**UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF**

# Monitoring of adverse events following praziquantel based treatment in pregnant women in Madagascar - a sub-study from the freeBILy clinical trial

**Dissertation**

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# 1 Abbreviations

| | |
|---|---|
| ARC | Clinical Research Associate (“Attaché de Recherche Clinique”) |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| APGAR | Apgar-Score |
| BNITM | Bernhard-Nocht-Institute for Tropical Medicine |
| CCA | Circulating Cathodic Antigen |
| CI | Confidence Interval |
| CICM | Charles Mérieux Centre of Infectious Disease |
| CPN | Antenatal Consultation (“*Consultation prénatale*”) |
| Co-ARC | Co-Clinical Research Associate (Co-Attaché de Recherche Clinique) |
| CRF | Case Report Form |
| CSB | Centre de Santé de Base / Health Care Centre |
| DALY | Disability-adjusted life-years |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| FDR | Foetal Death Rate |
| freeBILy | Fast and reliable easy-to-use-diagnostics for eliminating Bilharzia in young children and mothers |
| GCP | Good Clinical Practice |
| GCS | Glasgow Coma Scale |
| HLGT | High-Level Group Term |
| HLT | High-Level Term |
| ICD | International Classification of Disease |
| ICH | International Council for Harmonisation |
| IQR | Interquartile Range |
| LFU | Lost to follow-up |
| LLT | Lowest Level Term |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MAR | Missing at Random |
| MCAR | Missing Completely at Random |
| MNAR | Missing Not at Random |
| MDA | Mass Drug Administration |
| MSSO | Maintenance and Support Services Organization |
| NA | Not Applicable |
| NNH | Number Needed to Harm |
| PCR | Polymerase Chain Reaction |

| | |
|---|---|
| PHCC | Primary Health Care Centre |
| PI | Principal Investigator |
| PID | Participant Identification Number |
| POC-CCA | Point-of-care Circulating Cathodic Antigen |
| PSAC | Preschool-age children |
| PT | Preferred Term |
| PZQ | Praziquantel |
| RCT | Randomized Controlled Trial |
| RDT | Rapid diagnostic test |
| SAC | School-age children |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| $SmTRPM_{PZQ}$ | Schistosome transient receptor potential channel |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TID | Tube Identification Number |
| UADR | Unexpected Adverse Drug Reaction |
| UI | Uncertainty Interval |
| UN IGME | United Nations Inter-Agency Group for Child Mortality Estimation |
| WASH | Water, Sanitation and Hygiene |
| WHO | World Health Organization |

# 2 Introduction

Schistosomiasis is a debilitating disease that is caused by trematodes of the genus *Schistosoma* affecting an estimated 200 million people worldwide with 779 million at risk in 78 reported countries of which about 90% are located in Sub-Saharan Africa (3, 4). This includes Madagascar, where 74% of all administrative districts report endemicity of the disease (2). On a global scale, it is estimated to be associated with 15 000 to 280 000 deaths per year and 3.31 million disability-adjusted life-years (DALYs) in 2010 (5, 6). Schistosomiasis is particularly associated with poverty and a lack of water, sanitation and hygiene (WASH) facilities (7). The aim of fighting schistosomiasis in endemic countries comes along with challenges on multiple levels. This includes measures of prevention by education about backgrounds of the disease and avoidance of contact with infested water, hygiene measures by introducing WASH facilities with low-threshold access, implying easy access with sufficient availability. The rationale behind this is to inhibit the reproductive cycle of *Schistosoma*, snail control programs of snails that disseminate cercariae in freshwater (Figure 1 and 2), as well as cost-efficient diagnostic and therapeutic means as a response to infection (8).

## 2.1 Life cycle of *Schistosoma spp*. and human infection

The reproductive cycle of *Schistosoma spp.* involves fresh water snails (Figure 1 and 2) as intermediary hosts that live in rivers and lakes, ponds and other mostly lentic fresh water bodies. The open water is contaminated by means of human open defecation and urination, which facilitates transmission (Figure 2) (1, 7). Therefore, in resource-limited countries typical ways of infection consist of washing clothes in contaminated lakes or rivers, farming, playing in water or swimming (7).

*Figure 1 Left: Biomphalaria sp., intermediate host for S. mansoni. Centre: Adults of S. mansoni, female resides in the gynecophoral canal of thicker male. Right: Bulinus sp., the intermediate host for S. haematobium and S. intercalatum; Source: DPDx (9)*

Furthermore, recent discoveries suggest the existence of hybrid *Schistosoma* species with multi-species coinfections and an overlapping transmission potential in cattle and humans, adding an additional route of transmission that can increase the overall burden of the disease (10). An intermediate stage of the *Schistosoma*, called cercariae, is disseminated by infested freshwater snails can penetrate human skin and infect humans (Figure 2). Once the human skin is penetrated, the cercariae develop to worms, dwell within the human blood vessel system and cause severe long-term consequences to the health of its host (8).

