EU Risk Management Plan (RMP) for Arpraziquantel

Active substance(s) (INN/Trade Name):	**Arpraziquantel**
Name of Company:	**Merck Europe B.V.** **Gustav Mahlerplein 102** **Ito Toren** **1082 MA Amsterdam** **Netherlands** **Telephone +49 61 51-72 0** **Telefax +49 61 51-72 69 14** **e-mail: GlobalDrugSafety@merckgroup.com**
RMP version to be assessed as part of this application:	
RMP version number:	**1.0**
Data lock point for this RMP:	**30 Mar 2023**
Date of final sign-off:	Document signed electronically, see date of eSignature at the end of the document
Rationale for submitting an updated RMP:	Version number of the RMP updated to integer number 1.0 for closing sequence (Procedure no.: EMEA/H/W/0004252/0000). No changes in content compared to version 0.3.
Summary of significant changes in this RMP:	Changes endorsed for RMP version 0.3: Addition of Important Potential Risks: "Seizures in patients with undiagnosed asymptomatic neurocysticercosis" and "Use in patients with undiagnosed acute schistosomiasis". Rewording of missing information "Use in children <1 year of age". Modification in Limitations to Detect Adverse Reactions in Clinical Trial Development Programs to harmonize RMP with Guidance on the format of RMP in the EU – integrated format (EMA/164014/2018).

Signatures

Name: Dr. Sabine Hackel, MD

EEA QPPV

Document signed electronically by the EEA QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved for use in the EEA by the Marketing Authorisation Holder´s QPPV. The electronic signature is available on file.

Name: PPD

PPD

(Contact person for this RMP)

Signature: **Document signed electronically**

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List of Abbreviations

AE	Adverse Event
BCRP	Breast Cancer Resistance Protein
CNS	Central Nervous System
CYP	Cytochrome P450
DDI	Drug-drug Interaction
HIV	Human Immunodeficiency Virus
L-PZQ	Levo-praziquantel
OATP1B1	Organic Anion Transporter Polypeptide 1B1
OATP1B3	Organic Anion Transporter Polypeptide 1B3
OCT1	Organic Cation Transporter 1
P-gp	P-glycoprotein
PSAC	Preschool Aged Children
PT	Preferred term
PV	Pharmacovigilance
PZQ	Praziquantel
rac-PZQ	Racemic Praziquantel
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

Part I: Product(s) Overview

Product(s) Overview

Active substance(s) (INN)	Arpraziquantel
Pharmacotherapeutic group(s) (ATC Code)	Anthelmintics, antitrematodals (ATC Code: P02BA03)
Scientific opinion applicant	Merck Europe B.V. Gustav Mahlerplein 102 Ito Toren 1082 MA Amsterdam Netherlands
Medicinal products to which this RMP refers	Arpraziquantel
Invented name(s) in the European Economic Area (EEA)	Arpraziquantel
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Anthelminthics, antitrematodals
	Summary of mode of action: Arpraziquantel drug substance is the R (−) enantiomer of PZQ. Praziquantel (rac-PZQ) is a racemic mixture of 2 enantiomers, R (−) PZQ (also known as levo-praziquantel or L-PZQ) and S (+) PZQ (also known as dextro-praziquantel or D PZQ), in a 1:1 ratio. The parasiticidal activity of rac-PZQ on Schistosoma worms resides mostly in R (−) PZQ. Rac-PZQ damages the syncytial tegument of the tapeworm at a sensitive site (a proliferation zone in the neck), resulting in disturbed permeability. In addition, rac-PZQ leads to contraction of the parasite musculature, with subsequent spastic paralysis. The mechanism of action of arpraziquantel is identical to that of rac-PZQ.
	Important information about its composition: Arpraziquantel is the drug substance. Other ingredients are mannitol, starch pregelatinized, sodium starch glycolate type A, maize starch, sucralose, silica colloidal anhydrous, sodium stearyl fumarate and vitamin E polyethylene glycol succinate.
Hyperlink to the product information	Arpraziquantel product information (Module 1.3.1)
Indication(s) in the EEA	Current: Arpraziquantel is indicated for the treatment of schistosomiasis caused by *Schistosoma mansoni* or *Schistosoma haematobium* in children aged 3 months to 6 years.
	Proposed: Not applicable.
Dosage in the EEA	Current: Arpraziquantel is to be taken orally after a meal. *S. mansoni* infection: The recommended target dose for arpraziquantel is a single dose of 50 mg/kg body weight. *S. haematobium* infection: The recommended target dose for arpraziquantel is a single dose of 60 mg/kg body weight. The use of arpraziquantel in children with mixed infection (*S. mansoni* and *S. haematobium*) has not been evaluated. However, the recommended dose for *S. haematobium* (60 mg/kg) is expected to be efficacious in these cases.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	Current: Dispersible tablet, 150 mg.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ATC=Anatomical Therapeutic Chemical Code; EEA=European Economic Area; EU=European Union; INN=international nonproprietary name; PI=prescribing information; rac-PZQ=racemic praziquantel; RMP=risk management plan; SmPC=summary of product characteristics

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication

Arpraziquantel (Levo-praziquantel [L-PZQ]) is indicated for the treatment of schistosomiasis caused by *Schistosoma mansoni* or *Schistosoma haematobium* in children aged 3 months to 6 years.

Incidence

Schistosomiasis, or bilharzia, is a tropical disease caused by worms of the genus Schistosoma. The main disease-causing species are *S. haematobium*, *S. mansoni*, and *Schistosoma japonicum* (Cioli 2014). Schistosomiasis remains one of the most prevalent parasitic diseases in developing countries, causing not just human morbidity, but also significant economic and public health consequences. Schistosomiasis is a severe chronic inflammatory disease, endemic in 78 developing countries with moderate to high transmission kinetics in 51 of these countries. The World Health Organization (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 (WHO 2022a, WHO 2022b). Typically, the infection rates increase from an early age to a peak at age 8–15 years and decrease again in adults (Gryseels 2006). There are a paucity of incidence estimates for preschool-aged children (PSAC) (under 6 years) (Osakunor 2018). Within this age group, a small number of individuals carry most of the parasites, indicating that schistosomes are over dispersed (Gryseels 1996).

Prevalence

Estimates show that schistosomiasis infected more than 140 million persons worldwide in 2017 (90% in sub-Saharan Africa) (GBD 2018). The prevalence of schistosomiasis in children is very high, accounting for about 50% of the total infected population, and many more are at risk of the disease (WHO 2018). PSAC are a high-risk group in areas endemic of schistosomiasis. In areas of Mali, Niger, Sudan, Uganda and Zimbabwe, the prevalence of the infection for children aged under 5 years in 2010 ranged from 18% to 63% (WHO 2010). For infants and young children, infection prevalence is closely related to that of the caregiver (Garba 2010). This disassociates as children grow older, become independent, and frequently visit contaminated water sources (Osakunor 2018).

Schistosomiasis is characterized by focal epidemiology and over dispersed population distribution, with higher infection rates in children than in adults. Complex immune mechanisms lead to the slow acquisition of immune protection, although innate factors also play a part. Acute schistosomiasis, a feverish syndrome also called Katayama fever, is mainly seen in nonimmune travelers after primary infection. Chronic schistosomal disease affects mainly individuals with long-standing infections in poor rural areas. Immunopathological reactions against schistosome eggs trapped in the tissues lead to inflammatory and obstructive disease through the development of granulomas in the urinary system (*S. haematobium*) or intestinal disease, hepatosplenic

inflammation, and liver fibrosis (*S. mansoni*) (Gryseels 2006). Published data on age-specific prevalence are rare. An epidemiological survey in an endemic country (Sudan) reported the prevalence of urogenital schistosomiasis and intestinal schistosomiasis in children aged 1 to 6 years (WHO 2010). The age-specific prevalence were 1 to 3 years (32.6%), 3 to 5 years (43.9%), and 5 to 6 years (60.9%) in a village endemic mainly for *S. haematobium*, and 1 to 3 years (18.2%), 3 to 5 years (63.2%), and 5 to 6 years (44.3%) in a village predominantly endemic for *S. mansoni* (WHO 2010).

