trans-4-OH-arpraziquantel to clinical activity

The major human metabolite trans-4-OH-arpraziquantel has weak in-vitro activity against *S. mansoni* and *S. haematobium* and is > 200-fold less active than arpraziquantel. In-vivo data indicate that trans-4-OH-praziquantel, the main human metabolite of rac-PZQ, contributes little or nothing to the overall pharmacological drug effect of rac-PZQ in nonclinical species (Meister *et al*., 2014; Kovac *et al*., 2017; Staudt *et al*., 1992; Xiao *et al*., 1991).

However, the plasma exposure to trans-4-OH-arpraziquantel in PSAC was substantially higher than that of arpraziquantel after dosing with the arpraziquantel paediatric formulation at 50 and 60 mg/kg in the Phase 3 study MS200661-0003. In addition, trans-4-OH-arpraziquantel is less plasma protein bound than arpraziquantel. To evaluate whether trans-4-OH-arpraziquantel could contribute to clinical activity of arpraziquantel, the relative contributions of each were assessed as the ratio of unbound AUC divided by the in-vitro activity against *S. mansoni* and *S. haematobium*. From these simplistic calculations, the percentage contribution of trans-4-OH-arpraziquantel was < 60.3% and 70.8% for *S. mansoni* and *S. haematobium*, respectively.

In contrast to *S. haematobium*, *S. mansoni* worms reside in the mesenteric veins so they are exposed to the higher pre-systemic arpraziquantel concentrations relative to the metabolite in plasma of the systemic circulation.

The effective contribution of trans-4-OH-arpraziquantel to efficacy in *S. mansoni* is therefore likely to be lower than calculated. When the equivalent calculation was performed for rac-PZQ (Cohort 2), the relative contribution of trans-4-OH-arpraziquantel to efficacy was 65% and 75% for *S. mansoni* and *S. haematobium*, respectively.

Table 24 Estimation of Potential Contribution of Trans-4-OH-Arpraziquantel to the Clinical Activity of Arpraziquantel in Preschool-Aged Children

Parameter	Arpraziquantel	Trans-4-OH-arpraziquantel
Geomean AUC (ng.h/mL)	523	83400
Human plasma fraction unbound	0.2	0.638
S. mansoni IC_{50} (ng/mL)	40	13400
S. haematobium IC_{50} (ng/mL)	7	1470
Activity contribution S. mansoni (%)	> 39.7	< 60.3
Activity contribution S. haematobium (%)	29.2	70.8

Source: refer to Study Reports MS200661-0003, DMPK 84-13, G-A-VIT-22-011, and Section 2.4.
Geomean AUC from n=15 participants in Cohort 4b dosed with 60 mg/kg arpraziquantel in MS200661-0003 where both arpraziquantel and trans-4-OH-arpraziquantel were measured.
In vitro activity against S. mansoni and S. haematobium assessed after 4 hours incubations.

The potential contribution of trans-4-OH-arpraziquantel to efficacy was assessed using box plots of trans-4-OH-arpraziquantel exposure vs. cure. Given the high cure rates, no obvious relationship was discernible between clinical response and exposure to trans-4-OH-arpraziquantel.

Secondary pharmacology

There have not been any clinical studies to explore the possibility of secondary pharmacodynamic effects in humans. In the Phase 1 study in humans, ECGs were obtained before dosing and at 4 h and 24 h post-dose as well as at 3-10 days post-dose. The CSR states that the Bazett formula was applied and traces were read manually by investigator/designate. However, the CSR also mentions that there were no significant changes in QTcF. The CSR reports that no clinically significant changes were observed. It appears that there was no collection of ECGs in Phase 2 and 3 studies in infected children.

Pharmacodynamic interactions with other medicinal products or substances

The artemisinins are known to have anti-trematodal effects, which is why the applicant removed any children who received any of these compounds for treatment of malaria from the primary analysis of efficacy.

Relationship between plasma concentration and effect

Exposure-efficacy analyses

S. mansoni worms reside in mesenteric veins and the pre-systemic/portal vein concentration is possibly the main driver for treatment efficacy. *S. haematobium* worms reside in urinary bladder veins and systemic exposure is possibly the main driver for treatment efficacy. Notwithstanding worm location, only systemic exposures in children in the Phase 3 study were available for characterisation of the exposure-efficacy relationship.

One of the objectives of the POPPK analysis was to estimate individual exposures to examine the arpraziquantel exposure-efficacy relationship in terms of cure/non-cure and individual egg reduction rate (iERR). The small sample size, high cure rate and the high parent exposure variability owing to the erratic profiles and limited PK sampling duration precluded a model-based exposure-efficacy analysis and only graphical analyses were performed.

The Box plots of arpraziquantel AUC and cure status, stratified by dose, visit, infection type and visit are shown below followed by corresponding box plots for trans-4-OH-arpraziquantel. There was no obvious relationship between cure status and exposure to arpraziquantel or trans-4-OH-arpraziquantel. There was also no obvious relationship between iERR (categorised as iERR < 90% or iERR > 90%) and exposure to either arpraziquantel or trans-4-OH-arpraziquantel (categorised as below or above the respective median exposure).

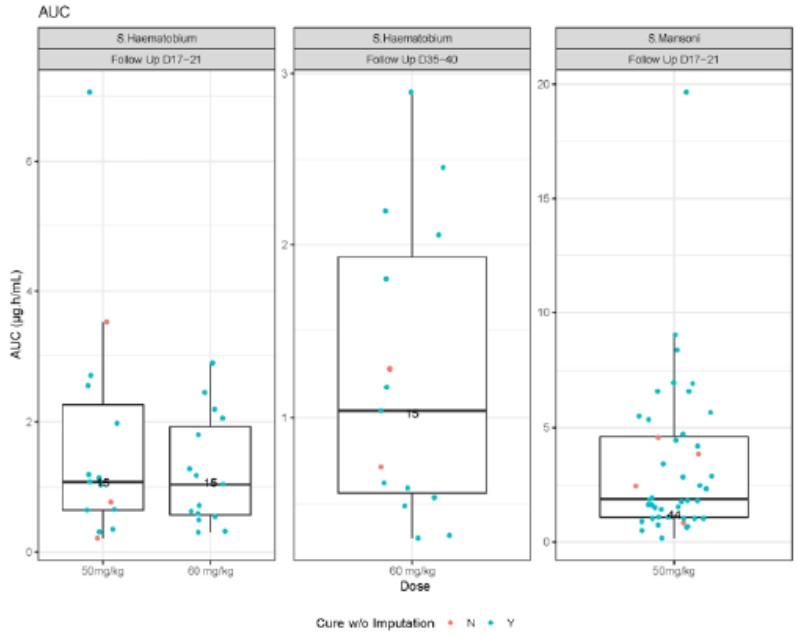


Figure 5 Box Plot of Arpraziquantel AUC by Visit, Infection type, Dose and Cure status

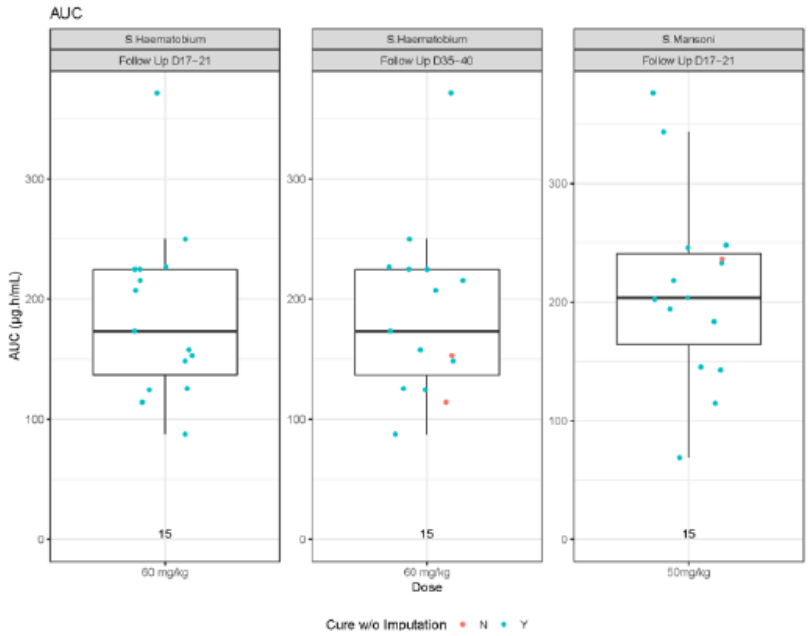


Figure 6 Box Plots of Trans-4-OH-arpraziquantel AUC by Visit, Infection type, Dose and Cure Status

Exposure-safety analyses

Box plots indicated that the incidence of TEAEs, treatment-related TEAEs, gastrointestinal TEAEs, and somnolence TEAEs was greater in participants infected with *S. mansoni*, particularly those with moderate/heavy intensity of infection and those with exposure of arpraziquantel above the median. Generally, the incidence of TEAEs, treatment-related TEAEs, gastrointestinal TEAEs and somnolence TEAEs was higher for either infection type when the arpraziquantel exposure (AUC or C_{max}) was above the median.

TEAEs and gastrointestinal TEAEs were of particular interest and logistic regression analyses were performed. Models were tested that evaluated the arpraziquantel exposure (AUC and C_{max}) in relation to the presence of an AE for an individual overall and which also included infection type as a covariate in the model. The analyses found that there was a higher probability of TEAEs and gastrointestinal TEAEs with increasing exposure of arpraziquantel. However, for gastrointestinal TEAEs, inclusion of infection type in the model indicated that an increased incidence of gastrointestinal TEAEs is related to infection with *S. mansoni*. Given that *S. mansoni* infected participants had a higher exposure than participants infected with *S. haematobium* this renders interpretation of the logistic regression analysis difficult.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Introduction

Much of the information on the PK of PZQ and its two enantiomers comes from the literature. In addition to published information, the applicant obtained PK data relevant to the 150 mg paediatric formulation in healthy S. African adults (Phase 1) and in infected children in endemic areas (Phase 3).

Given the well-established use of rac-PZQ, the aim was to identify doses using the L-PZQ paediatric formulation that provided similar plasma levels to those achieved when using the recommended dose of the licensed racemate and to descriptively compare the efficacy of the selected dose(s) of L-PZQ with that of a licensed racemate. In this regard, the Phase 1 study used 500 mg Cysticide tablets and the Phase 3 study used 600 mg Biltricide tablets as the licensed comparator, which was considered acceptable.

BCS classification

The applicant relies on a BCS class II classification for arpraziquantel. The in-vitro study 14MERCDP1R1 evaluated the permeability of arpraziquantel across Caco-2 cells, indicating that the P_{app} AB ranged from 40.5 to 47.5 x 10^{-6} cm/min and exceeded the high permeability positive control minoxidil, suggesting that arpraziquantel is a high permeability drug. However, based on the ICH M9, the assessment of permeability should preferentially be based on the extent of absorption derived from human PK studies (e.g. absolute bioavailability or mass balance). No absolute bioavailability nor mass balance studies were performed by the applicant.

A human mass balance study with rac-PZQ was performed by Patzschke *et al*. (1979). Results indicated that following oral doses of 14 and 46 mg/kg ^{14}C, 84% and 80% of administered

radioactivity, respectively, was recovered in urine in the 4 following days as the sum of unchanged praziquantel and metabolites.
The threshold to claim that a drug is highly permeable was not attained (85%) but can be explained by the absence of collection of ^{14}C recovery in the faeces. All together arpraziquantel is probably a BCS class II drug although a BCS class IV cannot be excluded.

Formulations
The three studies EMR200661-001, MS200661-0005 and MS200661-0003 each used one arpraziquantel formulation (TF1, TF2 and TF3, respectively). Furthermore, PK samples were collected in a different manner (e.g. K_3-EDTA, Na-heparinized and Li-heparin, respectively) and analyte concentrations were determined by various bioanalytical methods with no cross-over validation. Nevertheless, the POPPK model was developed only with PK data from MS200661-0003 so the matter is not further pursued.

The applicant states that the in-vitro dissolution profiles of TF2 and TF3 batches in biorelevant media can be regarded as similar, which is agreed. No comparative bioavailability study was performed to compare the three formulations and support extrapolation of PK properties / findings collected with TF1 to TF3, noting that there are no PK data available for TF2. However, the application rests mainly on the Phase 3 study, conducted with TF3 as intended for the market.

General PK properties of PZQ and/or L-PZQ

It has been reported that L-PZQ is not very highly bound to human plasma proteins (~80%) with lower binding of trans-4-OH-arpraziquantel.

Based on the joint POPPK model, using Phase 3 data from infected children, arpraziquantel Vc/F was estimated at 28.2 L (IIV of 2000%). Using the POPPK model for arpraziquantel alone, Vc/F was estimated at 57.9 L (allometric scaling with fixed exponent to 1 and by considering a median BW of 17.5 kg). However based on the results from the Phase 1 study performed in adults, with the NCA approach, Vz/F ranged from 4478 to 7155 L (Cohort A, C1, C2, E) and was 3685 L (range min max: 846-20100 L for Cohort B, Biltricide). Furthermore, based on the developed POPPK model by Falcoz *et al*. (PK data from adults and children where racemate PZQ was administered), Vtot/F was ~23643 L (allometric scaling with fixed exponent to 1 and by considering a median BW of 22 kg). To note, in this model no IIV for Vc/F or Vp/F was estimated, only an IIV on F (or BA) shared with CL/F, Vc/F and Vp/F. Therefore, based on the POPPK model from Falcoz *et al*., one can derive the Vtot/F for children with a median BW of 17.5 kg (~18806 L).

There is a discrepancy between estimates of V/F between the developed POPPK model and those estimated from Falcoz *et al*. as well as those estimated by NCA approach in EMR200661-001. The applicant attributes the different estimates of apparent distribution volume to the fact that these parameters have been characterised using data from different parts of the concentration versus time curve, dataset and conditions. This is agreed. However, the more relevant comparison between the value for V/F (57.9 L with 220% of IIV) with that of Falcoz *et al.* (1752 L without IIV) suggests that the fixed effect (V/F) estimated by Falcoz *et al.* would have been lower than 1752 L with a large random effect (IIV) or in contrast the one estimated by the PopPK model is too low. Furthermore the developed POPPK model developed by Falcoz *et al* used PK data from both adults and children whereas the model developed by the applicant used only PK data from children.

The published human mass balance study with ^{14}C-labelled rac-PZQ suggested that most (80%) of the administered dose of radioactivity was eliminated in urine and mostly within 24 h but a tiny fraction

(<0.02%) of this was associated with unchanged PZQ. The study indicated that elimination of rac-PZQ is almost completely via metabolism.

It seems that PZQ undergoes extensive first-pass hepatic metabolism so that most of the active parent drug does not reach the systemic circulation. It is expected that L-PZQ is also mainly cleared through metabolism. Small differences in first pass metabolism between individuals could result in substantially different L-PZQ exposures and explain at least in part the high IIV reported in the literature that was also observed in the applicant's studies.

For *S. mansoni*, considerable concentrations of L-PZQ may be expected in the mesenteric veins where the adult worms reside such that the high first pass metabolism should not be of importance to efficacy. For *S. haematobium*, only the L-PZQ that reaches the systemic circulation can exert efficacy against adult worms residing in the veins draining the bladder. The applicant considers that the low systemic bioavailability and high IIV for L-PZQ are not clinically relevant in light of the cure rates obtained. See further below and in section 3.

Phase 1 study
The PK data from rats suggested similar exposures were achieved when dosing with x mg/kg racemate or x/2 mg/kg L-PZQ. On this basis, the Phase 1 study primarily assessed the relative bioavailability of L-PZQ after a 20 mg/kg dose using the 150 mg paediatric formulation and after a 40 mg/kg dose using 500 mg Cysticide tablets. Table 9.2 in the CSR shows the number of whole tablets that were given to achieve as close to 20 mg/kg L-PZQ as possible. Generally, the administered doses in mg/kg approximated closely to the 20 mg/kg target dose. Statistical analyses used the adjusted parameter values.

In this primary comparison, the overall calculated relative bioavailability of L-PZQ when given as 20 mg/kg L-PZQ was ~40% of that when the same dose of L-PZQ was delivered using the racemate. The C_{max} was also lower when dosing with L-PZQ while dosing as the racemate gave a longer $t_{1/2}$ and slower clearance of L-PZQ.

There is no evidence of in-vivo inter-conversion between the two enantiomers. Therefore, it seems these results reflected an interaction between the two enantiomers in humans that yields higher exposures to L-PZQ when it is dosed with D-PZQ vs. dosing with L-PZQ alone. The finding led to selection of L-PZQ doses >20 mg/kg for the Phase 2 study.

The applicant states that the underlying mechanism for the lower L-PZQ exposures when the same dose is given alone rather than as racemate is unknown. However, several authors have investigated the phenomenon. It seems that L-PZQ is the preferred substrate for CYP1A1, 1A2, 2C9 and 2D6 while D-PZQ was preferred for CYP3A7 and 3A4, 3A5 and 2C19 had similar efficiency in metabolizing both PZQ enantiomers. Data from incubations of PZQ enantiomer mixtures with CYP2C9, 2C19, 3A4 and 3A5 were best fitted using models of competitive inhibition between the enantiomers. Overall, it seems that administration of L-PZQ as the racemate leads to slower elimination and therefore higher plasma exposures to L-PZQ compared to administration of L-PZQ alone.

The plasma exposure to the major metabolite (L)-trans-OH-PZQ was much greater than that to the parent compound L-PZQ regardless of dosing with L-PZQ alone or with the racemate. However, reflecting the lower bioavailability of L-PZQ when it was dosed alone, there was a somewhat lower $AUC_{0-\infty}$ of the metabolite after dosing with L-PZQ (116298.3 h*ng/mL) vs. dosing with the racemate (148768.7 h*ng/mL). The variability in $AUC_{0-\infty}$ for the metabolite, and generally the IIV for other PK parameters, was much less than observed for the parent compound.

Dose selection and dosing conditions for Phase 2 took into account the supra-proportionality for the L-PZQ adjusted C_{max} and AUC across the 10, 20 and 30 mg/kg doses after dose normalisation as well as the food effect observed when dosing L-PZQ alone as TF1. Administration of the L-PZQ 150 mg formulation directly in the mouth of adults gave broadly comparable but slightly higher (upper 90% CI for AUC GMR 134%) exposure compared to dosing after dispersion in water. However, the latter approach was taken in Phase 2 and 3 for the L-PZQ paediatric formulation and for the racemate tablets for reasons of palatability and ease of administration across the age range.

Overall, the Phase 1 study supported the doses and dosing conditions that were applied in Phase 2.

Phase 3 study
In African children infected with *S. mansoni* or *S. haematobium*, those assigned to the L-PZQ 150 mg formulation received either 50 mg/kg or 60 mg/kg as a single dose dispersed in water and taken after food. Venous blood samples for PK were obtained from the PK subset of 67 subjects, with variable numbers per cohort. The sampling scheme did not cover the terminal elimination phase and not all subjects had PK sampling up to 12 h post-dose. The observed data for L-PZQ underlined the variability in plasma profiles, many of which showed multiple peaks, and high inter-individual variability. The geometric mean AUC_{0-t} and C_{max} values after administration of 40 mg/kg Biltricide (i.e. 20 mg/kg L-PZQ) were around 17% and 19% of those who received 50 mg/kg L-PZQ alone, which was lower than the anticipated ratio of 40%.

To explore whether pre-systemic factors or differences in systemic elimination could explain the unexpectedly low plasma exposures in the Biltricide group in the Phase 3 study, the trans-4-OH-arpraziquantel/arpraziquantel ratios as a metric for metabolic clearance were compared between the rac-PZQ and arpraziquantel groups. The applicant concluded that there was similar metabolic clearance, suggesting that the most plausible potential reason for the lower-than-expected exposure of both arpraziquantel and the metabolite after administration of rac- PZQ was reduced absorption. This could be due to the omission of taste-masking additives, leading to incomplete ingestion of the dose.

By using the general formula of relative bioavailability $F_r = (AUC_{test}/AUC_{ref})*(D_{ref}/D_{test})$, the data from adults in EMR200661-001 in Cohort B (Ref) and Cohort A (test) suggest that F_r can be estimated at 39.5% (cross-over study design). By applying the same approach to MS200661-0003 (parallel design), considering Cohort 1b (Ref) and Cohort 1a (test) and applying the assumption of similar median BW, Fr can be estimated at 230%. The applicant attributed the discrepancy between the relative bioavailability of 39.5% in adults and 230% in children to the non-linear PK behaviour of the drug as a supra-proportional increase was demonstrated in adults (from 10 to 30 mg/kg) and the fact that exposure to Biltricide was unexpectedly low, which is agreed.

Although the geometric mean AUC_{0-t} and C_{max} after administration of 50 mg/kg L-PZQ in children aged 2-3 years were higher than those in children aged 4-6 years, the variability was large and the range of systemic exposures overlapped between the cohorts. Nevertheless, an effect age on L-PZQ exposures could not be excluded. With only two subjects sampled in Cohort 3 (3-24 months), no comment can be made on relative exposures for children aged < and > 2 years.

With no evidence of inter-conversion between L-PZQ and D-PZQ *in vivo*, and in keeping with the concept of competitive elimination of enantiomers, the PK data from the group that received the racemate indicated that the geometric mean AUC_{0-t} for D-PZQ was ~5.4-fold that for L-PZQ.

POPPK analysis
The POPPK model was built on a limited dataset due to the small number in the PK subset.

Arpraziquantel and its main metabolite were modelled simultaneously using a compartmental approach. The POPPK model has only a descriptive purpose and results from this analysis were used in the SmPC to reflect the Vc/F, CL/F and half-life estimates of arpraziquantel in the PSAC population.

The dataset used had a minimum weight ~8.5 kg and minimum age ~10 months. The applicant seeks approval from 3 months and 5 kg. Moreover, with almost no observed PK data in children aged <2 years, support for use below this age and at the lower weight range relies on the POPPK-predicted exposures and the limited safety and efficacy data available for these younger and lighter children.

The single covariate included in the final model was body weight, with effects on L-PZQ and trans-4-OH-arpraziquantel apparent clearance and volume parameters fixed at the allometric scaling exponents, 0.75 and 1, respectively. The POPPK model estimates for the L-PZQ AUC_{0-24} geometric mean (CV%) were 1.84 (129) µg.h/mL and 0.965 (86.4) µg.h/mL after 50 mg/kg and 60 mg/kg doses, respectively. Trans-4-OH-arpraziquantel AUC_{0-24} geometric means (CV%) were much higher at 195 (44.3) µg.h/mL and 175 (38.1) µg.h/mL after 50 mg/kg and 60 mg/kg doses, respectively. The AUC ratios (metabolite to parent) ratios ranged between 37.5 and 512. From simulated single dose concentration-time profiles, the applicant concluded that there was no relevant difference between L-PZQ AUC and C_{max} after administration of 50 mg/kg and 60 mg/kg doses, consistent with a relative dose difference (20%) below the IIV for apparent clearance (135%).

The applicant points to a published POPPK model for L-PZQ based on data from 493 children aged 2-15 years with *S. mansoni* or *S. haematobium.* Bioavailability decreased slightly in children with dose increases (dose range 20 to 60 mg/kg) and by 35% in adults with multiple dosing (3 doses of 25 mg/kg). Arpraziquantel clearance for the combined children and adult population was estimated to be 657 L/h.

Given the data from the applicant's Phase 3 study, it cannot be ruled out that the lack of difference in plasma L-PZQ between groups that received 50 mg/kg or 60 mg/kg L-PZQ could in part reflect lower bioavailability at the higher dose. Nevertheless, no firm conclusions can be drawn from the limited dataset in Phase 3. Also, despite the applicant's impression that there was no clear difference in plasma exposures to L-PZQ between the two dose groups, the efficacy data do support a 60 mg/kg dose for *S. haematobium*.

Special populations

Based on what is known about metabolism and excretion, renal impairment is not expected to affect L-PZQ PK but increased plasma exposures in subjects with moderate or severe liver dysfunction cannot be ruled out based on the literature. The target population for arpraziquantel is not expected to include large numbers with such degrees of hepatic impairment and it is unclear if the higher exposures that have been reported would be associated with a marked reduction in tolerability. Nevertheless, the SmPC recommends caution when using arpraziquantel in children with severe hepatic impairment and/or hepatosplenic schistosomiasis.

In the POPPK model, the scatterplots of model-derived individual L-PZQ AUC and dose-normalised AUC vs. weight did not show a consistent trend across the weight range. Furthermore, the distribution of body weight adjusted apparent clearance showed considerable overlap across the weight categories indicating no clinically relevant PK differences across the body weight range for PSAC.

Age and gender were not significant covariates in the POPPK analysis after the effect of body weight was considered in the model allometrically with standard allometric exponents (1.0 for apparent volume and 0.75 for apparent clearance).

Effect of disease factors
When taking into account the variability and ranges, the L-PZQ C_{max}, t_{max} and AUC_{0-t} were broadly similar regardless of infection with *S. mansoni* or *S. haematobium*.

The majority of infections in the PK population was light (58%) and 23/31 with moderate/heavy infection were infected with *S. mansoni*. The POPPK model did not find that infection intensity influenced the L-PZQ PK parameters in the population studied, all of whom were <6 years old.

Drug-drug interactions
The *in-vitro* data, which are described and considered in detail in the nonclinical report, generally suggest that L-PZQ is more likely to be a victim than a perpetrator of DDIs. However, an effect of co-administrations on systemic L-PZQ concentrations may not necessarily have an effect on efficacy at least against *S. mansoni* unless the interaction occurs at the level of gut absorption so that concentrations are reduced in the mesenteric veins. If co-administration leads to a reduction in plasma L-PZQ, a reduction in efficacy against *S. haematobium* cannot be dismissed. If co-administration leads to an increase in L-PZQ in plasma, an effect on safety cannot be ruled out.

As a victim, published data for rac-PZQ indicate that concomitant administration with strong and moderate CYP inhibitors (such as ketoconazole, grapefruit juice, cimetidine and albendazole) lead to AUC ratio increases up to 2-fold, i.e. weak to moderate effects. Induction of multiple CYP enzymes led to clear decreases in exposure. For example, the arpraziquantel AUC decreased by 4-fold when given with efavirenz and rac-PZQ was reduced > 5-fold by rifampicin. Inducers of CYP isoenzymes (especially 2C9, 2C19 and 3A4/5), such as phenytoin and carbamazepine, may substantially reduce L-PZQ levels in plasma by induction of first-pass hepatic metabolism. Also, it may be important to note that dexamethasone administered 24 h before rac-PZQ reduced bioavailability by approximately 50%. Praziquantel plasma levels are also reduced by chloroquine and glucose.

The applicant concluded that the risk of a clinically relevant DDI via transporter inhibition by arpraziquantel cannot be excluded for sensitive substrates of P-gp, OATP1B1, OATP1B3 and OCT1. Also, arpraziquantel and trans-4-OH-apraziquantel were shown to exert weak time-dependent inhibition of CYP3A4/5 based on results with midazolam and testosterone as substrates. The applicant considered that a clinically relevant time dependent inhibition by arpraziquantel or trans-4-OH-arpraziquantel is unlikely for CYP2D6 and 3A4/5 but cannot be excluded. As a single dose treatment with a short half-life, it is not anticipated that L-PZQ will have a clinically relevant induction effect.

Although not all the *in-vitro* studies used maximum drug concentrations that met the recommended levels in CHMP guidance, the important conclusions have been reflected in section 4.5 of the SmPC. The content of this section also reflects the medicinal products most likely to be co-administered with arpraziquantel. Importantly, co-administration with strong inducers of CYP450 isoenzymes has been contraindicated.

Pharmacodynamics

In light of the longstanding clinical experience with rac-PZQ and the literature pertaining to the two enantiomers, it is acceptable that the applicant did not conduct additional studies to explore the primary pharmacology of arpraziquantel against trematodes, including *Schistosoma* spp.

Whereas the adult worms of *S. mansoni* and *S. haematobium* reside in different venous distributions in humans, their life cycles are otherwise similar. Accumulated evidence suggests that rac-PZQ causes the adult worms to loosen their grip on the wall of veins. The mechanism appears to involve alterations in schistosomal glucose metabolism following induction of changes in intracellular calcium concentrations.

Several publications have concluded that arpraziquantel (L-PZQ) is the biologically active enantiomer against schistosome worms. For example, in studies that investigated the effect of PZQ on Ca^{2+} entry and *S. mansoni* adult worm paralysis, arpraziquantel was 50-fold more active (based on EC_{50}) than S-(+)-PZQ and about 35-fold more active than the major metabolite trans-4-OH-arpraziquantel. However, the efficacy of rac-PZQ and L-PZQ against *S. mansoni* does not appear to be directly related to plasma exposures. Rather, the applicant opines that the high arpraziquantel concentrations available before hepatic first-pass metabolism in the liver drives the efficacy against *Schistosoma mansoni* adult worms residing in the mesenteric veins.

Based on IC_{50} values determined for adult *Schistosoma haematobium*, L-PZQ was much more active than D-PZQ. In hamsters, L-PZQ resulted in a WBR of 98.5% after a dose of 125 mg/kg. In comparison, 250 mg/kg rac-PZQ resulted in a WBR of 99.3% while D-PZQ at 125 mg/kg showed a WBR of 46.7%. The calculated eudysmic ratio was 5.17.

Although the nonclinical data suggested that the major human metabolite of L-PZQ (trans-4-OH-arpraziquantel) has weak in-vitro and in-vivo activity against *S. mansoni* and *S. haematobium*, the applicant has considered the PK data for the metabolite.

Noting that the plasma exposure to trans-4-OH-arpraziquantel in the Phase 3 study was substantially higher than that of arpraziquantel and that the major metabolite has lower binding to plasma proteins, the applicant conducted some calculations to assess the potential contribution of the metabolite to clinical efficacy. From these simplistic calculations, the percentage contribution of trans-4-OH-arpraziquantel was < 60.3% and 70.8% for *S. mansoni* and *S. haematobium*, respectively. Since *S. mansoni* worms reside in the mesenteric veins, so would be exposed to high arpraziquantel concentrations, the contribution of trans-4-OH-arpraziquantel to efficacy against *S. mansoni* is probably lower then estimated. In contrast, since *S. haematobium* worms reside in urinary bladder veins, it is proposed that systemic exposure is likely to be the main driver for efficacy against this species.

While the applicant did attempt to examine the relationship between plasma concentrations of L-PZQ and trans-4-OH-arpraziquantel and efficacy, the exercise was limited by the PK subset sample size, high cure rate and the high parent exposure variability. Therefore, the relationship between plasma concentrations and efficacy against the two species remains unclear.

Furthermore, the applicant attempted an analysis of the arpraziquantel exposure-safety relationship. The box plots indicated that the incidence of TEAEs, treatment-related TEAEs, gastrointestinal and somnolence TEAEs was greater in children infected with *S. mansoni*, especially if there was a moderate/heavy intensity of infection, and those with arpraziquantel plasma concentrations (AUC and

C_{max}; using POPPK model) above the median. However, it is uncertain to what extent the gastrointestinal AEs were related to the species rather than to the treatment.

2.6.4. Conclusions on clinical pharmacology

Arpraziquantel (L-PZQ) appears to be the driver of the clinical efficacy of rac-PZQ. The relationship between the plasma concentrations of L-PZQ and either safety or efficacy is unclear. There are several reasons for this, including but not confined to, the high variability in PK for parent drug in the target population and the difference in location of the adult worms. Nevertheless, the efficacy of rac-PZQ is well established against both species. With high CV% values and few data in the youngest children, the use of arpraziquantel from 3 months and 5 kg is based on the POPPK-predicted exposures.