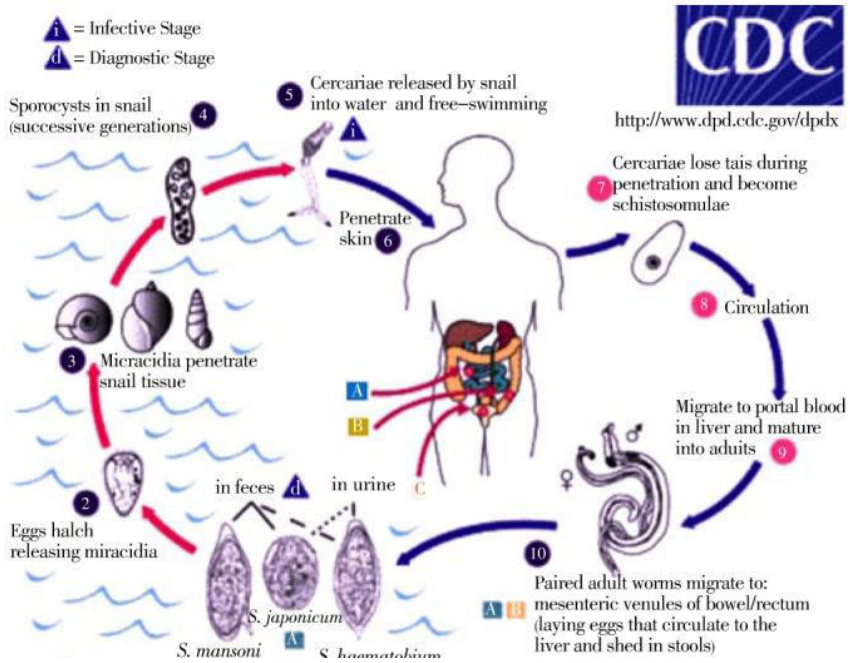


*Figure 2 Life cycle of Schistosoma spp.; Source: Gundamaraju, 2014, p. 2 (1)*

The infection is generally divided into three specific states: Acute infection, established active infection and late chronic infection. The acute infection can present itself a wide range of symptoms such as a skin rash in the beginning, then fever, fatigue and intestinal symptoms such as diarrhoea and abdominal pain (8). The established active infection typically shows inflammatory and immunological reactions of schistosome eggs trapped in host tissue of the gastrointestinal system in case of *S. mansoni* and urogenital system in case of *S. haematobium (8, 11)*. In the late chronic state of infection and depending on the *Schistosoma* species, complications of internal organs occur such as intestinal or urogenital bleeding, liver fibrosis and bladder cancer (8).

## 2.2 Diagnostic solutions to detect *Schistosoma spp*.

In endemic and resource-limited regions, where diagnostic solutions are typically needed most, they are usually limited to unspecific clinical symptoms such as fatigue, fever, anaemia, haematuria or physical or psychological developmental delays in children (12). Standard diagnostics also include microscopic analyses of stool (e.g. “Kato-Katz”) or urine samples as possibility to diagnose the typical parasitic egg shedding of the host (13). In a high-resource context, where schistosomiasis is typically not endemic and largely imported by travellers who have visited endemic regions, multiple different laboratory diagnostics are generally available based on serology or polymerase chain reaction (PCR) (14, 15). The full spectrum of diagnostic possibilities is, however, often not available in a resource-limited setting. The need of a cost-effective and reliable rapid diagnostic test (RDT) to fill the gap for this environment becomes evident. Therefore, the development and use of RDTs should generally be encouraged. A point of care diagnostic test for the circulating cathodic antigen (POC-CCA) to diagnose schistosomiasis in urine samples is commercially available. However, the test has major limitations as it presents a suboptimal test performance with regards to specificity in different study groups, among these relevant subgroups such as pregnant women and under three year old children with false-positive results and a specificity around 81% according to Marti et al. (16). Other authors have also questioned the test performance of the POC-CCA test particularly in areas of low endemicity (13, 17). The results regarding the test performance suggest more research and development is needed in the field of RDTs for schistosomiasis.

## 2.3 Treatment recommendation for schistosomiasis

In regions and communities of high endemicity and little diagnostic capacities, health care providers rely on mass drug administrations (MDA) campaigns as recommended by the World Health Organization (WHO) guidelines rather than a test-based treatment strategy (18, 19). However, for vulnerable populations, a test-based treatment strategy could be a solution to prevent excessive treatment. But in absence of an adapted diagnostic solution, it is hard at the current state of the art to determine feasibility and effectiveness. The WHO also recognized the need to include preschool-age children (PSAC) from endemic areas in treatment programs since 2010 (20). A recent WHO guideline from 2022 strongly recommends annual preventive chemotherapy in communities with ≥ 10% prevalence as treatment program with a single dose of praziquantel (PZQ) at ≥ 75% treatment coverage in all age groups from two years, adults and pregnant women after first trimester and lactating women (21). Despite new recommendations by WHO, outdated strategies such as treatment of only selected groups such as school-age children (SAC) and adults considered to be at risk in endemic areas, still remain widely adopted (22, 23). An additional drug formula for PSAC, was tested in a phase III study in 2021, for children aged three months to six years, with high efficacy and a favourable safety profile for children infected with *Schistosoma* in Ivory Coast and Kenya (24). The treatment of the target populations, however, remains a challenge as multiple barriers exist, which include concerns about treating women of reproductive age, exclusion of children younger than four years who clearly experience infection and