Mortality

Mortality has been estimated at 280,000 deaths/year in Sub-Saharan Africa, while the overall level of disability caused by schistosomiasis has been re-evaluated and extended to include previously neglected effects of chronic infection like anemia, growth stunting, nutritional status and diminished physical and cognitive fitness (Assis 1998, Ezeamama 2018). The mortality due to schistosomiasis varies between 24,067 and 200,000 deaths globally per year (WHO 2018). There are no data on the overall or the age-specific mortality estimates for schistosomiasis in children aged under 6.

Demographics of the population in the proposed indication and risk factors for the disease

At the World Health Assembly in 2001, Resolution A 54.19 was put forward, which urged endemic countries to start seriously tackling worms, specifically schistosomiasis and soil transmitted helminths, with a global target to treat at least 75% of all school aged children who are at risk of morbidity from schistosomiasis and soil transmitted helminths by the year 2010 (WHA54 R 2001). The WHO roadmap for 2020-2030 has established the target of eliminating schistosomiasis as a public health problem (defined as <1% proportion of heavy intensity infections) by 2030, and one of the strategies for achieving it is extending the Mass Drug Administration to PSAC; for this specific purpose, the arpraziquantel pediatric formulation will play a cornerstone role (WHO 2021).

The main existing treatment options

Since no vaccine exists against schistosomiasis and the mollusks acting as intermediate hosts are not easy to attack, chemotherapy has been the main approach for schistosomiasis control. Praziquantel (PZQ) or racemic-Praziquantel (hereafter referred to as rac-PZQ) was the first anthelminthic drug to fulfill WHO's requirements for treatment of a broad range of parasitic infections. The efficacy of rac-PZQ in the approved indications, treatment of infections due to trematodes (such as schistosomiasis) and cestodes, as well as infections caused by larvae of *Taenia solium* in the central nervous system (CNS; neurocysticercosis), is well-established. Rac-PZQ damages the syncytial tegument of the tapeworm at a sensitive site (a proliferation zone in the neck), resulting in disturbed permeability. In addition, rac-PZQ leads to contraction of the parasite musculature, with subsequent spastic paralysis (Park 2019).

The current standard treatment for schistosomiasis, rac-PZQ, is available for adults and school-aged children. However, these tablets are not suitable for use in younger children due to their size and bitter taste. A formulation suitable for PSAC is not available, and adequate clinical data are lacking in this population. A new treatment based on rac-PZQ, appropriate for children at the age of 3 months to 6 years, would permit accurate dosing and enhanced compliance in these patients, covering a highly unmet medical need.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

There are 3 distinct phases of clinical disease progression: acute infection, established active infection and late chronic infection. Acute schistosomiasis occurs mainly in nonimmune travelers to schistosomiasis-endemic areas after a primary infection; common presenting symptoms are myalgia, abdominal pain in the right upper quadrant, diarrhea (with or without blood), fatigue, malaise, fever and, in case of *S. haematobium* infection, hematuria (blood in urine). Established active and late chronic disease affects mainly individuals from poor rural areas with long-standing infections. In established active and late chronic infections, immunopathological reactions against schistosome eggs trapped in host tissues lead to inflammatory and obstructive disease; the tissues and organs affected depend on the infecting Schistosoma species, as the worms nest in different preferential anatomical locations. Late chronic infection with *S. mansoni*, *S. guineensis*, *S. intercalatum*, *S. mekongi* and *S. japonicum* (which all reside in the mesenteric veins of the bowel) causes intestinal disease, and advanced disease involves the liver and spleen (hepato-splenic schistosomiasis) inducing portal hypertension and its associated consequences in the long-term such as development of ascites, portosystemic shunts that induce hematemesis, as well as liver failure. Late chronic infection with *S. haematobium* (which nests in the pelvic venous plexus) causes urogenital schistosomiasis, which mainly involves lesions of the bladder wall that can progress to bladder cancer, in addition to lesions in the cervix, fallopian tubes and ovaries that lead to infertility. Morbidity is particularly severe in high intensity infections (infections with high worm burden), most importantly with *S. mansoni* and *S. japonicum*. Schistosomiasis is also associated with undernutrition, exercise intolerance (that is, decreased ability to perform physical exercise at what would be considered the normally expected level or duration), diarrhea (sometimes bloody), chronic pain and anemia, and urogenital schistosomiasis may be a factor in the spread of human immunodeficiency virus (HIV) (McManus 2018). Cross-sectional studies showed that *S. mansoni* infection was significantly associated with low levels of hemoglobin (Fetene 2021) and that the prevalence of anemia of inflammation increases with *S. mansoni* infection intensity (Butler 2012).

Important comorbidities

- HIV
- Tuberculosis
- Malaria
- Opportunistic infections (e.g., fungal, or protozoan infections) related to HIV
- Bacteremia and bacteriuria

Schistosomiasis often occurs alongside other infectious diseases, with a wide range of coinfecting organisms. In addition to its direct morbidities, schistosomiasis can affect immunological and physiological relations between the host and coinfecting pathogens. Thus, better control of schistosomiasis could provide adjunctive benefits in such areas. The most compelling example might be the effect of schistosomiasis on susceptibility to HIV infection. Among women with female genital schistosomiasis, the inflammation, friability, and neovascularization of the genital epithelial tissue can lead to a compromised physical barrier to exposure to HIV through sexual activity. In population-based studies, female genital schistosomiasis has been associated with a 3 to 4 times increased risk of HIV infection. This effect is compounded by increased concentrations of CD4-positive cells in semen of men with high intensity *S. haematobium* infection. Furthermore, during active schistosomiasis, CD4-positive cells are more susceptible to HIV infection due to increased concentrations of coreceptors, providing more targets for HIV infection. HIV-positive people who have delayed treatment for schistosomiasis have a more rapid increase of viral load and CD4-positive T-cell loss than those treated early for schistosomiasis. However, a randomized trial detected no significant effect of schistosome or other helminth infection on the length of time before patients with HIV became eligible for antiretroviral therapy. So far, no studies have been done of pediatric HIV and schistosomiasis coinfection, in which perinatally acquired HIV infection would normally precede schistosomiasis (Colley 2014).

Schistosomiasis could also alter the immune responses to coinfecting pathogens, allergens, or vaccines. The immunoregulatory responses during schistosome infection could downregulate T-helper-1-type immune response associated with control of viral or protozoan infections or interfere with immunization. In one of the most studied coinfections, schistosomiasis seems to modulate malaria, but studies have yielded conflicting results. In some studies, malaria prevalence, anemia, and pathological effects are higher in children with schistosomiasis than in children without schistosomiasis, whereas antimalarial immune responses are diminished. However, other studies report either no effect or even a protective effect of schistosome infection on malaria, accompanied by increased immune responses. Schistosome and malaria-related antigens can cross-react to a degree that further complicates the situation. The schistosome species involved could have an important effect - *S. haematobium* could promote protective responses whereas *S. mansoni* increases susceptibility to malaria. This difference could be a result of whether malaria sporozoites pass through a liver micro-environment immunologically affected by *S. mansoni* egg granulomas (Colley 2014). Observational studies conducted between 2016 and 2018 in *S. mansoni* infected school aged children in *S. mansoni* endemic area of Cameroon showed a significant reduction in anti-poliovirus Immunoglobulin G antibodies in comparison to uninfected controls (Musaigwa 2022).

Schistosomiasis perturbs the immune system and increases the risk of tuberculosis progression. A study from Tanzania reported a coinfection with *S. mansoni* in 34% of hospitalized patients with tuberculosis (Range 2007). In addition, observational studies showed that schistosomiasis reduces the host's immune response to the *bacille calmette–guerin* (BCG) vaccine, which has been widely used against *Mycobacterium tuberculosis*, and hence may lower the efficacy of the vaccine (Li 2013).

People with urinary schistosomiasis are vulnerable to bacterial infection when the mucosal barrier is broken down (Kone 2022). Bacterial infection complicates the course of people with urinary schistosomiasis because the otherwise so-called normal flora of the urinary tract has a way of entering and invading the underlying internal tissues due to the regular wear and tear of the epithelium by the spiny Schistosoma eggs.