2.6.5. Clinical efficacy

Clinical studies

The efficacy of arpraziquantel (L-PZQ) was evaluated in two clinical studies (Phase 2 - 0005 and Phase 3 - 0003) in children infected with *S. mansoni* or *S. haematobium* aged 3 months to 6 years.

Table 25 Studies supporting the efficacy of arpraziquantel (L-PZQ)

Feature	MS200661-0005 Part 1	MS200661-0005 Part 2	MS200661-0003
Study start	12 June 2016		02 Sep 2019
Study end	17 Nov 2018		07 Aug 2021
Number of Study Centers	1		2
Location(s)	District Hospital of Man Ivory Coast		District Hospital of Man, Homa Bay Hospital Ivory Coast, Kenya
Setting	Outpatient		Outpatient
Type	Prospective clinical Phase 2		Prospective clinical Phase 3
Design	Open-label		Open-label, confirmatory
Study Objective	Dose finding	Efficacy and Safety	Efficacy and Safety
Statistical considerations	Clinical CRs, i.e., the proportions of participants cured, assessed by Kato-Katz 14 to 21 days after treatment for S. mansoni were calculated for each treatment arm on the mITT population; 95% CIs were calculated using the Clopper-Pearson (exact) method.		Clinical CRs, i.e., the proportions of participants cured, (as assessed by the Kato-Katz method 17 to 21 days after treatment for S. mansoni; 17 to 21 days as well as 35 to 40 days after treatment by urine filtration for S. haematobium). The 95% CIs were calculated based on the Clopper-Pearson (exact) method.

Population	Participants aged 2 to 6 years with a diagnosis of S. mansoni infection	Participants aged 3 to 24 months with a diagnosis of S. mansoni infection	Participants aged 3 months to 6 years with a diagnosis of S. mansoni or S. haematobium infection
arpraziquantel dose[a]	30, 45, or 60 mg/kg	50 mg/kg	50 mg/kg, 60 mg/kg
rac-PZQ ODT dose[a]	40 mg/kg, 60 mg/kg		
Biltricide dose[a]	3 × 20 mg/kg TID, 40 mg/kg		40 mg/kg[b]
Duration of treatment	Single day, multiple or single dose treatment	Single day, single dose treatment	Single day, single dose treatment
Diagnosis Inclusion Criteria	S. mansoni positive diagnosis (> 1 egg in stool/1 occasion) according to WHO classification		Cohorts 1, 2, and 3: S. mansoni positive diagnosis (≥ 1 egg in stool/1 occasion) according to WHO classification Cohort 4: S. haematobium positive diagnosis (≥ 1 egg in urine/1 occasion) according to WHO classification
Primary endpoint	Clinical CR (as assessed by Kato-Katz method)		Clinical CR (as assessed by Kato-Katz method or urine filtration method)
Additional efficacy endpoints	ERR, CR (as assessed by POC-CCA® test)		ERR, CR (as assessed by POC-CCA test for S. mansoni-infected children)

2.6.5.1. Dose response study

Study MS200661-0005

This randomised, open-label explored the safety and efficacy of various doses of rac-PZQ and L-PZQ compared to licensed rac-PZQ (Biltricide) tablets in PSAC with *S. mansoni* in the Ivory Coast.

Part 1 compared Biltricide at two recommended doses with various doses of rac-PZQ and L-PZQ administered as paediatric formulation in children aged 2-6 years. Randomisation to one of the 7 cohorts was stratified by infection severity to achieve ~40% moderate/heavy and ~60% light infections.

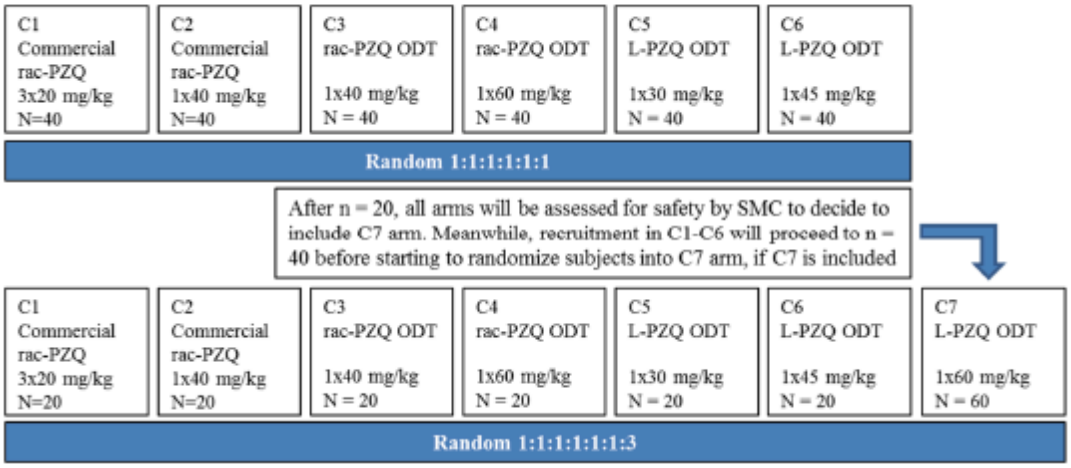


Figure 7 Schematic Representation of Part 1 of the Study

Part 2 assessed the safety and efficacy of the formulation and mg/kg dose selected from Part 1 in children aged 3-24 months infected with *S. mansoni.*

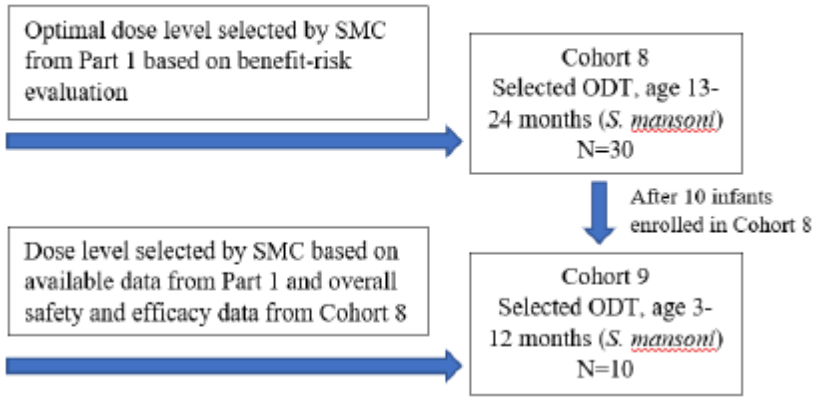


Figure 8 Schematic Representation of Part 2 of the Study

Eligible children were aged 2-6 years and at least 8 kg (Part 1) and 3-24 months and at least 4 kg (Part 2). All had *S. mansoni* mono-infection with positive egg counts in stool (>1 egg/1 occasion) and infection loads were classified using WHO criteria as:

- light (1-99 eggs per gram of stool)
- moderate (100-399 eggs per gram of stool)
- heavy (≥ 400 eggs per gram of stool) infections

Children were excluded if they had treatment within 4 weeks prior to study screening with PZQ, other anti-helminthic, anti-malarial or anti-retroviral compounds or other medication that might affect the PK of PZQ (e.g. carbamazepine, phenytoin, glucocorticosteroids, chloroquine, rifampicin, cimetidine).

Children with a positive malaria Rapid Diagnostic Test (RDT) result were treated according to national guidelines. Children who required malaria treatment after receiving study treatment were not withdrawn from the study. However, because some anti-malarial agents (artemisinin derivatives) have activity against *S. mansoni*, children treated with an artemisinin after receiving assigned study drug were excluded from the primary efficacy analysis.

Treatments were as shown in the figures above.

- rac-PZQ and L-PZQ tablets were 150 mg strength and administered as a mg/kg single dose
- commercial rac-PZQ was Biltricide 600 mg scored tablets dosed at 40 mg/kg or 3 x 20 mg/kg (total 60 mg/kg)

The target doses were calculated but then there was some rounding to enable dosing with multiples of whole 150 mg tablets and whole, ½ or ¼ tablets of Biltricide as needed.

The 150 mg tablets were dispersed in water. Biltricide 600 mg tablets were crushed and suspended in water. Dosing occurred after a meal of composition dictated by local customs and kept the same for all subjects in the 2-6 years age group.

The objectives and endpoints are summarised in *Table **22***.
The primary efficacy endpoint (clinical CR defined as no *S. mansoni* eggs in the stools 14-21 days after treatment) was assessed by the Kato-Katz method and was conducted at the study site hospital. Egg counts per gram of stool were determined at Screening and at 14-21 days after treatment. At each time point two stool samples were collected from each subject on different days within a maximum of five days apart. Three Kato-Katz thick smears were prepared from each stool sample and read under the microscope. Eggs per gram of stool was calculated as the sum of egg counts per subject obtained from two stool samples with three Kato-Katz thick smears each, multiplied by a factor of four.

For each treatment arm, the CR corresponded to the percentage of subjects becoming egg-negative 14-21 days after treatment. If no stool sample was collected at 14-21 days after treatment, the subject was imputed as uncured.

Table 26 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
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*.	Efficacy: • Clinical cure defined as no parasite eggs in the stools (*S. mansoni* infections) 14-21 days after treatment. Egg counts were determined by the Kato-Katz method.

Secondary	
Part 1: • To determine the safety of different doses of rac-PZQ ODT and L-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* • To explore the dose-response relationship for L-PZQ ODT and rac-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* • To assess the efficacy and safety of rac-PZQ commercial tablet at 20 mg/kg tid dose administration and at 40 mg/kg single dose administration in children aged 2 to 6 years infected with *S. mansoni* • To assess the acceptability in terms of ease of administration of the rac-PZQ ODT and L-PZQ ODT in children aged 2 to 6 years infected with *S. mansoni* Part 2: • To assess the acceptability in terms of ease of administration of the selected ODTs (rac-PZQ or L-PZQ) in 3- to 24-month infants infected with *S. mansoni* • To explore the dose- response relationship for L-PZQ ODT and rac-PZQ ODT in 3- to 24-month infants infected with *S. mansoni*	Efficacy: • Egg Reduction Rate (ERR, %) calculated based on the arithmetic (and geometric) mean egg count per gram of stool before and 14-21 days after treatment (as determined by Kato-Katz method). • Cure defined as absence of parasite antigens in the urine as assessed by the commercially available POC-CCA assay for *S. mansoni*. Safety and tolerability: • Changes in laboratory safety parameters and vital signs (body temperature, blood pressure and pulse rate) • Occurrence, nature, severity and outcome of adverse events • Occurrence of Adverse Drug Reactions per treatment group

The study was exploratory such that there was no hypothesis testing for the primary endpoint. The sample size was based on the minimum number of subjects to reach a meaningful precision of the CR in each arm, taking into account the stratification factor. A minimum clinical meaningful CR was considered as equal to 70%. With 50 evaluable subjects enrolled, stratified as 40% moderate/heavy and 60% light, the corresponding 95% CI lower bound of an observed CR of 70% would be above ~58%, depending on potential difference between the strata. Assuming an approximate 17% dropout rate, 60 subjects per arm were to be randomised to ensure at least 50 evaluable subjects per arm.

A statistical analysis plan (SAP) describing the rules and conventions for presentation and analysis of data was prepared and signed off (V 2.0, 31 January 2018) before conducting any formal analyses.

Three analysis sets were employed:

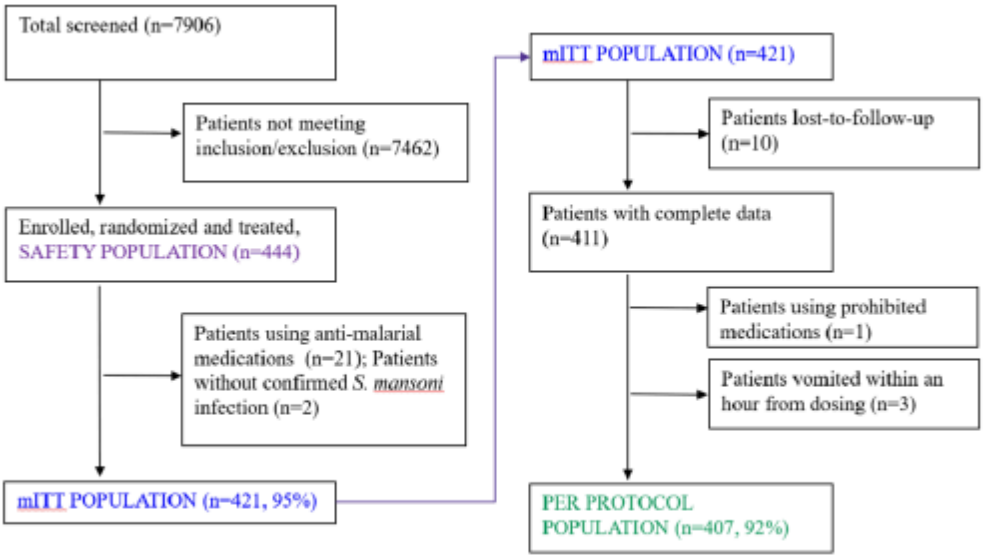
- Safety analysis set defined as all subjects who took any dose
- Modified intention-to-treat analysis set (mITT) population included all randomised subjects who had a baseline measurement for the efficacy variable. Children who required anti-malarial treatment following IMP administration were excluded from the mITT analysis set
- Per protocol analysis set (PP) included mITT subjects who did not take any prohibited medications or had any other clinically important protocol deviations, including vomiting within the first hour of dosing

There was no hypothesis testing. Efficacy data were analysed descriptively. Point estimates and 95% confidence intervals (CI) were calculated for each treatment arm. The calculation of 95% CIs for CRs relied on the Clopper-Pearson (exact) method. For egg reduction rates, the CIs were calculated by a resampling approach as outlined in the SAP.

The primary analysis was based on the mITT analysis population with imputations and observed data (i.e. mITT without imputation) were analysed as a sensitivity analysis.

Results

There were 444 children enrolled and treated in Part 1, of which 23 were excluded from the efficacy analysis set (mITT population) mainly because of concomitant anti-malarial medication.



Note: Percentages were out of n=444 treated. Reasons for exclusions are hierarchical, i.e., subjects with multiple reasons are not counted more than once.

Figure 9 Disposition of Subjects: Part 1

In Part 2, the high screen failure rate reflected very low infection rates in children aged 3-24 months.

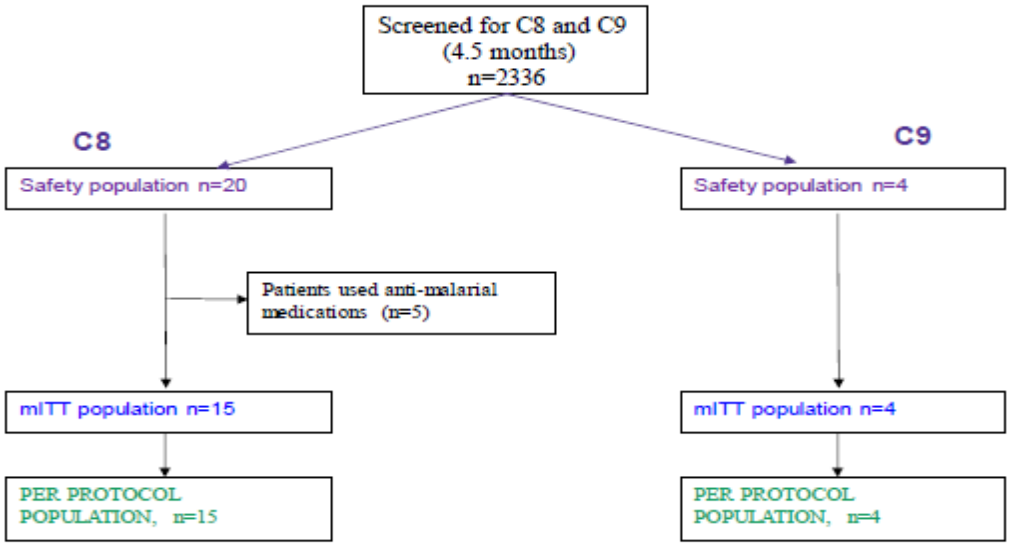


Figure 10 Disposition of Subjects: Part 2

All subjects were black, 53.8% were male and Cohorts 1-7 were balanced with respect to median age, weight, height and BMI. Most subjects in Part 1 (60.8%) had light infection.

Table 27 Infection Load at Baseline (Stratification) Part 1 and Part 2 – Safety Analysis Set

Infection intensity	Cohort 1[a] (N=60) n (%)	Cohort 2[a] (N=60) n (%)	Cohort 3[a] (N=60) n (%)	Cohort 4[a] (N=60) n (%)	Cohort 5[a] (N=60) n (%)	Cohort 6[a] (N=60) n (%)	Cohort 7[a] (N=60) n (%)	Cohort 8[a] (N=20) n (%)	Cohort 9[a] (N=4) n (%)	Total (N=444) n (%)
Light	36 (60.0)	35 (58.3)	36 (60.0)	35 (58.3)	36 (60.0)	36 (60.0)	36 (60.0)	16 (80.0)	4 (100.0)	270 (60.8)
Moderate/Heavy	24 (40.0)	25 (41.7)	24 (40.0)	24 (40.0)	23 (38.3)	24 (40.0)	24 (40.0)	4 (20.0)	0	172 (38.7)
Negative	0	0	0	1 (1.7)	1 (1.7)	0	0	0	0	2 (0.5)

Source: Table 15.1.4.3

[a] Cohort 1: Biltricide 3x20 mg/kg; Cohort 2: Biltricide 40 mg/kg; Cohort 3: rac-PZQ ODT 40 mg/kg; Cohort 4: rac-PZQ ODT 60 mg/kg; Cohort 5: L-PZQ ODT 30 mg/kg; Cohort 6: L-PZQ ODT 45 mg/kg; Cohort 7: L-PZQ ODT 60 mg/kg; Cohort 8: L-PZQ ODT 50 mg/kg; Cohort 9: L-PZQ ODT 50 mg/kg.

The primary analysis was based on the mITT analysis set with imputation of missing data. The CR in all cohorts was ≥70 %, with the highest CR in Cohort 6 (L-PZQ 45 mg/kg), Cohort 7 (L-PZQ 60 mg/kg) and Cohort 1 (Biltricide 3 x 20 mg/kg). The lowest CR was observed in Cohort 2 (Biltricide 1x 40 mg/kg) but CIs overlapped for all cohorts. The results for the mITT population without imputation and PP population gave similar findings.

Table 28 Overall Clinical Cure Rate (%) by Kato-Katz Method (Point Estimate and Exact 95% confidence interval – mITT and PP analysis sets)

Analysis set	Cohort 1[a] (N=57)	Cohort 2[a] (N=58)	Cohort 3[a] (N=58)	Cohort 4[a] (N=58)	Cohort 5[a] (N=56)	Cohort 6[a] (N=57)	Cohort 7[a] (N=58)	Cohort 8[b] (N=15)	Cohort 9[b] (N=4)
mITT with imputation	89.5 [78.5, 96.0]	74.1 [61.0, 84.7]	81.0 [68.6, 90.1]	79.3 [66.6, 88.8]	78.6 [65.6, 88.4]	86.0 [74.2, 93.7]	89.7 [78.8, 96.1]	93.3 [68.1, 99.8]	100 [39.8, 100]
mITT without imputation	91.1 [80.4, 97.0]	79.6 [66.5, 89.4]	82.5 [70.1, 91.3]	79.3 [66.6, 88.8]	81.5 [68.6, 90.7]	89.1 [77.8, 95.9]	89.7 [78.8, 96.1]	93.3 [68.1, 99.8]	100 [39.8, 100]
PP	90.7 [79.7, 96.9]	79.6 [66.5, 89.4]	82.5 [70.1, 91.3]	79.3 [66.6, 88.8]	81.5 [68.6, 90.7]	89.1 [77.8, 95.9]	91.1 [80.4, 97.0]	93.3 [68.1, 99.8]	100 [39.8, 100]

Source: Tables 15.2.1.1a, 15.2.1.2a and 15.2.1.3a

[a] Part 1: Cohort 1 (2-6 years): Biltricide 3x20 mg/kg; Cohort 2: Biltricide 40 mg/kg; Cohort 3: rac-PZQ ODT 40 mg/kg; Cohort 4: rac-PZQ ODT 60 mg/kg; Cohort 5: L-PZQ ODT 30 mg/kg; Cohort 6: L-PZQ ODT 45 mg/kg; Cohort 7: L-PZQ ODT 60 mg/kg.

[b] Part 2: Cohorts 8 (13-24 months) and 9 (3-12 months): L-PZQ ODT 50 mg/kg.

In Part 2, Cohorts 8 and 9 (L-PZQ 50 mg/kg) had CRs above 90% (14/15 and 4/4 subjects).

Following stratification of the analysis sets (see table for strata), regression analysis revealed that infection intensity appeared to be the only significant covariate (apart from treatment) with respect to CR. Generally, CRs were higher in light infections vs. moderate/heavy infections, with an estimated odds ratio (moderate/heavy vs. light) of 0.37 (95% CI: 0.21 – 0.63).

Age was not a significant covariate but all children aged <2 years received L-PZQ at 50 mg/kg. The odds ratio for cure when comparing 2-4 and 4-6 year-olds was 1.31 (95% CI 0.68, 2.54), which suggests that the lower age group was not more difficult to cure when given same treatment.

Logistic regression found no significant association between treatment and CR. Dose level was associated with increased CR with borderline significance while adjusting for formulation (odds ratio per 10 mg/kg increase: 1.28; 95% CI: 1.00, 1.64).

Table 29 Clinical Cure Rate by Sub-group using Kato-Katz Method, Stratified by Infection Intensity, Age Group and Gender (Point Estimate and 95% Confidence Interval) – mITT Analysis Set (with Imputation)

Stratification	Cohort 1[a] (N=57)	Cohort 2[a] (N=58)	Cohort 3[a] (N=58)	Cohort 4[a] (N=58)	Cohort 5[a] (N=56)	Cohort 6[a] (N=57)	Cohort 7[a] (N=58)	Cohort 8[b] (N=15)	Cohort 9[b] (N=4)
Overall (no stratification)	89.5 [78.5, 96.0]	74.1 [61.0, 84.37]	81.0 [68.6, 90.1]	79.3 [66.6, 88.8]	78.6 [65.6, 88.4]	86.0 [74.2, 93.7]	89.7 [78.8, 96.1]	93.3 [68.1, 99.8]	100 [39.8, 100]
Light infection	91.7 [77.5, 98.2]	85.7 [69.7, 95.2]	82.9 [66.4, 93.4]	85.7 [69.7, 95.2]	84.8 [68.2, 94.9]	94.3 [80.8, 99.3]	94.3 [80.8, 99.3]	100 [71.5, 100]	100 [39.8, 100]
Moderate/ Heavy infection	85.7 [63.7, 97.0]	56.5 [34.5, 76.8]	78.3 [56.3, 92.5]	69.6 [47.1, 86.8]	69.6 [47.1, 86.8]	72.7 [49.8, 89.3]	82.6 [61.2, 95.0]	75.0 [19.4, 99.4]	ND
Age 2 – 4 years	94.1 [71.3, 99.9]	71.4 [41.9, 91.6]	90.9 [58.7, 99.8]	88.2 [63.6, 98.5]	84.2 [60.4, 96.6]	92.9 [66.1, 99.8]	87.5 [61.7, 98.4]	0.00[c] [0.00, 97.5]	ND
Age 4 – 6 years	87.5 [73.2, 95.8]	75.0 [59.7, 86.8]	78.7 [64.3, 89.3]	75.6 [59.7, 87.6]	75.7 [58.8, 88.2]	83.7 [69.3, 93.2]	90.5 [77.4, 97.3]	ND	ND
Male	94.6 [81.8, 99.3]	58.1 [39.1, 75.5]	76.9 [56.4, 91.0]	76.0 [54.9, 90.6]	82.4 [65.5, 93.2]	89.3 [71.8, 97.7]	90.9 [75.7, 98.1]	100.0 [66.4, 100.0]	100.0 [29.2, 100.0]
Female	80.0 [56.3, 94.3]	92.6 [75.7, 99.1]	84.4 [67.2, 94.7]	81.8 [64.5, 93.0]	72.7 [49.8, 89.3]	82.8 [64.2, 94.2]	88.0 [68.8, 97.5]	83.3 [35.9, 99.6]	100.0 [2.5, 100.0]

Source: Tables 15.2.1.1a, 15.2.1.1b, 15.2.1.1c and 15.2.1.1d . ND=Not done.

[a] Part 1: Cohort 1 (2-6 years): Biltricide 3x20 mg/kg; Cohort 2: Biltricide 40 mg/kg; Cohort 3: rac-PZQ ODT 40 mg/kg; Cohort 4: rac-PZQ ODT 60 mg/kg; Cohort 5: L-PZQ ODT 30 mg/kg; Cohort 6: L-PZQ ODT 45 mg/kg; Cohort 7: L-PZQ ODT 60 mg/kg.

[b] Part 2: Cohorts 8 (13-24 months) and 9 (3-12 months): L-PZQ ODT 50 mg/kg.

[c] Estimates based on a single participant.

The CRs based on POC-CCA at Day 14 -21 were noticeably lower than CRs assessed by the Kato-Katz method for the primary analysis, which may reflect the higher sensitivity of the POC CCA test as reported in the literature. All cohorts presented CRs below 60% except Cohort 7 which achieved a CR of 72.4% (CI 59.1-83.3). In Cohort 9, none of 4 subjects was cured when diagnosed by POC-CCA but the POC-CCA test has not been clinically validated in infants and toddlers (i.e. results could be false positives). There was a clear increase in POC CCA CR over time (Day 2, 8 and 14-21) in general.

Table 30 Clinical Cure Rate by POC-CCA Method (Point Estimate and 95% Confidence Interval) – mITT Analysis Set with Imputation

Trial day	Cohort 1[a] (N=57)	Cohort 2[a] (N=58)	Cohort 3[a] (N=58)	Cohort 4[a] (N=58)	Cohort 5[a] (N=56)	Cohort 6[a] (N=57)	Cohort 7[a] (N=58)	Cohort 8[b] (N=15)	Cohort 9[b] (N=4)
Day 2	14.0 [6.3, 25.8]	5.2 [1.1, 14.4]	5.2 [1.1, 14.4]	13.8 [6.1, 25.4]	7.1 [2.0, 17.3]	10.5 [4.0, 21.5]	19.0 [9.9, 31.4]	33.3 [11.8, 61.6]	0.0 [0.0, 60.2]
Day 8	49.1 [35.6, 62.7]	27.6 [16.7, 40.9]	32.8 [21.0, 46.3]	31.0 [19.5, 44.5]	28.6 [17.3, 42.2]	49.1 [35.6, 62.7]	65.5 [51.9, 77.5]	53.3 [26.6, 78.7]	0.0 [0.0, 60.2]
Day 14-21	57.9 [44.1, 70.9]	36.2 [24.0, 49.9]	41.4 [28.6, 55.1]	52.2 [41.5, 68.3]	42.9 [29.7, 56.8]	61.4 [47.6, 74.0]	72.4 [59.1, 83.3]	66.7 [38.4, 88.2]	0.0 [0.0, 60.2]

Source: Table 15.2.2.1a

[a] Part 1: Cohort 1 (2-6 years): Biltricide 3x20 mg/kg; Cohort 2: Biltricide 40 mg/kg; Cohort 3: rac-PZQ ODT 40 mg/kg; Cohort 4: rac-PZQ ODT 60 mg/kg; Cohort 5: L-PZQ ODT 30 mg/kg; Cohort 6: L-PZQ ODT 45 mg/kg; Cohort 7: L-PZQ ODT 60 mg/kg.

[b] Part 2: Cohort 8 (13-24 months): L-PZQ ODT 50 mg/kg; Cohort 9 (3-12 months): L-PZQ ODT 50 mg/kg.

The group mean ERRs were calculated as arithmetic mean based ERR (ERRA) and geometric mean based ERR (ERRG). With and without imputation (Tables 1 and 2), high ERRG and ERRA were observed across all cohorts. Proportions with iERR ≥ 90% were mostly close to or >90% for all treatments.

Table 31 Egg Reduction Rate – mITT Analysis set (with imputation)

Characteristic/ Statistics	Cohort 1 Bilitricide 3x20 mg/kg (N=57)	Cohort 2 Bilitricide 40 mg/kg (N=58)	Cohort 3 rac-PZQ ODT 40 mg/kg (N=58)	Cohort 4 rac-PZQ ODT 60 mg/kg (N=58)	Cohort 5 L-PZQ ODT 30 mg/kg (N=56)	Cohort 6 L-PZQ ODT 45 mg/kg (N=57)	Cohort 7 L-PZQ ODT 60 mg/kg (N=58)	Cohort 8 L-PZQ ODT 50 mg/kg (N=15)	Cohort 9 L-PZQ ODT 50 mg/kg (N=4)
Group arithmetic mean based ERR(a)									
n(%)	57 (100)	58 (100)	58 (100)	58 (100)	56 (100)	57 (100)	58 (100)	15 (100)	4 (100)
Point estimate	99.5	83.2	97.6	96.2	99.3	74.8	96.8	99.7	100
95% CI	[98.3, 99.9]	[63.7, 97.3]	[92.6, 99.6]	[89.5, 99.4]	[98.2, 99.8]	[43.2, 99.8]	[88.9, 99.9]	[98.8, 100]	[100, 100]
Group geometric mean based ERR(a)									
n(%)	57 (100)	58 (100)	58 (100)	58 (100)	56 (100)	57 (100)	58 (100)	15 (100)	4 (100)
Point estimate	99.7	98.3	99.2	99.2	99.4	99.3	99.6	99.8	100
95% CI	[99.3, 99.9]	[96.7, 99.2]	[98.4, 99.7]	[98.4, 99.6]	[98.7, 99.8]	[98.4, 99.8]	[99.0, 99.9]	[99.3, 100]	[100, 100]
Individual ERR (%)(b)									
n (missing)	57 (0)	58 (0)	58 (0)	58 (0)	56 (0)	57 (0)	58 (0)	15 (0)	4 (0)
Mean ±SD	97.28 ±14.00	88.31 ±32.07	94.53 ±18.04	95.77 ±16.32	93.64 ±21.88	95.98 ±18.55	95.56 ±25.12	99.77 ±0.89	100 ±0
Median	100	100	100	100	100	100	100	100	100
Q1; Q3	100; 100	99.75; 100	100; 100	100; 100	100; 100	100; 100	100; 100	100; 100	100; 100
Min; Max	0.0; 100	-50.0; 100	0.0; 100	-13.0; 100	0.0; 100	0.0; 100	-85.7; 100	96.6; 100	100; 100
Proportion of iERR ≥ 90% (%)									
n(%)	54 (94.7)	48 (82.8)	52 (89.7)	53 (91.4)	50 (89.3)	55 (96.5)	55 (94.8)	15 (100)	4 (100)
Point estimate	94.7	82.8	89.7	91.4	89.3	96.5	94.8	100	100
95% CI	[85.4, 98.9]	[70.6, 91.4]	[78.8, 96.1]	[81.0, 97.1]	[78.1, 96.0]	[87.9, 99.6]	[85.6, 98.9]	[78.2, 100]	[39.8, 100]

(a) ERR is the relative difference in group means of egg counts before and after treatment. For each cohort, at each time point group mean is mean of eggs/gram across all subjects.

(b) iERR is the relative difference in egg/gram before and after treatment for each subject and was summarized across all subjects in each cohort.

CIs for group mean based ERRs were calculated using bootstrapping approach. CIs for proportion of iERR≥90% were calculated using Clopper-Pearson method.