may be at greatest risk for morbidity, individual-level refusal based on lack of knowledge regarding infection status, and the misconception that schistosomiasis is not an important cause of morbidity and mortality (18). Closing treatment gaps by expanding access to the affected populations, including PSAC, remains essential as leaving out these age groups from treatment and monitoring worsens health inequities and has negative long-term consequences for sustainable schistosomiasis control (23).

### 2.4 Drug characteristics of praziquantel

The drug of choice for chemotherapy to treat schistosomiasis is PZQ. It was discovered in 1972 and approved for human use in the 1980s for therapy against schistosomiasis and other parasitic flatworms (25). It is known to be a typically effective treatment with little side effects. Due to its effectivity, safety and overall importance as drug, praziquantel has also become part of the "Model List of Essential Medicines" by WHO (26). Despite its widespread use for decades, the physiological effect of PZQ has long remained elusive. A study from 2020 elucidated a relevant schistosome ion channel $\mathrm{SmTRPM}_{\mathrm{PZQ}}$, that is activated by PZQ and elicits a transient $Ca^{2+}$ signal in schistosomes, which perturbs physiological calcium homeostasis and causes contractile paralysis and tegument damage of the parasites (25). Interestingly, PZQ is also known to have less impact against juvenile worms and overall effectivity of PZQ depends on age of infection, the sex of the worms and their state of pairing (25, 27). This likely plays a role in case of failure to cure an infection after PZQ treatment. Nevertheless, treatment remains generally effective with an estimated cure rate after single dose of 40mg/kg PZQ of 89.2% (95% CI: 85.4-93.1) and 93.6% (95% CI: 80.6-106.0) for *S. mansoni* and *S. haematobium*, respectively (28). Overall, PZQ is generally considered a safe drug even though data in specific vulnerable groups remains scarce.

### 2.5 Safety and tolerability in clinical trials

In clinical research, particularly in later stage trials, the evaluation of safety and tolerability of a drug represents a crucial aspect. It allows exploration of potential adverse effects as suggested by guidelines. Safety and tolerability of a drug includes data of adverse events and serious adverse events of a clinical trial. An adverse event (AE) is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (29). In other words, it is possible to be any sign or symptom emerging after a drug administration that does not need to be associated with it. In addition, there is a classification of serious adverse events (SAEs) or serious adverse drug reactions (SADRs) which are associated with death, are life-threatening, require hospitalization, result in permanent disability or congenital anomalies (29). It is also important to determine the expectedness of a reaction, which for example leads to the definition of an unexpected adverse drug reactions (UADR) (29). Fatal or life-threatening UADRs are subject to expedite reporting to regulatory authorities as they can lead to suspension of clinical investigations. Regulatory agencies should, accordingly, be notified no later than seven calendar days after first knowledge by the legal representatives of the studies. Within an additional eight calendar days, a clinical report should be submitted (29). The regulatory definition of tolerability is defined by

the guideline of the International Council for Harmonisation (ICH): “The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject” (30). Therefore, whether a drug is considered tolerable or not is unequivocally determined by the subject exposed to the drug under investigation. And tolerability needs to be discerned from safety, which by ICH is defined by the medical risk that the subject is exposed to by intake of the drug rather than the subjective impression of a drug effect. The medical risk includes an extensive overview and assessment by means of validated laboratory values, vital signs, clinical adverse events and other available diagnostic tests, such as ECGs (30). It becomes evident that safety and tolerability cannot be used interchangeably. However, there still exists much ambiguity around the term tolerability in clinical research with regards to its actual objectivity and standardization. Stanulovic et al. published a systematic review to assess the approach of how tolerability is defined in clinical research and concluded that e.g. “good tolerability” is a common, almost colloquial, but inappropriate summary conclusion vaguely referring to acceptable safety profile, while not actually referring to tolerability (31). In line with this reasoning of tolerability and an appropriate analysis of withdrawals, Ioannidis et al. also suggest a description of withdrawals due to harms and the experience of the treatment in a clinical trial (32).

## 2.6 Adverse drug reactions of praziquantel

The product monograph of PZQ reports known adverse drug reactions (ADRs) of unknown frequency that are based on spontaneous reports sorted by categories of the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Classes (SOCs) (33-35). MedDRA® is a subscription-based, clinically validated international medical terminology dictionary in order to harmonize communication of clinical safety information throughout all clinical study phases, developed by ICH (34, 36). According to the product monograph of PZQ, the ADRs in Table 1 have been observed (37). It is, however, unclear whether the ADRs have a direct link with the PZQ administration, destruction of parasites in the body of the host or no association since symptoms of the infestation may also occur. A mixture of the aforementioned causes of similar symptoms makes it unreliable to determine a distinct source (35). Also, sequelae of chronic infections can also cause signs or symptoms that are not directly infection or drug-related.