A prior infection with *Schistosoma* often influences the subsequent infection by a protozoan (e.g., Entamoeba, Leishmania and Toxoplasma), bacterium (e.g., *Helicobacter pylori* and *Staphylococcus aureus*) or another helminth (e.g., Fasciola and Echinostoma) (Abruzzi 2011). There is also an association between schistosomiasis and eumycetoma, a neglected fungal disease that frequently occurs in the tropics (Hellemond 2013). PSAC with indolent schistosomiasis were at higher risk of acquiring pneumonia and severe pneumonia (Mduluza-Jokonya 2020).

In addition, schistosomiasis can negatively impact child development and learning (Ezeamama 2018, King 2020, Mutapi 2021).

Part II: Module SII - Nonclinical Part of the Safety Specification

Key relevant safety findings from nonclinical studies are presented below:

Safety pharmacology

A variety of safety pharmacological tests were conducted with rac-PZQ in different animal species which covered the effects on cardiovascular and renal function, on the CNS and on blood parameter effects. Overall, the oral administration of rac-PZQ had no acute pharmacological safety effects in animals which would suggest a risk for human patients. The central nervous symptoms that occurred at high intravenous doses were considered to be an expression of nonspecific, cerebral intoxication at sublethal doses.

The safety pharmacology endpoints with respect to cardiovascular, respiratory, CNS and renal function were also covered in the repeated-dose toxicity studies in rats and dogs. No prohibitive findings were detected.

In addition, in the clinical studies performed with arpraziquantel, no harmful cardiovascular, respiratory, or CNS effects were detected.

Drug-drug interactions

The potential of arpraziquantel to be a victim or perpetrator of a drug-drug interaction (DDI) has been assessed with in vitro studies.

As a potential victim of a DDI, the major Cytochrome P450 (CYP) isozymes metabolizing arpraziquantel are CYP 1A2, 2C9, 2C19 and 3A4/5 isoforms. Arpraziquantel is not a substrate of efflux transporters P-gp, breast cancer resistance protein (BCRP) or hepatic uptake transporters organic anion transporter polypeptide 1B1 (OATP1B1), organic anion transporter polypeptide 1B3 (OATP1B3) or organic cation transporter 1 (OCT1).

As a perpetrator of DDI, arpraziquantel does not induce CYP1A2 but does induce CYP3A4 in vitro. However, as a single-dose treatment these observations are unlikely to be clinically relevant. The DDI for a theoretical maximum arpraziquantel dose of 1,800 mg (60 mg/kg) through reversible inhibition can be excluded for all CYP isoforms. A clinically relevant time-dependent inhibition by arpraziquantel or trans-4-Hydroxy-arpraziquantel is excluded for CYP isoforms 1A2, 2B6, 2C8, 2C9, and 2C19 and considered unlikely for CYP2D6 and CYP3A4/5. However, the risk of a clinically relevant DDI via transporter inhibition by arpraziquantel could not be excluded for co-administered substrates of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OCT1.

Toxicity

Nonpivotal toxicity studies with rac-PZQ and essential bridging studies on repeat-dose toxicity with arpraziquantel are used to assess the safety profiles of rac-PZQ and arpraziquantel. These studies show a comparable toxicological profile for rac-PZQ and arpraziquantel.

Single-dose toxicity

Single-dose toxicity studies in mice, rats, rabbits, and dogs indicate that the acute toxicity of rac-PZQ is low after single oral, intramuscular, intraperitoneal, or subcutaneous administration. In dogs, a lethal dose could not be established due to the emetic effect of rac-PZQ in this species. The lethal dose (LD_{50}) values were >2,000 mg/kg in all other species tested, irrespective of the route of administration.

Repeat-dose toxicity

Measured parameters in the repeat-dose toxicity studies up to 13 weeks duration in rats and dogs with rac-PZQ included clinical signs, body weight, food consumption, ophthalmology, clinical pathology (hematology, serum chemistry, urinalysis), gross pathology, organ weights and microscopic pathology. Rac-PZQ was well tolerated in all species and did not produce macroscopic or microscopic lesions up to the highest doses tested. Transient signs of vomiting and depressed appetite were seen in dogs. There were no biologically relevant rac-PZQ-related changes in body weights, food consumption, electrocardiography, ophthalmoscopy, or neurological function (in dogs). Increased organ weights at high doses (rat: liver, kidney, spleen, heart, thyroid, and adrenals; dog: liver) were without histological correlate and are not considered to be adverse.

In the pivotal 4-week repeat-dose toxicity study in rats, arpraziquantel and rac-PZQ were compared and showed a comparable toxicological profile. The main findings observed with either compound were slight increases in serum and urinary calcium and serum inorganic phosphorus at the different doses tested. These changes, in the absence of corresponding pathomorphological changes, were not considered toxicologically relevant. Slight increases of liver and thyroid weights were determined in all treatment groups except of the lowest arpraziquantel dose group (15 mg/kg). The thyroid follicular cell hypertrophy/hyperplasia observed with both arpraziquantel and rac-PZQ at the 300 mg/kg is considered an adaptive response due to liver metabolism induction and showed full recovery. These changes, often observed in laboratory animals following repeated administration of a xenobiotic compound, are not considered relevant for the clinical situation of arpraziquantel, where the drug is intended for use as a single oral dose. The no-observed-adverse-effect level (NOAEL) of arpraziquantel and rac-PZQ were considered to be

300 mg/kg/day. The study findings show that the toxicological information available with rac-PZQ can be extrapolated to arpraziquantel.

Since no effects on lymphoreticular tissues were described in the repeat-dose toxicity studies, an adverse effect on the immune system seems to be very unlikely.

Genotoxicity and carcinogenicity

Almost all in vitro and in vivo genotoxicity assays indicate that rac-PZQ lacks mutagenic potential. In one publication, rac-PZQ has been described to act as a weak co-mutagen which increased the mutagenicity of several chemical mutagens and carcinogens in bacteria and in animal cells. In another published study with a questionable design and interpretation of the results, the authors concluded rac-PZQ be a hepatotoxic, genotoxic, and carcinogenic drug.

Long-term studies with weekly oral administration of up to 250 mg/kg in rats and hamsters did not show a carcinogenic potential of rac-PZQ. In a literature study in rats, rac-PZQ at very high doses was concluded to have a hepatocarcinogenesis-promoting potential while in another published study in Syrian hamsters, no such promoting potential for hepatocarcinogenesis was observed.

The genotoxicity and carcinogenicity of rac-PZQ was reviewed by the International Commission for Protection Against Environmental Mutagens and Carcinogens and by the Committee for Veterinary Medicinal Products of the European Agency for the Evaluation of Medicinal Products. Committee for Veterinary Medicinal Products concluded that rac-PZQ is not a mutagenic substance and revealed no treatment-related effects in tumor incidence, latency, and multiplicity. International Commission for Protection Against Environmental Mutagens and Carcinogens concluded that rac-PZQ appears not to present a genotoxic risk to humans exposed to the prescribed once-a-day treatment for different types of schistosomiasis.

In conclusion, rac-PZQ does not present a genotoxic or carcinogenic risk.

Reproductive toxicology

Rac-PZQ did not impair male and female fertility in rats and was not teratogenic in rats and rabbits at doses of up to 300 mg/kg/day. In rabbits, body weight development and food consumption of maternal animals treated with rac-PZQ were lower as compared to controls. In a peri postnatal study, rac-PZQ did not negatively affect the development of the conceptus and the offspring until sexual maturity when administered in daily oral doses to pregnant/lactating Wistar rats from closure of the hard palate through weaning. The offspring of these rats were raised without treatment, paired and their progeny F1 raised for 28 days. No adverse effects on the reproductive ability of the F1 generation as well as on the development of the F2 generation were seen.

Juvenile toxicity

The results obtained from toxicity studies with rac-PZQ, including 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 pediatric population.

Other toxicity-related information or data

Rac-PZQ did not show any sensitizing properties in Guinea pigs and humans.

In vitro, arpraziquantel has lower cytotoxicity than S-(+)-PZQ and similar cytotoxicity as rac-PZQ.