Source Output ID: t-15-2-3-1a-newerr

Table 32 Egg Reduction Rate – mITT Analysis set (without imputation)

Characteristic/ Statistics	Cohort 1 Bilitricide 3x20 mg/kg (N=57)	Cohort 2 Bilitricide 40 mg/kg (N=58)	Cohort 3 rac-PZQ ODT 40 mg/kg (N=58)	Cohort 4 rac-PZQ ODT 60 mg/kg (N=58)	Cohort 5 L-PZQ ODT 30 mg/kg (N=56)	Cohort 6 L-PZQ ODT 45 mg/kg (N=57)	Cohort 7 L-PZQ ODT 60 mg/kg (N=58)	Cohort 8 L-PZQ ODT 50 mg/kg (N=15)	Cohort 9 L-PZQ ODT 50 mg/kg (N=4)
Group arithmetic mean based ERR(a)									
n(%)	56 (98.2)	54 (93.1)	57 (98.3)	58 (100)	54 (96.4)	55 (96.5)	58 (100)	15 (100)	4 (100)
Point estimate	99.8	98.1	99.1	96.2	99.6	99.1	96.8	99.7	100
95% CI	[99.5, 100]	[95.3, 99.5]	[98.1, 99.7]	[89.5, 99.4]	[98.9, 99.9]	[97.5, 99.9]	[88.9, 99.9]	[98.8, 100]	[100, 100]
Group geometric mean based ERR(a)									
n(%)	56 (98.2)	54 (93.1)	57 (98.3)	58 (100)	54 (96.4)	55 (96.5)	58 (100)	15 (100)	4 (100)
Point estimate	99.8	99.1	99.4	99.2	99.6	99.6	99.6	99.8	100
95% CI	[99.5, 100]	[98.3, 99.6]	[98.8, 99.7]	[98.4, 99.6]	[99.1, 99.8]	[99.2, 99.9]	[99.0, 99.9]	[99.3, 100]	[100, 100]
Individual ERR (%)(b)									
n (missing)	56 (1)	54 (4)	57 (1)	58 (0)	54 (2)	55 (2)	58 (0)	15 (0)	4 (0)
Mean ±SD	99.02 ±4.95	94.85 ±21.76	96.19 ±12.99	95.77 ±16.32	97.11 ±12.39	99.47 ±1.86	95.56 ±25.12	99.77 ±0.89	100 ±0
Median	100	100	100	100	100	100	100	100	100
Q1; Q3	100; 100	100; 100	100; 100	100; 100	100; 100	100; 100	100; 100	100; 100	100; 100
Min; Max	66.7; 100	-50.0; 100	33.3; 100	-13.0; 100	16.7; 100	91.7; 100	-85.7; 100	96.6; 100	100; 100
Proportion of iERR ≥ 90% (%)									
n(%)	54 (94.7)	48 (82.8)	52 (89.7)	53 (91.4)	50 (89.3)	55 (96.5)	55 (94.8)	15 (100)	4 (100)
Point estimate	96.4	88.9	91.2	91.4	92.6	100	94.8	100	100
95% CI	[87.7, 99.6]	[77.4, 95.8]	[80.7, 97.1]	[81.0, 97.1]	[82.1, 97.9]	[93.5, 100]	[85.6, 98.9]	[78.2, 100]	[39.8, 100]

(a) ERR is the relative difference in group means of egg counts before and after treatment. For each cohort, at each time point group mean is mean of eggs/gram across all subjects.

(b) iERR is the relative difference in egg/gram before and after treatment for each subject and was summarized across all subjects in each cohort.

CIs for group mean based ERRs were calculated using bootstrapping approach. CIs for proportion of iERR≥90% were calculated using Clopper-Pearson method.

Source Output ID: t-15-2-3-1b-newerr

The applicant and SMC concluded that a single dose of L-PZQ 45 mg/kg provided an acceptable CR as assessed by Kato-Katz method and safety profile in 2-6 year-olds infected with *S. mansoni.*

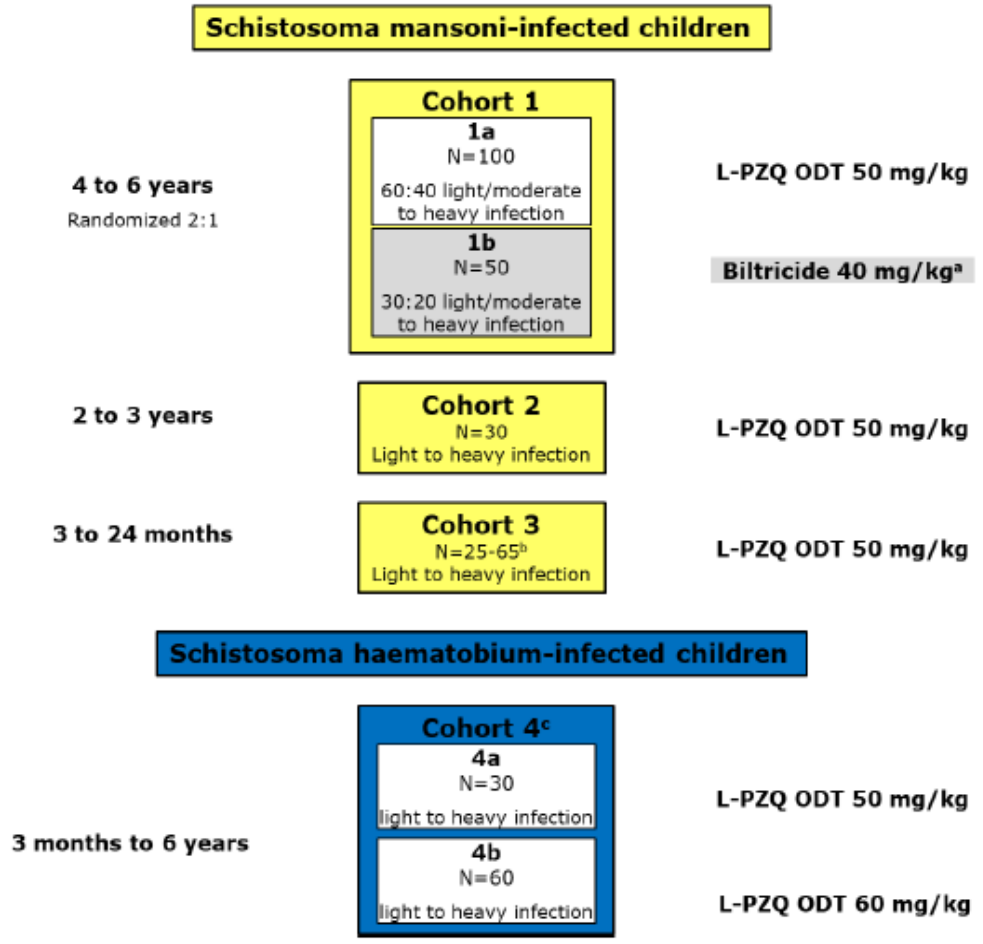
For ease of dose calculation, 50 mg/kg of L-PZQ was selected for Part 2 in subjects aged 3-24 months and the results in Cohorts 8 and 9 were considered to further support this dose.

CRs were significantly higher among subjects with light infection vs. moderate/heavy infections. CRs assessed by the POC-CCA method and egg reduction rates followed similar trends to CRs determined by the Kato-Katz method although CRs by POC-CCA were consistently lower for all cohorts. Generally, results from the different analysis population sets were consistent. In summary, the 50 mg/kg L-PZQ dose (rounded up from 45 mg/kg) was selected for treatment of *S. mansoni* in the Phase 3 study as described below. The same dose was used initially in children with *S. haematobium* but during the study a decision was taken to assess a slightly higher (60 mg/kg) dose for treatment of this species for reasons explained below.

2.6.5.2. Main study

Study MS200661-0003

The applicant conducted a single pivotal efficacy study in Kenya and Ivory Coast in 2019-2021. An IDMC reviewed the safety data and the efficacy data of Cohort 4 after 30 children had received 50 mg/kg L-PZQ to decide if the dose should be increased to 60 mg/kg L-PZQ.



a Biltricide label at study start included only children ≥ 4 years old, but it can be used to treat children below this age under medical supervision.

b N=41 was initially planned in order to have 65 participants in this age group in the pooled analysis with Phase 2, MS200661-0005, Cohorts 8 and 9 (n=24). However, due to enrollment challenges and based on feedback received during scientific advice with EMA (EMA/CHMP/SAWP/470033/2020), n ≥ 10 in Cohort 3 was considered appropriate by the sponsor.

c After review of efficacy and safety data for the first 30 enrolled participants in Cohort 4a, the IDMC recommended to increase L-PZQ ODT dose to 60 mg/kg in Cohort 4b.

IDMC=Independent Data Monitoring Committee, L-PZQ=levorotatory enantiomer of praziquantel, ODT=orodispersible tablet(s).

Figure 11 Design Diagram

Methods

- **Study Participants**

Eligible subjects were male and female African children as follows:

- Aged 3 months to 6 years
  - Cohort 1: 4 to 6 years of age
  - Cohort 2: 2 to 3 years of age
  - Cohort 3: 3 to < 24 months of age
  - Cohort 4: 3 months to 6 years of age
- Minimum body weight 8.0 kg if aged 2-6 years or 5.0 kg if aged 3 to < 24 months
- Minimum Hb 10 g/dL

Cohorts 1, 2 and 3
Children were *S. mansoni* positive defined as positive egg count in stool (≥ 1 egg/1 occasion) according to WHO classification (2002): light (1 to 99 eggs/g of faeces), moderate (100 to 399 eggs/g of faeces) and heavy (≥ 400 eggs/g of faeces).

Cohort 4
Children were *S. haematobium* positive defined as positive egg counts in urine (≥ 1 egg/10 mL of urine) according to WHO classification (2002) of light (< 50 eggs/10 mL of urine) and heavy (≥ 50 eggs/10 mL of urine).

Exclusions included:

- Children with predefined medical conditions that could negatively affect treatment, assessment and completion of study.
- Protocol-defined concomitant treatment within 2 weeks prior to enrolment with medication that might have affected the metabolism of PZQ, such as certain anti-epileptics (e.g. carbamazepine or phenytoin), glucocorticosteroids (e.g. dexamethasone), chloroquine, rifampicin or cimetidine.
- Treatment with PZQ within 4 weeks prior to screening.
- Hypersensitivity to PZQ or any of the excipients.
- Mixed S. mansoni and S. haematobium infections.

- **Treatments**

Subjects received a single treatment with assigned medication on Day 1 as follows:

Cohort 1 (150): aged 4 to 6 years with *S. mansoni* randomised in a 2:1 ratio to 50 mg/kg L-PZQ (Cohort 1a: 100) or 40 mg/kg Biltricide (Cohort 1 b: 50). There was randomisation in Cohort 1 only in a 2:1 ratio to L-PZQ or Biltricide. This was conducted via a computer-generated randomisation list integrated into the electronic data capturing system. Randomisation was stratified according to light or moderate/heavy intensity of infection.

Cohort 2 (30): aged 2 to 3 years with *S. mansoni* received 50 mg/kg L-PZQ

Cohort 3 (18): aged 3 to < 24 months with *S. mansoni* received 50 mg/kg L-PZQ

Cohort 4 (90): aged 3 months to 6 years with *S. haematobium*
Cohort 4a (30): 50 mg/kg L-PZQ

Cohort 4b (60): 60 mg/kg L-PZQ

Enrolment into the different cohorts occurred in parallel except for 4a and 4b (see further below).

As in Phase 2, the target doses were calculated but then there was some rounding to enable dosing with multiples of whole 150 mg tablets and whole, ½ or ¼ tablets of Biltricide as needed. See Table 37 below for the actual mg/kg doses administered after applying rounding of doses.

- **Objectives/Outcomes/endpoints**

The study objectives, endpoints and statistical methods are summarised in the table below.

Table 33 Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints (Outcome Measures)	Statistical Methods
Primary		
Efficacy		
To assess the efficacy of: • a single dose (50 mg/kg) of L-PZQ ODT in Cohort 1a. • a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide – internal control) in Cohort 1b. as assessed by CR 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni.	Clinical cure was defined as no parasite eggs in the stool 17 to 21 days after treatment (first sample taken between Days 17 and 21, and the remaining in a window of 5 days after the first one). Egg counts were determined by the Kato-Katz method: One stool sample was collected during the prescreening period (Days -28 to -1) and the second one within a maximum of 5 days thereafter as baseline. Two additional stool samples were collected between Days 17 to 21 after dosing to determine efficacy: the first one was collected within the 17- to 21-day window and the second one within a maximum of 5 days following collection of the 1st sample. Three Kato-Katz thick smears (41.7 mg) were prepared from each stool sample.	No hypothesis testing was performed. Point estimates and corresponding 2-sided 95% CIs were determined. Participants cured of infection during the study were labeled as "responders". Responders were defined as participants with no parasite eggs (as determined by Kato-Katz method) in the End-of-Study stool samples, 17 to 21 days after treatment, according to the eCRF page "End-of-Study (Days 17 to 21)". The proportion of responders in each cohort was determined based on a binomial distribution. Exact 95% CIs were calculated based on the Clopper-Pearson method. Point estimates and corresponding 95% CIs were presented for CR, in terms of proportion of responders, by cohort. Response was listed by cohort and participant. Estimates of CR were presented graphically in the form of forest plots presenting point estimates and 95% CIs. For mITT analysis tables were presented with imputation and without imputation. If the End-of-Study Kato-Katz egg count was missing, it was imputed using the LOCF approach. Participants with missing data were considered non-responders.

Objectives	Endpoints (Outcome Measures)	Statistical Methods
Secondary		
Efficacy		
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as assessed by CR 17 to 21 days after treatment, in: • children 2 to 3 years of age infected with S. mansoni (Cohort 2). • children 3 to < 24 months of age infected with S. mansoni (Cohort 3).	Same as for Cohort 1.	CR as assessed by the Kato-Katz method for Cohorts 2 and 3. Statistical methods are the same as for Cohort 1.
To assess the efficacy of a single dose (50 or 60 mg/kg based on IDMC recommendation) of L-PZQ ODT as assessed by CRs 17 to 21 days and 35 to 40 days after treatment, in children 3 months to 6 years of age infected with S. haematobium (Cohort 4a and 4b, respectively).	Clinical cure was defined as no parasite eggs in the urine samples at follow-up. Egg counts were determined by urine examination using the urine filtration technique: The first sample was collected during the prescreening period (Days -28 to -1) and the second and the third one within a maximum of 5 days thereafter as baseline. At the End-of-Study Visit (between Days 17 and 21) Cohort 4 participants were asked to provide 3 urine samples (about 10 mL each): the first one was collected within the 17- to 21-day window and the other 2 within a maximum of 5 days following collection of the first sample, for analysis by the filtration method. Similarly, at the Extended Follow-up Visit, Cohort 4 participants treated at 60 mg/kg L-PZQ ODT were asked to provide 3 additional urine samples (about 10 mL each) on different days between Days 35 and 40 (first sample taken between days 35 and 40, while the remaining samples are taken in a 5-day window timeframe after the first sample), for efficacy assessment by the filtration method. The urine samples were filtered through a filter mesh. This mesh was then examined under the microscope for S. haematobium egg count.	CR as determined by urine filtration technique for Cohort 4. Statistical methods are the same as for Cohort 1.

Objectives	Endpoints (Outcome Measures)	Statistical Methods
To assess the efficacy of: • a single dose (50 mg/kg) of L-PZQ ODT in Cohort 1a. • a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide – internal control) in Cohort 1b. as assessed by ERR 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni.	ERR from pretreatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohort 1.	The group/collective ERR was determined for Cohorts 1a and 1b as follows: Step 1: Calculated the arithmetic group mean and geometric group mean egg counts (epg) at each visit. Step 2: Calculated group ERR for each treatment group: • ERR_A (%) = relative difference expressed in percent between the posttreatment mean egg count and the pretreatment mean egg count • ERR_G (%) = relative difference expressed in percent between the geometric mean posttreatment egg count and geometric mean pretreatment egg count. In addition: iERR was calculated for each participant: • iERR (%) = relative difference expressed in percent between the posttreatment egg count and the pretreatment egg count. Point and interval estimates of ERR_A, ERR_G and proportion of individuals with iERR ≥ 90% were presented by treatment group. 95% CIs of ERR_A and ERR_G were calculated by bootstrapping. The CI for proportion of individuals with iERR ≥ 90% was calculated using Clopper-Pearson method. In the analysis with imputation, if the End-of-Study Kato-Katz egg count was missing, it was imputed using the LOCF approach.

Objectives	Endpoints (Outcome Measures)	Statistical Methods
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as determined by ERR in children: • children 2 to 3 years of age infected with S. mansoni (Cohort 2). • children 3 months to < 24 months of age infected with S. mansoni (Cohort 3). • children 3 months to 6 years of age infected with S. haematobium (Cohort 4a). To assess the efficacy of a single dose (60 mg/kg based on IDMC recommendation) of L-PZQ ODT as determined by ERR in children: • children 3 months to 6 years of age infected with S. haematobium (Cohort 4b).	ERR from pretreatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohorts 2 and 3 and the urine filtration method for Cohort 4. Additionally, ERR from pretreatment to 35 to 40 days after treatment, using parasite egg counts as determined by the urine filtration method for Cohort 4 participants.	Statistical methods are the same as for Cohort 1. For Cohort 4b, if egg counts were missing only at Extended Follow-up Visit, in the analysis with imputation, it was imputed by taking the value from End-of-Study Visit.
To assess the CR as demonstrated with use of the commercially available POC-CCA® test in children 3 months to 6 years of age, infected with S. mansoni (Cohorts 1, 2, and 3).	One urine sample was collected 17 to 21 days after treatment. Cure is defined as absence of test line in the POC-CCA® test cassette (i.e., no Schistosoma antigens detected).	CR as assessed by the POC-CCA® method for Cohorts 1, 2, and 3 was analyzed in the same manner as the primary endpoint, with proportion cured and its 95% CI.
Safety		
To assess the safety of a single dose (50 mg/kg) of L-PZQ ODT in: • children 4 to 6 years of age infected with S. mansoni (Cohort 1a). • children 2 to 3 years of age infected with S. mansoni (Cohort 2). • children 3 months to < 24 months of age infected with S. mansoni (Cohort 3). • children 3 months to 6 years of age infected with S. haematobium (Cohort 4a). To assess the safety of a single dose (60 mg/kg based on IDMC recommendation) of L-PZQ ODT in: • children 3 months to 6 years of age infected with S. haematobium (Cohort 4b).	Safety and tolerability assessments (from first treatment to planned End-of-Study Visit): • Occurrence, nature, severity, and outcome of AEs. • Occurrence of treatment-related AEs. • Changes in laboratory safety parameters (hematology, biochemistry, urinalysis) and vital signs (body temperature, blood pressure and pulse rate).	• All safety analyses were performed on the Safety population, which included all participants who received a dose of study treatment. • Participants were analyzed according to the actual treatment they received. • Descriptive statistics were provided for safety and tolerability endpoints.

Objectives	Endpoints (Outcome Measures)	Statistical Methods
Acceptability		
To assess acceptability in terms of ease of administration of the selected L-PZQ ODT (Cohorts 1a, 2, 3, and 4) and commercial PZQ tablet (Cohort 1b).	• Reaction to study intervention administration (e.g., spitting, crying) were recorded to describe tolerability as assessed by nurse/site staff for all children enrolled in the study. • Palatability assessment using a human gustatory sensation test (100-mm VAS) scoring modified by the incorporation of a 3-point facial hedonic scale for all children 5 and 6 years of age enrolled in the study.	Recorded reactions to study intervention are listed and were summarized as appropriate.
Pharmacokinetics		
To assess the concentration-time profile of praziquantel following the administration of L-PZQ ODT formulation and Biltricide formulation in a subset of children.	Concentrations of both enantiomers, and if appropriate, PK parameters (e.g., C_{max}, t_{max}, AUC_{0-t}).	• Plasma concentrations were summarized and are tabulated using descriptive statistics. • All PK parameters were calculated using standard non-compartmental methods and the actual administered dose.

The egg counts were determined by the Kato-Katz method. One stool sample was collected during the pre-screening period (Days -28 to -1) and the second within a maximum of 5 days thereafter as baseline. Two stool samples were collected between Days 17 to 21 after dosing to determine efficacy (i.e. at EOS visit). The first one was collected within the 17- to 21-day window and the second one within a maximum of 5 days following collection of the first sample. Three Kato-Katz thick smears (41.7 mg) were prepared from each stool sample.

- **Sample size**

The integrated analysis plan (IAP) states the target sample sizes but with no justification since there was no formal hypothesis testing.

- **Statistical methods**

The planned analyses described in the final version of the IAP are summarised in Table 1 above. The analysis populations (ITT, mTT and PP) were defined as described for the Phase 2 study.

The primary endpoint (cure rate [CR]) was defined as the proportion of participants with no parasite eggs in stool at the EOS visit, which occurred 17 to 21 days after treatment (first sample taken between Days 17 and 21; second sample in a window of 5 days after the first one). The primary analysis compared CRs in Treatment groups 1a and 1b. Point estimates and corresponding 2-sided 95% CIs were determined. Participants cured of infection during the study were counted as responders.

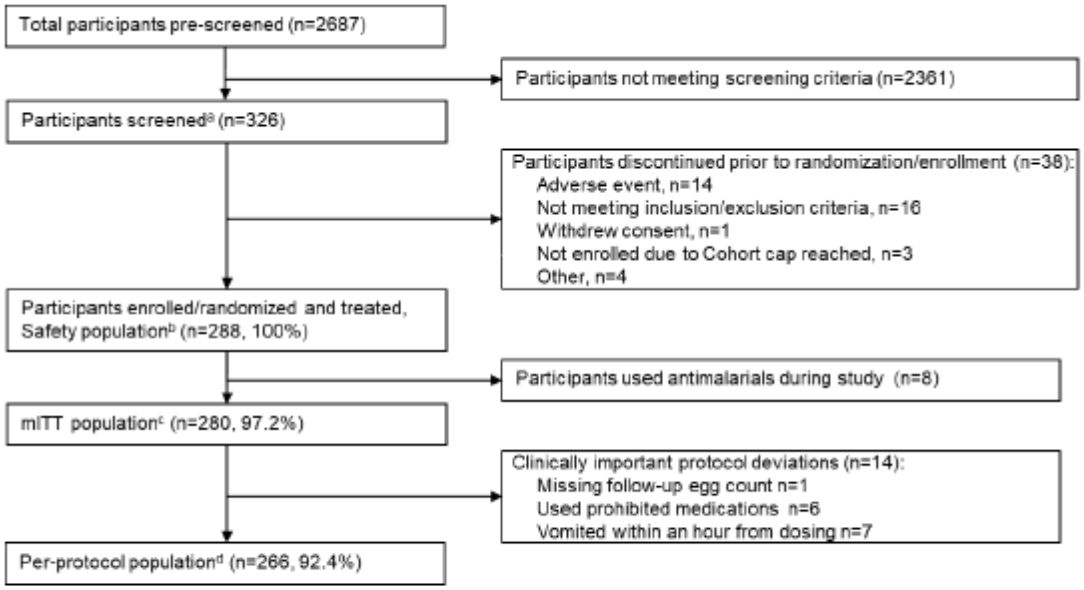
Point estimates and corresponding 95% CIs were presented for CRs. Exact 95% CIs were calculated based on the Clopper-Pearson method. For the mITT population the tables were presented with imputation and without imputation. If the End-of-Study Kato-Katz egg count was missing, it was imputed using the LOCF approach. Participants with missing data were counted as non-responders.

The secondary analyses were conducted in the other cohorts, all of which had no control group. There was no hypothesis testing and the aim was to broadly compare the observed CRs with those obtained in Treatment groups 1a and 1b. The same approach was taken to determining responders and 95% CI were calculated around the response rates.

Results

- **Participant flow**

  The table and figure below summarise participant flow for Cohorts 1-4. Only one randomised and treated subject (in Cohort 1b) failed to complete the study.



Source: Tables 8.1.1.1, 8.1.1.3, and 8.1.2.1
mITT=modified intent-to-treat.

a All participants who signed the informed consent.
b All participants who received 1 dose of study intervention.
c All enrolled participants who received 1 dose of study intervention and had baseline measurement, excluding those who used anti-malaria treatment after enrollment/randomization.
d All participants who were in the mITT population and had ≥ 1 postbaseline measurement without any clinically important protocol deviations.

Figure 12 Participant Disposition for Participants Enrolled into Cohorts 1 to 4

- **Recruitment**

The majority (189; 67.5%) was enrolled in Kenya and all Cohort 4 subjects were enrolled in Kenya due to the epidemiology of *S. haematobium*.

- **Conduct of the study**

An IDMC meeting was held on 09 March 2020 and a recommendation was given to increase the dose of L-PZQ in Cohort 4b to 60 mg/kg, which was implemented by the sponsor. Other changes implemented after the first interim analysis were:

- Addition of a second time point to assess efficacy at 5th week post-treatment in Cohort 4b.
- Addition of PK sampling in a subset of participants in Cohorts 1b and 4b.
- Addition of the second interim analysis in Cohort 4b after 30 participants had received 60 mg/kg L-PZQ.

- **Numbers analysed**

The proportions of male and female participants were similar. All participants were Black. In Cohort 4, the majority was aged 4 to 6 years, consistent with *S. haematobium* disease epidemiology.

The target for Cohort 1 of 40% moderate/heavy infections and 60% light infections was achieved. The proportions with light infection were comparable between Cohort 1a (59/98 [60.2%]) and Cohort 1b (27/48 [56.3%]). Light infection predominated in Cohort 3 (14/18 [77.8%]) and in Cohort 4a (18/29 [62.1%]) and Cohort 4b (52/58 [89.7%]). In contrast, Cohort 2 had a higher proportion with moderate or heavy infection (58.6% [17/29]) due to the presence of hotspots in the Kenya districts where screening was performed.
Numbers for predefined populations are shown below.

Table 34 Populations

	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n (%)	Cohort 1b 4 to 6 yrs Bilitricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)	Total N=288 n (%)
Number of participants in:							
SCR population[a]							326
Safety population[b]	100 (100)	50 (100)	30 (100)	18 (100)	30 (100)	60 (100)	288 (100)
mITT population[c]	98 (98.0)	48 (96.0)	29 (96.7)	18 (100)	29 (96.7)	58 (96.7)	280 (97.2)
PP population[d]	94 (94.0)	44 (88.0)	28 (93.3)	15 (83.3)	28 (93.3)	57 (95.0)	266 (92.4)
PK population[e]	17 (17.0)	10 (20.0)	9 (30.0)	2 (11.1)	14 (46.7)	15 (25.0)	67 (23.3)

Source: Table 8.1.1.3

L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet(s), PK=pharmacokinetic(s), PP=per protocol, SCR=screening.

[a] All participants who signed the informed consent.
[b] All participants who received 1 dose of study intervention.
[c] All enrolled participants who received 1 dose of study intervention and had baseline measurement, excluding those who used anti-malaria treatment after enrollment/randomization.
[d] All participants who are in the mITT population and had ≥ 1 postbaseline measurement without any clinically important protocol deviations.
[e] All participants who received 1 dose of active study intervention and provided ≥ 1 measurable postdose concentration, did not take prohibited medications/foods/fluids or experience any same-day diarrhea or vomiting after study intervention administration.

- **Outcomes and estimation**

Whereas all randomised subjects received their assigned single dose calculated by body weight, the table below shows the actual doses administered taking into account limitations of breakage of tablets

to deliver the calculated doses. The mean and median doses in mg/kg were close to the targeted mg/kg doses but the ranges indicate that some children received 10-15 mg/kg more than the target for their cohort. Also, some children assigned to 50 mg/kg L-PZQ received <45 mg/kg.

Table 35 Study Intervention Compliance – Safety Population

	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n (%)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)
Compliance with treatment, n (%)						
100%	100 (100)	50 (100)	30 (100)	18 (100)	30 (100)	60 (100)
Actual dose received (mg/kg)						
Mean ±SD	51.7 ± 4.96	40.9 ± 3.33	52.3 ± 4.22	51.7 ± 4.85	52.0 ± 4.38	63.2 ± 5.01
Median	51.0	41.0	52.5	52.3	51.3	62.9
Min; Max	44.4; 61.4	35.4; 54.7	46.5; 61.8	42.9; 59.4	44.6; 61.1	54.0; 75.0
Total dose received (mg)						
Mean ±SD	901.5 ± 167.19	708.0 ± 109.43	700.0 ± 106.67	475.0 ± 92.75	860.0 ± 204.43	1167.5 ± 265.03
Median	750.0	750.0	750.0	450.0	825.0	1050.0
Min; Max	750; 1350	450; 900	450; 1050	300; 600	450; 1200	600; 1950

- **Efficacy analyses**

Efficacy against *Schistosoma mansoni*

The clinical CRs by the Kato-Katz method in *S. mansoni*-infected children who received 50 mg/kg L-PZQ were ≥ 87% with the lower bounds of the 95% CI exceeding 70% (Cohorts 1a, 2 and 3). The CRs in Cohort 1 were comparable for 50 mg/kg L-PZQ and 40 mg/kg Biltricide. One subject was lost to follow-up from Cohort 1b, so there is almost no difference between the results for the mITT population with and without imputation.

Moreover, the point estimates for CRs in Cohorts 2 and 3, as well as for the pooled data in children aged from 3-24 months who received 50 mg/kg L-PZQ in Cohort 3 in the Phase 3 study and in Cohorts 8 and 9 in the Phase 2 study, were all above 90%.

Table 36 Overall Clinical Cure Rate (%) in S. mansoni-Infected Participants – mITT and PP Populations

Population Point Estimate (%) [95% CI]	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg (N=98)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg (N=48)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg (N=29)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=18)	Pooled Cohorts 8, 9 and 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=37)
mITT with imputation	87.8 [79.6, 93.5]	81.3 [67.4, 91.1]	93.1 [77.2, 99.2]	94.4 [72.7, 99.9]	94.6 [81.8, 99.3]
mITT without imputation*	87.8 [79.6, 93.5]	83.0 [69.2, 92.4]	93.1 [77.2, 99.2]	94.4 [72.7, 99.9]	94.6 [81.8, 99.3]
	*(N=94)	*(N=44)	*(N=28)	*(N=15)	*(N=34)
PP	88.3 [80.0, 94.0]	81.8 [67.3, 91.8]	96.4 [81.7, 99.9]	93.3 [68.1, 99.8]	94.1 [80.3, 99.3]

Source: Tables 8.2.1.1, 8.2.1.2, 8.2.1.3, 8.2.1.5, 8.2.1.6, and 8.2.1.7 from MS200661-0003 CSR; Exact 95% CIs were calculated based on the Clopper-Pearson method.
*Represent the total number of participants in the PP population.
CI=confidence interval, mITT=modified intent-to-treat, ODT=orodispersible tablet, PP=per protocol.
* Only 1 participant from Cohort 1b was lost to follow-up and was imputed.
Note: Cohorts 1, 2, and 3 from this study and Cohorts 8 and 9 from the Phase 2 Study MS200661-0005. CRs were based on Kato-Katz.

Efficacy against *Schistosoma haematobium*

The CR in Cohort 4a (50 mg/kg L-PZQ) was 58.6% [38.9, 76.5%] at Week 3. The increase in L-PZQ dose to 60 mg/kg resulted in a CR for Cohort 4b of 86.2% [74.6, 93.9%] at Week 3 and 94.8% [85.6, 98.9%] at Week 5. The CRs in the PP population were similar to those in the mITT population.