*Table 1 Observed adverse drug reactions of praziquantel according to product monograph; Source : Bayer Inc. (37)*

| **System Organ Class** | **Adverse Drug Reaction (unknown frequency)** |
|---|---|
| Cardiac Disorders | Arrhythmia |
| Gastrointestinal Disorders | Gastrointestinal and abdominal pains |
| | Nausea |
| | Vomiting |
| | Anorexia |
| | Diarrhoea (very rarely bloody diarrhoea) |
| General Disorders and Administration Site Conditions | Asthenia |
| | Feeling unwell |
| | Fever |
| | Fatigue |
| Immune System Disorders | Jarisch-Herxheimer Reaction |
| | Allergic reaction |
| | Polyserositis |
| | Eosinophilia |
| Musculoskeletal, Connective Tissue and Bone | Myalgia |
| Nervous System Disorders | Headache |
| | Dizziness |
| | Vertigo |
| | Somnolence |
| | Seizures |
| Skin and Subcutaneous Tissue Disorders | Urticaria |
| | Rash |
| | Pruritus |

A systematic review and meta-analysis from 2021 investigated relevant adverse effects among individuals, including adults, as well as SAC and PSAC, treated with a 40mg/kg single dose PZQ in Ethiopia (28). Any AE was reported by a total of 88.7% (95% CI: 86.7-90.4) among all 1217 individuals treated. It concluded an incidence of 69.2% (95% CI: 66.5-71.8) abdominal pain/cramps, 36.2% (95% CI: 33.4-39.0) diarrhoea, 28.3% (95% CI: 25.8-30.9) headache, 29.7% (95% CI: 27.0-32.6) nausea and 25.1% (95% CI: 22.6-27.6) vomiting, 28.2 (95% CI: 25.2-41.4) dizziness, 25.7% (95% CI: 25.7-29.6) fever, 23.5% fatigue (95% CI: 19.9-27.3) and 16.6 (95% CI: 14.5-18.9) bloody stool as common AEs after PZQ administration (28). The signs and symptoms were reported to be observed for the first four hours after drug administration and quickly resolved.

## 2.7 Praziquantel use during pregnancy

PZQ is a drug of choice for treatment of schistosomiasis infection and has been authorized to be used as medicine since 1980 in Germany (38). However, according to the product monograph no sufficient and well-controlled studies have been conducted with PZQ in pregnant women (37, 38). Additionally, an increase in the miscarriage rate was found in rats at three times the single human therapeutic dose (37). However, results from animal studies don't necessarily reproduce similar results in humans. Nevertheless, PZQ should only be used in women of reproductive age and pregnant women after careful considerations of the risk-benefit profile of the treatment (35). Since 2006, however, the WHO recommends the use of PZQ in pregnant and breastfeeding women in MDA for schistosomiasis in endemic countries, while stressing the need for more research and randomized controlled trials (RCTs) to evaluate the safety and efficacity as countries have been reluctant to implement this policy due to lasting safety concerns (19). A previous study from 2016 was able to produce reassuring data concerning safety with no increased foetal loss and teratogenicity during PZQ use in pregnant women, despite the fact that the number of women treated (N=370) and their intensity of infection remains too low to have a conclusive assessment on safety and tolerability (39). Reassuringly, according to the WHO and over more than three decades of post-market experience, no reports of SAEs relevant to human pregnancy have been published, e.g. abortions, stillbirths or congenital anomalies (19).