Nitroso-praziquanamine has been identified as a drug substance related impurity in the drug product. According to the results of a good laboratory practice-compliant Bacterial Reverse Mutation Assay (Ames Test), nitroso-praziquanamine was mutagenic in TA1535 in the presence of 30% hamster S9 in the preincubation setting at a concentration of 2,000 µg/plate. An acceptable intake for nitroso-praziquanamine of 1,500 ng/day was established by EMA. The content of this impurity is controlled at the drug substance and drug product level and no additional risk is foreseen.

Overall, the nonclinical safety information available with rac-PZQ and arpraziquantel suggests no anticipated safety concerns regarding the use of arpraziquantel in the targeted pediatric population at an age of 3 months to 6 years infected with Schistosoma.

Part II: Module SIII - Clinical Trial Exposure

In total, 732 pediatric participants aged 3 months to 6 years were included in the pooled Safety Analysis Population across the Phase 2 (MS200661-0005) and Phase 3 (MS200661-0003) studies, including 442 participants who received at least one dose of arpraziquantel (Table 1). The other 290 participants received either Biltricide® or other rac-PZQ products. Treatment compliance was 100% in 442 participants who received arpraziquantel, 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. L-PZQ 50 mg/kg was selected from Part 1 of the MS200661-0005 study for the Part 2 (24 months or younger) and for the initial dose of MS200661-0003 study.

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

Table 1 Study Intervention Exposure (Safety Analysis Population)

	L-PZQ (mg/kg)				
Category Statistic	**30 (n=60)**	**45 (n=60)**	**50 (n=202)**	**60 (n=120)**	**Total (n=442)**
Actual dose received (mg/kg)					
n (%)	60 (100.0)	60 (100.0)	202 (100.0)	120 (100.0)	442 (100.0)
Mean ± SD	30.14 ± 2.84	45.55 ± 2.80	51.43 ± 4.78	61.92 ± 4.25	50.59 ± 10.63
Median	30.51	45.32	50.97	61.70	50.97
Q1; Q3	28.04; 32.35	43.12; 48.04	47.47; 55.26	58.46; 64.29	45.45; 58.33
Min; Max	24.2; 35.2	40.8; 50.4	40.0; 61.8	54.0; 75.0	24.2; 75.0

L-PZQ (mg/kg)					
Category Statistic	**30 (n=60)**	**45 (n=60)**	**50 (n=202)**	**60 (n=120)**	**Total (n=442)**
Total dose received (mg)					
n (%)	60 (100.0)	60 (100.0)	202 (100.0)	120 (100.0)	442 (100.0)
Mean ± SD	480.0 ± 106.2	720.0 ± 122.9	779.7 ± 224.0	1,062.5 ± 241.8	807.7 ± 275.4
Median	450.0	750.0	750.0	1,050.0	750.0
Q1; Q3	450.0; 600.0	600.0; 750.0	600.0; 1,049.9	900.0; 1,200.0	600.0; 1,050.0
Min; Max	300; 750	450; 1050	300; 1350	600; 1950	300; 1950

L-PZQ=levo-praziquantel; SD=standard deviation

Demographics and baseline characteristics for the Safety Analysis Population are summarized in Table 2. All (100%) participants were Black or African American. In each group, overall, most participants were within the age range of 4 to ≤6 years and most had a light infection at baseline (64.9%). As stated above, L-PZQ 50 mg/ was the selected formulation/dose from MS200661-0005 study Part 1 to be used in Part 2 and in the MS200661-0003 study, therefore, this dose group had the highest proportion of children 3 to 24 months (20.3%) compared with other groups.

Table 2 Demographics and Other Baseline Characteristics (Safety Analysis Population)

L-PZQ (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 species, n (%)					
S. mansoni	60 (100.0)	60 (100.0)	172 (85.1)	60 (50.0)	352 (79.6)
S. haematobium	0	0	30 (14.9)	60 (50.0)	90 (20.4)
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)

L-PZQ (mg/kg)					
Category Statistic	**30 (n=60)**	**45 (n=60)**	**50 (n=202)**	**60 (n=120)**	**Total (n=442)**
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

BMI=Body Mass Index; L-PZQ=Levo-praziquantel; SD=standard deviation

a "6 years" includes participants who are aged 6 years and 11 months.

b Light infection: 1−99 eggs/gram of feces for *S. mansoni* infection, or 1−49 eggs/10 mL of urine for *S. haematobium* infections. Moderate/Heavy infection: ≥100 eggs/gram of feces for *S. mansoni* infection, or ≥50 eggs/10 mL of urine for *S. haematobium* infections.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 3 Exclusion Criteria in the Pivotal Clinical Studies Across the Development Program

Exclusion criteria	Reason for exclusion	Missing information Yes/No (If no rationale)
Children <3 months and above 6 years.	Standard inclusion criteria for clinical studies in preschool aged children aged 3 months to 6 years only.	No/ Not relevant for the treatment of the target population in clinical practice.
Mixed *S. mansoni and S. haematobium* infections.	Aim was to investigate efficacy and safety of L-PZQ in *S. mansoni* or *S. haematobium* infected children.	No/ To get a clear data with respect to efficacy and safety of L-PZQ in *S. mansoni* or *S. haematobium* infected children, the patients with only a single schistosomal infection were included in the study. As per SmPC Section 4.2 "Posology and method of administration" the recommended dose for *S. haematobium* (60 mg/kg) is expected to be efficacious in mixed infection cases, which covers the risk and its management.

Exclusion criteria	Reason for exclusion	Missing information Yes/No (If no rationale)
History of hypersensitivity to PZQ or any of the excipients.	Standard exclusion criteria in clinical studies.	No/ SmPC Section 4.3 "Contraindications" covers the risk and its management.
Any predefined medical conditions, like: • Participants with seizures and/or medical history of seizures and/or other signs of potential CNS involvement • Participants with known cysticercosis, or with signs or symptoms (e.g., subcutaneous nodules) suggestive of cysticercosis.	• Avoid factors that may confound understanding of arpraziquantel's safety profile. • In rare individual cases with coexisting neurocysticercosis, convulsions have occurred with rac-PZQ treatment. Symptoms present due to the increased intracranial pressure caused by the disease may be temporarily intensified during the treatment with rac-PZQ due to the inflammation developed by the host in response to the killing of *Taenia solium cysticerci*.	No/ SmPC Sections 4.3 "Contradictions" and 4.4 "Special warnings and precautions for use" cover the risk and its management.
Protocol defined concomitant treatment within 2 weeks prior to enrollment with medication that might have affected the metabolism of PZQ, such as certain antiepileptics (e.g., carbamazepine or phenytoin), glucocorticosteroids (e.g., dexamethasone), chloroquine, rifampicin, or cimetidine.	Concomitant administration of strong cytochrome P450 inducers, such as rifampicin, carbamazepine, and phenytoin, is contraindicated as therapeutically effective plasma levels may not be achieved (effects of arpraziquantel may be reduced). Concomitant administration of other moderate cytochrome P450 inducers, for example, systemic dexamethasone, may also reduce plasma concentrations of arpraziquantel (effects of arpraziquantel may be reduced).	No/ SmPC Sections 4.3 "Contradictions" and 4.5 "Interaction with other medicinal products and other forms of interaction" cover the risk and its management.
Fever, defined as temperature >37.5°C axillary or oral.	Standard exclusion criteria in clinical studies.	No/ SmPC Section 4.8 "Undesirable effects" states pyrexia as expected adverse reaction.

CNS=central nervous system; PZQ=praziquantel; rac-PZQ=racemic praziquantel; SmPC=summary of product characteristics

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

In total, 732 pediatric participants aged 3 months to 6 years were included in the pooled Safety Analysis Population across the Phase 2 and Phase 3 studies, including 442 participants who received a dose of arpraziquantel. The ability to detect rare adverse reactions is therefore limited.

Considering arpraziquantel's short half-life and single dose recommendation, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure seem to be not relevant.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 4 Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure
Children	Children aged 3 months to 6 years were included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	**Patients with hepatic impairment:** Data with rac-PZQ indicates that caution is warranted in patients with severe hepatic insufficiency or in patients with hepatosplenic schistosomiasis. Due to reduced drug metabolization in the liver, considerably higher and sustained plasma concentrations of unmetabolized arpraziquantel may occur, leading to a prolonged plasma half-life. In such cases, treatment should be carried out on an inpatient basis. **Patients with renal impairment:** After oral administration, rac-PZQ is extensively metabolized and approximately 80% of drug related material is excreted via the kidneys. Excretion might be delayed in patients with impaired kidney function.