Table 37 Overall Clinical Cure Rate (%) in S. haematobium-infected Participants – mITT and PP Populations

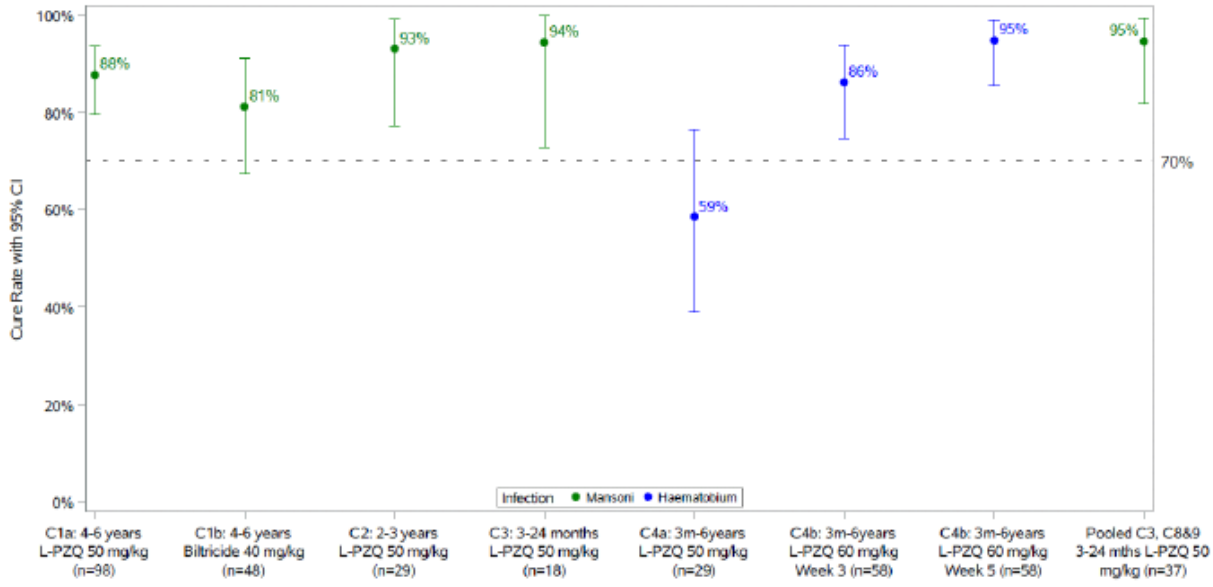
Population Point Estimate (%) [95% CI]	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg Week 3 (N=29)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg	
		Week 3 (N=58)	Week 5 (N=58)
mITT	58.6 [38.9, 76.5]	86.2 [74.6, 93.9]	94.8 [85.6, 98.9]
	*(N=28)	*(N=57)	*(N=57)
PP	57.1 [37.2, 75.5]	86.0 [74.2, 93.7]	94.7 [85.4, 98.9]

Source: Tables 8.2.1.1, 8.2.1.2, and 8.2.1.3 from MS200661-0003 CSR; Exact 95% CIs were calculated based on the Clopper-Pearson method.
* Represent the total number of participants in the PP population.
CI=confidence interval, CR=cure rate, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet, PP=per protocol.
Note: CR was based on urine filtration and no imputation was done as no missing follow-up egg count.

Efficacy across all cohorts

The figure below summarises the point estimates and the 95% CI.

With the exception of Cohort 4a, with a Week 3 CR suggesting that 50 mg/kg L-PZQ may be suboptimal for *S. haematobium*, the lower bounds of the 95% CI around the point estimates for CRs in the L-PZQ groups are consistently above 70%.



Source: Tables 8.2.1.1 and 8.2.1.5.
CI=confidence interval, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat.

Figure 13 Overall Clinical Cure Rate (%) – mITT Population

CRs for *S. mansoni* by subgroups

The next table shows the CR for each cohort according to infection intensity, gender and country.

There were comparable clinical CRs between L-PZQ and Biltricide within Cohort 1 for those with light infection although the CR was numerically higher with L-PZQ. The CRs were lower but very similar for L-PZQ and Biltricide for those with moderate/heavy infections (CR 76.9% and 76.2%). A higher CR with L-PZQ in those with light infection was observed in Cohort 2. This pattern was not seen in the smaller numbers in Cohort 3. It was seen when data from Cohort 3 were pooled with Cohorts 8 and 9 from the Phase 2 study (light infection 96.6% vs. moderate/heavy infection 87.5%) but only 8 subjects had moderate/heavy infection.

There was no apparent effect of gender on CRs. The applicant considered that the slightly higher CRs in Ivory Coast could be due to the higher density of persistent hotspots in Kenya where transmission is high, increased risk of reinfection and higher parasite heterogeneity in terms of maturity.

Table 38 Clinical Cure Rate (%) in S. mansoni-Infected Participants, Stratified by Infection Intensity, Age Group, Gender, and Country – mITT Population (with Imputation)

Subgroup Point Estimate (%) [95% CI] n	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg (N=98)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg (N=48)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg (N=29)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=18)	Pooled Cohorts 8, 9 and 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=37)
Light infection[a]	94.9 [85.9, 98.9] n=59	85.2 [66.3, 95.8] n=27	100 [73.5, 100] n=12	92.9 [66.1, 99.8] n=14	96.6 [82.2, 99.9] n=29
Moderate/heavy infection[b]	76.9 [60.7, 88.9] n=39	76.2 [52.8, 91.8] n=21	88.2 [63.6, 98.5] n=17	100 [39.8, 100] n=4	87.5 [47.4, 99.7] n=8
Male	91.7 [80.0, 97.7] n=48	88.9 [70.8, 97.7] n=27	92.9 [66.1, 99.8] n=14	100 [59.0, 100] n=7	100 [82.4, 100] n=19
Female	84.0 [70.9, 92.8] n=50	71.4 [47.8, 88.7] n=21	93.3 [68.1, 99.8] n=15	90.9 [58.7, 99.8] n=11	88.9 [65.3, 98.6] n=18
Kenya	83.7 [69.3, 93.2] n=43	78.3 [56.3, 92.5] n=23	91.7 [73.0, 99.0] n=24	91.7 [61.5, 99.8] n=12	91.7 [61.5, 99.8] n=12
Ivory Coast	90.9 [80.1, 97.0] n=55	84.0 [63.9, 95.5] n=25	100 [47.8, 100] n=5	100 [54.1, 100] n=6	96.0 [79.7, 99.9] n=25

Source: Tables 8.2.2.1 and 8.2.2.5 (infection intensity), 8.2.4.1 and 8.2.4.5 (gender), and 8.2.5.1 and 8.2.5.5 (country) from MS200661-0003 CSR; Exact 95% CIs were calculated based on the Clopper-Pearson method.

CI=confidence interval, CSR=clinical study report, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.

Note: Cohorts 1, 2, and 3 from this study and Cohorts 8 and 9 from the Phase 2 Study MS200661-0005. Cure rates were based on Kato-Katz. Cohort 8 and 9 participants from Phase 2 Study MS200661-0005 were recruited in Ivory Coast only.

[a] Light infection: 1-99 eggs per gram of stool.

[b] Moderate infection: 100-399 eggs per gram of stool; Heavy infection: ≥ 400 eggs per gram of stool.

CRs for *S. haematobium* by subgroups

Reflecting disease epidemiology in the PSAC population, enrolment occurred only in Kenya and few subjects had moderate/heavy infections. The observed CR was higher in Cohort 4a for light infection (66.7%) compared to heavy infection (45.5%). In Cohort 4b the CRs were 86.5% at Week 3 and 94.4% at Week 5 for light infections compared to CRs for heavy infections that were 83.3% and 100% at respective visits. However, sample sizes in Cohorts 4a and 4b for heavy infections are small.

The majority in Cohort 4 (67/87 [77%]) was aged 4 to 6 years. Despite the small sample size aged 2 to 4 years, the CR in this age group did not show a relevant difference to the 4 to 6 years group.

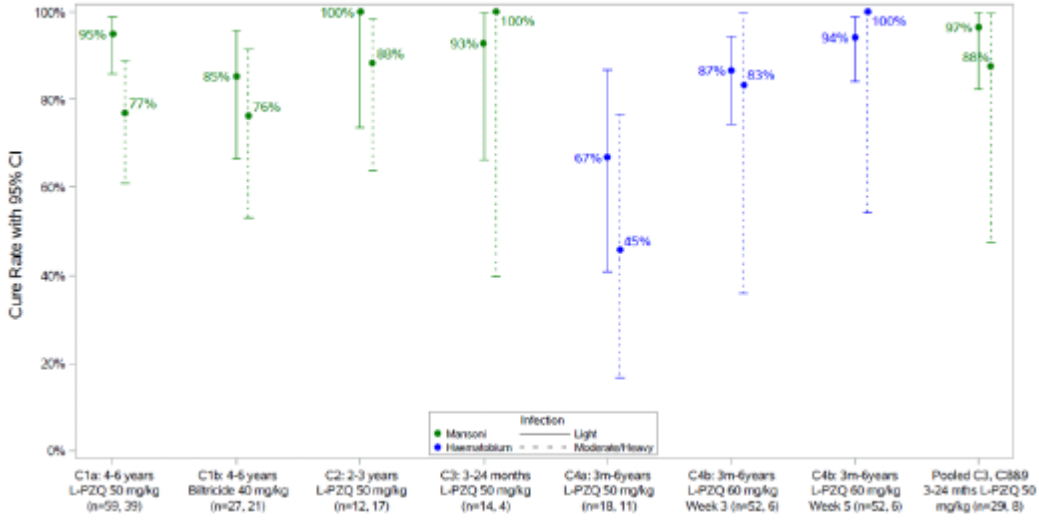
In Cohort 4b, the CRs were higher at Week 5 vs. Week 3, which the applicant considers may reflect the longer host parasite lifecycle in *S. haematobium* with a longer period required for egg clearance.

Table 39 Clinical Cure Rate (%) in S. haematobium-Infected Participants, Stratified by Infection Intensity, Age Group, and Gender – mITT Population.

Stratification Point Estimate (%) [95% CI] n	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg Week 3 (N=29)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg	
		Week 3 (N=58)	Week 5 (N=58)
Light infection[a]	66.7 [41.0, 86.7] n=18	86.5 [74.2, 94.4] n=52	94.2 [84.1, 98.8] n=52
Heavy infection[b]	45.5 [16.8, 76.6] n=11	83.3 [35.9, 99.6] n=6	100 [54.1, 100] n=6
Age 4 to 6 years	52.4 [29.8, 74.3] n=21	87.0 [73.7, 95.1] n=46	95.7 [85.2, 99.5] n=46
Age 2 to 3 years	71.4 [29.0, 96.3] n=7	80.0 [44.4, 97.5] n=10	90.0 [55.5, 99.8] n=10
Age 3 to < 24 months	100 [2.5, 100] n=1	100 [15.8, 100] n=2	100 [15.8, 100] n=2
Male	60.0 [36.1, 80.9] n=20	90.6 [75.0, 98.0] n=32	93.8 [79.2, 99.2] n=32
Female	55.6 [21.2, 86.3] n=9	80.8 [60.7, 93.5] n=26	96.2 [80.4, 99.9] n=26

Source: Tables 8.2.2.1 (infection intensity), 8.2.3.1 (age), and 8.2.4.1 (gender) from MS200661-0003 CSR;
Exact 95% CIs were calculated based on the Clopper-Pearson method.
CI=confidence interval, CSR=clinical study report, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.
Note: Cure rate was based on urine filtration.
[a] Light infection: 1-49 eggs/10 mL of urine.
[b] Heavy infection: ≥ 50 eggs/10 mL of urine.

CRs across all cohorts by infection intensity



Source: Tables 8.2.2.1 and 8.2.2.5.
CI=confidence interval, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat.

Figure 14 Clinical Cure Rate (%) by Infection Intensity – mITT Population

Egg reduction rate (ERR)

Schistosoma mansoni

For the mITT population, the ERRG and ERRA were near or above 95% except for Cohort 2, in which the ERRG was 99.6% but the ERRA was 88.5%. The lower ERRA in Cohort 2 was due to a subject who vomited within an hour from dosing who had an egg count of 1148 at follow-up. After exclusion of this subject, the PP population had an ERRA of 97.7%. The proportions with an iERR ≥ 90% were above 91% for all cohorts. For the pooled Cohort 3 with Cohorts 8 and 9 from the Phase 2 study the ERRA was 97.2%, the ERRG was 99.6% and proportion with an iERR ≥ 90% was 97.3%.

Table 40 Egg Reduction Rate (%) in S. mansoni-infected Participants – mITT Population with Imputation

Point Estimate (%) [95% CI]	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg (N=98)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg (N=48)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg (N=29)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=18)	Pooled Cohorts 8, 9 and 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=37)
ERR_A	99.5 [98.8, 99.9]	99.2 [97.6, 99.8]	88.5 [56.4, 100]	95.6 [77.0, 100]	97.2 [88.9, 100]
ERR_G	99.7 [99.5, 99.9]	99.5 [98.9, 99.8]	99.6 [98.5, 100]	99.3 [96.6, 100]	99.6 [98.7, 100]
Proportion of iERR ≥ 90%	94.9 [88.5, 98.3]	91.7 [80.0, 97.7]	93.1 [77.2, 99.2]	94.4 [72.7, 99.9]	97.3 [85.8, 99.9]

Source: Tables 8.2.8.1 and 8.2.8.4 from MS200661-0003 CSR.

CI=confidence interval, CSR=clinical study report, ERR=egg reduction rate, ERR_A=group arithmetic mean-based ERR, ERR_G=group geometric mean-based ERR, iERR=individual egg reduction rate, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.

ERR is the relative difference in group means of egg counts before and after treatment. For each cohort, at each time point group mean is the mean of eggs/gram of feces across all participants.

iERR is the relative difference in eggs/gram of feces before and after treatment for each participant.

CIs for group mean-based ERRs were calculated using bootstrapping approach. CIs for proportion of iERR ≥ 90% were calculated using Clopper-Pearson method.

Note: Cohorts 1, 2, and 3 from this study and Cohorts 8 and 9 from Phase 2 Study MS200661-0005. Egg counts were based on Kato-Katz method.

The next table shows the ERRs by infection intensity, age group, gender and country.

For the mITT population, ERRG and ERRA as determined by Kato-Katz were close to or above 90% for all subgroups in all cohorts. The proportions with an iERR ≥ 90% were close to or above 90% for all cohorts except for Cohort 1b 40 mg/kg Biltricide in the Ivory Coast, where the proportion with an iERR ≥ 90% was 84%.

In the subgroups pooled across Cohort 3 and Cohorts 8 and 9 from Phase 2 study MS200661-0005, the observed ERRA, ERRG and proportion with iERR ≥ 90% were consistently above 90%.

Table 41 Egg Reduction Rate (%) in S. mansoni-infected Participants, Stratified by Infection Intensity, Age Group, Gender, and Country – mITT Population with Imputation

Subgroup Point Estimate (%) [95% CI], n		Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg (N=98)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg (N=48)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg (N=29)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=18)	Pooled Cohorts 8, 9 and 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=37)
Light infection[a]	ERR_A	99.0 [97.0, 100] n=59	89.3 [72.2, 99.6] n=27	100 [100, 100] n=12	76.9 [17.2, 100] n=14	91.0 [68.0, 100] n=29
	ERR_G	99.7 [99.2, 100]	98.6 [96.1, 99.8]	100 [100, 100]	98.3 [91.5, 100]	99.4 [97.5, 100]
	Proportion of iERR ≥ 90%	94.9 [85.9, 98.9]	85.2 [66.3, 95.8]	100 [73.5, 100]	92.9 [66.1, 99.8]	96.6 [82.2, 99.9]
Moderate/heavy infection[b]	ERR_A	99.6 [98.8, 99.9] n=39	99.8 [99.7, 100] n=21	88.1 [53.1, 100] n=17	100 [100, 100] n=4	99.8 [99.3, 100] n=8
	ERR_G	99.9 [99.7, 100]	99.9 [99.7, 100]	99.7 [98.6, 100]	100 [100, 100]	99.9 [99.5, 100]
	Proportion of iERR ≥ 90%	94.9 [82.7, 99.4]	100 [83.9, 100]	88.2 [63.6, 98.5]	100 [39.8, 100]	100 [63.1, 100]
Male	ERR_A	99.7 [99.1, 100] n=48	99.5 [97.5, 100] n=27	87.5 [29.4, 100] n=14	100 [100, 100] n=7	100 [100, 100] n=19
	ERR_G	99.8 [99.5, 100]	99.6 [98.8, 100]	99.7 [97.9, 100]	100 [100, 100]	100 [100, 100]
	Proportion of iERR ≥ 90%	95.8 [85.7, 99.5]	92.6 [75.7, 99.1]	92.9 [66.1, 99.8]	100 [59.0, 100]	100 [82.4, 100]
Female	ERR_A	99.3 [97.8, 99.9] n=50	98.7 [95.4, 99.9] n=21	91.5 [75.7, 100] n=15	90.2 [14.3, 100] n=11	94.1 [71.4, 100] n=18
	ERR_G	99.6 [99.2, 99.9]	99.4 [98.2, 99.9]	99.5 [97.8, 100]	98.3 [88.6, 100]	99.0 [95.6, 100]
	Proportion of iERR ≥ 90%	94.0 [83.5, 98.7]	90.5 [69.6, 98.8]	93.3 [68.1, 99.8]	90.9 [58.7, 99.8]	94.4 [72.7, 99.9]
Kenya	ERR_A	99.6 [98.8, 100] n=43	99.8 [99.7, 100] n=23	88.3 [55.0, 100] n=24	95.3 [74.3, 100] n=12	95.3 [71.8, 100] n=12
	ERR_G	99.8 [99.6, 100]	99.8 [99.6, 99.9]	99.6 [98.5, 100]	99.4 [95.3, 100]	99.4 [95.3, 100]
	Proportion of iERR ≥ 90%	97.7 [87.7, 99.9]	100 [85.2, 100]	91.7 [73.0, 99.0]	91.7 [61.5, 99.8]	91.7 [61.5, 99.8]
Ivory Coast	ERR_A	98.9 [97.4, 99.9] n=55	93.2 [79.7, 99.8] n=25	100 [100, 100] n=5	100 [100, 100] n=6	99.7 [99.1, 100] n=25
	ERR_G	99.5 [99.0, 99.9]	98.9 [96.5, 99.9]	100 [100, 100]	100 [100, 100]	99.8 [99.4, 100]
	Proportion of iERR ≥ 90%	92.7 [82.4, 98.0]	84.0 [63.9, 95.5]	100 [47.8, 100]	100 [54.1, 100]	100 [86.3, 100]

Source: Tables 8.2.9.1 and 8.2.9.4 (infection intensity), 8.2.11.1 and 8.2.11.4 (gender), and 8.2.12.1 and 8.2.12.4 (country) from MS200661-0003 CSR.

CI=confidence interval, CSR=clinical study report, ERR=egg reduction rate, ERR_A=group arithmetic mean-based ERR, ERR_G=group geometric mean-based ERR, iERR=individual egg reduction rate, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.

Note: Cohorts 1, 2, and 3 from this study and Cohorts 8 and 9 from the Phase 2 Study MS200661-0005. Egg counts were based on Kato-Katz method.

[a] Light infection: 1-99 eggs per gram of stool.

[b] Moderate infection: 100-399 eggs per gram of stool; Heavy infection: ≥ 400 eggs per gram of stool.

Schistosoma haematobium

For the mITT population, ERRG and ERRA were close to or above 98% for Cohorts 4a and 4b. The proportions with an iERR ≥ 90% were close to or above 93% for both cohorts.

Table 42 Egg Reduction Rate (%) in S. haematobium-Infected Participants – mITT Population

Point Estimate (%) [95% CI]	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg Week 3 (N=29)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg	
		Week 3 (N=58)	Week 5 (N=58)
ERR_A	99.4 [98.8, 99.8]	99.2 [98.2, 99.8]	99.3 [97.6, 100]
ERR_G	99.1 [98.2, 99.6]	98.8 [97.5, 99.7]	99.4 [98.2, 100]
Proportion of iERR ≥ 90%	93.1 [77.2, 99.2]	94.8 [85.6, 98.9]	98.3 [90.8, 100]

Source: Table 8.2.8.1 from MS200661-0003 CSR.

CI=confidence interval, CSR=clinical study report, ERR=egg reduction rate, ERR_A=group arithmetic mean-based ERR, ERR_G=group geometric mean-based ERR, iERR=individual egg reduction rate, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.

ERR is the relative difference in group means of egg counts before and after treatment. For each cohort, at each time point group mean is the mean of eggs/gram of feces across all participants.

iERR is the relative difference in eggs/gram of feces before and after treatment for each participant.

CIs for group mean-based ERRs were calculated using bootstrapping approach. CIs for proportion of iERR ≥ 90% were calculated using Clopper-Pearson method.

Note: Egg counts were based on urine filtration.

The table below shows the ERRs by subgroups, where the ERRG and ERRA were close to or above 97% and proportions with an iERR ≥ 90% were close to or above 90%.

Table 43 Egg Reduction Rate (%) in S. haematobium-Infected Participants, Stratified by Infection Intensity, Age Group, and Gender – mITT Population and Imputation

Subgroup Point Estimate (%) [95% CI] n		Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg Week 3 (N=29)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg	
			Week 3 (N=58)	Week 5 (N=58)
Light infection[a]	ERR_A	97.7 [94.8, 99.6] n=18	98.9 [97.6, 99.7] n=52	98.6 [95.5, 100] n=52
	ERR_G	98.1 [95.6, 99.6]	98.7 [97.1, 99.6]	99.1 [97.3, 100]
	Proportion of iERR ≥ 90%	88.9 [65.3, 98.6]	94.2 [84.1, 98.8]	98.1 [89.7, 100]
Heavy infection[b]	ERR_A	99.8 [99.5, 99.9] n=11	99.5 [97.5, 100] n=6	100 [100, 100] n=6
	ERR_G	99.8 [99.5, 99.9]	99.7 [98.3, 100]	100 [100, 100]

Subgroup Point Estimate (%) [95% CI] n		Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg Week 3 (N=29)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg	
			Week 3 (N=58)	Week 5 (N=58)
	Proportion of iERR ≥ 90%	100 [71.5, 100]	100 [54.1, 100]	100 [54.1, 100]
Age 4 to 6 years	ERR_A	99.4 [98.5, 99.8] n=21	99.4 [98.4, 99.9] n=46	99.3 [97.3, 100] n=46
	ERR_G	99.2 [98.2, 99.7]	99.0 [97.8, 99.8]	99.4 [98.0, 100]
	Proportion of iERR ≥ 90%	90.5 [69.6, 98.8]	95.7 [85.2, 99.5]	97.8 [88.5, 99.9]
Age 2 to 3 years	ERR_A	99.9 [98.4, 100] n=7	97.8 [86.7, 100] n=10	99.7 [98.3, 100] n=10
	ERR_G	99.4 [97.4, 100]	97.3 [84.0, 100]	99.5 [97.6, 100]
	Proportion of iERR ≥ 90%	100 [59.0, 100]	90.0 [55.5, 99.7]	100 [69.2, 100]
Age 3 to < 24 months	ERR_A	100 [100, 100] n=1	100 [100, 100] n=2	100 [100, 100] n=2
	ERR_G	100 [100, 100]	100 [100, 100]	100 [100, 100]
	Proportion of iERR ≥ 90%	100 [2.5, 100]	100 [15.8, 100]	100 [15.8, 100]
Male	ERR_A	99.5 [98.8, 99.9] n=20	99.8 [99.2, 100] n=32	99.9 [99.6, 100] n=32
	ERR_G	99.3 [98.2, 99.8]	99.6 [98.9, 100]	99.8 [99.3, 100]
	Proportion of iERR ≥ 90%	90.0 [68.3, 98.8]	100 [89.1, 100]	100 [89.1, 100]
Female	ERR_A	98.8 [97.7, 99.8] n=9	97.7 [94.8, 99.7] n=26	97.8 [91.2, 100] n=26
	ERR_G	98.6 [96.9, 99.8]	97.0 [92.6, 99.5]	98.6 [94.4, 100]
	Proportion of iERR ≥ 90%	100 [66.4, 100]	88.5 [69.8, 97.6]	96.2 [80.4, 99.9]

Source: Tables 8.2.9.1 (infection intensity), 8.2.10.1 (age), and 8.2.11.1 (gender) from MS200661-0003 CSR.

CI=confidence interval, CSR=clinical study report, ERR=egg reduction rate, ERR_A=group arithmetic mean-based ERR, ERR_G=group geometric mean-based ERR, iERR=individual egg reduction rate, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.

Note: Egg counts were based on urine filtration.

[a] Light infection: 1 to 49 eggs/10 mL of urine.

[b] Heavy infection: ≥ 50 eggs/10 mL of urine.

CRs based on POC-CCA

All cohorts presented CRs per POC-CCA around 60%, ranging from 55% to 72% with the lowest value observed in Cohort 1b (40 mg/kg Biltricide). The applicant states that the lower CR based on POC-CCA compared to the clinical CR has been ascribed in the literature to the higher sensitivity of this technique for diagnosis in both high and low endemic epidemiological settings.

Table 44 Cure Rate (%) by POC-CCA Method at Week 3 – mITT Population

	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg (N=98)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg (N=48)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg (N=29)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=18)	Pooled Cohorts 8, 9 and 3 3 to 24 mths L-PZQ ODT 50 mg/kg (N=37)
Point estimate (%) [95% CI]	64.3	55.3	62.1	72.2	62.2
	[54.0, 73.7]	[40.1, 69.8]	[42.3, 79.3]	[46.5, 90.3]	[44.8, 77.5]

Source: Tables 8.2.7.1 and 8.2.7.3 from MS200661-0003 CSR; Clopper-Pearson exact 95% CIs.

CI=confidence interval, CSR=clinical study report, L-PZQ=levorotatory enantiomer of praziquantel, mITT=modified intent-to-treat, ODT=orodispersible tablet.

- **Summary of main efficacy results**

The CR based on Kato-Katz method at 17 to 21 days after treatment of *S. mansoni* in children aged 4 to 6 years (Cohort 1a) was 88% [80, 94%], and was similar to the CR observed for commercially available Biltricide at the 40 mg/kg standard dose (Cohort 1b): 81% [67, 91%]. The CRs observed in the PP population were close or similar to those observed for the mITT population.

Across all age groups the CRs were close to or above 90% for *S. mansoni* (50 mg/kg L-PZQ) and *S. haematobium* (60 mg/kg L-PZQ).

For *S. haematobium* the CR was higher with L-PZQ 60 mg/kg compared to 50 mg/kg (59% [39, 77%] and 86% [75, 94%], respectively, at Week 3). A higher CR was observed with 60 mg/kg at Week 5 (95% [86, 99%]) compared to Week 3.

The CRs tended to be lower in moderately/heavily infected vs. lightly infected children.

A high ERR was observed across all cohorts: ERRG were all around 99%; proportions with iERR ≥ 90% were all > 90%.

CRs as determined by POC-CCA were generally lower than those determined using the Kato-Katz method but showed similar patterns across age groups.

On pooling the data for Cohort 3 from this study and Cohorts 8 and 9 from the Phase 2 study, the CR with 50 mg/kg L-PZQ in children aged 3 to 24 months was similar to that in other age groups (94.6% with 95% CI [81.8, 99.3%]). In this pooled group, ERRG was 99.6% and the proportion with iERR ≥ 90% was 97.3%.

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy.

Table 45 Summary table of efficacy for trial MS200661-0003

Title: An open-label, Phase 3 efficacy and safety study of L-praziquantel orodispersible tablets (L-PZQ ODT) in Schistosoma-infected children 3 months to 6 years of age, including a 2:1 randomised, controlled cohort of *Schistosoma mansoni*-infected children 4 to 6 years of age treated with L-PZQ ODT or commercial PZQ (Biltricide)			
Study identifier	PACTR 201810634034543 Clinical Trials.gov: NCT03845140		
Design	Open label, partly randomised (Cohort 1 only) Phase 3 pivotal efficacy study		
	Duration of main phase:		2 September 2019 initiation 7 August 2021 (LPLV) 22 June 2022 CSR date
Hypothesis	No formal hypothesis testing in any cohort		
Treatment groups	L-PZQ 50 mg/kg		Single dose in Cohorts 1a, 2, 3 all with *S. mansoni* Cohort 4a with *S. haematobium*
	Biltricide 40 mg/kg		Single dose in Cohort 1b *S. mansoni*
	L-PZQ 60 mg/kg		Single dose in Cohort 4b *S. haematobium*
Endpoints and definitions	Primary Clinical cure rate	CR	Based on Kato Katz method for *S. mansoni* CR was defined as no parasite eggs in stools obtained 17-21 days post-treatment and within the next 5 days For *S. haematobium*, Week 3 CR was defined as no parasite eggs in urine samples (3 samples starting at day 17-21 and 5 days apart); repeated to derive Week 5 CR starting with samples obtained starting days 35-40
	Secondary Egg reduction rate	ERR	Egg counts determined as for the primary endpoint
Database lock	28 September 2021		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified Intent to Treat (mITT) 3 weeks after treatment for all Cohorts 5 weeks after treatment for *S. haematobium* (Cohort 4) only			
Descriptive statistics and estimate variability	Treatment group	L-PZQ 50 mg/kg	Biltricide 40 mg/kg	L-PZQ 60 mg/kg
	Number of subjects	**Cohort 1a N=98**	**Cohort 1b N=48**	**Cohort 4b N-58**
	S. mansoni CR (95% CI) With imputation Without imputation	87.8 (79.6, 93.5) 87.8 (79.6, 93.5)	81.3 (67.4, 91.1) 83.0 (69.2, 92.4)	N/A
	ERRA ERRG Proportion of iERR ≥90%	99.5 (98.8, 99.9) 99.7 (99.5, 99.9) 94.9 (88.5, 98.3)	99.2 (97.6, 99.8) 99.5 (98.9, 99.8) 91.7 (80.0, 97.7)	N/A
	S. mansoni CR (95% CI) With imputation Without imputation	**Cohort 2 N=29** 93.1 (77.2, 99.2) 93.1 (77.2, 99.2)	N/A	N/A
	S. mansoni CR (95% CI) With imputation Without imputation	**Cohort 3 N=18** 94.4 (72.7, 99.9) 94.4 (72.7, 99.9)	N/A	N/A
	S. haematobium CR (95% CI)	**Cohort 4a N=29** Week 3 58.6 (38.9, 76.5)	N/A	**Cohort 4b N=58** Week 3 86.2 (74.6, 93.9) Week 5 94.8 (85.6, 98.9)

2.6.6. Discussion on clinical efficacy

Biltricide tablets contain 600 mg rac-PZQ and are recommended for treatment of schistosomiasis from 4 years of age (from 1 year US and Germany) with posology given from 20 kg body weight. The tablets are scored and are broken to achieve the recommended doses by weight band, including administration of ¼ tablets for some children. Cysticide tablets contain 500 mg racemic PZQ and are scored, with a similar need to break them to achieve the calculated dose. The tablets and fragments are recommended to be swallowed whole. In routine practice, it seems that it is not unusual that tablets are crushed and administered as a slurry, but this has a bitter taste and may result in dose rejection and/or vomiting.

The prescribing information for Biltricide and Cysticide recommends use only from the age of 4 years (Biltricide from 1 year and Cysticide from 2 years in Germany) and the dose for treating schistosomiasis is 3 x 20 mg/kg on one day, regardless of the species. However, the WHO recommends a single dose of 40 mg/kg every 1-3 years, including PSAC from 2 years regardless of species as an alternative.