## 2.8 Schistosomiasis in Madagascar

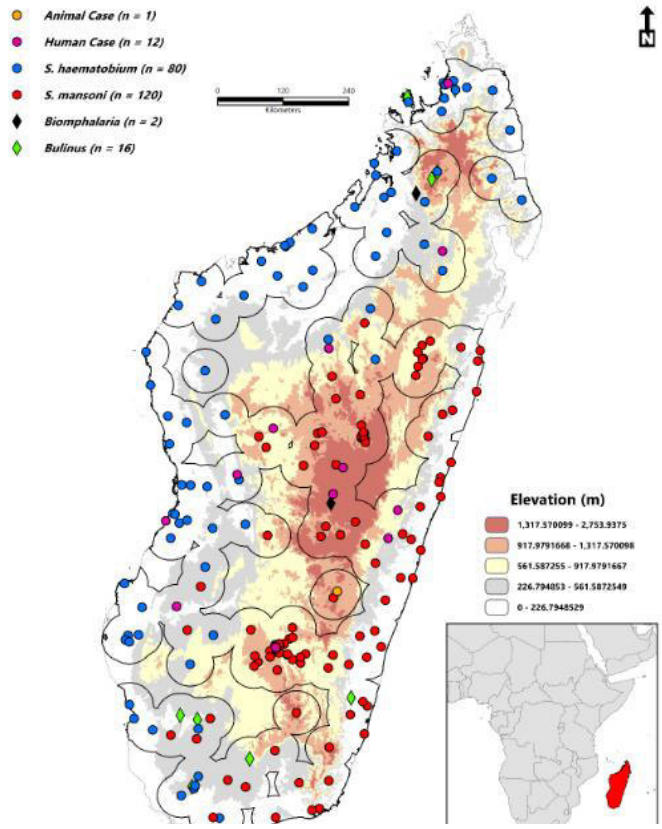


*Figure 3 Geographic distribution of occurrence data (n=231) in comparison to the predominant topographic characteristics of Madagascar; Source: Mark A. Deka, 2022, p. 3 (2)*

In Madagascar, endemicity of schistosomiasis is reported in 74% of all administrative districts (2). Two species of *Schistosoma* are prevalent in Madagascar, namely *S. haematobium* and *S. mansoni (2, 40).* Concerning vector snails, *Bulinus* and *Biompholaria* species (Figure 1), which are responsible for *S. haematobium* and *S. mansoni* transmission, have been reported in multiple locations in Madagascar (Figure 3) (2). *S. haematobium*, cause of urogenital schistosomiasis, is predominantly prevalent in the western and northern districts of the island, whereas *S. mansoni,* cause of intestinal schistosomiasis, is predominantly prevalent in the eastern and southern districts of the island and in the central highland's districts (Figure 3) (2, 40). An overlapping endemicity of both species is reported in districts of the north-central and south-west (40, 41). In rural Madagascar, schistosomiasis is suspected to be overall widespread with PCR test results from pregnant Madagascan women from 2010 suggesting a prevalence of up to 69,1% (42). Recent data published in 2023 from Gruninger et al. based on PCR results of adults also suggests a high prevalence of 61.3% *S. haematobium* in north-western peri-urban area Ankazomborona, 50.2% prevalence *S. mansoni* in north-western highlands urban area Tsiroanomandidy and 59.5% prevalence *S. mansoni* in the south-central highland rural area Andina (43). It becomes clear that schistosomiasis is widespread in Madagascar and a considerable part of the Madagascan population is likely at risk, while disregarding specific risk factors for infection. Overall, the task of fighting diseases and promoting health combined with a struggling health care system in Madagascar is creating a highly challenging environment for the Madagascan people and healthcare stakeholders (44, 45).

## 2.9 The freeBILy trial in Madagascar

The overarching trial that is providing data on safety and tolerability for this thesis is freeBILy. It is a phase III randomized controlled clinical trial for pregnant women and their children that are positively diagnosed with schistosomiasis in Madagascar (46). The sub-study concerning safety and tolerability is embedded in the freeBILy trial. The study objectives of freeBILy are concerning the assessment of the impact of a test-based treatment strategy on the health of mothers and children as well as sensitivity and specificity of the POC-CCA rapid test and other secondary objectives such as cost-effectiveness of the strategy. The intervention arm included the test-based treatment strategy whereas the control arm followed national guidelines, which did not include a test and treat strategy but treatment of symptomatic cases. Positively diagnosed pregnant women were treated with PZQ. The size of the trial with 5114 pregnant women recruited, of which 2346 were allocated to the intervention arm, may provide valuable information about less frequent adverse events occurring after PZQ administration in pregnant women. Furthermore, the published freeBILy study protocol was recently cited to call for insights on additional safety information that will further inform guidelines (46, 47).

### 2.9.1 freeBILy study design

freeBILy is a cluster randomized trial that recruited 5114 pregnant women in their 5$^{th}$ to 6$^{th}$ month of pregnancy (Figure 4 and 5). The study was running from 11 April 2019 until 1 September 2022. Participants were recruited in 42 sites in the provinces of Antananarivo and Fianarantsoa in the Madagascar highlands. The women and their children were followed up for 24 months after birth with four scheduled visits after recruitment. Visits were normally incorporated in regular ante- or postnatal woman and childcare. Participants could also consult study personnel for unscheduled visits in case of adverse events or questions.