L-PZQ=levo-praziquantel; rac-PZQ=racemic praziquantel.

Part II: Module SV – Post Authorisation Experience

Not applicable.

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Arpraziquantel has no known potential for illegal purposes, e.g., as a recreational drug or to facilitate assault.

Potential for transmission of infectious agents

Not applicable.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

No important identified risks so far.

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.

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Treatment during intraocular cysticercosis

Convulsions have occurred during rac-PZQ treatment in patients with coexisting cysticercosis. The increased intracranial pressure caused by neurocysticercosis may be temporarily intensified during treatment with rac-PZQ due to the host inflammatory response to destruction of *Taenia solium* cysticerci. Another manifestation of cysticercosis is, intraocular cysticercosis, presenting with visual impairment and ocular inflammation depending on the location of the cyst. In eye, *T. solium* can affect any part from eyelids, conjunctiva, anterior chamber, uvea, vitreous, retina, extraocular muscles to even optic nerve (Pushker 2001). Coinfection of neurocysticercosis and intraocular cysticercosis is a common presentation in clinical practice. The diagnosis of intraocular cysticercosis has special importance due to high risk of visual impairment. The possible mechanism of visual loss can be due to either compression from enlarging cyst or inflammatory reaction to cyst wall and toxic material released from dying cyst (Rath 2010).

Early surgical excision of intraocular cysticercosis cyst was the treatment of choice (Steinmetz 1989). If there is coinfection with intraocular and intracranial cysticercus, the complete intraocular cyst must be removed completely by surgery before anthelminthic treatment is started as lysis and degeneration of the cyst may induce further intraocular inflammatory reactions and result in loss of vision. (Natarajan 1999, Jain 2015)

As per the Summary of Product Characteristics (SmPC) in Section 4.3 arpraziquantel is contraindicated in patients with “known or suspected cysticercosis” and as per Section 4.4 there is a special warning and precaution. Another manifestation of cysticercosis is intraocular cysticercosis presenting with visual impairment and ocular inflammation depending on the location of the cyst. The intraocular cyst must be removed by surgery before anthelminthic treatment is started as lysis and degeneration of the cyst may induce further intraocular inflammatory reactions and result in loss of vision.”

Reason for not including an identified or potential risk in the list of Safety Concerns in the RMP:

The above risk requires no further characterization. It is adequately communicated via routine risk minimization activities within the SmPC and Package Leaflet.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important potential risk 1

- **Seizures in patients with undiagnosed asymptomatic neurocysticercosis**

The anthelminthic treatment may disrupt the usual stable, noninflammatory host–parasite relationship, initiating an acute immune response, which has been attributed to inflammation secondary to killing of the cysticerci. As all parasites are affected at the same time, clinical deterioration is frequent (Del Brutto 2014, Fogang 2015).

Benefit-risk impact

There may be a risk of seizures in patients with a medical history of seizures or other CNS disorders. Hence, patients with history of seizures and with other CNS symptoms, cysticercosis should be ruled out first before commencing the treatment with arpraziquantel. The risk of arpraziquantel "Seizures in patients with undiagnosed asymptomatic neurocysticercosis" is unlikely to impact the benefit-risk balance of arpraziquantel. (Section SVII.3.1.1.1).

Important potential risk 2

- **Use in patients with undiagnosed acute schistosomiasis**

Racemic praziquantel is not effective during acute schistosomiasis due to lack of activity against migrating schistosomulae.

The use of racemic praziquantel in the acute phase of schistosomiasis may be associated with clinical deterioration (paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions). These reactions may lead to potentially life-threatening events (e.g. respiratory failure, encephalopathy, myocarditis and/or cerebral vasculitis). The risk for these reactions may be higher in non-immune travelers.

Benefit-risk impact

The reactions predominantly occurring in patients treated during the acute phase of schistosomiasis could potentially be severe or life-threatening. The benefit of arpraziquantel for treating schistosomiasis is considered to outweigh the risk of reactions. The risk of arpraziquantel "Use in patients with undiagnosed acute schistosomiasis" is unlikely to impact the benefit-risk balance of arpraziquantel (Section SVII.3.1.1.2).

Missing information 1

- **Use in patients with impaired kidney function**

After oral administration, rac-PZQ is extensively metabolized and approximately 80% of drug-related material is excreted via the kidneys (Patzschke 1979); thus, the same is hypothesized for arpraziquantel. Delayed excretion is to be expected in patients with impaired kidney function.

Benefit-risk impact

Since no participant with impaired kidney function was included in the study, the impact of arpraziquantel in children with impaired renal function is unknown, although no child experienced kidney impairment during the study and accumulation of arpraziquantel is not expected. Therefore, this topic has been classified as missing information in the list of safety concerns (Section SVII.3.2.1).

Missing information 2

- **Use in patients with hepatic impairment**

Due to reduced drug metabolization in the liver, considerably higher and sustained plasma concentrations of unmetabolized arpraziquantel may occur, leading to a prolonged plasma half-life. In such cases, treatment should be carried out on an inpatient basis.

Benefit-risk impact

Since no participant with liver dysfunction was included in the study therefore, the impact of arpraziquantel in these children is unknown, although no child experienced hepatic impairment during the study. Therefore, this topic has been classified as missing information in the list of safety concerns (Section SVII.3.2.2).

Missing information 3

- **Use in children <1 year of age**

The safety data for use of arpraziquantel in children <1 year of age was limited to 7 children. Based on all available safety data it was confirmed that the adverse reaction profile is similar across all age groups and no safety issue was observed during the clinical development.

Benefit-risk impact

Since a limited number of participants (N=7) of this age group were exposed to arpraziquantel, the impact of arpraziquantel use in children <1 year of age is also limited, although no child experienced any severe TEAE, and no major safety concern was identified. Therefore, this topic has been classified as missing information in the list of safety concerns (Section SVII.3.2.3).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

No important identified risks so far.

SVII.3.1.1 Important Potential Risks

SVII.3.1.1.1 Seizures in Patients with Undiagnosed Asymptomatic Neurocysticercosis

Potential mechanisms

The anthelminthic treatment may disrupt the usual stable, noninflammatory host–parasite relationship, initiating an acute immune response, which has been attributed to inflammation secondary to killing of the cysticerci. As all parasites are affected at the same time, clinical deterioration is frequent (Del Brutto 2014, Fogang, 2015).

Evidence source(s) and strength of evidence

Epilepsy is the most common symptom of neurocysticercosis, mainly when the location is in the parenchyma (Sierra 2017). Two retrospective studies found marked improvement in the associated seizure disorders among patients with parenchymal neurocysticercosis in favor of anthelminthic treatment using praziquantel and albendazole (Vazquez 1992, Brutto 1992). A randomized controlled study in 1995, by contrast, showed no difference in the proportion of patients free of seizures during the entire follow-up period treated with albendazole, praziquantel, or corticosteroids alone (Carpio 1995). Later, multiple randomized studies of anthelminthic treatment in viable parenchymal neurocysticercosis consistently demonstrate that antiparasitic treatment decreases the burden of parasites and results in fewer seizures relapse, making antiparasitic treatment a preferred approach in most neurocysticercosis cases (Garcia 2004, Garcia 2014). Studies focusing on undiagnosed and asymptomatic neurocysticercosis are lacking.

Characterization of the risk

Clinical studies of arpraziquantel did not include participants with seizures and/or medical history of seizures, other signs of potential CNS involvement, or participants with known cysticercosis or signs/symptoms (e.g., subcutaneous nodules) suggestive of cysticercosis. Two participants in the arpraziquantel group had a medical history of seizures (Phase 2 study MS200661-0005) or other signs of CNS involvement, but no participant had experienced a CNS event during the studies.