L-PZQ is the active moiety within the racemate. The aim of the L-PZQ programme was to provide an appropriate formulation and tablet size for oral dosing of pre-school age children in endemic areas with a minimum age for use of 3 months. A dispersible/orodispersible tablet (DT/ODT) formulation was selected as potentially appropriate, and Phase 1 results suggested it was preferable to disperse the tablets in water prior to administration rather than using direct dispersion in the mouth. The poor palatability of the tablets reported by adults when they were disintegrated in the mouth was reinforced by a published study of palatability in Tanzanian school age children from 6 years (Mahende *et al*., 2021). In the Phase 2 and 3 studies, the tablets were dispersed in water and administered using a cup in all age groups.

The efficacy of arpraziquantel was evaluated in children infected with *S. mansoni* or *S. haematobium* and resident in endemic areas. The Phase 2 dose-finding and formulation-finding study was confined to children infected with *S. mansoni* and suggested that the minimum L-PZQ dose should be 45 mg/kg. The Phase 3 study used a rounded up 50 mg/kg L-PZQ target dose for *S. mansoni* and evaluated 50 mg/kg and 60 mg/kg L-PZQ as the target doses for *S. haematobium*.

The Phase 2 and Phase 3 studies were the subject of several requests for CHMP scientific advice and the final design and analysis of these studies was in keeping with the advice given. It was agreed that the focus of the clinical programme would be to establish appropriate mg/kg doses for the L-PZQ. Although there is no proven direct link between plasma exposures to L-PZQ and efficacy against schistosomiasis, the PK findings raised the possibility that giving L-PZQ alone at the same dose delivered by the racemate could lead to lower efficacy compared to the racemate. Hence, the arpraziquantel dose is more than half of the L-PZQ dose that is administered using the racemate.

The Phase 2 and Phase 3 studies were both open-label. After discussions during scientific advice, the open-label design was accepted because the efficacy endpoints were laboratory parameters and laboratory staff were not aware of treatment assignments. During the procedure, the applicant provided full details of the laboratories involved in Kenya and Ivory Coast, the laboratory methods and the quality control procedures in place, including second readings and resolution of discrepancies between readers. In summary, the processes put in place were deemed acceptable.

In Phase 2 and Phase 3, the dosing instructions were to disperse the tablets in water and there was no alternative mode of administration offered. Therefore, no patient was treated by L-PZQ tablets by

direct dispersion in the mouth in Phase 2 or 3 clinical studies. The applicant confirmed that all children received their dose as tablets dispersed in water and administered via a cup.

Design and conduct of clinical studies

Phase 2 study 0005

Conducted between 2016 and 2018 at a single centre in the Ivory Coast, the study enrolled children with *S. mansoni* infections.

In Part 1, children aged 2-6 years were randomised (20-40 per group) to commercial rac-PZQ tablets (3 x 20 mg/kg or 1 x 40 mg/kg), paediatric formulations of rac-PZQ (40 mg/kg or 60 mg/kg) or L-PZQ (30 mg/kg, 45 mg/kg or 60 mg/kg). The doses were selected because of varying opinions regarding the optimal dose of licensed racemate, especially for children aged <4 years, and to determine an appropriate dose of L-PZQ when given alone using the paediatric formulation. In Part 2, Cohort 8 (L-PZQ 50 mg/kg, age 13-24 months) and Cohort 9 (L-PZQ 50 mg/kg, age 3-12 months) the number of subjects planned was 30 and 10, respectively.

The calculated mg/kg doses were rounded to the next/closest value so that doses could be delivered using whole 150 mg tablets, which were dispersed in water prior to administration. The applicant provided the exact dosing instructions by body weight that were given to study staff along with a tabulation of the mean, median and range of actual mg/kg doses delivered for Cohorts 1-9 in the Phase 2 study. In Part 2, in which the target dose was 50 mg/kg, the instructions were slightly different to those applied in Phase 3. Among the children in Cohorts 8 and 9 who received a target dose of 50 mg/kg, the calculated actual doses administered were from 40 mg/kg to 57.7 mg/kg.

The level of infection in the children enrolled into the study was classified using the WHO criteria and there was stratification at randomisation by infection load. The exclusion criteria were in line with the prescribing information for the racemate. Screening and treatment for malaria was implemented at screening/pre-study and children treated with an artemisinin after receiving assigned study drug were removed from the primary efficacy analysis due to the possible confounding effect of anti-schistosomal activity of the artemisinins.

The primary efficacy endpoint for treatment of *S. mansoni* infections was clinical cure, defined as no eggs found in stools obtained 14-21 days after the single dose treatment. Importantly, the cure rate depended on two samples collected on different days and up to 5 days apart. Three Kato-Katz thick smears were prepared from each stool sample and eggs per gram of stool was calculated as the sum of egg counts per subject obtained from two stool samples with three Kato-Katz thick smears each, multiplied by a factor of four. If no stool sample was collected at 14-21 days after treatment, the subject was imputed as uncured. It was agreed during scientific advice that the most important secondary efficacy endpoint was the egg reduction rate (ERR) from baseline to 14-21 days after treatment. This was calculated based on the arithmetic mean and geometric mean egg count per gram of stool for each treatment arm.

It was agreed that the study was exploratory with no hypothesis testing required for the primary endpoint, so the sample size was based mainly on feasibility considerations. Nevertheless, the applicant prepared a statistical analysis plan (SAP). The primary analysis was conducted in the mITT set, defined as all randomised subjects who had a baseline measurement for the efficacy variable, excluding those who received anti-malarial treatment following dosing. The primary analysis included imputation of missing data (last observation carried forward) and those with missing follow-up egg counts were imputed as not cured. The primary analysis was repeated without imputation.

Phase 3 study 0003

The single pivotal efficacy study was conducted in Kenya and Ivory Coast in 2019-2021. Based on the results with 45 mg/kg in Phase 2, children aged 3 months to 6 years with *S. mansoni* received a target dose of 50 mg/kg L-PZQ using the tablets administered after dispersion in water. The minimum body weight for enrolment was 5 kg for those aged <24 months and 8 kg from 2 years of age.

As per CHMP advice, there was randomisation to L-PZQ or racemate (2:1) only in Cohort 1 aged 4-6 years. Although the Phase 2 study suggested that 3 x 20 mg/kg on one day might be somewhat better than 1 x 40 mg/kg in children aged 2-6 years, the Biltricide dose in Cohort 1 was 40 mg/kg. This dose is recommended by the WHO and the literature gives variable results for different Biltricide doses and according to the infection (*S. mansoni* or *S. haematobium*). See further below on the between-group comparisons that were made.

For children with *S. haematobium*, in accordance with the protocol, the IDMC reviewed the safety and efficacy data of Cohort 4 after 30 children had received 50 mg/kg L-PZQ and recommended that the dose should be increased to 60 mg/kg L-PZQ.

The classification of infection load for *S. mansoni* and *S. haematobium* followed WHO criteria and stratification at randomisation by load was applied to Cohort 1 since only this Cohort was randomised. As in Phase 2, exclusions were kept to a minimum.

The primary endpoint for groups infected with *S. mansoni* was the cure rate at day 17-21 after treatment (compared to days 14-21 in Phase 2). Apart from the time window applied, this endpoint was determined as in Phase 2. The primary analysis for those with *S. mansoni* compared Cohorts 1a and 1b (i.e. L-PZQ vs. Biltricide). However, as was agreed at the time of scientific advice, there was no formal hypothesis testing. The ERR was the main secondary endpoint as in Phase 2.

The primary endpoint for those with *S. haematobium* was the cure rate as assessed at 17 to 21 days and 35 to 40 days after treatment, where clinical cure was defined as no parasite eggs in urine using the urine filtration technique. The application of an assessment at two time points up to ~6 weeks post-treatment was appropriate for this species.

Efficacy data and additional analyses

Phase 2 study 0005

In children aged 2-6 years, the mean and median weights were ~15-16 kg and for Cohorts 8 and 9 (3-24 months) values were ~9 kg. A detailed analysis of the actual mg/kg doses administered indicated that the mean and median values were very close to the target values. In accordance with the stratification, close to 60% in Cohorts 1-7 had a light infection whereas the majority in Cohorts 8-9 had light infections.

The overall CR in all cohorts was ≥70%. The lowest CR (74%) was observed in Cohort 2 with 40 mg/kg Biltricide but the 95% CI around the cure rates overlapped for all cohorts. Given the results across Cohort 1 as well as the result for Cohort 6 and the high cure rates in Cohorts 8-9, it was considered reasonable to select a 50 mg/kg dose for *S. mansoni* in Phase 3. This conclusion was supported by similar findings for the analysis of cure rates in the mITT population without imputation.

Regression analysis revealed that infection intensity appeared to be the only significant covariate (apart from treatment) with respect to CR.
However, even in those with moderate/heavy infections, the cure rates for the L-PZQ groups fell between those for 3x20 mg/kg (85.7%) and 1x40 mg/kg (56.5%) Biltricide, ranging from 69-82%.

The CRs based on POC-CCA at Day 14 -21 were noticeably lower than CRs assessed by the Kato-Katz method for the primary analysis, which may reflect the higher sensitivity of the POC CCA test as reported in the literature. However, the POC CCA results suggested broad comparability between the Biltricide groups and the groups that received at least 45 mg/kg arpraziquantel. There was an increase in POC CCA CR over time (Day 2, 8 and 14-21).

The Egg Reduction Rates (ERR) per geometric mean (ERRgm) and per arithmetic mean (ERRam) in the mITT population were close to or >90% except for Cohort 2 (Biltricide 40 mg/kg). Without imputation, high ERRG and ERRA were observed across all cohorts (> 95%) for all the study interventions.

The applicant concluded that a single dose of L-PZQ 45 mg/kg provided an acceptable CR as assessed by Kato-Katz method with an acceptable safety profile in 2-6 year-olds infected with *S. mansoni.* For ease of dose calculation, 50 mg/kg of L-PZQ was selected for Part 2 in subjects aged 3-24 months and the results in Cohorts 8 and 9 were considered to further support this dose.

In summary, the 50 mg/kg L-PZQ dose (rounded up from 45 mg/kg) was selected for treatment of *S. mansoni* in the Phase 3 study. Initially, the same dose was used in children with *S. haematobium* but, it was later increased to 60 mg/kg for reasons explained below.

Phase 3 study 0003

The majority (67.5%) were enrolled in Kenya and all Cohort 4 subjects were enrolled in Kenya due to the epidemiology of *S. haematobium*. In Cohort 4 (3 months to 6 years of age), the majority was aged 4 to 6 years, consistent with the epidemiology of *S. haematobium*.

The target for Cohort 1 of 40% moderate/heavy infections and 60% light infections was achieved. Light infection predominated in Cohort 3 (14/18 [77.8%]) and in Cohort 4a (18/29 [62.1%]) and Cohort 4b (52/58 [89.7%]). In contrast, Cohort 2 had a higher proportion with moderate or heavy infection (58.6% [17/29]) due to the presence of hotspots in some Kenya districts.

As in Phase 2, there was a mg/kg rounded dose schema. The SmPC reflects the dose schema exactly as applied in Phase 3, which was slightly different to that applied in Phase 2 for the 50 mg/kg and 60 mg/kg target dose groups. The actual mean and median mg/kg doses delivered across Cohorts 1-4 were mostly very close to the targeted mg/kg doses. However, the ranges indicate that some children received up to 7 mg/kg below the target for their cohort while some others received up to 15 mg/kg more than the target for their cohort.

- ***Schistosoma mansoni***

The clinical CRs by the Kato-Katz method in *S. mansoni*-infected children who received 50 mg/kg L-PZQ were ≥ 87% with the lower bounds of the 95% CI exceeding 70% (Cohorts 1a, 2 and 3). The CRs in Cohort 1 were broadly comparable for 50 mg/kg L-PZQ and 40 mg/kg Biltricide.

One subject was lost to follow-up from Cohort 1b, so there is almost no difference between the results for the mITT population with and without imputation.

Within Cohort 1 the CRs were lower but very similar for L-PZQ and Biltricide for those with moderate/heavy infections (CR 76.9% and 76.2%) vs. those with light infections.

The point estimates for CRs in Cohorts 2 and 3, as well as for the pooled data in children aged from 3-24 months who received 50 mg/kg L-PZQ in Cohort 3 or in Cohorts 8 and 9 in the Phase 2 study, were all above 90%. A higher CR with L-PZQ in those with light infection was observed in Cohort 2. This pattern was not seen in the smaller numbers in Cohort 3. It was seen when data from Cohort 3 were pooled with Cohorts 8 and 9 from the Phase 2 study (light infection 96.6% vs. moderate/heavy infection 87.5%) but only 8 subjects had moderate/heavy infection.

While the study was not powered for the comparison between Cohort 1a and 1b or for comparisons between the other cohorts with *S. mansoni* and the licensed racemate, and while the comparisons should take account of the different levels of infection, the study suggested that 50 mg/kg L-PZQ administered as paediatric formulation was likely to be at least as efficacious as 40 mg/kg of the racemate (CR 81% with a lower bound of the 95% CI just below the target 70%). Noting that 3x20 mg/kg of the racemate appeared possibly more efficacious than 1x40 mg/kg in Phase 2, a cross-study comparison (which must be viewed with due caution) suggested that the point estimate CR and lower bounds of the 95% CI for Cohorts 1a, 2 and 3 were broadly comparable with the results for 3x20 mg/kg racemate.

The results for the CR were supported by those for the ERR. For the mITT population, the ERRG and ERRA were near or above 95% except for Cohort 2, in which the ERRG was 99.6% but the ERRA was 88.5%. The lower ERRA in Cohort 2 was due to a subject who vomited within an hour from dosing who had an egg count of 1148 at follow-up. After exclusion of this subject, the PP population had an ERRA of 97.7%. The proportions with an iERR ≥ 90% were close to or above 90% for all cohorts except for Cohort 1b 40 mg/kg Biltricide in the Ivory Coast, where the proportion with an iERR ≥ 90% was 84%. In the subgroups pooled across Cohort 3 and Cohorts 8 and 9 from the Phase 2 study, the observed ERRA, ERRG and proportion with iERR ≥ 90% were consistently above 90%.

CRs as determined by POC-CCA were generally lower than those determined using the Kato-Katz method but showed similar patterns across age groups.

- ***Schistosoma haematobium***

There was no control group for the evaluation of efficacy against *Schistosoma haematobium.* The optimum dose of racemate for treating this species is unclear from the literature. With a 58.8% CR in Cohort 4a (50 mg/kg L-PZQ) at Week 3, the IDMC recommended an increase in dose to 60 mg/kg, which seems appropriate. The 60 mg/kg dose resulted in a CR of 86.2% [74.6, 93.9%] at Week 3 and 94.8% [85.6, 98.9%] at Week 5. The higher CR at Week 5 vs. Week 3 may reflect the longer host parasite lifecycle in *S. haematobium* and a longer period for egg clearance.

The observed CR was higher in Cohort 4a for light infection (66.7%) compared to heavy infection (45.5%). In Cohort 4b the CRs were 86.5% at Week 3 and 94.4% at Week 5 for light infections compared to CRs for heavy infections that were 83.3% and 100% at respective visits. However, sample sizes in Cohorts 4a and 4b for heavy infections are small.

For the mITT population, ERRG and ERRA were close to or above 98% for Cohorts 4a and 4b. The proportions with an iERR ≥ 90% were close to or above 93% for both cohorts.

Generally, the findings support use of 50 mg/kg L-PZQ for treatment of *S. mansoni* and 60 mg/kg for treatment of *S. haematobium* in children aged from 3 months to 6 years. In this regard, it is

acknowledged that there are relatively few data in children aged <2 years, especially for *S. haematobium*. Specifically, 37 children aged <2 years were treated for *S. mansoni* based on pooled data of three cohorts in Phase 2 and 3 while there were only 2 children aged <2 years treated for *S. haematobium* in Phase 3. This anticipated paucity of data was discussed during scientific advice in light of the age distribution of infections by the two species. However, the few efficacy data that are available, together with POPPK modelling that suggests a broad comparability in systemic exposures when mg/kg dosing is applied, do support an expectation of efficacy.

2.6.7. Conclusions on the clinical efficacy

The clinical development programme was focussed on determining a safe and effective dose of L-PZQ when administered as paediatric formulation to pre-school age children resident in areas where *S. mansoni* or *S. haematobium* is/are endemic. Due to the existing information available for the licensed racemate, and for feasibility reasons, it was agreed with the applicant in scientific advice that a modest development programme could suffice.

Although the CHMP strongly recommended comparisons with licensed racemate in Phase 2 and 3, the optimal dose of racemate remains unverified for either species and opinions vary on the doses to be applied by weight and/or age band, noting that the prescribing information anyway restricts use to a minimum of 4 years whereas there is a perceived need to have a formulation and posology that can be used from infancy up to 6 years. As a result, and for feasibility reasons, it was not possible to identify a justifiable non-inferiority margin to be applied to the clinical CRs. During scientific advice, the CHMP reached agreement with the applicant on a target 70% lower bound of the 95% CI around the point estimates for CR that could support a recommendation for dosing. This was based on multiple literature reports and it was taken forward to Phase 3 having viewed the results from Phase 2.

While there is a paucity of data (PK and efficacy) in children aged <24 months, and especially in those aged <12 months, there is no reason identified to preclude the use of arpraziquantel in accordance with the proposed minimum age of 3 months, with posology given from 5 kg.

Overall, the results of the programme support an expectation that 50 mg/kg L-PZQ administered as paediatric formulation can achieve a CR for *S. mansoni* that is at least comparable with that achieved with either 3x20 mg/kg or 1x40 mg/kg of the racemate. Furthermore, that 60 mg/kg L-PZQ administered as paediatric formulation will be highly efficacious for treatment of *S. haematobium*.

When viewed by infection load, it remains the case that these doses should provide an acceptable level of efficacy even in moderate/heavy infections. However, information appears in the SmPC on outcomes according to estimated pre-treatment parasite loads.

Noting the palatability of the tablets if left to disintegrate in the mouth in adults and in children aged from 6 years, along with the actual mode of administration used in Phase 2 and 3 (dispersal in water and administration via a cup), arpraziquantel should only be given after dispersal in water and should then be administered using a syringe or a cup depending on the opinion of the treating physician as to which is most appropriate for the individual child. Due to a perceived risk of choking in small children and due to lack of any clinical experience in the target age range, the tablets are not recommended for disintegration in the mouth.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In total, 732 paediatric participants aged 3 months to 6 years were included in the pooled Safety Analysis Population across the Phase 2 (study MS200661-0005) and Phase 3 (study MS200661-0003) studies, including 442 participants who received at least one dose of arpraziquantel. The other 290 participants either received Biltricide (n=170) or rac-PZQ ODT (n=120). Treatment compliance was 100%, as expected for single-dose studies.

In the Phase 2 Study MS200661-0005, a total of 444 children aged 3 months to 6 years were enrolled, treated, and included in the Safety Population with Parts 1 and 2 of the study including 420 and 24 participants, respectively. A total of 434 (97.7%) participants completed the study.

Cohort	Product	Dosage	Safety Analysis Set (N)
Cohort 1 (reference therapy)	rac-PZQ oral tablets (Biltricide 600 mg)	20 mg/kg, tid every 4 hours	60
Cohort 2 (reference therapy)	rac-PZQ oral tablets (Biltricide 600 mg)	40 mg/kg, single dose	60
Cohort 3	rac-PZQ ODT	40 mg/kg, single dose	60
Cohort 4	rac-PZQ ODT	60 mg/kg, single dose	60
Cohort 5	L-PZQ ODT	30 mg/kg, single dose	60
Cohort 6	L-PZQ ODT	45 mg/kg, single dose	60
Cohort 7	L-PZQ ODT	60 mg/kg, single dose	60
Cohort 8	L-PZQ ODT	50 mg/kg, single dose	20
Cohort 9	L-PZQ ODT	50 mg/kg, single dose	4

In the Phase 3 Study MS200661-0003, a total of 288 children aged 3 months to 6 years were enrolled, treated, and included in the Safety Population. A total of 287 (99.7%) participants completed the study.

Phase 3 study

There was complete adherence to assigned treatment in the Phase 3 study as shown in the table.

Table 46 Study Intervention Compliance – Safety Population

	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n (%)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)
Compliance with treatment, n (%)						
100%	100 (100)	50 (100)	30 (100)	18 (100)	30 (100)	60 (100)
Actual dose received (mg/kg)						
Mean ±SD	51.7 ± 4.96	40.9 ± 3.33	52.3 ± 4.22	51.7 ± 4.85	52.0 ± 4.38	63.2 ± 5.01
Median	51.0	41.0	52.5	52.3	51.3	62.9
Min; Max	44.4; 61.4	35.4; 54.7	46.5; 61.8	42.9; 59.4	44.6; 61.1	54.0; 75.0
Total dose received (mg)						
Mean ±SD	901.5 ± 167.19	708.0 ± 109.43	700.0 ± 106.67	475.0 ± 92.75	860.0 ± 204.43	1167.5 ± 265.03
Median	750.0	750.0	750.0	450.0	825.0	1050.0
Min; Max	750; 1350	450; 900	450; 1050	300; 600	450; 1200	600; 1950

Demographics and baseline characteristics (Safety Analysis Population- pooled data from the Phase 2 and 3 studies

L-PZQ ODT (mg/kg)					
Category Statistic	**30 (n=60)**	**45 (n=60)**	**50 (n=202)**	**60 (n=120)**	**Total (n=442)**
Age categories, n (%)	60 (100.0)	60 (100.0)	202 (100.0)	120 (100.0)	442 (100.0)
3 to < 24 months	0 (0.0)	0 (0.0)	41 (20.3)	2 (1.7)	43 (9.7)
≥ 2 to < 4 years	19 (31.7)	16 (26.7)	39 (19.3)	27 (22.5)	101 (22.9)
≥ 4 to ≤ 6 years[a]	41 (68.3)	44 (73.3)	122 (60.4)	91 (75.8)	298 (67.4)
≥ 2 to ≤ 6 years[a]	60 (100.0)	60 (100.0)	161 (79.7)	118 (98.3)	399 (90.3)
Age (years)					
Mean ± SD	4.68 ± 1.274	4.79 ± 1.097	4.12 ± 1.797	5.00 ± 1.381	4.53 ± 1.585
Median (min; max)	4.73 (2.0; 6.8)	4.80 (2.2; 6.8)	4.59 (0.3; 6.8)	5.06 (1.1; 6.9)	4.87 (0.3; 6.9)
Gender, n (%)	60 (100.0)	60 (100.0)	202 (100.0)	120 (100.0)	442 (100.0)
Male	37 (61.7)	28 (46.7)	106 (52.5)	67 (55.8)	238 (53.8)
Female	23 (38.3)	32 (53.3)	96 (47.5)	53 (44.2)	204 (46.2)
Infection severity, n (%)[b]	60 (100.0)	60 (100.0)	202 (100.0)	120 (100.0)	442 (100.0)
Light	36 (60.0)	36 (60.0)	125 (61.9)	90 (75.0)	287 (64.9)
Moderate/heavy	23 (38.3)	24 (40.0)	77 (38.1)	30 (25.0)	154 (34.8)
Missing	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Height (cm)					
Mean ± SD	101.5 ± 10.7	101.8 ± 9.0	97.6 ± 14.1	106.2 ± 11.8	101.1 ± 12.9
Median	103.0	102.0	101.0	107.0	103.0
Min; Max	80; 119	80; 124	64; 130	75; 146	64; 146
Weight (kg)					
Mean ± SD	15.86 ± 2.93	15.83 ± 2.68	15.10 ± 3.87	17.17 ± 3.78	15.86 ± 3.68
Median	15.95	15.55	15.50	17.15	16.00
Min; Max	10.5; 23.4	10.8; 23.6	6.9; 24.5	8.0; 33.8	6.9; 33.8
BMI (kg/m^2)					
Mean ± SD	15.36 ± 1.40	15.25 ± 1.41	15.68 ± 1.53	15.11 ± 1.26	15.43 ± 1.44
Median	15.05	15.25	15.60	14.90	15.20
Min; Max	12.7; 20.3	12.8; 18.8	10.5; 22.6	12.5; 19.4	10.5; 22.6

Phase 1 study

There were 36 subjects exposed to at least four doses of assigned treatment and 34 subjects received all five dosage forms. Of the two subjects, who withdrew for personal reasons after completing four treatments, one did not receive treatment C2 (30 mg/kg arpraziquantel dispersed in water and taken after a meal) and one did not receive treatment D (20 mg/kg arpraziquantel dispersed in water and not taken after a meal).

2.6.8.2. Adverse events

Phase 3 study

The table summarises the safety profile. TEAEs and related TEAEs are defined as in the footnote.

Table 47 Overview of Treatment emergent Adverse Events – Safety Population

	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n (%)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)	Total N=288 n (%)
Number of participants with:							
Any TEAE	66 (66.0)	31 (62.0)	20 (66.7)	14 (77.8)	9 (30.0)	28 (46.7)	168 (58.3)
Any drug-related TEAE	31 (31.0)	14 (28.0)	16 (53.3)	4 (22.2)	0	5 (8.3)	70 (24.3)
Any serious TEAE	0	0	0	0	0	1 (1.7)	1 (0.3)
Any severe TEAE	1 (1.0)	1 (2.0)	1 (3.3)	0	0	1 (1.7)	4 (1.4)
Any drug-related severe TEAE	0	0	1 (3.3)	0	0	0	1 (0.3)

Source: Table 8.3.1.1

MedDRA version 24.0

L-PZQ=levorotatory enantiomer of praziquantel, MedDRA=Medical Dictionary for Regulatory Activities, ODT=orodispersible tablet(s), TEAE=treatment-emergent adverse event.

NOTE: TEAEs are defined as those events with onset dates/time occurring after study intervention administration or events that worsen after study intervention administration. Related TEAEs are events with reported relationship missing, unknown or yes.

For the most common TAEs reported, the incidence of abdominal pain was similar between Cohorts 1a (23.0%) and 1b (20.0%) compared to 30% in Cohort 2. However, this was not reported in the youngest cohort (3), nor was the incidence higher with 60 mg/kg. Somnolence occurred at comparable rates in Cohorts 1a and 1b (6-8%) and 3 (11%), but the rate was much higher in Cohort 2 (26.7%).

Table 48 Most Commonly Reported TEAEs (≥5% of Participants Overall) by System Organ Class and Preferred Term – Safety Population

Primary System Organ Class Preferred Term	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n %	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)	Total N=288 n (%)
Participants with ≥ 1 TEAE	66 (66.0)	31 (62.0)	20 (66.7)	14 (77.8)	9 (30.0)	28 (46.7)	168 (58.3)
Gastrointestinal disorders	**31 (31.0)**	**15 (30.0)**	**13 (43.3)**	**3 (16.7)**	**2 (16.7)**	**4 (6.7)**	**68 (23.6)**
Abdominal pain	23 (23.0)	10 (20.0)	9 (30.0)	0	0	2 (3.3)	44 (15.3)
Diarrhoea	18 (18.0)	3 (6.0)	4 (13.3)	2 (11.1)	0	2 (3.3)	29 (10.1)
Vomiting	8 (8.0)	5 (10.0)	4 (13.3)	1 (5.6)	1 (3.3)	0	19 (6.6)
Nervous system disorders	**9 (9.0)**	**3 (6.0)**	**8 (26.7)**	**2 (11.1)**	**0**	**2 (3.3)**	**24 (8.3)**
Somnolence	8 (8.0)	3 (6.0)	8 (26.7)	2 (11.1)	0	1 (1.7)	22 (7.6)
Infections and infestations	**30 (30.0)**	**17 (34.0)**	**11 (36.7)**	**9 (50.0)**	**8 (26.7)**	**16 (26.7)**	**91 (31.6)**
Upper respiratory tract infection	4 (4.0)	1 (2.0)	3 (10.0)	1 (5.6)	5 (16.7)	3 (5.0)	17 (5.9)

Incidences of the most commonly reported TEAEs were similar between Cohorts 1a and 1b except for diarrhoea, being three times more common with arpraziquantel vs. Biltricide. However, rates for diarrhoea after arpraziquantel were lower in the younger cohorts. The limited data from Cohorts 4a and 4b do not point to a major difference in safety profile although the proportion reporting at least one AE was higher with 60 mg/kg vs. 50 mg/kg.

TEAEs by Severity

Overall, the severity of TEAEs was mostly mild (143/288 [49.7%] participants) or moderate (56/288 [19.4%] participants). Only 4/288 (1.4%) participants experienced severe TEAEs. The severe TEAEs included 2 events of malaria for 1 participant from each Cohort 1a and 4b, respectively, rash reported for 1 participant in Cohort 1b, and abdominal pain for 1 participant in Cohort 2. The only severe event considered to be related to study intervention was the event of abdominal pain reported for 1 participant in Cohort 2, and the only severe event reported as an SAE was malaria reported for 1 participant in Cohort 4b.

Drug-related TEAEs

Overall, ≥ 1 drug related TEAE was reported for 70/288 (24.3%) across cohorts. The most commonly reported drug related TEAE was abdominal pain (41/288 [14.2%]).

Table 49 Most Commonly Reported Drug-related TEAEs (≥5% of Participants Overall) by Primary System Organ Class and Preferred Term – Safety Population

Primary System Organ Class Preferred Term	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n %	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)	Total N=288 n (%)
Participants with ≥ 1 event	29 (29.0)	13 (26.0)	16 (53.3)	4 (22.2)	0	4 (6.7)	66 (22.9)
Gastrointestinal disorders	**28 (28.0)**	**13 (26.0)**	**13 (43.3)**	**3 (16.7)**	**0**	**3 (5.0)**	**60 (20.8)**
Abdominal pain	21 (21.0)	9 (18.0)	9 (30.0)	0	0	2 (3.3)	41 (14.2)
Diarrhoea	16 (16.0)	3 (6.0)	4 (13.3)	2 (11.1)	0	2 (3.3)	27 (9.4)
Vomiting	7 (7.0)	4 (8.0)	4 (13.3)	1 (5.6)	0	0	16 (5.6)
Nervous system disorders	**7 (7.0)**	**3 (6.0)**	**8 (26.7)**	**2 (11.1)**	**0**	**1 (1.7)**	**21 (7.3)**
Somnolence	7 (7.0)	3 (6.0)	8 (26.7)	2 (11.1)	0	1 (1.7)	21 (7.3)

Except for treatment-related diarrhoea, the proportions with other commonly reported drug-related TEAEs were similar between Cohorts 1a and 1b and lower than in Cohort 2. In Cohort 4, low numbers reported treatment-related TEAEs with 60 mg/kg arpraziquantel vs. none with 50 mg/kg. Only one drug related TEAE was severe, this being the case of abdominal pain as reported above.

Table 50 Number of Participants with Drug-related TEAEs by Worst Severity by Cohort and Overall – Safety Population

	Participants with ≥ 1 Event			
Cohort	N	Mild n (%)	Moderate n (%)	Severe n (%)
Overall	N=288	61 (21.2)	23 (8.0)	1 (0.3)
Cohort 1a (4 to 6 yrs) 50 mg/kg L-PZQ ODT	N=100	27 (27.0)	12 (12.0)	0
Cohort 1b (4 to 6 yrs) 40 mg/kg Biltricide	N=50	12 (24.0)	3 (6.0)	0
Cohort 2 (2 to 3 yrs) 50 mg/kg L-PZQ ODT	N=30	13 (43.3)	8 (26.7)	1 (3.3)
Cohort 3 (3 to 24 mths) 50 mg/kg L-PZQ ODT	N=18	4 (22.2)	0	0
Cohort 4a (3 mths to 6 yrs) 50 mg/kg L-PZQ ODT	N=30	0	0	0
Cohort 4b (3 mths to 6 yrs) 60 mg/kg L-PZQ ODT	N=60	5 (8.3)	0	0

AESIs

AESIs were pre-defined in the protocol (diarrhoea, nausea, vomiting, headache, dizziness, inflammation and abdominal pain). Of these, the most common (as above) was abdominal pain and most reports of abdominal pain were considered treatment-related. No events of dizziness and inflammation were reported. The incidence of the most commonly reported AESIs (≥ 5%) was higher in the *S. mansoni* cohorts (Cohorts 1a, 1b, 2, and 3) than in the *S. haematobium* cohorts (Cohorts 4a and 4b). No events

of abdominal pain were reported in Cohort 3 and no events of abdominal pain and diarrhoea were reported in Cohort 4a.