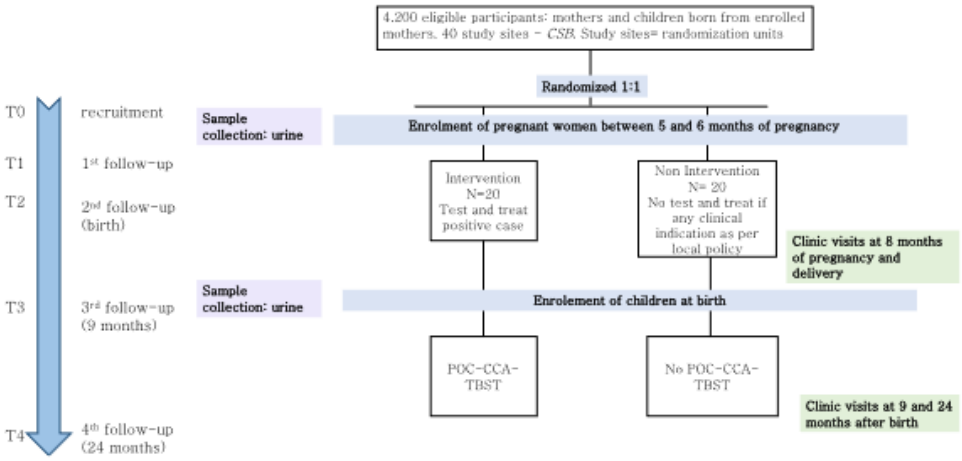


*Figure 4 Cluster randomized trial study design. The CSBs, randomly allocated between intervention and non-intervention, represent the randomization units. At the 5th or 6th month of pregnancy (T0), women will be enrolled in the study and consent for their children will be asked. At T0 and 9 (T3) and 24 (T4) months after birth, urine samples will be collected. At delivery (T2), children will formally become part of the study. Source: Fusco et al., 2021, p. 4 (46)*

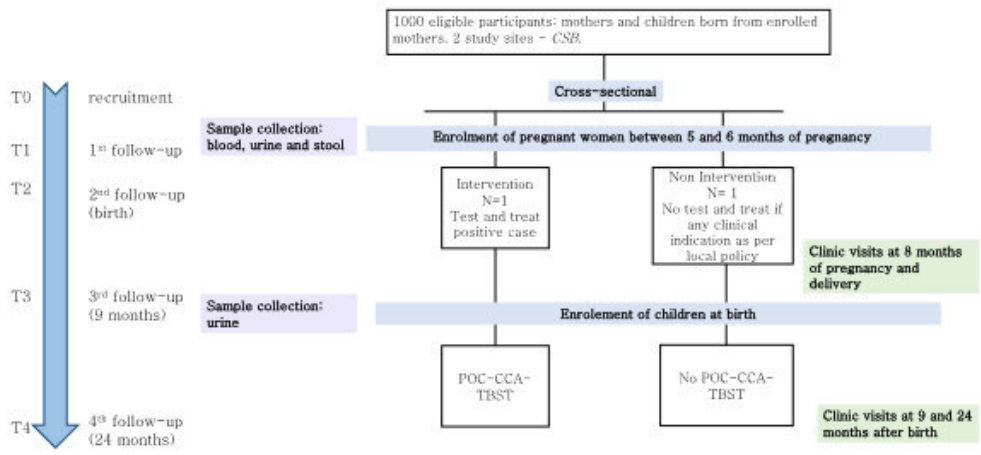


*Figure 5 Design of the cross-sectional study. The two non-randomized CSBs Andina and Imerintsiatosika were selected as the intervention and non-intervention sites, respectively. At the 5th or 6th month of pregnancy (T0), women will be enrolled in the study and consent for their children will be asked. At T0, blood, urine and stool samples will be collected. At the end of the study, the sample will be analysed with the tests described in Table 1. At 8 months of pregnancy (T1) and 9 (T3) and 24 (T4) months after birth, urine samples will be collected. At delivery (T2), children will formally become part of the study. Source: Fusco et al.,2021, p.5 (46)*

*Table 2 Scheme of scheduled visits. T0 mother's enrolment at 5th or 6th month of pregnancy; T1 pre-delivery follow up at the 8th month of pregnancy; T2 delivery follow up at birth and inclusion of children; T3 follow up 9 month after delivery; and, T4 final follow up 24 months after delivery; Source: Fusco et al., 2021, p.7 (46)*

| Scheme of scheduled visits | | | |
|---|---|---|---|
| Type of activity | Subjects | Intervention | Control |
| Visit | women | T0, T1, T2, T3, T4 | T0, T1, T2, T3, T4 |
| POC-CCA | women | T0, T3, T4 | T4 |
| Treatment of positive cases | women | T0, T3, T4 | T4 |

The type of activities that are relevant for this study during scheduled visits of freeBILy are depicted in Table 2. These include, apart from completion of Case Report Forms (CRF), POC-CCA test and treatment of positive cases according the protocol.

### 2.9.2 Inclusion and exclusion criteria

The target population for this exploratory sub-study consists of pregnant Madagascan women in their 5th to 6th month of pregnancy according to weeks of amenorrhea during recruitment, who are 16 years of age or older and live in the zone of the consulted health centre (CSB) that is also serving for regular antenatal care visits. Participants agree to attend follow-up visits at the CSB of recruitment up until 24 months of age of the child and accept a possible treatment in CSBs. Furthermore, the exclusion criteria must not be fulfilled to enroll to the freeBILy trial (Table 3). These include previous enrollment in the study, presence of a congenital anemia, having received a blood transfusion in the past and known episodes of epilepsy or convulsive episodes. Fever during the consultation for enrollment represents a temporary exclusion criterion, among other definite exclusion criteria (Table 3). Minors need to have additional consent of their legal guardian in order to

be able to participate. After delivery of the child, the child is also being followed up for visits until the age of 24 months.