Risk factors and risk groups

Neurocysticercosis is a major cause of acquired epilepsy in most of the developing world and has been considered as the single cause explaining the increased incidence and prevalence of epilepsy in these regions (Blocher 2011, Carabin 2011, Del Brutto 2005, Medina 2005, Preux 2005,

Villaran 2009, Del Brutto 2014). Seizures may occur at any stage of cysticerci involution within the brain parenchyma, from viable cysts to calcifications. Unhygienic practices resulting in ingestion of *T. solium* eggs directly from a Taenia carrier, or less often by contaminated food, are causal factors for cysticercosis. Neurocysticercosis is common where there is clustering of conditions favoring the transmission of *T. solium*, including low level of education, poverty, deficient disposal of human feces, slaughtering of pigs without veterinary control, and presence of free-roaming pigs around households.

Most factors associated with seizures in neurocysticercosis are similar to those in other epilepsies, including number of prior seizures, length of seizure-free period and length of using antiepileptic drugs before withdrawal (Nash 2004, Brutto 1994, Herrick 2020). Therapy with the cysticidal drug albendazole, disrupting the stable neurocysticercosis disease due to secondary inflammation, is an additional risk factor (Nash 2011).

Preventability

Arpraziquantel is contraindicated in children with known or suspected cysticercosis.

Seizures have occurred during rac-PZQ treatment in patients with coexisting cysticercosis. The increased intracranial pressure caused by neurocysticercosis may be temporarily intensified during treatment with rac-PZQ due to the host inflammatory response to destruction of *Taenia solium cysticerci*.

Patients with seizures and/or a medical history of seizures and/or other signs of potential CNS involvement can be treated with arpraziquantel, but there is an increased risk for seizures and an undiagnosed asymptomatic neurocysticercosis should be ruled out before commencing the treatment with arpraziquantel.

Any early symptoms suggestive of seizures in patients with co-existing neurocysticercosis should be investigated and if conclusive, corticosteroid therapy may be initiated along with medications to prevent or alleviate seizures that have commenced.

Impact on the benefit-risk balance of the product

There may be a risk of seizures in patients with a medical history of seizures or other CNS disorders. Hence, patients with history of seizures and with other CNS symptoms, cysticercosis should be ruled out first before commencing the treatment with arpraziquantel. The risk of arpraziquantel “Seizures in patients with undiagnosed asymptomatic neurocysticercosis” is unlikely to impact the benefit-risk balance of arpraziquantel.

Public health impact

If treated appropriately, the seizures in patients with co-existing neurocysticercosis should resolve. If untreated, the seizures may progress to a life-threatening condition and the underlying neurocysticercosis may further deteriorate. The prognosis of epilepsy depends on multiple factors related to degree of infection and host response to parasite. Nearly 85% of patients with a solitary cerebral cysticercus granuloma have a favorable seizure outcome following resolution of the lesion, but the prognosis of epilepsy in patients with multiple cysts and residual calcifications is

not as benign. However, given that no participant had a CNS event during the studies, there is no relevant impact on public health.

SVII.3.1.1.2 Use in Patients with Undiagnosed Acute Schistosomiasis

Potential mechanisms

Rac-PZQ is not effective against migrating schistosomulae. Accordingly, rac-PZQ is ineffective during acute schistosomiasis.

In addition, the use of rac-PZQ in the acute phase of schistosomiasis may be associated with clinical deterioration (paradoxical reactions, serum sickness, Jarisch-Herxheimer-like reactions). These reactions may lead to potentially life-threatening events (e.g. respiratory failure, encephalopathy, myocarditis and/or cerebral vasculitis). The risk for these reactions may be higher in non-immune travelers.

Evidence source(s) and strength of evidence

No studies were found reporting the burden and risk of undiagnosed acute schistosomiasis in PSAC.

Characterization of the risk

Acute schistosomiasis (Katayama syndrome/fever) is a systemic hypersensitivity reaction to the migrating schistosomula that occurs a few weeks to months after a primary infection. Most persons recover spontaneously from the acute stage after 2 to 10 weeks, but some develop a persistent and more serious disease (Gryseels 2006).

Acute schistosomiasis is rarely reported in people living in endemic regions who are repeatedly exposed to schistosomes. This trend might reflect a chronic immunomodulation by repeated schistosome exposure. Maternal infection may already sensitise the foetus to schistosome antigens in utero, altering the developing immune system so that on exposure to cercariae, pre-existing polarised immunity modulates the inflammatory response (Freer 2018).

Diagnosis of schistosomiasis in young children is problematic as there is no “gold-standard” diagnostic test. The detection of infections in PSAC is somewhat different to older children as the adult worm pairs are themselves maturing into full fecundity, so egg detection methods perform poorly having a significant time-delay lagging the patency of either antibody or antigen methods (Poole 2014).

If untreated, schistosomiasis can persist for years, and chronic infection can lead to an increased risk of liver fibrosis or bladder cancer. Antiparasitic treatment is recommended even in cases of probable diagnosis because of the variable performance of the tools available to confirm schistosomiasis diagnosis and the risks associated with delayed treatment. This approach is possible due to the efficacy of PZQ and its good safety profile (Comelli 2023).

Several published articles reported on the use of praziquantel in SAC and PSAC with acute schistosomiasis:

- Alqahtani (2017) conducted a retrospective case series including 9 school aged children (SAC) who were diagnosed with acute intestinal schistosomiasis. Infected children were treated with PZQ oral dose of 20 mg/kg every 8 hours for a day, and none of these children presented late complications of schistosomiasis after 3 months of follow up.
- Cavalcanti (2021) followed a group of 7 children (a toddler, 5 PSAC and one pre-adolescent) with acute schistosomiasis clinical manifestations for 2 years after treatment. The long-term follow-up after treatment with 3 doses of PZQ (80 mg/kg/dose), showed high cure rates (CR) as demonstrated by the DNA-based assay as well as reduced levels of side effects. The results suggest that high dose and repeated treatment with PZQ might be effective for AS in young children. The author's results suggest that an anti-helminthic drug regimen including a high dose of PZQ (80 mg/kg) and more than a single oral dose might be efficient to treat acute schistosomiasis in the pediatric and adolescent group.
- Namwanje (2011) conducted a randomized clinical trial in Uganda to determine the safety of PZQ alone or in combination with mebendazole in the treatment of *S. mansoni* and soil-transmitted helminthiasis in children aged 1 to 4 years. The overall prevalence of S. mansoni was 21.8% (130 over 596 children included). The age distribution was as following: N=6 for 1-year-old; N=11 for 2-year-old; N=32 for 3-year-old and N=81 for 4-year-old). Of these 130 children, 19.2% (25) had heavy infections, 20.8% (27) had moderate infections, while 60.0% (78) were lightly infected. No serious adverse events were reported or observed after treatment. PZQ with or without mebendazole was well tolerated in small children in the study area.
- Mutapi (2015) demonstrated that children as young as 4 months mounted schistosome-specific antibody responses. These studies showed that children aged 5 years were already immunologically primed to kill parasites damaged by PZQ and that immune-compromisation did not affect PZQ efficacy.

The first infection event in most endemic areas occurs early at the pre-school age, but to date, no specific studies in PSAC with acute schistosomiasis have been published. In studies of SAC, protective immunity against schistosomiasis is characterized by a dynamic shift in the balance between effector and regulatory (humoral and cellular) immune responses, with effector responses surpassing the regulatory responses as infection progresses (Osakunor 2018).

Clinical studies of arpraziquantel did not include participants with undiagnosed acute schistosomiasis. No event of sudden inflammatory immune response suspected to be caused by the release of schistosomal antigens (due to undiagnosed acute schistosomiasis) has been reported.

Risk factors and risk groups

Acute schistosomiasis is a toxemic and allergic reaction to the migrating and maturing larvae of Schistosoma. It is also known as Katayama syndrome/fever and mainly seen in nonimmune individuals after their first exposure to schistosomes.

In most cases, especially in people living in endemic areas, symptomatic acute schistosomiasis is not observed, and the disease reaches a stage of established active infection, with mature adult worms and well-established egg production (McManus 2018).