Reactions to study intervention administration

It seems that the study site nurses recorded "reactions to study intervention administration" in all cohorts. Overall, 85/288 (29.5%) had some reaction to study intervention administration, of which the most common were abdominal pain, diarrhoea and crying. There did not seem to be a relationship between reactions to study intervention administration and type of treatment or dose. Rates did vary by age group.

Table 51 Reaction to Study Intervention Administration by Cohort – Safety Population

Reaction	Cohort 1a 4 to 6 yrs L-PZQ ODT 50 mg/kg N=100 n (%)	Cohort 1b 4 to 6 yrs Biltricide 40 mg/kg N=50 n (%)	Cohort 2 2 to 3 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 3 3 to 24 mths L-PZQ ODT 50 mg/kg N=18 n (%)	Cohort 4a 3 mths to 6 yrs L-PZQ ODT 50 mg/kg N=30 n (%)	Cohort 4b 3 mths to 6 yrs L-PZQ ODT 60 mg/kg N=60 n (%)	Total N=288 n (%)
Any reaction	31 (31.0)	16 (32.0)	18 (60.0)	10 (55.6)	2 (6.7)	8 (13.3)	85 (29.5)
Crying	1 (1.0)	4 (8.0)	8 (26.7)	8 (44.4)	2 (6.7)	2 (3.3)	25 (8.7)
Spitting	1 (1.0)	3 (6.0)	6 (20.0)	6 (33.3)	0	3 (5.0)	19 (6.6)
Diarrhoea	16 (6.0)	3 (6.0)	4 (13.3)	2 (11.1)	0	2 (3.3)	27 (9.4)
Sleepiness	7 (7.0)	3 (6.0)	7 (23.3)	2 (11.1)	0	1 (1.7)	20 (6.9)
Abdominal pain	21 (21.0)	9 (18.0)	9 (30.0)	0	0	2 (3.3)	41 (14.2)
Fever	1 (1.0)	1 (2.0)	0	0	0	0	2 (0.7)
Vomiting	7 (7.0)	4 (8.0)	4 (13.3)	1 (5.6)	0	0	16 (5.6)
Other	3 (3.0)	1 (2.0)	0	0	0	1 (1.7)	5 (1.7)

Palatability was assessed only in children aged 5-6 years using a human gustatory sensation test (100-mm VAS) modified by the incorporation of a 3-point facial hedonic scale. The palatability score ranged from 0 to 100, with a higher score indicating better taste. Arpraziquantel had a higher score than Biltricide, which may have contributed to the lower incidence of crying and spitting.

Table 52 Palatability Assessment by Treatment – Safety Population (5 to 6 years of age)

Statistics	L-PZQ ODT 50 mg/kg N=86	L-PZQ ODT 60 mg/kg N=35	Biltricide 40 mg/kg N=35	Total N=156
n (%)	86 (100)	35 (100)	34 (97.1)	155 (99.4)
Mean ±SD	70.9 ±26.79	81.4 ±17.96	55.3 ±30.33	69.8 ±27.24
Median	85.5	88.0	50.0	84.0
Min; Max	4; 95	25; 98	8; 93	4; 98

Source: Table 8.3.6.6

L-PZQ=levorotatory enantiomer of praziquantel, Max=maximum, Min=minimum, ODT=orodispersible tablet(s), SD=standard deviation.

Palatability was assessed only for participants in Cohorts 1 and 4 with age 5 to 6 years.

Phase 2 study

The first table below summarises the safety data from this study. The second table summarises the most commonly reported TEAEs.

Table 53 Overview of the Incidence of Treatment Emergent Adverse Events – Safety Analysis Set

Number of Subjects With	Cohort 1[a] (N=60) n (%)	Cohort 2 (N=60) n (%)	Cohort 3 (N=60) n (%)	Cohort 4 (N=60) n (%)	Cohort 5 (N=60) n (%)	Cohort 6 (N=60) n (%)	Cohort 7 (N=60) n (%)	Cohort 8 (N=20) n (%)	Cohort 9 (N=4) n (%)
Any TEAE	34 (56.7)	38 (63.3)	35 (58.3)	40 (66.7)	35 (58.3)	39 (65.0)	45 (75.0)	16 (80.0)	4 (100.0)
Any Study Drug-related TEAE[b]	10 (16.7)	11 (18.3)	7 (11.7)	16 (26.7)	8 (13.3)	2 (3.3)	13 (21.7)	3 (15.0)	1 (25.0)
Any Serious TEAE	1 (1.7)	0	1 (1.7)	0	0	0	0	0	0
Any Study Drug-related Serious TEAE	0	0	1 (1.7)	0	0	0	0	0	0
Any TEAE Leading to Death	0	0	0	0	0	0	0	0	0
Any Study Drug-related TEAE Leading to Death	0	0	0	0	0	0	0	0	0

Source: Table 15.3.1.1
TEAE=Treatment Emergent Adverse Event.
[a] Cohort 1: Biltricide 3x20 mg/kg; Cohort 2: Biltricide 40 mg/kg; Cohort 3: rac-PZQ ODT 40 mg/kg; Cohort 4: rac-PZQ ODT 60 mg/kg; Cohort 5: L-PZQ ODT 30 mg/kg; Cohort 6: L-PZQ ODT 45 mg/kg; Cohort 7: L-PZQ ODT 60 mg/kg; Cohort 8: L-PZQ ODT 50 mg/kg; Cohort 9: L-PZQ ODT 50 mg/kg.
[b] Probable or possible relationship with IMP according to Investigator.

Table 54 Overview of Adverse Events Most Commonly Reported by Preferred Term (PT) and Treatment Group – Safety Analysis Set

Number of Subjects With	Cohort 1[a] (N=60) n (%)	Cohort 2[a] (N=60) n (%)	Cohort 3[a] (N=60) n (%)	Cohort 4[a] (N=60) n (%)	Cohort 5[a] (N=60) n (%)	Cohort 6[a] (N=60) n (%)	Cohort 7[a] (N=60) n (%)	Cohort 8[a] (N=20) n (%)	Cohort 9[a] (N=4) n (%)	Total (N=444) N (%)
Any TEAE	34 (56.7)	38 (63.3)	35 (58.3)	40 (66.7)	35 (58.3)	39 (65.0)	45 (75.0)	16 (80.0)	4 (100.0)	286 (64.4)
Anemia	15 (25.0)	25 (41.7)	23 (38.3)	22 (36.7)	18 (30.0)	22 (36.7)	29 (48.3)	5 (25.0)	4 (100.0)	163 (36.7)
C-reactive protein increased	7 (11.7)	4 (6.7)	10 (16.7)	8 (13.3)	7 (11.7)	14 (23.3)	6 (10.0)	0	0	56 (12.6)
Bronchitis	9 (15.0)	7 (11.7)	3 (5.0)	5 (8.3)	4 (6.7)	3 (5.0)	8 (13.3)	2 (10.0)	0	41 (9.2)
Malaria	5 (8.3)	3 (5.0)	5 (8.3)	1 (1.7)	4 (6.7)	4 (6.7)	2 (3.3)	5 (25.0)	1 (25.0)	30 (6.8)
Abdominal pain	5 (8.3)	3 (5.0)	3 (5.0)	5 (8.3)	4 (6.7)	0	6 (10.0)	1 (5.0)	0	27 (6.1)
Pyrexia	7 (11.7)	3 (5.0)	3 (5.0)	1 (1.7)	3 (5.0)	2 (3.3)	0	1 (5.0)	0	20 (4.5)
Diarrhea	1 (1.7)	1 (1.7)	1 (1.7)	4 (6.7)	4 (6.7)	1 (1.7)	1 (1.7)	1 (5.0)	0	14 (3.2)
Vomiting	1 (1.7)	3 (5.0)	0	1 (1.7)	1 (1.7)	1 (1.7)	4 (6.7)	1 (5.0)	1 (25.0)	13 (2.9)
Abdominal distention	1 (1.7)	2 (3.3)	0	3 (5.0)	1 (1.7)	1 (1.7)	4 (6.7)	0	0	12 (2.7)
Lymphocytosis	0	0	0	0	0	0	0	7 (35.0)	4 (100.0)	11 (2.5)
Rhinitis	1 (1.7)	1 (1.7)	0	3 (5.0)	0	0	3 (5.0)	0	1 (25.0)	9 (2.0)
Urinary tract infection	1 (1.7)	1 (1.7)	0	0	0	1 (1.7)	0	3 (15.0)	1 (25.0)	7 (1.6)
Transaminases increased	4 (6.7)	1 (1.7)	1 (1.7)	0	1 (1.7)	0	0	0	0	7 (1.6)

The most commonly reported AE was anaemia in 163/444 total subjects (36.7%), with the highest incidence in Cohorts 9 (4/4) and 7 (29/60; 48.8%). C-reactive protein increased was reported for 56 subjects (12.6%), with the highest incidence in Cohort 6 (14/60; 23.3%). Other commonly reported AEs included several types of infections as well as abdominal pain (6.1%), diarrhoea (3.2%), vomiting (2.9%) and abdominal distention (2.7%). Lymphocytosis (2.5%) was exclusively reported in Cohorts 8 and 9.

Five (2.5%) of those who received arpraziquantel reported severe TEAEs, including C-reactive protein increased (n=2), leukocyturia (n=2) and thrombocytopenia (n=1).

Table 55 Overview of Treatment Emergent Adverse Events by Treatment and Worst intensity – Safety Analysis Set

Number of Subjects With	Bilbricide (N=120)			rac-PZQ (N=120)			L-PZQ (N=204)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
At least one event	51 (42.5)	34 (28.3)	2 (1.7)	42 (35.0)	39 (32.5)	2 (1.7)	88 (43.1)	63 (30.9)	5 (2.5)
Anemia	21 (17.5)	19 (15.8)	0	20 (16.7)	25 (20.8)	0	43 (21.1)	35 (17.2)	0
Thrombocytopenia	0	0	0	0	1 (0.8)	0	0	0	1 (0.5)
Abdominal distension	3 (2.5)	0	0	3 (2.5)	0	0	6 (2.9)	0	0
Abdominal pain	4 (3.3)	3 (2.5)	0	5 (4.2)	3 (2.5)	0	7 (3.4)	4 (2.0)	0
Diarrhea	2 (1.7)	0	0	2 (1.7)	3 (2.5)	0	6 (2.9)	1 (0.5)	0
Pyrexia	2 (1.7)	8 (6.7)	0	1 (0.8)	3 (2.5)	0	3 (1.5)	3 (1.5)	0
Bronchitis	11 (9.2)	5 (4.2)	0	5 (4.2)	3 (2.5)	0	12 (5.9)	5 (2.5)	0
Malaria	7 (5.8)	1 (0.8)	0	4 (3.3)	1 (0.8)	0	8 (3.9)	8 (3.9)	0
Rhinitis	2 (1.7)	0	0	3 (2.5)	0	0	3 (1.5)	1 (0.5)	0
C-reactive protein increased	5 (4.2)	5 (4.2)	1 (0.8)	3 (2.5)	15 (12.5)	0	10 (4.9)	15 (7.4)	2 (1.0)
Transaminase increased	3 (2.5)	1 (0.8)	1 (0.8)	0	0	1 (0.8)	0	1 (0.5)	0
Leukocyturia	0	0	0	0	0	1 (0.8)	0	2 (1.0)	2 (1.0)

There were 77 drug-related TEAEs reported for 71/444 (16.0%) subjects of which most were of mild intensity (n=47; 61.0%) or moderate intensity (n=29; 37.7%) and only one was severe.

Abdominal pain was the most commonly reported drug-related TEAE with an overall incidence of 27/444 (6.1%) subjects. Cohort 7 had the highest reporting rate for abdominal pain (6/60; 10.0%) with no reports in Cohorts 6 and 9. The second most common drug-related TEAE was vomiting. Again, the highest incidence was in Cohort 7 (4/60; 6.7%). Other commonly reported drug-related TEAEs across all cohorts included diarrhoea (2.5%), pyrexia (2.0%) and transaminases increased (0.7%).

Table 56 Overview of Drug-related Adverse Events Most Commonly Reported by Preferred Term (PT) and Treatment Group – Safety Analysis Set

Number of Subjects With	Cohort 1[a] (N=60) n (%)	Cohort 2[a] (N=60) n (%)	Cohort 3[a] (N=60) n (%)	Cohort 4[a] (N=60) n (%)	Cohort 5[a] (N=60) n (%)	Cohort 6[a] (N=60) n (%)	Cohort 7[a] (N=60) n (%)	Cohort 8[a] (N=20) n (%)	Cohort 9[a] (N=4) n (%)	Total (N=444) N (%)
Any drug-related TEAE	10 (16.7)	11 (18.3)	7 (11.7)	16 (26.7)	8 (13.3)	2 (3.3)	13 (21.7)	3 (15.0)	1 (25.0)	71 (16.0)
Abdominal pain	5 (8.3)	3 (5.0)	3 (5.0)	5 (8.3)	4 (6.7)	0	6 (10.0)	1 (5.0)	0	27 (6.1)
Vomiting	1 (1.7)	3 (5.0)	0	1 (1.7)	1 (1.7)	1 (1.7)	4 (6.7)	1 (5.0)	1 (25.0)	13 (2.9)
Diarrhea	0	1 (1.7)	1 (1.7)	4 (6.7)	3 (5.0)	1 (1.7)	1 (1.7)	0	0	11 (2.5)
Pyrexia	4 (6.7)	1 (1.7)	2 (3.3)	0	1 (1.7)	0	0	1 (5.0)	0	9 (2.0)
Transaminases increased	1 (1.7)	1 (1.7)	1 (1.7)	0	0	0	0	0	0	3 (0.7)

The pre-defined AESIs were the same as in Phase 3 (see above). Of these, abdominal pain was the AESI most often reported (6.1%; all considered drug-related), followed by diarrhoea (3.2%; 11/14 considered drug-related) and vomiting (2.9%; all considered drug-related).

Table 57 Overview of Adverse Events of Special Interest by Preferred Term (PT) and Treatment Group – Safety Analysis Set

Number of Subjects With	Cohort 1[a] (N=60) n (%)	Cohort 2[a] (N=60) n (%)	Cohort 3[a] (N=60) n (%)	Cohort 4[a] (N=60) n (%)	Cohort 5[a] (N=60) n (%)	Cohort 6[a] (N=60) n (%)	Cohort 7[a] (N=60) n (%)	Cohort 8[a] (N=20) n (%)	Cohort 9[a] (N=4) n (%)	Total (N=444) n (%)
Abdominal pain	5 (8.3)	3 (5.0)	3 (5.0)	5 (8.3)	4 (6.7)	0	6 (10.0)	1 (5.0)	0	27 (6.1)
Diarrhea	1 (1.7)	1 (1.7)	1 (1.7)	4 (6.7)	4 (6.7)	1 (1.7)	1 (1.7)	1 (5.0)	0	14 (3.2)
Vomiting	1 (1.7)	3 (5.0)	0	1 (1.7)	1 (1.7)	1 (1.7)	4 (6.7)	1 (5.0)	1 (25.0)	13 (2.9)
Nausea	0	0	0	0	0	0	2 (3.3)	0	0	2 (0.5)
Headache	0	1 (1.7)	0	0	0	0	0	0	0	1 (0.2)

Phase 1 study

Of 34 subjects who received any dose, 23 (63.9%) reported 55 TEAEs; 8 (22.2%) subjects reported 12 TEAEs during treatment A, 17 (47.2%) subjects reported 23 TEAEs during treatment B, 4 (22.2%) subjects reported 5 TEAEs during treatment C1, 4 (23.5%) subjects reported 7 TEAEs during treatment C2, 5 (14.3%) subjects reported 7 TEAEs during treatment D and 1 (2.8%) subject reported 1 TEAE during treatment E.

Only TEAEs belonging to the SOC "gastrointestinal disorders" were reported across all five treatments. The remaining TEAEs included fatigue dizziness, dysgeusia and headache (all considered related), influenza, tonsillitis, excoriation, musculoskeletal pain and oropharyngeal pain (all not considered related). Headache was the most commonly reported TEAE (27 of 55 TEAEs).

The second table below shows drug-related TEAEs, which occurred in 19 (52.8%) subjects. All TEAEs were considered mild in intensity, except for 4 moderate TEAEs, 2 during treatment B (headache and abdominal pain upper) and 2 during treatment C2 (headache). No new type of AEs was observed after treatment with the paediatric formulation of L-PZQ. All TEAEs were resolved by the end of the trial.

Table 58 Summary of Treatment – Emergent Adverse Events by Treatment

	Treatment A (N = 36)	Treatment B (N = 36)	Treatment C1 (N = 18)	Treatment C2 (N = 17)	Treatment D (N = 35)	Treatment E (N = 36)
No. of TEAEs	**E**	**E**	**E**	**E**	**E**	**E**
Any TEAEs	12	23	5	7	7	1
Serious TEAEs	0	0	0	0	0	0
TEAEs Resulting in Discontinuation	0	0	0	0	0	0
TEAEs Of Severe Intensity	0	0	0	0	0	0
IMP-related TEAEs	9	23	2	4	4	1
No. of Subjects Experiencing TEAEs	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAEs	8 (22.2%)	17 (47.2%)	4 (22.2%)	4 (23.5%)	5 (14.3%)	1 (2.8%)
Serious TEAEs	0	0	0	0	0	0
TEAEs Resulting in Discontinuation	0	0	0	0	0	0
TEAEs Of Severe Intensity	0	0	0	0	0	0
IMP-related TEAEs	7 (19.4%)	17 (47.2%)	1 (5.6%)	3 (17.6%)	4 (11.4%)	1 (2.8%)

N = number of subjects, E = number of AEs; TEAE = treatment-emergent adverse events

A = MSC2499550A formulation at 20 mg/kg dispersed in water, after a meal

Table 59 Summary of Treatment-Related Treatment-Emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Treatment A (N = 36)	Treatment B (N = 36)	Treatment C1 (N = 18)	Treatment C2 (N = 17)	Treatment D (N = 35)	Treatment E (N = 36)	Total (N = 36)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with events and total events	7 (19.4) 9	17 (47.2) 23	1 (5.6) 2	3 (17.6) 4	4 (11.4) 4	1 (2.8) 1	19 (52.8) 43
Gastrointestinal Disorder	2 (5.6) 2	6 (16.7) 9	1 (5.6) 1	2 (11.8) 2	0	1 (2.8) 1	9 (25.0) 15
Abdominal Discomfort	0	1 (2.8) 1	1 (5.6) 1	0	0	0	2 (5.6) 2
Abdominal Pain Upper	0	1 (2.8) 2	0	0	0	0	1 (2.8) 2
Diarrhoea	1 (2.8) 1	0	0	0	0	0	1 (2.8) 1
Dyspepsia	1 (2.8) 1	0	0	1 (5.9) 1	0	1 (2.8) 1	1 (2.8) 3
Nausea	0	5 (13.9) 5	0	1 (5.9) 1	0	0	5 (13.9) 6
Vomiting	0	1 (2.8) 1	0	0	0	0	1 (2.8) 1
General Disorders and Administration site conditions	1 (2.8) 1	0	1 (5.6) 1	0	0	0	1 (2.8) 2
Fatigue	1 (2.8) 1	0	1 (5.6) 1	0	0	0	1 (2.8) 2
Nervous System Disorders	6 (16.7) 6	13 (36.1) 14	0	1 (5.9) 2	4 (11.4) 4	0	14 (38.9) 26
Dizziness	0	1 (2.8) 1	0	0	0	0	1 (2.8) 1
Dysgeusia	0	1 (2.8) 1	0	0	0	0	1 (2.8) 1
Headache	6 (16.7) 6	11 (30.6) 12	0	1 (5.9) 2	4 (11.4) 4	0	12 (33.3) 24

N = The number of subjects dosed with each treatment, or the number of subjects in the safety population for the total summary; n = Number of subjects with specific adverse event; % = calculated using the number of subjects dosed with each treatment, or the number of subjects in the safety population for the total summary as the denominator (n/N*100), E = Number of AEs

A = MSC2499550A formulation at 20 mg/kg dispersed in water, after a meal

B = Current PZQ formulation (Cysticide®) at 40 mg/kg given with water after a meal

C = MSC2499550A formulation at 10 (C1) or 30 (C2) mg/kg (randomized 1 to 1) given dispersed in water, after a meal

D = MSC2499550A formulation at 20 mg/kg given dispersed in water without a meal

E = MSC2499550A formulation at 20 mg/kg directly disintegrated in the mouth without water after a meal

2.6.8.3. Serious adverse event/deaths/other significant events

Phase 3 study

There were no deaths. One subject in Cohort 4b (S. haematobium treated with 60 mg/kg arpraziquantel) had a SAE of severe malaria considered unrelated to treatment. The SAE started on Day 16 and resolved with sequelae on Day 23. In accordance with the protocol, this subject continued in the study after successful treatment for malaria but was excluded from the mITT population.

Phase 2 study
There were no deaths. There were two SAEs reported. Both involved increased transaminases in one subject in Cohort 1 and one subject in Cohort 3. The SAE in Cohort 1 had onset prior to administration of Biltricide.

The SAE in Cohort 3 (rac-PZQ 40 mg/kg) had onset 20 days after treatment and was considered related to study treatment by the investigator but not by the sponsor. This subject was enrolled into Cohort 3 on 19 October 2016 and increased levels of transaminases were detected at the Day 14-21 follow up visit on 07 November 2016. The ALT was 44 x ULN and the AST was 51 x ULN. The subject had 4000 malaria trophozoites/µL detected on 16 November 2016. An ultrasound performed on 16 November 2016 demonstrated hepatic fibrosis and a moderately enlarged spleen, consistent with hepatosplenic schistosomiasis although (other than HBV and HCV, for which tests were negative) alternative explanations could not be ruled out. The applicant's position was based on the subject's history and the fact that no cases of elevated transaminases have been reported in humans who have received PZQ.
Phase 1 study
There were no deaths or SAEs.

2.6.8.4. Laboratory findings

Phase 3 study

Safety laboratory tests (haematology, biochemistry, urinalysis) were performed pre dose on day 1 (i.e. 12 hours post dose).

Investigators reviewed abnormal results and assigned them as clinically significant according to their opinion. Clinically significant abnormal laboratory findings were reported as TEAEs if they were associated with clinical signs and symptoms, led to treatment discontinuation, or were otherwise considered medically important by the Investigator.

Across cohorts, no haematology parameters showed clinically relevant changes over time. TEAEs to haematology parameters were lymphocytosis (in 13/288 [4.5%]), anaemia (8/288 [2.8%]), neutropenia (6/288 [2.1%]), neutrophil count decreased (1/288 [0.3%]), hypochromic anaemia (2/288 [0.7%]) and thrombocytosis (1/288 [0.3%]). Some of these findings were related to malaria in 12 (4.2%) subjects across the arpraziquantel groups.

Across cohorts, no biochemistry or urinalysis parameters (some of which were influenced by the underlying infection) showed clinically relevant changes over time. One subject had a TEAE (non-drug-related) of transaminases increased.

Phase 2 study

In each of Cohorts 1-7, 22/60 subjects were evaluated for a change in laboratory parameters from baseline by sampling either at Day 14 - 21 or, by amendment, at the end of confinement visit (Day 2, at least 16 h after the only or last dose of assigned treatment).

Laboratory abnormalities most often reported as TEAEs were anaemia (163), C-reactive protein increased (56), lymphocytosis (11) and transaminases increased (7; 3 of which were considered drug-related, with one in each of Cohorts 1, 2 and 3). Thrombocytosis was also reported for two subjects in

Cohort 8 and in none of the other cohorts. Severe thrombocytopenia (31 x 10x9/L on day 20) considered unrelated to drug was reported for one subject in Cohort 5 with a low baseline value (185 10x9/L). There was one case of thrombocytopenia in Cohort 4 was considered drug-related. This was of moderate severity but asymptomatic and the result came from the sample taken on Day 2. The day 2 level (93 10x9/L) had decreased from baseline (230 x 109/L on Day 1). The CSR states that sample clumping cannot be ruled out.

The CSR points out that some of these laboratory TEAEs were due to results from day of treatment samples. Of the 46 TEAEs which were not from samples taken prior to IMP administration 29 were mild, 16 moderate and one 33 of the 46 TEAEs had an outcome of unknown, 8 were not recovered/not resolved and 5 were resolved.

Table 60 Overview of Most Frequent Laboratory Investigation Adverse Events by Treatment Group – Safety Analysis Set

Number of Subjects With	Cohort 1[a] (N=60) n (%)	Cohort 2[a] (N=60) n (%)	Cohort 3[a] (N=60) n (%)	Cohort 4[a] (N=60) n (%)	Cohort 5[a] (N=60) n (%)	Cohort 6[a] (N=60) n (%)	Cohort 7[a] (N=60) n (%)	Cohort 8[a] (N=20) n (%)	Cohort 9[a] (N=4) n (%)	Total (N=444) n (%)
Anemia	15 (25.0)	25 (41.7)	23 (38.3)	22 (36.7)	18 (30.0)	22 (36.7)	29 (48.8)	5 (25.0)	4 (100.0)	163 (36.7)
C-reactive protein increased	7 (11.7)	4 (6.7)	10 (16.7)	8 (13.3)	7 (11.7)	14 (23.3)	6 (10.0)	0	0	56 (12.6)
Lymphocytosis	0	0	0	0	0	0	0	7 (35.0)	4 (100)	11 (2.4)
Transaminases increased	4 (6.7)	1 (1.7)	1 (1.7)	0	1 (1.7)	0	0	0	0	7 (1.6)

Source: Table 15.3.1.2

[a] Cohort 1: Biltricide 3x20 mg/kg; Cohort 2: Biltricide 40 mg/kg; Cohort 3: rac-PZQ ODT 40 mg/kg; Cohort 4: rac-PZQ ODT 60 mg/kg; Cohort 5: L-PZQ ODT 30 mg/kg; Cohort 6: L-PZQ ODT 45 mg/kg; Cohort 7: L-PZQ ODT 60 mg/kg; Cohort 8: L-PZQ ODT 50 mg/kg; Cohort 9: L-PZQ ODT 50 mg/kg.

Safety laboratory measurements which demonstrated notable changes over time included lymphocyte percentage, ALT, AST, CRP, leucocytes in urine and nitrates in urine. The changes were of a small magnitude within the normal range or marginally exceeded the normal range and did not represent any time or dose-dependent relationship.

Clinically significant abnormalities were determined by investigators as in Phase 3.

Of the 4530 individual haematology parameter abnormalities per reference range reported, 417 (9%) in 180 subjects were considered clinically significant. Anaemia was the most frequent laboratory abnormality in all cohorts, likely reflecting repeated malaria episodes in many subjects.

There were 2482 individual chemistry parameter abnormalities per laboratory reference range reported. The AST and ALT reference range for the study was 4.7 to 15.3 U/L while the generally used range is 5 to 41 U/L for ALT and 5 to 42 U/L for AST. Of these, 138 were considered clinically significant and 76 subjects had at least one abnormality recorded as TEAE including hypoproteinaemia, AST and/or ALT increased, creatinine increased, C-reactive protein increased and hyperglycaemia.

Three of the 32 TEAEs reflecting samples taken after IMP administration were considered drug-related (see above re transaminases increased). The subject in Cohort 1 and an increase of mild severity from normal baseline values (reaching ALT 72 U/L and AST 86 U/L) starting 2 two days after dosing that

resolved. The subject in Cohort 2 had increases on day 20 moderate severity (ALT 96 U/L vs. baseline 30 U/L and AST 103 U/L vs. baseline 54 U/L). The subject in Cohort 3 had a SAE (see section 4.4).

Of the 32 reported chemistry abnormality TEAEs 12 were mild, 17 moderate and 3 severe (the SAE of drug-related transaminases increased and two TEAEs of CRP increase). These CRP increases occurred in conjunction with malaria.

There were 29 urinalysis abnormalities considered clinically significant and TEAEs were reported for 17 subjects, including UTI (7), leukocyturia (5), proteinuria (2) and nitrate positive urine (3).

Phase 1 study
There were no notable changes from baseline (screening) in any of the laboratory parameters in any subject at any time point. None of the abnormal laboratory parameters was considered by the Investigator to be clinically significant so none was reported as a TEAE.

2.6.8.5. Safety in special populations

Age

When safety results in the Safety Analysis Population were analysed by age, the only notable observations were that a larger proportion of younger participants reported TEAEs in general compared with older children and a higher incidence of somnolence specifically was observed: 4.7% in participants aged 3 months to < 24 months (L-PZQ only), 8.9% in participants aged 2 to < 4 years (L-PZQ only), 2.7% in participants aged 4 to 6 years in the L-PZQ group and 2.2% in participants aged 4 to 6 years in the Biltricide group. This trend of having more somnolence cases in the youngest children may be explained by the higher sensitivity to develop dehydration in the context of suffering gastrointestinal events such as vomiting and diarrhoea.

The rest of the AEs, including gastrointestinal events, were generally balanced across the different treatment interventions and age categories.

Table 61 Overview of TEAEs – SAF Analysis Set (Age Category: 3 months < 24 months)

	L-PZQ ODT		
Subjects with:	50 mg/kg (N=41) n (%)	60 mg/kg (N=2) n (%)	Total (N=43) n (%)
Any TEAE	32(78.0)	2(100.0)	34(79.1)
Any trial drug related TEAE	8(19.5)	0	8(18.6)
Any serious TEAE	0	0	0
Any trial drug related serious TEAE	0	0	0
Any Severe TEAE	0	0	0
Any trial drug related Severe TEAE	0	0	0
Any TEAE leading to treatment discontinuation	0	0	0
Any TEAE leading to death	0	0	0
Any trial drug related TEAE leading to death	0	0	0

Table 62 Overview of TEAEs – SAF Analysis Set (Age Category: 2 Years to 4 Years)

	L-PZQ ODT				
Subjects with:	30 mg/kg (N=19) n (%)	45 mg/kg (N=16) n (%)	50 mg/kg (N=39) n (%)	60 mg/kg (N=27) n (%)	Total (N=101) n (%)
Any TEAE	11(57.9)	11(68.8)	23(59.0)	18(66.7)	63(62.4)
Any trial drug related TEAE	0	0	16(41.0)	3(11.1)	19(18.8)
Any serious TEAE	0	0	0	0	0
Any trial drug related serious TEAE	0	0	0	0	0
Any Severe TEAE	1(5.3)	1(6.3)	1(2.6)	0	3(3.0)
Any trial drug related Severe TEAE	0	0	1(2.6)	0	1(1.0)
Any TEAE leading to treatment discontinuation	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0
Any trial drug related TEAE leading to death	0	0	0	0	0

Table 63 Overview of TEAEs – SAF Analysis Set (Age Category: 4 Years to 6 Years)

	L-PZQ ODT				
Subjects with:	30 mg/kg (N=41) n (%)	45 mg/kg (N=44) n (%)	50 mg/kg (N=122) n (%)	60 mg/kg (N=91) n (%)	Total (N=298) n (%)
Any TEAE	24 (58.5)	28 (63.6)	73 (59.8)	53 (58.2)	178 (59.7)
Any trial drug related TEAE	8 (19.5)	2 (4.5)	31 (25.4)	15 (16.5)	56 (18.8)
Any serious TEAE	0	0	0	1 (1.1)	1 (0.3)
Any trial drug related serious TEAE	0	0	0	0	0
Any Severe TEAE	1 (2.4)	1 (2.3)	1 (0.8)	2 (2.2)	5 (1.7)
Any trial drug related Severe TEAE	0	0	0	0	0
Any TEAE leading to treatment discontinuation	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0
Any trial drug related TEAE leading to death	0	0	0	0	0

Sex

When safety results in the Safety Analysis Population were analysed by sex, no noteworthy differences were observed in TEAEs.