*Table 3 Inclusion and exclusion criteria for the freeBILy-trial, Source: Fusco et al., 2021, p.6 (46)*

| Eligibility criteria for participation in the study |
|---|
| INCLUSIONS CRITERIA |
| • Informed consent signed (from the parents for minors)<br>• Expected residency in the area of the study site for the next 24 months<br>• Pregnant women between their 5th and 6th months of pregnancy<br>• Children born from an enrolled mother, including twins<br>• Willingness to comply with the protocol requirements including: sampling and treatment for both mothers and children |
| EXCLUSIONS CRITERIA |
| • Fever (temporary exclusion)<br>• History of transfusion<br>• History of congenital anaemia<br>• Epileptic or convulsive episodes<br>• Non-pregnant women<br>• Pregnant women younger than 16 years old<br>• Pregnant women who have not completed their 4th month of pregnancy<br>• Pregnant women over their 6th month of pregnancy<br>• Pregnant women who do not live in the area of the CSB<br>• Children born from mothers not enrolled in the study<br>• Children born in a CSB different from the ones in which the mothers were enrolled |

### 2.9.3 freeBILy study sites

The study was conducted in the provinces of Antananarivo and Fianarantsoa in Madagascar and incorporated in the local ante- and postnatal care of the selected CSBs. In three study regions 42 study sites were selected for recruitment. The study sites are depicted in Table 4 and 5.

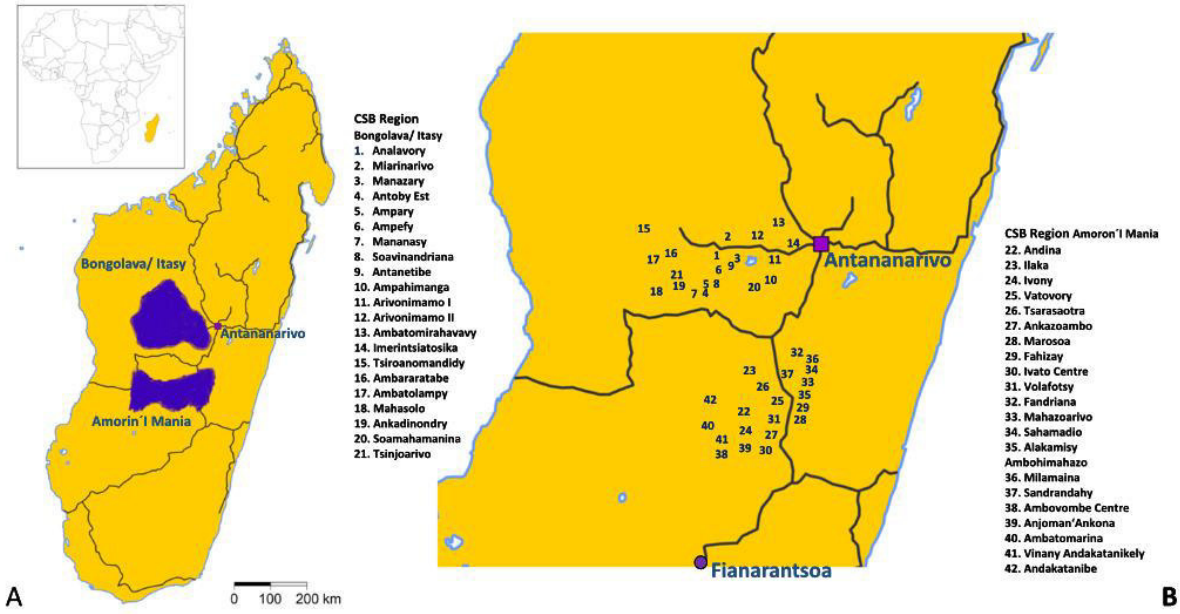


*Figure 6 Distribution of the freeBILy study sites across the regions of Bongolava, Itasy and Amoron'i Mania in Madagascar. In **A**, the geographic locations of these regions of Madagascar are depicted. In **B**, the full list of study sites and their distribution within the regions of Bongolava, Itasy and Amoron'I Mania are given. Source: Fusco et al., 2021, p.4 (46)*

*Table 4 Study sites in province Antananarivo (For CSB numbers: Figure 6)*

| CSB Number | Site Name | Abbreviation | Allocation |
|---|---|---|---|
| 1 | Analavory | TA | Intervention |
| 2 | Mianarivo | TB | Control |
| 3 | Manazary | TC | Control |
| 4 | Antoby Est | TD | Control |
| 5 | Ampary | TE | Control |
| 6 | Ampefy | TF | Intervention |
| 7 | Mananasy | TG | Control |
| 8 | Soavinandriana | TH | Control |
| 9 | Antanetibe | TI | Control |
| 10 | Ampahimanga | TJ | Control |
| 11 | Arivonimamo I | TK | Control |
| 12 | Arivonimamo II | TL | Intervention |
| 13 | Ambatomirahavavy | TM | Intervention |
| 14 | Imerintsiatosika | TN | Control |
| 15 | Tsiroanomandidy Ville | TO | Intervention |
| 16 | Ambararatabe | TP | Intervention |
| 17 | Ambatolampy / Ambohitrakely | TQ | Intervention |
| 18 | Mahasolo | TR | Control |
| 19 | Ankadinondry | TS | Intervention |
| 20 | Soamahamanina | TT | Intervention |
| 21 | Tsinjoarivo | TU | Intervention |