In schistosome-endemic areas, a significant amount of the exposure to infection in PSAC is passive (i.e., use of contaminated water at home or children being bathed/sitting in a basin of fresh water while the guardian performs domestic chores), particularly in the youngest children. Exposure becomes more active as the children grow (e.g., accompanying caregivers to water sources for domestic chores). Therefore, in the early years of infants and young children, exposure to infection is closely linked to that of the caregiver. This disassociates as children grow older, become independent, and frequently visit contaminated water sources with friends and/or older siblings (Osakunor 2018).

Preventability

Early care for and attention in PSAC may provide an opportunity to treat schistosomiasis-associated anemia, reduce occult blood loss and reduce inflammatory responses. Treatment of schistosomiasis has the dual benefit of treating inflammation due to infection and maximizing the efficacy of childhood vaccinations. Early treatment of children in Schistosoma-endemic regions may therefore enhance downstream benefits of vaccine programmes, improve educational attainment and cognitive ability, as well as improve overall health outcomes (Mdulaza 2017).

The use of arpraziquantel may theoretically be associated with deterioration of the patient's medical condition with symptoms similar to an allergic reaction mainly in the acute phase of schistosomiasis (where the worms begin to produce eggs). This could lead to potentially life-threatening events such as lung failure, encephalopathy (brain disease), and/or cerebral vasculitis (inflammation of blood vessels in the brain).

To prevent such scenario the use of arpraziquantel is contraindicated in patients with known or suspected acute schistosomiasis. Patients with symptoms such as skin lesions (pruritus, skin eruption), fever, cough, abdominal pain and diarrhea should not be treated with arpraziquantel.

Impact on the benefit-risk balance of the product

The reactions predominantly occurring in patients treated during the acute phase of schistosomiasis could potentially be severe or life-threatening. The benefit of arpraziquantel for treating schistosomiasis condition is considered to outweigh the risk of reactions predominantly occurring during the acute phase of schistosomiasis that can be managed in clinical practice.

No participant had an event due to undiagnosed schistosomiasis during the clinical studies of arpraziquantel.

The risk of arpraziquantel "Use in patients with undiagnosed acute schistosomiasis" is unlikely to impact the benefit-risk balance of arpraziquantel.

Public health impact

If appropriate diagnosis of acute schistosomiasis is performed, a precise treatment and dose can be given to the patient which can reduce the transmission of schistosomiasis to others in endemic areas, can improve the affected patient's quality of life by alleviation of symptoms such as fever and abdominal pain, and prevent the progression of acute schistosomiasis to the chronic form of

the disease, which can cause severe organ damage. However, if acute schistosomiasis remains undiagnosed, the arpraziquantel treatment could lead to potentially life-threatening events such as lung failure, encephalopathy (brain disease), and/or cerebral vasculitis (inflammation of blood vessels in the brain). However, given that no participant had an event due to undiagnosed acute schistosomiasis during the studies, there is no relevant impact on public health.

SVII.3.2 Presentation of the Missing Information

SVII.3.2.1 Use in Patients with Impaired Kidney Function

Evidence source

After oral administration, rac-PZQ is extensively metabolized and approximately 80% of drug-related material is excreted via the kidneys (Patzschke 1979); thus, the same is hypothesized for arpraziquantel. More than 80% of administered rac-PZQ and its metabolites are excreted in urine within 4 days and more than 90% of the renal excretion occurs within the first 24 hours. Delayed excretion is to be expected in patients with impaired kidney function. However, accumulation of unchanged drug is not expected.

The number of children with a medical history of renal and urinary disorders, specifically considering hematuria, was 1.4% among L-PZQ treated participants, and the number of individual PTs TEAEs within the System Organ Class of “Renal and urinary disorders” was 3.4%. Nephrotoxic effects are not known.

Anticipated risk/consequence of the missing information

Patients with impaired kidney function are expected to have delayed metabolic clearance and increased exposure to arpraziquantel. The efficacy and safety of arpraziquantel is unknown in this population as patients with active or a history of any impaired kidney function were excluded from the clinical studies. Therefore, no dosage recommendation can be made for arpraziquantel in patients with renal impairment.

SVII.3.2.2 Use in Patients with Hepatic Impairment

Evidence source

Arpraziquantel is rapidly metabolized by the cytochrome P450 enzyme system and undergoes a high first pass effect in the liver. Trans-4-hydroxy-arpraziquantel (major metabolite) has weak in vitro activity against *S. mansoni* and *S. haematobium* and may contribute to clinical activity.

Anticipated risk/consequence of the missing information

Due to reduced drug metabolization in the setting of decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis, higher and sustained plasma concentrations of unmetabolized arpraziquantel may occur, leading to a prolonged plasma half-life. Hence, treatment should be conducted on an inpatient basis.

In clinical studies of arpraziquantel, participants with pre-existing hepatic insufficiency were excluded based on exclusion criteria. Participants' liver function test results were monitored, and no important liver-associated safety signals were identified in the Safety Analysis Population. Arpraziquantel should be used with caution in patients with severe hepatic insufficiency and in patients with hepatosplenic schistosomiasis as no data are available.

SVII.3.2.3 Use in Children <1 Year of Age

Evidence source

During the clinical development program, a total of 7 children <1 year of age were exposed to arpraziquantel.

In Part 2 of the Company-sponsored clinical study MS200661-0005, a total of 4 infant participants (age ranging from 5 to 11 months) received arpraziquantel treatment. PPD

In the Company-sponsored clinical study MS200661-0003, a total of 3 infant participants (age ranging from 4 to 11 months) received arpraziquantel treatment. PPD

No cases were retrieved from the cumulative search of the Company safety database concerning use in children <1 year of age.

Overall, the reported safety data are in line with the known safety profile of arpraziquantel and the benefit-risk balance remains positive and unchanged. Routine PV activities are considered sufficient for monitoring of safety related to arpraziquantel use in children <1 year of age.

Based on the guideline EMEA/CHMP/EWP/147013/2004 efficacy and safety of a product can be influenced by the age of children.

Children show rapid developmental changes in absorption, distribution, metabolism, and excretion, and it is important to consider that there may be large pharmacokinetic and pharmacodynamics differences among preterm infants and within infants over time, depending on their gestational or postconceptional age (gestational age + postnatal age).

Factors such as gestational age, postnatal age, birth and body weight, renal function, S-albumin, concomitant medication, other diseases, etc., influence the pharmacokinetic in pediatric population. Particularly the pharmacokinetic in children aged <1 year is the least predictable within this group (guideline EMEA/CHMP/EWP/147013/2004).

Thus, every drug, including arpraziquantel, may present with a different efficacy and safety profile in children <1 year age.

The safety data for use of arpraziquantel in children <1 year of age was limited to 7 children. Based on all available safety data it was confirmed that the adverse reaction profile is generally similar

across all age groups and no safety issue was observed during the clinical development. There is in general a paucity of studies and quality data assessing the safety and efficacy of PZQ in this age group (Keiser 2011). Very few articles were published in the literature about the safety of anthelminthics including PZQ in children <1 year of age are presented below:

A study assessed parasitological cure and putative side effects in a prospective cohort of *S. mansoni* infected children (aged 5 months to 7 years old) in lakeshore settings of Uganda. The findings show that PZQ treatment of young children resulted in satisfactory cure rates, and marked reduction in egg-output, with only mild and transient reported side effects (Sousa-Figueiredo 2012).

An interventional study assessed the safety and efficacy of PZQ syrup (Epiquantel®) in 243 PSAC in 3 villages of Niger, thereof, 21 (12.7%) aged between 1 to 23 months. No serious AEs were observed throughout the study. The overall proportion of children experiencing at least 1 AE after treatment was 34.2%. Most of the AEs occurred within 4 h after drug administration (32.5%), while the proportion of AEs 24-h post treatment was considerably lower (6.2%). There was no difference in the occurrence of AEs in relation to age ($\chi 2=0.11$, $p=0.991$ for the occurrence of at least 1 AE). The most common AE was abdominal pain (30.6%), followed by bloody diarrhea (16.2%) and sleepiness (15.3%). The proportion of children vomiting was 7.1%. Three out of the 18 reported bloody diarrheal episodes occurred within 4 h post treatment, as reported to the study physician. Thirteen children reported fever, all occurring within the first 4 h post-treatment (Garba 2013).