Infection Intensity

Table 64 Study Intervention-Related Treatment-Emergent Adverse Events in ≥2% of Participants, Light infection Intensity (Safety Analysis Population)

	Biltricide (mg/kg)			Rac-PZQ ODT (mg/kg)			L-PZQ ODT (mg/kg)				
	3×20 (n = 36) n (%)	40 (n = 64) n (%)	Total (n = 100) n (%)	40 (n = 36) n (%)	60 (n = 35) n (%)	Total (n = 71) n (%)	30 (n = 36) n (%)	45 (n = 36) n (%)	50 (n = 125) n (%)	60 (n = 90) n (%)	Total (n = 287) n (%)
Any study intervention-related TEAE	6 (16.7)	12 (18.8)	18 (18.0)	2 (5.6)	4 (11.4)	6 (8.5)	2 (5.6)	1 (2.8)	16 (12.8)	11 (12.2)	30 (10.5)
Blood and lymphatic system disorders	0	0	0	0	1 (2.9)	1 (1.4)	0	0	1 (0.8)	0	1 (0.3)
Thrombocytopenia	0	0	0	0	1 (2.9)	1 (1.4)	0	0	0	0	0
Gastrointestinal disorders	2 (5.6)	9 (14.1)	11 (11.0)	0	2 (5.7)	2 (2.8)	1 (2.8)	1 (2.8)	9 (7.2)	9 (10.0)	20 (7.0)
Abdominal pain	1 (2.8)	3 (4.7)	4 (4.0)	0	2 (5.7)	2 (2.8)	0	0	4 (3.2)	5 (5.6)	9 (3.1)
Diarrhea	0	0	0	0	0	0	1 (2.8)	0	1 (0.8)	2 (2.2)	4 (1.4)
Vomiting	1 (2.8)	5 (7.8)	6 (6.0)	0	0	0	0	1 (2.8)	4 (3.2)	3 (3.3)	8 (2.8)
General disorders and administration site conditions	4 (11.1)	2 (3.1)	6 (6.0)	1 (2.8)	0	1 (1.4)	1 (2.8)	0	1 (0.8)	0	2 (0.7)
Pyrexia	4 (11.1)	2 (3.1)	6 (6.0)	1 (2.8)	0	1 (1.4)	1 (2.8)	0	1 (0.8)	0	2 (0.7)
Investigations	1 (2.8)	1 (1.6)	2 (2.0)	1 (2.8)	0	1 (1.4)	0	0	0	0	0
Transaminases increased	1 (2.8)	1 (1.6)	2 (2.0)	1 (2.8)	0	1 (1.4)	0	0	0	0	0
Nervous system disorders	0	1 (1.6)	1 (1.0)	0	0	0	0	0	4 (3.2)	2 (2.2)	6 (2.1)
Somnolence	0	0	0	0	0	0	0	0	4 (3.2)	1 (1.1)	5 (1.7)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (2.9)	1 (1.4)	0	0	0	0	0
Cough	0	0	0	0	1 (2.9)	1 (1.4)	0	0	0	0	0

Table 65 Study Intervention-Related Treatment-Emergent Adverse Events in ≥2% of Participants, Moderate/heavy infection intensity (Safety Analysis Population)

	Biltricide (mg/kg)			Rac-PZQ ODT (mg/kg)			L-PZQ ODT (mg/kg)				
	3×20 (n = 24) n (%)	40 (n = 46) n (%)	Total (n = 70) n (%)	40 (n = 24) n (%)	60 (n = 24) n (%)	Total (n = 48) n (%)	30 (n = 23) n (%)	45 (n = 24) n (%)	50 (n = 77) n (%)	60 (n = 30) n (%)	Total (n = 154) n (%)
Any study intervention-related TEAE	4 (16.7)	13 (28.3)	17 (24.3)	5 (20.8)	11 (45.8)	16 (33.3)	6 (26.1)	1 (4.2)	39 (50.6)	7 (23.3)	53 (34.4)
Gastrointestinal disorders	4 (16.7)	13 (28.3)	17 (24.3)	4 (16.7)	11 (45.8)	15 (31.3)	6 (26.1)	1 (4.2)	38 (49.4)	6 (20.0)	51 (33.1)
Abdominal pain	4 (16.7)	9 (19.6)	13 (18.6)	3 (12.5)	3 (12.5)	6 (12.5)	4 (17.4)	0	27 (35.1)	3 (10.0)	34 (22.1)
Diarrhea	0	4 (8.7)	4 (5.7)	1 (4.2)	4 (16.7)	5 (10.4)	2 (8.7)	1 (4.2)	21 (27.3)	1 (3.3)	25 (16.2)
Gastrointestinal inflammation	0	0	0	0	3 (12.5)	3 (6.3)	0	0	0	0	0
Haematochezia	1 (4.2)	1 (2.2)	2 (2.9)	1 (4.2)	0	1 (2.1)	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0	1 (1.3)	2 (6.7)	3 (1.9)
Vomiting	0	2 (4.3)	2 (2.9)	0	0	0	1 (4.3)	0	10 (13.0)	1 (3.3)	12 (7.8)
General disorders and administration site conditions	0	0	0	1 (4.2)	0	1 (2.1)	0	0	1 (1.3)	0	1 (0.6)
Pyrexia	0	0	0	1 (4.2)	0	1 (2.1)	0	0	1 (1.3)	0	1 (0.6)
Nervous system disorders	0	3 (6.5)	3 (4.3)	0	0	0	0	0	14 (18.2)	0	14 (9.1)
Headache	0	0	0	0	0	0	0	0	1 (1.3)	0	1 (0.6)
Somnolence	0	3 (6.5)	3 (4.3)	0	0	0	0	0	13 (16.9)	0	13 (8.4)

Hepatic impairment

The safety of arpraziquantel in participants with hepatic impairment was not investigated in a dedicated clinical study, and no participants with hepatic impairment were included in the Safety Analysis Population.

Renal impairment

The effect of renal impairment on the PK of arpraziquantel has not been investigated.

2.6.8.6. Immunological events

Rash (not related), urticaria (related, mild in severity) and pruritus (related moderate in severity) were reported in the studies. Urticaria and pruritus are listed in section 4.8 of the SmPC with the frequency uncommon. Severe allergic reactions were not reported in studies performed by the applicant.

Severe allergic reactions were reported in patients receiving racemic praziquantel, as discussed in the literature and therefore they may occur in patients treated with arpraziquantel. Therefore, the risk for development of severe allergic reactions in patients receiving arpraziquantel cannot be excluded.

Further, as indicated by the applicant the risk of development of allergic reactions could be higher in pre-school aged children, compared to other age groups. In the meta-analysis of clinical trials of praziquantel comparing 503 pre-school aged children (PSAC) and 1,504 school children, the cumulative incidence of itching/rash was higher in pre-school aged children than in school children (8.6% versus 5.5%, respectively).

Paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions, potentially leading to life-threatening events were reported in patients treated with racemic praziquantel for acute schistosomiasis. It seems (Osakunor, 2018) that the first infection event in most endemic areas occurs early at the pre-school age. Acute schistosomiasis is typically seen in non-immune individuals.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No new data were provided in relation to drug-drug interactions.

2.6.8.8. Discontinuation due to adverse events

Phase 1, 2 and 3 studies
There were no discontinuations of treatment or study due to AEs.

2.6.9. Discussion on clinical safety

The most relevant safety data come from the Phase 3 study (MS200661-0003) with supportive data for the final dose regimens coming from the Phase 2 study (MS200661-0005).

In total 732 paediatric participants aged 3 months to 6 years were included across the Phase 2 (study MS200661-0005) and Phase 3 (study MS200661-0003) studies, including 442 participants who received at least one dose of arpraziquantel.

In total, 202 children were exposed to the target dose of 50 mg/kg and 120 children were exposed to the dose 60mg/kg. Additional 120 children received doses lower than these recommended in the SmPC. It is noted that most children treated with arpraziquantel were within the 4 to 6 years age group (122 (60%) children for the 50mg/kg dose and 91(76%) for the 60mg/kg dose) (for younger age groups see below).

In general, there are some differences in the safety profile of L-PZQ and Biltricide recorded in the Phase 2 study as compared to the Phase 3 study. For example, in Phase 2 study anaemia was reported by up to 48% of children whereas in Phase 3 only up to 4% of patients. Abdominal pain was one of the most frequently reported PT in Phase 3 study (up to 23%), whereas in Phase 2 was reported less frequently (up to 10%). Somnolence was not reported in Phase 2 study. These differences could be explained by differences in the definition of TEAEs in these 2 paediatric studies. In Phase 2 study but not in Phase 3 study laboratory abnormalities at baseline were classified as TEAEs. Further, intrinsic, or environmental factors may have also contributed to these differences including infection type and intensity and different locations where these studies were performed.

Common AEs

In **MS200661-0003 (Phase 3)** study, 58.3% of subjects reported ≥ 1 TEAE. The incidence of ≥1 TEAE was similar between Cohorts 1a and Cohorts 1b (66% versus 62% respectively). The highest frequency of TEAE (77.8%) was reported in Cohort 3 (aged 3 to 24 months and receiving L-PZQ DT 50 mg/kg) however, taking into consideration a small number of participants included in this cohort this result needs to be interpreted with caution. TEAEs within the SOC Infections and infestations was reported the most frequently followed by the SOC Gastrointestinal disorders and Nervous system disorders.

At the PT level abdominal pain was the most frequently reported (15.3%) followed by diarrhoea (10.1%), somnolence (7.6%), vomiting (6.6%) and upper respiratory tract infection (5.9%).

In relation to the PT abdominal pain the incidence was similar in Cohorts 1a and Cohorts 1b (23% and 20% respectively) and slightly higher as reported in 30 % participants in the 2 to 3 years age group (Cohort 2). Abdominal pain was only reported 2 children in the youngest age groups.

In study MS200661-0003 Cohort 2 (13/30 [43.3%] participants) had the highest incidence of gastrointestinal disorders claimed, as probably related to the higher baseline infection intensity. Cohort 2 (8/30 [26.7%] participants) had also the highest incidence of somnolence compared to 6% in Cohort 1b and 8% in Cohort 1a (all *S. mansoni* cohorts) with respectively 43.8% and 39.8% of patients with moderate/heavy infection intensity.

In **MS200661-0005 (Phase 2)** study, 286 (64%) among all the 444 treated subjects reported at least one TEAE. All subjects (4, 100%) in Cohort 9 reported TEAEs and 45 (75.0%) and 16 (80.0%) in Cohorts 7 and 8, respectively. The incidence of TEAEs in the other cohorts varied between 56.7% and 66.7%.

TEAEs within the SOC Blood and lymphatic system disorders were the most frequently reported in all cohorts and the incidence of TEAEs within this SOC ranged from 25% in Cohort 1 to 100% in Cohort 9 (i.e. AEs were reported for all 4 children enrolled to this cohort). Within the SOC Blood and lymphatic system disorders anaemia was most frequently reported. The second most common SOC was the SOC Gastrointestinal disorders. Abdominal pain, vomiting, diarrhoea was most frequently reported however, the frequency of these AEs was lower than seen in the Phase 3 study (less than 10 % in any treatment group). In relation to the SOC Infections and infestations, bronchitis, malaria and rhinitis was the most frequently seen in these patients.

TEAEs by severity
The majority of TEAEs were mild or moderate.
The number of severe TEAE reported across studies was small. In MS200661-0003 study only 4/288 (1.4%) participants experienced severe TEAEs including 2 events of malaria for 1 participant from each Cohort 1a and 4b, respectively, rash reported for 1 participant in Cohort 1b, and abdominal pain for 1 participant in Cohort 2.
In MS200661-0005 study severe TEAEs were reported in 9 children (2%) including 5 enrolled to the L-PZQ treatment group. In the L-PZQ group severe cases of C-reactive protein increased (n=2), leukocyturia (n=2), and thrombocytopenia (n=1) were reported.

Related TEAEs
In MS200661-0003 study, the majority of the Drug Related TEAEs were within the SOC Gastrointestinal disorders (abdominal pain, diarrhoea, nausea, vomiting). Other Drug Related TEAEs included Lymphocytosis, Eyelid oedema, Pyrexia, Gastroenteritis, Headache, Urticaria which were reported by one or two patients only. One male subject aged 5 years in Cohort 1a (L-PZQ) had a drug-related TEAE of lymphocytosis that was considered mild 53.9% with onset one day after treatment.

In MS200661-0005 study, a total of 71 (16.0%) subjects were considered to have at least one drug-related TEAE. Similar as in the Phase 3 study, drug-related TEAE were most frequently reported within the SOC Gastrointestinal disorders. Other drug-related TEAE included pruritus, pyrexia and transaminases increased, thrombocytopenia, and cough (only pruritus and pyrexia were reported in the L-PZQ treatment groups).

Serious adverse events and deaths

In total, 3 SAEs were reported including one case of severe malaria and 2 cases of increased transaminases in one subject in Cohort 1 and one subject in Cohort 3 in the Phase 2 study. No deaths were reported.

Safety profile of L-PZQ as compared to Biltricide-pooled safety analysis
No major differences were identified between these two products. The frequency of TEAEs and drug related TEAEs were similar between groups. TEAEs were reported in 62.2% of patients treated with L-PZQ as compared to 59.4% of patients receiving Biltricide. Drug related TEAE were reported in 18.8% patients on L-PZQ and 20.6% on Biltricide**.** Serious and severe AEs were reported by small and similar percentage of patients. One SAE was reported for a patient on L-PZQ and one for a patient on Biltricide Severe AEs were reported in 1.8% of patients in each group. At the PT level, abdominal pain, vomiting, and pyrexia occurred with similar frequencies on L-PZQ and on Biltricide in the pooled safety analysis.

Diarrhoea and somnolence occurred with a higher frequency in the L-PZQ treated patients as compared to those treated with Biltricide (7.5%, 4.3% versus 2.9%, 1.8%, respectively). Some differences were noted for PTs within the SOC Infections and infestations but with no clear pattern (bronchitis occurred more frequently in the Biltricide group but urinary tract infection (URTI) occurred more frequently in the L-PZQ group).

The remaining PTs were reported in a small number of children therefore no firm conclusion could be made.

Immunological events

Allergic reactions

Rash (not related), urticaria (related, mild in severity) and pruritus (related, moderate in severity) were reported in the studies. Severe allergic reactions were not reported in studies performed by the applicant.

Severe allergic reactions were reported in patients receiving racemic praziquantel as discussed in the literature and therefore they may occur in patients treated with arpraziquantel. Therefore, the risk for development of severe allergic reactions in patients receiving arpraziquantel cannot be excluded.
Further, as indicated by the applicant the risk of development of allergic reactions could be higher in preschool aged children compared to other age groups. In the meta-analysis of clinical trials of praziquantel comparing 503 preschool aged children and 1,504 school children, the cumulative incidence of itching/rash was higher in pre-school aged children than in school children (8.6% versus 5.5%, respectively).

Section 4.4 of the SmPC was updated highlighting this potential risk.

Acute schistosomiasis

The applicant was asked to justify the lack of contraindication in the treatment of acute schistosomiasis. As indicated in section 4.4, racemic praziquantel is not effective during acute schistosomiasis due to lack of activity against migrating schistosomulae. Further, the use during the acute schistosomiasis could lead to significant and life-threatening consequences. In response to these concerns, the applicant agreed to add in section 4.3 and 4.4, a contraindication regarding the use in children with known, or suspected acute schistosomiasis.

Further, the applicant indicated that children under 2 years of age often have low infection intensities (defined by concentration of schistosome ova excretion) and traditional diagnostic methods lack sensitivity for such low-intensity infections (Freer 2018). Thus, the applicant completed the warning in

section 4.4 with the inclusion of the most common clinical manifestations of AS to support identifying of such children.

Finally, "Use of arpraziquantel in patients with undiagnosed acute schistosomiasis" was added as asked as an important potential risk in the list of safety concerns of the RMP for further risk characterisation.

Paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions, potentially leading life-threatening events were reported in patients treated with racemic praziquantel for acute schistosomiasis.

The applicant indicated that within chronically exposed populations, Katayama syndrome caused by *S. mansoni* and *S. haematobium* is rarely reported. A potential explanation for this phenomenon, as provided by the applicant, is that in-utero sensitisation might decrease the severity of common symptoms of Katayama syndrome in chronically exposed populations however, it is also likely that these cases from endemic areas are underdiagnosed.

Therefore, it is considered that the available data are insufficient to claim that Katayama syndrome is not occurring within chronically exposed populations. Further, as first infection event in most endemic areas occurs early at the pre-school age, this population of patients could be at higher risk of development of this event however there is no data to confirm or reject this. The CHMP recommended that this uncertainty be reflected in the SmPC: *The risk for these reactions may be higher in non-immune patients. As the first infection event in most endemic areas occurs early at the pre-school age, theoretically, the risk of Katayama syndrome could be higher in pre-school aged children; however, there are no data to confirm or reject this.*

Any cases of severe allergic reactions, paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions reported post marketing will be monitored and presented in PSUR.

Safety profile in younger age groups

In total, in Phase 2 and 3 studies (MS200661-0003 and MS200661-0005) 101 children were within 2 to 4 age group (including 39 and 27 children exposed to the 50 mg/kg and 60 mg/kg dose of L-PZQ, respectively) and 43 children were younger than 2 years of age (including 41 receiving the 50 mg/kg dose of L-PZQ and 2 receiving the 60 mg/kg dose of L-PZQ). Seven children included in the arpraziquantel development programme were younger than 1 year of age.

When the safety results were analysed by age, no major differences were noted (with exception of somnolence which was reported more frequently in younger children). Somnolence was reported in 4.7% children aged 3 months to < 24 months (L-PZQ only), in 8.9% children aged 2 to < 4 years (L-PZQ DT only) and in less than 2.7% children aged 4 to 6 years of age.

The literature data available for racemic praziquantel do not indicate major differences in the safety profile in pre-school aged children as compared to older children and adults. The meta-analysis of studies which enrolled 1,694 PSAC (Zwang, 2014) indicated that AEs reported in this age-group were mild and transient. In another study, which recruited 234 PSAC treated at a dose of 40 mg/kg (Coulibaly, 2012), most of the AEs were observed within the first 4 hours after treatment and they were transient and of mild intensity (with the only exception of face and body inflammation (4 events) that was graded as moderately severe). Other AEs included abdominal pain, diarrhoea, nausea, vomiting, dizziness, fever, fatigue, and headache. Further review of the literature safety data on the use in the youngest age group which included 25 children aged 5–24 months exposed to praziquantel in Sousa-Figueiredo study (2012) and 21 children aged between 1 and 23 months treated with praziquantel syrup does not reveal any new significant safety findings. Abdominal pain, bloody

diarrhoea and sleepiness were the most common adverse events reported in these studies, but these were transient and self-limiting.

Of note, racemic praziquantel is approved in some EU countries for the use in children aged 1 and above.

The applicant considered that safety events expected in young children are anticipated to follow the same distribution and severity as in older children and adults, with the possible exception of a higher incidence of allergic reactions (see above).

Although it can be agreed the safety profile of arpraziquantel when used in children aged 2 and below seems to be similar to the safety profile of arpraziquantel when used in older age groups, the available data are limited and therefore they need to be interpreted with caution. This is particularly relevant for children younger than 1 year of age.

Section 4.4 of the SmPC was updated to indicate that the data for children < 1 year of age is limited and that caution is required when arpraziquantel is used in these patients.

In addition, the applicant agreed to update the RMP and include the use of arpraziquantel in children < 1 year of age as missing information.

Cohorts 4a and 4b investigating the effect of L-PZQ on *S. haematobium*

It is noted that in general, the frequency of reported TEAE was slightly lower in Cohorts 4a and 4b as compared to other cohorts. ≥1 TEAE was reported in 30% of children receiving the dose 50 mg/kg and 46% of children receiving the dose 60 mg/kg. AEs within the SOC Gastrointestinal disorders were reported only in 6 patients in total including 2 who reported abdominal pain. The applicant considered that these differences in reporting could be attributable to the fact that *S. haematobium* causes urogenital schistosomiasis and not intestinal schistosomiasis.

Somnolence was also less frequently reported in these cohorts (i.e. it was reported by one patient only).
Other AEs which were seen in Cohorts 4a and 4b including those reported with a higher frequency as compared to other groups (i.e. lymphocytosis, neutropenia, gastritis, fatigue, wound sepsis, haematuria, rhinitis allergic and dermatitis allergic) are not particularly concerning as they were reported by a small number of participants, were not severe or serous. Only one severe event was malaria reported for 1 participant in Cohort 4b.

The limited data collected in this Phase 3 study seems to indicate that the safety profile of L-PZQ given at the dose up to 60 mg/kg and when used for the treatment of *S. haematobium* is not different as compared with L-PZQ given at the dose 50 mg/kg and used for the treatment of *S. mansoni*.

Effects on CNS

Co-existing cysticercosis

As stated in section 4.3 of the SmPC, the product is contraindicated in children with known or suspected cysticercosis. A relevant warning is also included in section 4.4 of the SmPC. Further, it was highlighted that in patients with a history of seizures and with other central nervous system symptoms, cysticercosis should be ruled out first before commencing the treatment with arpraziquantel.

As there is a concern that the product could be used in patients with undiagnosed asymptomatic neurocysticercosis (it is believed that asymptomatic neurocysticercosis is occurring in 50% of patients), the RMP was updated with the following potential risk: seizures in undiagnosed asymptomatic neurocysticercosis. This risk will be monitored post-marketing.

Seizures

Seizures were not reported in studies performed by the applicant. It was noted that in the product information for racemic praziquantel, seizures were listed as adverse drug reactions with unknown frequency. There are limited data indicating that there could be an increased risk of seizures not only in case of cysticercosis. Racemic praziquantel therapy can exacerbate central nervous system disorders in patients with other parasitosis with cerebral localisation. The warning proposed by the applicant was considered confusing since by being global and not confined to patients with parasitosis with CNS localisation, it tended to convey the idea that the drug itself could decrease seizure threshold. The applicant was therefore recommended to update the proposed warning to include in the SmPC that racemic praziquantel can exacerbate central nervous system disorders in patients with other parasitosis with cerebral localisation**.**

Laboratory findings

Safety laboratory tests (haematology, biochemistry, urinalysis) were performed both paediatric studies but, the observation period was short. In the initial Phase 2 protocol, safety laboratory tests (haematology, biochemistry, urinalysis) were scheduled at Screening (Day 1) and at the End of Study Visit (Day 14 to 21). During the protocol amendment this was changed to safety laboratory testing to be performed at the End of Confinement (Day 2) and optionally at the Day 8 if required for AE follow up. In the Phase 3 study MS200661-0003 the safety laboratory evaluations were conducted at ~12 h post-dose. The approach taken by the applicant was based on the fact that, the half-life of the study treatments is short (Biltricide 1 to 2.5 h and L-PZQ 3 h) although it is not fully clear if this observation period was sufficient to capture laboratory AEs with late onset.

In the Phase 3 study TEAEs related to laboratory abnormalities were reported infrequently. Lymphocytosis was reported in 4.5% of participants followed by anaemia (2.8%) and neutropenia (2.1%). One case of lymphocytosis was considered related to the study treatment by investigators. One subject had a TEAE (non-drug-related) of transaminases increased.

In the Phase 2 study TEAE laboratory abnormalities were reported more frequently. These differences could be partially explained by differences in the definition of TEAEs in these two paediatric studies. In the Phase 2 study but not in Phase 3 study laboratory abnormalities at baseline (reported on the same day but prior to the IMP administration) were classified as TEAEs. In this study, anaemia was most frequently reported (in 36.7% of children), followed by CRP increase (in 12 % of children) whereas other PTs were reported by a small number of patients. Four cases were considered as drug-related (one case of thrombocytopenia and three cases of transaminases increased), and two case were considered as serious (two cases of transaminases increased).

One case of thrombocytopenia (drop from 230 10x9/L on Day 1 to 93 10x9/L on Day 2) in Cohort 4 was considered related to the study treatment by the investigator (but not by the applicant). In this study there was another case of severe thrombocytopenia (drop to 31 10x9/L) in the subject in Cohort 5 which occurred 20 days after IMP administration. The applicant considers these two cases to be

procedure-related however, as assessments were not repeated no firm conclusion regarding causality could be made. The applicant agreed to monitor cases of thrombocytopenia and present them in the PSUR.

Liver safety

A total of 12 transaminases increased TEAEs, including 2 serious TEAEs, were reported during Phases 2 and 3 study conduct. 2 cases were considered as severe and serious.

Nine of these TEAEs were assessed as unrelated to study drug with plausible alternative explanations provided.

Three cases (one case in each severity category i.e. mild, moderate and serious) were considered as related all these cases were from rec-PZQ groups.

A serious and related case of transaminases increased was reported in Phase 2 study in the rac−PZQ DT 40 mg/kg group in a participant. During the day 14 to 21 follow up visit increased levels of transaminases were detected (ALT levels were 44×ULN and the AST 51×ULN). Although this case was considered related to the treatment by the investigator, it was not considered related by the applicant due to ongoing malarial infection which could contribute to this increase in levels of transaminases. For this case it is not clear why it was classified as severe and serious this is not apparent from the description provided by the applicant.

The second case of serious transaminases increased was not considered related to the study treatment as this event in fact was reported prior to the administration of study treatment.

The literature data are limited and do not provide strong evidence that PZQ is leading to increases in transaminases (however, it needs to be noted that and most controlled trials of this agent have used one day courses without serum aminotransferase monitoring). In the preclinical studies the effect on liver was only seen at very high doses (≥ 1,000 mg/kg), significantly exceeding clinical doses.

Therefore, it is considered that, based on the available evidence, no update to the SmPC was considered necessary. However, any reported cases of transaminases increases will be monitored and presented in the next PSUR for further review.

Arrhythmia
It is noted that in the product information for Biltricide arrhythmia is listed as an adverse drug reaction with unknown frequency. No cases of arrhythmia were reported in studies performed by the applicant. In the RMP the applicant provided justification for not including this risk in the list of safety concern, which is acceptable. Nevertheless, any cases of arrhythmia reported post-marketing in children will be presented and discussed in PSUR.

Adverse reactions in children treated with arpraziquantel

The following ADR are listed in the SmPC for arpraziquantel: abdominal pain, diarrhoea, vomiting and somnolence (frequency common), headache, nausea, urticaria, pruritus and pyrexia with frequency uncommon).

These were selected based on the fact that they were considered related to the study treatment by investigators. Further, these ADRs are listed in the product information for racemic praziquantel.

Related TEAEs (i.e. gastroenteritis and lymphocytosis) identified in the arpraziquantel development programme, were not considered as ADR by the applicant and this could be accepted as the data are too limited to make conclusion regarding causality.

2.6.10. Conclusions on the clinical safety

In general, no major safety concerns were identified in studies MS200661-0003 and MS200661-0005 in children aged 3 months to 6 years. The majority of TEAEs were mild or moderate. The number of severe TEAEs reported across studies was small. There were no deaths; serious adverse events were reported in three patients (one case of severe malaria and 2 cases of increased transaminases). There were no major differences in the safety profile of L-PZQ as compared to Biltricide.

However, the safety data for use of arpraziquantel in children less than 1 years of age is limited and this was highlighted in the SmPC. In addition, a contraindication for the use in children with known or suspected acute schistosomiasis was added as a result of the assessment further to a CHMP recommendation, together with a warning in section 4.4 of the SmPC. Patients with acute schistosomiasis would be required to be identified clinically based on the most common clinical manifestations of acute schistosomiasis, such as skin lesions (pruritus, skin eruption), fever, cough, abdominal pain and diarrhoea.

2.7. Risk Management Plan

2.7.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Seizures in patients with undiagnosed asymptomatic neurocysticercosis • Use in patients with undiagnosed acute schistosomiasis
Missing information	• Use in patients with impaired kidney function • Use in patients with hepatic impairment • Use in children <1 year of age

2.7.2. Discussion on safety specification

The applicant agreed to add "Use in children < 1 year" as missing information in the RMP. Additionally, the applicant stated that this topic will be discussed in the upcoming PSUR.

In addition, the applicant provided a discussion on local feasibility of additional pharmacovigilance activities regarding use in children < 1 year, highlighting the following:

- New studies to collect additional safety data in these very young patients are not considered feasible due to the difficulty to identify appropriate sites where this patient population could be reasonably quickly enrolled.
- < 2 years old children will be treated through a test and treat approach in healthcare facilities via healthcare providers (not via Mass Drug Administration)
- The exposure of arpraziquantel in children < 1 year of age will be very limited in initial 3 - 4 years of country access to arpraziquantel.

- The applicant believes a careful feasibility assessment in the various countries considering local infrastructure and collaboration opportunities with NTD network is required prior to the initiation of any additional pharmacovigilance activity.
- The applicant proposes to include the use of arpraziquantel in children < 1 year under close monitoring to ensure monitoring of these small children and confirm the positive benefit-risk balance.

2.7.3. Conclusions on the safety specification

The proposals provided by the applicant were accepted. The use of arpraziquantel in children < 1 year should be under close monitoring and the data should be presented and discussed in each PSUR. In addition, feasibility for the initiation of any additional pharmacovigilance activity should be discussed locally in countries where the product will be used in this age group and these discussions should be reported at each PSUR. The applicant committed to this.

2.7.4. Pharmacovigilance plan

Routine pharmacovigilance activities will be applied throughout to manage the safety of arpraziquantel.

Specific adverse reaction follow-up questionnaires are not planned.

Other forms of routine pharmacovigilance activities are not planned.

No additional Pharmacovigilance Activities are planned.

2.7.5. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimization activities
Seizures in patients with undiagnosed asymptomatic neurocysticercosis	Routine Risk Communication: • SmPC Section 4.4 • Package Leaflet Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None.
Use in patients with undiagnosed acute schistosomiasis	Routine Risk Communication: • SmPC Section 4.3 and 4.4 • Package Leaflet Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None.
Use in patients with impaired kidney function	Routine Risk Communication SmPC Section 4.2 and 5.2 Routine risk minimization activities recommending specific clinical measures to address the risk: None.
Use in patients with hepatic impairment	Routine Risk Communication: • SmPC Sections 4.2 and 4.4 • Package Leaflet Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None.
Use in children <1 year of age	Routine Risk Communication: • SmPC Section 4.2 • Package Leaflet Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None.

Additional risk minimisation measures

No additional risk minimisation measures are planned nor necessary for the safe and effective use of the product. The PRAC, having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the approved indications.

2.7.6. Conclusion

As the population of children under 1 year of age is a part of the proposed indication, the proposal to include children < 1 year of age as Missing information in the RMP was questioned. It was recommended that any limitation of efficacy and safety data in this population be reflected in the SmPC.

Significant and potentially life-threatening complications in patients with undiagnosed acute schistosomiasis and risk of seizures in patients with undiagnosed asymptomatic neurocysticercosis should not be added to the list of safety concerns in the RMP. These safety concerns will be monitored in PSURs.

At present, no additional Phase IV activities and risk minimisation measures are proposed.