Anticipated risk/consequence of the missing information

The metabolism changes, particularly in age group with age <1 year. Thus, there is an increased risk for AEs in this age group.

Part II: Module SVIII – Summary of the Safety Concerns

Table 5 Summary of Safety Concerns

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

Part III: Pharmacovigilance Plan (Including Post Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities will be applied throughout to manage the safety of arpraziquantel:

Specific adverse reaction follow-up questionnaires:

Specific adverse reaction follow-up questionnaires are not planned.

Other forms of routine pharmacovigilance activities:

Other forms of routine pharmacovigilance activities are not planned.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimization Plan (Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1 Routine Risk Minimization Measures

Table 6 Description of Routine Risk Minimization 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 Sections 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.

SmPC=summary of product characteristics

V.2 Additional Risk Minimization Measures

Not applicable.

V.3 Summary of Risk Minimization Measures

Table 7 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Seizures in patients with undiagnosed asymptomatic neurocysticercosis	Routine Risk Minimization Measures: • *SmPC Section 4.4* • *Package Leaflet Section 2* Additional Risk Minimization Measures: *None*	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: *None* Additional Pharmacovigilance Activities: *None*
Use in patients with undiagnosed acute schistosomiasis	Routine Risk Minimization Measures: • *SmPC Section 4.3 and 4.4* • *Package Leaflet Section 2* Additional Risk Minimization Measures: *None*	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: *None* Additional Pharmacovigilance Activities: *None*
Use in patients with impaired kidney function	Routine Risk Minimization Measures: • *SmPC Sections 4.2 and 5.2* Additional Risk Minimization Measures: *None*	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: *None* Additional Pharmacovigilance Activities: *None*
Use in patients with hepatic impairment	Routine Risk Minimization Measures: • *SmPC Sections 4.2 and 4.4* • *Package Leaflet Section 2* Additional Risk Minimization Measures: *None*	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: *None* Additional Pharmacovigilance Activities: *None*
Use in children <1 year of age	Routine Risk Minimization Measures: • *SmPC Section 4.2* • *Package Leaflet Section 2* Additional Risk Minimization Measures: *None*	Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: *None* Additional Pharmacovigilance Activities: *None*

SmPC=summary of product characteristics

Part VI: Summary of the Risk Management Plan

Summary of the risk management plan (RMP) for Arpraziquantel

This is a summary of the RMP for arpraziquantel. The RMP details important risks of arpraziquantel, how these risks can be minimized, and how more information will be obtained about arpraziquantel risks and uncertainties (missing information).

Arpraziquantel's SmPC and its Package Leaflet give essential information to healthcare professionals and patients on how Arpraziquantel should be used.

This summary of the RMP for Arpraziquantel should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of arpraziquantel's RMP.

I. The Medicine and What it is Used for

Arpraziquantel is authorized for the treatment of schistosomiasis caused by *S. mansoni* or *S. haematobium* in children aged 3 months to 6 years (see SmPC for the full indication). It contains arpraziquantel as the active substance and it is given by oral route.

Further information about the evaluation of arpraziquantel's benefits can be found in arpraziquantel's European Public Assessment Report, including its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of arpraziquantel, together with measures to minimize such risks and the proposed studies for learning more about arpraziquantel risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine Risk Minimization Measures.

If important information that may affect the safe use of arpraziquantel is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of arpraziquantel are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of arpraziquantel. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
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

II.B Summary of Important Risks

Important Potential Risk: Seizures in patients with undiagnosed asymptomatic neurocysticercosis	
Evidence for linking the risk to the medicine	Literature review
Risk factors and risk groups	Neurocysticercosis is a major cause of acquired epilepsy in most of the developing world and has been considered as the single cause explaining the increased incidence and prevalence of epilepsy in these regions. Seizures may occur at any stage of Cysticerci involution within the brain parenchyma, from viable cysts to calcifications. Unhygienic practices resulting in ingestion of *T. solium* eggs directly from a Taenia carrier, or less often by contaminated food, are causal factors for cysticercosis. Neurocysticercosis is common where there is clustering of conditions favoring the transmission of *T. solium*, including low level of education, poverty, deficient disposal of human feces, slaughtering of pigs without veterinary control, and presence of free-roaming pigs around households. Therapy with the cysticidal drug albendazole, disrupting the stable neurocysticercosis disease due to secondary inflammation, is an additional risk factor.
Risk Minimization Measures	Routine Risk Minimization Measures: • SmPC Section 4.4 • Package Leaflet Section 2 Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None.

Important Potential Risk: Seizures in patients with undiagnosed asymptomatic neurocysticercosis	
Additional Pharmacovigilance Activities	None.

Rac-PZQ=racemic praziquantel; SmPC=summary of product characteristics

Important Potential Risk: Use in patients with undiagnosed acute schistosomiasis	
Evidence for linking the risk to the medicine	No studies were found reporting the burden and risk of undiagnosed acute schistosomiasis in PSAC.
Risk factors and risk groups	Acute schistosomiasis is a toxemic and allergic reaction to the migrating and maturing larvae of Schistosoma. It is also known as Katayama fever and mainly seen in nonimmune individuals after their first exposure to schistosomes. In most cases, especially in people living in endemic areas, symptomatic acute schistosomiasis is not observed, and the disease reaches a stage of established active infection, with mature adult worms and well-established egg production (McManus 2018). In schistosome-endemic areas, a significant amount of the exposure to infection in PSAC is passive (i.e., use of contaminated water at home or children being bathed/sitting in a basin of fresh water while the guardian performs domestic chores), particularly in the youngest children. Exposure becomes more active as the children grow (e.g., accompanying caregivers to water sources for domestic chores). Therefore, in the early years of infants and young children, exposure to infection is closely linked to that of the caregiver. This disassociates as children grow older, become independent, and frequently visit contaminated water sources with friends and/or older siblings (Osakunor 2018).
Risk Minimization Measures	Routine Risk Minimization Measures: • SmPC Section 4.3 and 4.4 • Package Leaflet Section 2 Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None.
Additional Pharmacovigilance Activities	None.

Rac-PZQ=racemic praziquantel; SmPC=summary of product characteristics

Missing information: Use in patients with impaired kidney function	
Evidence for linking the risk to the medicine	Rac-PZQ is extensively metabolized and excreted via kidneys (Patzschke 1979) and thus same is hypothesized for arpraziquantel.
Risk factors and risk groups	The patients with impaired kidney function are expected to have delayed excretion.
Risk Minimization Measures	Routine Risk Minimization Measures: • SmPC Sections 4.2 and 5.2 Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None.
Additional Pharmacovigilance Activities	None.

Rac-PZQ=racemic praziquantel; SmPC=summary of product characteristics

Missing information: Use in patients with hepatic impairment	
Evidence for linking the risk to the medicine	Arpraziquantel undergoes first pass effect in liver and hence hepatic insufficiency, hepatosplenic schistosomiasis may lead to prolonged plasma half-life.
Risk factors and risk groups	The patients with pre-existing severe hepatic insufficiency or in patients with hepatosplenic schistosomiasis.
Risk Minimization Measures	Routine Risk Minimization Measures: • SmPC Sections 4.2 and 4.4 • Package Leaflet Section 2 Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None.
Additional Pharmacovigilance Activities	None.

SmPC=summary of product characteristics

Missing information: Use in children with <1 year of age	
Evidence for linking the risk to the medicine	Due to a small number of children in this age group with age <1 year been exposed to arpraziquantel in clinical studies, safety data in this age group is limited.
Risk factors and risk groups	The metabolism changes, particularly in age group with age <1 year. Thus, there is an increased risk for AEs in this age group.
Risk Minimization Measures	Routine Risk Minimization Measures: • SmPC Section 4.2 • Package Leaflet Section 2 Routine Pharmacovigilance Activities beyond adverse reactions reporting and signal detection: None.
Additional Pharmacovigilance Activities	None.

AE=adverse event; SmPC=summary of product characteristics

II.C Post Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of Arpraziquantel.

II.C.2 Other Studies in the Post Authorisation Development Plan

There are no studies required for Arpraziquantel.

Part VII Annexes

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Not applicable

Annex 6 Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable

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