The CHMP considers the risk management plan version 1.0 acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant are in line with the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 14 December 2023.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

2.9. Product information

2.9.1. User consultation

A user testing of the package leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Development was promoted by a general lack of a suitable presentation of rac-PZQ for children aged <4 years and the fact that in those children the available presentations may require breakage into ¼ tablets and have a bitter taste that limits dose adherence. The applicant proposed that Arpraziquantel (L-PZQ) 150 mg dispersible tablets should be indicated for the treatment of schistosomiasis caused by *Schistosoma mansoni*, *Schistosoma haematobium* in children aged 3 months to 6 years (weighing at least 5 kg). The age and weight limits reflected development of arpraziquantel specifically to provide a suitable formulation and tablet size to achieve the targeted mg/kg doses in PSAC.

3.1.1. Disease or condition

Schistosomiasis (bilharzia) results from infection by parasitic flatworms (blood flukes). The infection is prevalent in tropical and subtropical areas without potable water and adequate sanitation. More than 90% of affected areas are in Africa. The disease comprises an acute phase that progresses to a severe chronic inflammatory disease and is endemic in 78 developing countries, with moderate to high transmission kinetics in 51 of these countries. The WHO estimated that 779 million people are at risk of acquiring a Schistosoma infection and in 2019 more than 236 million people required preventative chemotherapy for schistosomiasis.

The prevalence of schistosomiasis in children < 14 years of age in endemic countries is high, accounting for approximately 50% of infections. A recent study published in 2020 found a pooled prevalence estimate of 19% for any Schistosoma species in pre-school aged children (PSAC) in sub-Saharan Africa (Kalinda). Studies in Nigeria, Ghana and Uganda (Odogwu 2006) identified infection with *S. mansoni* and *S. haematobium* in very early childhood. In a study in Niger, the prevalence of schistosome infection among children < 5 years of age exceeded the recommended threshold for large-scale administration of racemic praziquantel (rac-PZQ).

Approximately 20 million people suffer severe consequences from the disease, with approximately 20,000 to 200,000 annual deaths. According to the WHO, this rate should have decreased considerably over the past decade with the increase in large-scale preventative chemotherapy campaigns. However, a major limitation to schistosomiasis control has been the limited availability of rac-PZQ and lack of a paediatric formulation suitable for young children. Data for 2020 show that only 31.9% of people requiring treatment were reached globally, with 44.9% of school-aged children requiring preventive chemotherapy for schistosomiasis being treated. The number of treatments and coverage was 27.1% lower in 2020 (76.9 million treated) than in 2019 (105.5 million treated), due mainly to control measures for the COVID-19 pandemic, which resulted in suspension of preventative chemotherapy in many countries and endemic areas.

Schistosomiasis presents mainly in intestinal or urogenital forms and is caused by six main Schistosoma species. Intestinal schistosomiasis is caused by *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis* (and related *S. intercalatum*) while urogenital schistosomiasis is caused by *S. haematobium*. The most prevalent species in sub-Saharan Africa are *S. mansoni* and *S. haematobium*.

The life cycle of the species that infect humans involves a snail development phase and a human phase. The adult worms develop in humans and fertilised eggs are excreted into the environment.

After completion of development within snails, the cercariae enter water sources. Infection of humans occurs via skin penetration during water exposures (e.g. bathing, agricultural work, fishing work). The disease manifestations in humans depend on whether adult worms reside in the mesenteric veins (*S. mansoni* and *S. japonicum*) or in the bladder venous plexus (*S. haematobium*). Trapping of some eggs in the organs (e.g. bowel, liver, lung, bladder, CNS) produces local symptoms through formation of granulomas resulting from the host inflammatory response.

The clinical manifestations of schistosomiasis can be acute (Katayama syndrome) and chronic. The incubation period of Katayama syndrome is typically 14 to 84 days. Symptoms may include fever, headache, myalgia, rash and respiratory (asthma-like) symptoms. For *S. mansoni*, clinical manifestations of chronic disease are blood in the stool, constipation, diarrhoea, and chronic inflammation, which can cause bowel wall ulceration, fibrosis, hyperplasia, polyposis, and portal hypertension accompanied by hepatosplenomegaly. Leukocytosis is frequent and eosinophilia occurs in almost 70% of infected patients. For *S. haematobium*, clinical manifestations of chronic disease include dysuria and haematuria, as well as injury to the genital tract and susceptibility to other infections, which can lead to bladder cancer in the long term.

Active infections acquired at early ages may aggravate the clinical significance of the disease in later life. In children, schistosomiasis is associated with severe consequences, including impairment of growth, cognition, development and physical fitness. There is also morbidity related to anaemia, malabsorption and hepatosplenic dysfunction. For example, a study of Brazilian school children with mild- to moderate-intensity schistosome infections (< 400 *S. mansoni* eggs/g stool) found that those treated for schistosome infection with oxamniquine for 1 year had greater measurements for weight, triceps skinfold thickness, mid-arm circumference, arm muscle area and BMI vs. those who were untreated. A meta-analysis of 30 studies reporting on 38,992 children aged 5-19 years found that Schistosoma infection or non-dewormed status was associated with educational, learning and memory deficits.

3.1.2. Available therapies and unmet medical need

Racemic praziquantel (rac-PZQ) was developed in the 1970s. It has been registered and marketed since 1980 as an anthelminthic drug (e.g. Biltricide or Cysticide) and is well established as the standard treatment for schistosomiasis. Preventive chemotherapy by mass drug administration with annual or biannual single doses of rac-PZQ is the cornerstone of the control of schistosomiasis since the WHO resolution in 2001, which urged endemic countries to treat at least 75% of all at-risk children of school age by 2010. Rac-PZQ 600 mg tablets are included in the WHO list of essential medicines for the treatment of schistosomiasis in adults and school-aged children at an annual or biannual single dose of 40 mg/kg according to the WHO Guideline for treatment and control of schistosomiasis. This strategy is recommended for all at-risk people aged ≥ 2 years of age, with treatment for children < 2 years of age considered on an individual clinical basis.

Currently, there is no acceptable paediatric formulation for PSAC. Commercially available rac-PZQ is composed of two enantiomers in a 1:1 ratio: R-(-)-PZQ (=L-PZQ) and S-(+)-PZQ. Arpraziquantel (R-[-]-PZQ) is the main biologically active form. The S-(+)-PZQ enantiomer has been reported to play an important role in the bitter taste of the drug and is not converted to R-(-)-PZQ *in vivo*. The marketed rac-PZQ tablets need to be divided, crushed, and given with water for dosing in young children. The intense bitter taste risks under-dosing due to gagging or vomiting, with negative implications for treatment adherence. In 2010, the WHO recommended the development of a water dispersible PZQ formulation for appropriate treatment of PSAC.

3.1.3. Main clinical studies

The Paediatric Praziquantel Consortium initially developed rac-PZQ and single active enantiomer (L-PZQ; arpraziquantel) dispersible/orodispersible tablets (DT/OTD). There were three clinical studies:

- Phase 1 relative bioavailability study (EMR200661-001) in healthy adult male participants comparing the pharmacokinetics (PK) of arpraziquantel (150 mg tablet) at a 20 mg/kg dose versus the marketed rac-PZQ Cysticide (500 mg tablet) at a 40 mg/kg dose and evaluating the taste of the arpraziquantel formulation.

- Phase 2 dose-finding study (MS200661-0005) in *S. mansoni*-infected children aged 2 to 6 years assessing arpraziquantel (30, 45, and 60 mg/kg) and rac-PZQ paediatric formulations (rac-PZQ DT 40 and 60 mg/kg and commercial rac-PZQ tablet [Biltricide] 3 × 20 mg/kg and 40 mg/kg). The selected dose of 50 mg/kg L-PZQ was evaluated in a small number aged 3 to 24 months.

- Phase 3 study (MS200661-0003) to demonstrate the efficacy and safety of L-PZQ in Schistosoma-infected children aged 3 months to 6 years. There was 2:1 randomisation of *S. mansoni*-infected children aged 4 to 6 years with L-PZQ 50 mg/kg or commercial rac-PZQ (Biltricide). A separate, non-randomised cohort of children 3 months to 6 years of age infected with *S. haematobium* was treated with arpraziquantel 50 or 60 mg/kg.

3.2. Favourable effects

The efficacy of L-PZQ (arpraziquantel) was evaluated in children infected with *S. mansoni* or *S. haematobium* and resident in endemic areas. The Phase 2 dose-finding and formulation-finding study was confined to children infected with *S. mansoni* and suggested that the minimum L-PZQ dose should be 45 mg/kg. The Phase 3 study used a rounded up 50 mg/kg L-PZQ target dose for *S. mansoni* and evaluated 50 mg/kg and 60 mg/kg L-PZQ target doses for *S. haematobium*.

Phase 2 study 0005

Conducted between 2016 and 2018 at a single centre in the Ivory Coast, the study enrolled children with *S. mansoni* infections. In Part 1, children aged 2-6 years were randomised (20-40 per group) to commercial rac-PZQ tablets (3 x 20 mg/kg or 1 x 40 mg/kg), paediatric formulation of rac-PZQ (40 mg/kg or 60 mg/kg) or paediatric formulation of L-PZQ (30 mg/kg, 45 mg/kg or 60 mg/kg). The level of infection in the children enrolled into the study was classified using the WHO criteria and there was stratification at randomisation by infection load.

The primary efficacy endpoint for treatment of *S. mansoni* infections was clinical cure, defined as no eggs found in stools obtained 14-21 days after the single dose treatment. The study was exploratory with no hypothesis testing required for the primary endpoint, so the sample size was based mainly on feasibility considerations. The primary analysis was conducted in the mITT set, defined as all randomised subjects who had a baseline measurement for the efficacy variable, excluding those who received anti-malarial treatment following dosing. The primary analysis included imputation of missing data (last observation carried forward). Those with missing egg counts were imputed as not cured.

In accordance with the stratification, close to 60% aged from 2 years had a light infection whereas the majority in Cohorts 8-9 had light infections. The overall CR in all cohorts was ≥ 70%. The lowest CR (74%) was observed with 40 mg/kg Biltricide but the 95% CI around the cure rates overlapped for all cohorts.

Regression analysis revealed that infection intensity appeared to be the only significant covariate (apart from treatment) with respect to CR. However, even in those with moderate/heavy infections, the cure rates for the L-PZQ groups fell between those for 3x20 mg/kg (85.7%) and 1x40 mg/kg (56.5%) Biltricide, ranging from 69-82%.

The CRs based on POC-CCA at Day 14 -21 were noticeably lower than CRs assessed by the Kato-Katz method for the primary analysis, which may reflect the higher sensitivity of the POC CCA test as reported in the literature. There was an increase in POC CCA CR over time (Day 2, 8 and 14-21). The Egg Reduction Rates (ERR) per geometric mean (ERRgm) and per arithmetic mean (ERRam) in the mITT population were close to or >90% except for Cohort 2 (Biltricide 40 mg/kg). Without imputation, high ERRG and ERRA were observed across all cohorts (> 95%) for all the study interventions.

The applicant concluded that a single dose of L-PZQ 45 mg/kg provided an acceptable CR as assessed by Kato-Katz method and safety profile in 2-6 year-olds infected with *S. mansoni.* For ease of dose calculation, 50 mg/kg of L-PZQ was selected for Part 2 in subjects aged 3-24 months and the results in this age range were considered to further support this dose for Phase 3.

Phase 3 study 0003

The single pivotal efficacy study was conducted in Kenya and Ivory Coast in 2019-2021. Children aged 3 months to 6 years with *S. mansoni* received a target dose of 50 mg/kg L-PZQ using the DTs administered after dispersion in water. The minimum body weight for enrolment was 5 kg.

There was randomisation to L-PZQ or racemate (2:1) in Cohort 1 aged 4-6 years. Although the Phase 2 study suggested that 3 x 20 mg/kg on one day might be somewhat better than 1 x 40 mg/kg in children aged 2-6 years, the Biltricide dose in Cohort 1 was 40 mg/kg. This dose is recommended by the WHO for routine population-based treatment at intervals. The literature gives variable results for different Biltricide doses and according to *S. mansoni* or *S. haematobium* infections.

For children with *S. haematobium*, the initial target dose was also 50 mg/kg. In accordance with the protocol, the IDMC reviewed the safety and efficacy data of Cohort 4 after 30 children had received 50 mg/kg L-PZQ DT and recommended that the target dose be increased to 60 mg/kg L-PZQ.

The classification of infection load for *S. mansoni* and *S. haematobium* followed WHO criteria and stratification at randomisation by load was applied to Cohort 1 since only this cohort was randomised. The primary endpoint for groups infected with *S. mansoni* was the cure rate at day 17-21 after treatment (compared to days 14-21 in Phase 2). The primary analysis for those with *S. mansoni* compared Cohorts 1a and 1b (i.e. L-PZQ vs. Biltricide) but there was no formal hypothesis testing. The ERR was the main secondary endpoint.

The primary endpoint for those with *S. haematobium* was the cure rate as assessed at 17 to 21 days and 35 to 40 days after treatment, where clinical cure was defined as no parasite eggs in urine using the urine filtration technique.

The target for Cohort 1 of 40% moderate/heavy infections and 60% light infections was achieved. Light infection predominated in Cohort 3 [77.8%], Cohort 4a [62.1%] and Cohort 4b [89.7%]. In contrast, Cohort 2 had a higher proportion with moderate or heavy infection (58.6%) due to the presence of hotspots in some Kenya districts.

Schistosoma mansoni
The clinical CRs by the Kato-Katz method in *S. mansoni*-infected children who received 50 mg/kg L-PZQ were ≥ 87% with the lower bounds of the 95% CI exceeding 70% (Cohorts 1a, 2 and 3). The CRs in Cohort 1 were broadly comparable for 50 mg/kg L-PZQ and 40 mg/kg Biltricide. One subject was lost to follow-up from Cohort 1b, so there is almost no difference between the results for the mITT population with and without imputation. Within Cohort 1 the CRs were lower but very similar for L-PZQ and Biltricide for those with moderate/heavy infections (CR 76.9% and 76.2%) vs. those with light infections.

The point estimates for CRs in Cohorts 2 and 3, as well as for the pooled data in children aged from 3-24 months who received 50 mg/kg L-PZ in Cohort 3 or in Cohorts 8 and 9 in the Phase 2 study, were all above 90%. A higher CR with L-PZQ in those with light infection was observed in Cohort 2. This pattern was not seen in the smaller numbers in Cohort 3, but it was seen when data from Cohort 3 were pooled with Cohorts 8 and 9 from the Phase 2 study (light infection 96.6% vs. moderate/heavy infection 87.5%) although only 8 subjects had moderate/heavy infection.

While the study was not powered for the comparison between Cohort 1a and 1b or for comparisons between the other cohorts with *S. mansoni* and the licensed racemate, and while the comparisons should take account of the different levels of infection, the study suggested that 50 mg/kg L-PZQ was likely to be at least as efficacious as 40 mg/kg of the racemate (CR 81% with a lower bound of the 95% CI just below the target 70%). Noting that 3x20 mg/kg of the racemate appeared possibly more efficacious than 1x40 mg/kg in Phase 2, a cross-study comparison (which must be viewed with due caution) suggested that the point estimate CR and lower bounds of the 95% CI for Cohorts 1a, 2 and 3 were broadly comparable with the results for 3x20 mg/kg racemate.

The results for the CR were supported by those for the ERR. For the mITT population, the ERRG and ERRA were near or above 95% except for Cohort 2, in which the ERRG was 99.6% but the ERRA was 88.5%. The lower ERRA in Cohort 2 was due to a subject who vomited within an hour from dosing who had an egg count of 1148 at follow-up. After exclusion of this subject, the PP population had an ERRA of 97.7%. The proportions with an iERR ≥ 90% were close to or above 90% for all cohorts except for Cohort 1b 40 mg/kg Biltricide in the Ivory Coast, where the proportion with an iERR ≥ 90% was 84%. In the subgroups pooled across Cohort 3 and Cohorts 8 and 9 from the Phase 2 study, the observed ERRA, ERRG and proportion with iERR ≥ 90% were consistently above 90%.

CRs as determined by POC-CCA were generally lower than those determined using the Kato-Katz method but showed similar patterns across age groups.

Schistosoma haematobium
There was no control group for the evaluation of efficacy against *Schistosoma haematobium.* The optimum dose of racemate for treating this species is unclear from the literature. With a 58.8% CR in Cohort 4a (50 mg/kg L-PZQ) at Week 3, the CR was also higher for light infection (66.7%) compared to heavy infection (45.5%).

The IDMC recommended an increase in dose to 60 mg/kg. The 60 mg/kg dose resulted in a CR of 86.2% [74.6, 93.9%] at Week 3 and 94.8% [85.6, 98.9%] at Week 5. The higher CR at Week 5 vs. Week 3 may reflect the longer host parasite lifecycle in *S. haematobium* and a longer period for egg clearance. With the 60 mg/kg dose, the CRs were 86.5% at Week 3 and 94.4% at Week 5 for light infections compared to CRs for heavy infections that were 83.3% and 100% at respective visits. However, sample sizes in Cohorts 4a and 4b for heavy infections are small.

For the mITT population, ERRG and ERRA were close to or above 98% for Cohorts 4a and 4b. The proportions with an iERR ≥ 90% were close to or above 93% for both cohorts.

Generally, the findings support target doses of 50 mg/kg L-PZQ for treatment of *S. mansoni* and 60 mg/kg for treatment of *S. haematobium* in children aged from 3 months to 6 years.

3.3. Uncertainties and limitations about favourable effects

The Phase 2 and Phase 3 studies were open label. After discussions during scientific advice, the open-label design was accepted because the efficacy endpoints were laboratory parameters and laboratory staff were not aware of treatment assignments. Full details of the laboratory methods and quality control procedures were provided and found satisfactory, including resolution of discrepant readings.

In Phase 2 and 3, the calculated mg/kg doses were rounded to the next/closest value so that doses could be delivered using whole 150 mg tablets, which were dispersed in water prior to administration. The actual doses administered to those who failed to clear the infection were compared to the actual doses given to those with clinical cure. There was no pattern found to suggest that those who failed to clear the infection were more likely to have received less than the target dose vs. those who did clear the infection, i.e. there was no clear dose-response relationship detected.

There are very limited efficacy data in children <2 years of age by species at the selected dose of L-PZQ (i.e., 37 children for *S. mansoni* in pooled data of three cohorts from Phase 2 and 3 and 2 children for *S. haematobium* from Phase 3). The SmPC recommends dispersion in the same minimum volumes advised during the Phase 3 study with administration via a syringe or cup, selected by the treating healthcare professional depending on the individual child. Due to the poor palatability of the tablets if left to disintegrate in the mouth and the risk of choking in young children, this alternative mode of administration, which was not used in Phase 2 or 3, is not to be allowed.

3.4. Unfavourable effects

The most relevant safety data supporting the use of arpraziquantel come from the Phase 3 study (MS200661-0003) with supportive data for the final dose regimens coming from the Phase 2 study (MS200661-0005). In these studies, the safety profile of arpraziquantel (L-PZQ) was compared to Biltricide tables given at the dose 40 mg/kg once daily or 20 mg/kg three times a day. The comparative safety data in these studies are only available for children from age 4 years and upwards.

In total 202 children were exposed to the target dose of 50 mg/kg and 120 children were exposed to the dose 60 mg/kg.

In the MS200661-0003 study, 58.3% of subjects reported ≥ 1 TEAE, TEAEs within the SOC Infections and infestations was reported the most frequently followed by the SOC Gastrointestinal disorders and Nervous system disorders. At the PT level abdominal pain was the most frequently reported (15.3%) followed by Diarrhoea (10.1%), Somnolence (7.6%), Vomiting (6.6%) and Upper respiratory tract infection (5.9%).

In the MS200661-0005 study, 286 (64%) among all the 444 treated subjects reported at least one TEAE. TEAEs within the SOC Blood and lymphatic system disorders were the most frequently reported in all cohorts. The second most common SOC was the SOC Gastrointestinal disorders. Abdominal pain, vomiting, diarrhoea was most frequently reported however, the frequency of these AEs was lower than seen in the Phase 3 study (less than 10% in any treatment group). Within the SOC Blood and lymphatic system disorders anaemia was most frequently reported.

The majority of TEAEs were mild or moderate.

The number of severe TEAE reported across studies was small. In MS200661-0003 study only 4/288 (1.4%) participants experienced severe TEAEs including 2 events of malaria for 1 participant from each Cohort 1a and 4b, respectively, rash reported for 1 participant in Cohort 1b, and abdominal pain for 1 participant in Cohort 2.

In the MS200661-0005 study severe TEAEs were reported in 9 children (2%) including 5 enrolled into the L-PZQ treatment group. In the L-PZQ group severe cases of C-reactive protein increased (n=2), leukocyturia (n=2), and thrombocytopenia (n=1) were reported.

In the MS200661-0003 study, the majority of the Drug Related TEAEs were within the SOC Gastrointestinal disorders (abdominal pain, diarrhoea, nausea, vomiting). Other Drug Related TEAEs included Lymphocytosis, Eyelid oedema, Pyrexia, Gastroenteritis, Headache, Urticaria which were reported by one or two patients only. One male subject aged 5 years in Cohort 1a (L-PZQ) had a drug-related TEAE of lymphocytosis that was considered mild 53.9% with onset one day after treatment.

In the MS200661-0005 study, a total of 71 (16.0%) subjects were considered to have at least one drug-related TEAE. Similar as in the Phase 3 study, drug-related TEAE were most frequently reported within the SOC Gastrointestinal disorders. Other drug-related TEAE included pruritus, pyrexia and transaminases increased, thrombocytopenia, and cough (only pruritus and pyrexia were reported in the L-PZQ treatment groups).

In total, 3 SAEs were reported including one case of severe malaria and 2 cases of increased transaminases in one subject in Cohort 1 and one subject in Cohort 3 in the Phase 2 study. No deaths were reported.

No major differences were identified between L-PZQ, as compared to Biltricide in the pooled safety analysis. The frequency of TEAEs and drug related TEAEs were similar between groups. TEAEs were reported in 62.2% of patients treated with L-PZQ as compared to 59.4% of patients receiving Biltricide. Drug related TEAE were reported in 18.8% patients on L-PZQ and 20.6% on Biltricide. Serious and severe AEs were reported by small and similar percentage of patients. One SAE was reported for a patient on L-PZQ and one for a patient on Biltricide. Severe AEs were reported in 1.8% of patients in each group. At the PT level, abdominal pain, vomiting and pyrexia occurred with similar frequencies.

Diarrhoea and somnolence occurred with a higher frequency in the L-PZQ treated patients as compared to those treated with Biltricide (7.5%, 4.3% versus 2.9%, 1.8%, respectively). Some differences were noted for PTs within the SOC Infections and infestations but with no clear pattern (bronchitis occurred more frequently in the Biltricide group but, URTI occurred more frequently in the L-PZQ group).

Rash (not related), urticaria (related, mild in severity) and pruritus (related, moderate in severity) were reported in the studies. Severe allergic reactions were not reported in studies performed by the applicant.

Severe allergic reactions were reported in patients receiving racemic praziquantel and therefore they may occur in patients treated with arpraziquantel.

Paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions, potentially leading life-threatening events were reported in patients treated with racemic praziquantel for acute schistosomiasis.

In Phase 3 study TEAEs related to laboratory abnormalities were reported infrequently. Lymphocytosis was reported in 4.5% of participants followed by anaemia (2.8%) and neutropenia (2.1%). One case of lymphocytosis was considered related to the study treatment by investigators. One subject had a

TEAE (non-drug-related) of transaminases increased. In Phase 2 study TEAE laboratory abnormalities were reported more frequently.

In this study anaemia was most frequently reported (in 36.7% of children), followed by CRP increase (in 12 % of children) whereas other PTs were reported by a small number of patients. Four cases were considered as drug-related (one case of thrombocytopenia and three cases of transaminases increased), and two case were considered as serious (two cases of transaminases increased).

3.5. Uncertainties and limitations about unfavourable effects

The safety data for use of arpraziquantel in children less than 2 years of age is limited. In the arpraziquantel development program 43 children were younger than 2 years of age (including 41 receiving the 50 mg/kg dose of L-PZQ and 2 receiving the 60 mg/kg dose of L-PZQ). Seven children were younger than 1 year of age. Although, the safety profile of arpraziquantel when used in children aged 2 and below seems to be similar to the safety profile of arpraziquantel when used in older age groups, the available data are limited and therefore they need to be interpreted with caution. This uncertainty is particularly relevant for children younger than 1 year of age. The SmPC has been updated indicating that the data for children under 1 are limited and the product should be used with caution in these patients. Furthermore, the safety when used in children under 1 will be monitored post-marketing and discussed in each PSUR.

Severe allergic reactions were not reported in studies performed by the applicant. However severe allergic reactions were reported in patients receiving racemic praziquantel and therefore they may occur in patients treated with arpraziquantel. Further, as indicated by the applicant the risk of development of allergic reactions could be higher in pre-school aged children, compared to other age groups. A relevant warning in this regard is included in the SmPC.

A contraindication for the use in children with known or suspected acute schistosomiasis was added to section 4.3. As explained in section 4.4, racemic praziquantel is not effective during acute schistosomiasis due to lack of activity against migrating schistosomulae. Further, the use during the acute schistosomiasis could lead to significant and life-threatening consequences. The most common clinical manifestations of acute schistosomiasis such as skin lesions (pruritus, skin eruption), fever, cough, abdominal pain, and diarrhoea were described in the SmPC. Paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions, potentially leading life-threatening events were reported in patients treated with racemic praziquantel for acute schistosomiasis. There are concerns that it could be used in patients with (undiagnosed) acute schistosomiasis leading to significant and potentially life-threatening complications. It is speculated that in-utero sensitisation might decrease the severity of symptoms of Katayama syndrome in chronically exposed populations, however the available data are insufficient to claim that severe Katayama syndrome is not occurring within chronically exposed populations. Further, as first infection event in most endemic areas occurs early at the pre-school age, this population of patients could be at higher risk of development of this event. However, there are no data to confirm or reject this. This uncertainty has been reflected in the SmPC.

There are uncertainties as to whether laboratory tests monitoring performed in the studies allows for identification of all relevant abnormalities. In the initial Phase 2 protocol, safety laboratory tests (haematology, biochemistry, urinalysis) were scheduled at Screening (Day 1) and at the End of Study Visit (Day 14 to 21). During the protocol amendment this was changed to safety laboratory testing to be performed at the End of Confinement (Day 2) and optionally at the Day 8 if required for AE follow up. In the Phase 3 study MS200661-0003 the safety laboratory evaluations were conducted at ~12 h post-dose. The approach taken by the applicant was based on the fact that, the half-life of the study

treatments is short (Biltricide 1 to 2.5 h and L-PZQ 3 h) although it is not fully clear if this observation period is sufficient to capture AEs with late onset.

There is a concern that the product could be used in patients with undiagnosed asymptomatic neurocysticercosis (it is believed that asymptomatic neurocysticercosis is occurring in 50% of patients), which could lead to seizures in these patients. This issue will be monitored post-marketing.

Seizures were not reported in studies performed by the applicant. It is noted that in the product information for racemic praziquantel seizures are listed as adverse drug reactions with unknown frequency. There are limited literature data indicating that there could be an increased risk of seizures not only in case of cysticercosis. A relevant warning was added to the SmPC in this regard.

No cases of arrhythmia were reported in studies performed by the applicant however it is noted that in the product information for racemic praziquantel arrhythmia is listed as an adverse drug reaction with unknown frequency. However, based on discussion provided by the applicant it was agreed that a warning is not warranted. However, all reported cases of cardiac arrhythmias in association with arpraziquantel will be monitored and presented in the next PSUR.

3.6. Effects Table

Effects Table for arpraziquantel for treatment of *S. mansoni* and *S. haematobium*

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Cure rate Cohort 1 4-6 years Cohort 2 2-4 years Cohort 3 3-24 months	Egg eradication *S. mansoni*	% (95% CI)	50 mg/kg L-PZQ 87.8 (79.6, 93.5) 93.1 (77.2, 99.2) 94.4 (72.7, 99.9)	Biltricide Cohort 1 81.3 (67.4, 91.1)	Not powered for comparative efficacy	Phase 3 study
ERRA ERRG Cohort 1 4-6 years	Arithmetic and geometric mean ERRs	% %	99.5 99.7	99.2 99.5		
Cure rate	Egg eradication *S. haematobium* Week 3 Week 5	% (95% CI)	60 mg/kg L-PZQ 86.2 (74.6, 93.9) 94.8 (85.6, 98.9)	none		Phase 3 study
Unfavourable Effects						
Any TEAE		n (%)	L-PZQ 275 (62.2)	Biltricide 101 (59.4)		Pooled Paediatric Studies
Any severe TEAE		n (%)	L-PZQ 8 (1.8)	Biltricide 3 (1.8)		Pooled Paediatric Studies
Any serious TEAE		n (%)	L-PZQ 1 (0.2)	Biltricide 1 (0.6)		Pooled Paediatric Studies
Abdomi-nal pain		n (%)	L-PZQ 45 (10.2)	Biltricide 18 (10.6)		Pooled Paediatric Studies

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Diarrhoea		n (%)	L-PZQ 33 (7.5)	Biltricide 5 (2.9)		Pooled Paediatric Studies
Anaemia		n (%)	L-PZQ 84 (19.0)	Biltricide 42 (24.7)	Overestimated as baseline abnormalities classified as TEAEs	Pooled Paediatric Studies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Since rac-PZQ has been in use for many years and commercial presentations are indicated for use from 4 years of age, the applicant's approach was firstly to select a dose of L-PZQ administered alone as 150 mg tablets to provide comparable systemic exposures to those achieved with racemate in adults (dosed as 1x40 mg/kg). With results indicating that the dose of L-PZQ given alone needed to be higher than that used when given as racemate, the applicant proceeded to a dose-finding study with an efficacy endpoint in PSAC infected with *S. mansoni*. When compared with 3x20 mg/kg or 1x40 mg/kg racemate, it appeared that a dose of at least 45 mg/kg L-PZQ would achieve a broadly comparable CR to the racemate.

For convenience, the target dose used in Phase 3 was 50 mg/kg for *S. mansoni*. This was also the starting dose used for *S. haematobium,* but the dose was later increased to 60 mg/kg due to week 3 CR that suggested that 50 mg/kg may be sub-optimal.

Generally, the findings support use of target doses of 50 mg/kg L-PZQ for treatment of *S. mansoni* and 60 mg/kg for treatment of *S. haematobium* in children aged from 3 months to 6 years. For both species, the CR may be slightly lower in moderate/heavy infections, but this also applies to use of the racemate. For *S. haematobium*, the CR may increase between weeks 3 and 5 post-dose due to clearance times.

In relation to safety, no major concerns were identified in studies MS200661-0003 and MS200661-0005 in children aged 3 months to 6 years. The majority of TEAEs were mild or moderate. The number of severe TEAE reported across studies was small. There were no deaths and serious adverse events were reported in three patients (one case of severe malaria and 2 cases of increased transaminases). There were no major differences in the safety profile of L-PZQ as compared to Biltricide. However, the safety data for use of arpraziquantel in children less than 1 years of age is limited and this is reflected in the SmPC.

3.7.2. Balance of benefits and risks

The balance of benefits and risks is considered to be favourable for arpraziquantel.

3.8. Conclusions

The overall benefit/risk balance of arpraziquantel is positive, subject to the conditions stated in the section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety, and efficacy, the CHMP adopts by consensus a scientific opinion as the benefit-risk balance of arpraziquantel in the treatment of schistosomiasis caused by *Schistosoma mansoni* or *Schistosoma haematobium* in children aged 3 months to 6 years is favourable.

The scientific opinion is subject to the attached product information and the following conditions.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the scientific opinion

- **Periodic Safety Update Reports**

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 14 December 2023.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every six months until otherwise agreed.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Scientific opinion Holder (SOH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.