*Table 5 Study sites in province Fianarantsoa (CSB numbers: Figure 6)*

| CSB Number | Site Name | Abbreviation | Allocation |
|---|---|---|---|
| 22 | Andina | FA | Intervention |
| 23 | Ilaka | FB | Control |
| 24 | Ivony | FC | Intervention |
| 25 | Vatovory | FD | Intervention |
| 26 | Tsarasaotra | FE | Intervention |
| 27 | Ankazoambo | FF | Intervention |
| 28 | Marasoa | FG | Intervention |
| 29 | Fahizay | FH | Control |
| 30 | Ivato Centre | FI | Intervention |
| 31 | Volafotsy | FJ | Control |
| 32 | Fandriana | FK | Intervention |
| 33 | Mahazoarivo | FL | Intervention |
| 34 | Sahamadio | FM | Control |
| 35 | Alakamisy Ambohazao | FN | Control |
| 36 | Milamaina | FO | Control |
| 37 | Sandrandahy | FP | Intervention |
| 38 | Ambovombe Centre | FQ | Control |
| 39 | Anjoman' Akona | FR | Control |
| 40 | Ambatomarina | FS | Control |
| 41 | Vinany Andakatanikely | FT | Intervention |
| 42 | Andakatanibe/Andakatany | FU | Control |

## 2.10 Scope of thesis and research questions

This thesis will focus on the safety and tolerability of PZQ use during pregnancy. This concerns crucial background information, whether the safety profile of MDA in pregnant women is favourable with regards to a potential over-treatment, while accepting potentially avoidable additional side-effects compared to a test-based treatment strategy. The overall goal is to provide further reassuring and valuable safety data to dispel doubts about PZQ treatment of pregnant women. Information on safety and tolerability will be drawn from available and preliminary clinical data of the freeBILy trial, which primarily investigates test-based PZQ treatment of pregnant women and their children. The following research questions are formulated:

**(1)** What is the safety and tolerability profile of PZQ in pregnant women in Madagascar?

**(2)** Are there different safety indicators observed within the freeBILy study population?

**(3)** Are any sociodemographic factors more frequently present in children with AE/SAEs?

**(4)** Is there a time dependency of different types of AEs after praziquantel administration, with particular interest in SAEs concerning prematurity and foetal death?

# 3 Materials and Methods

## 3.1 Materials

### 3.1.1 Urine collection

*Table 6 Used material for urine collection on site*

| Collection kit containing the necessary material | Producer |
|---|---|
| 40 ml urine cup for the mother | According to local availabilities |
| Pre-printed labels for identification | Charles Mérieux Center of Infectious Disease (CICM) |

### 3.1.2 POC-CCA rapid test

*Table 7 Diagnostic material*

| Diagnostic test | Producer | Batch number | Content | Expiry date |
|---|---|---|---|---|
| Schisto POC-CCA® cassette-based test kit | ICT INTERNATIONAL, Noordhoek, South Africa | 200326039 | • 25 x test cassettes each individually packaged<br>• 1 x instructions for use<br>• 25 x pipettes | 03/2022 |
| G score panels | Leiden University Medical Centre, Leiden, Netherlands | | Panel of 10 cassettes stored in a light-tight bag | |

### 3.1.3 Drugs

*Table 8 Drugs*

| Drug | Producer |
|---|---|
| Praziquantel Tablets USP 600mg | MACLEODS PHARMACEUTICALS LIMITED, Mumbai, India |

### 3.1.4 Forms and documents

*Table 9 Used forms and study documents*

| Document/form | Explanation |
|---|---|

| | |
|---|---|
| Case Report Forms (CRFs) | Documents used in clinical trials to document participant's data in a standardized design that facilitates data collection and analysis (48). For each participant pre-printed personalized CRFs were provided in folders at the study sites. CRFs may be adapted according to needs with a standardized process involving authorization by principal investigators and circulation of new version. |
| SOP_SAE_FRA_v.1.3 | Standard Operating Procedure (SOP) for AEs and SAEs |
| 07_freeBILy_*Imprevue*_v2.8 | CRF for unscheduled Visits |
| 10_freeBILy_*Evènement indésirable*_v2.5 | CRF for AEs and SAEs |
| REC_MeC_28_FRA | SAE Clinical Report CRF (Appendix Figure 13) |
| *Fiche de Notification des Effets Indésirables Des Médicaments/Vaccins* | Notification sheet for ADRs in Madagascar by the Ministry of Health Madagascar/Centre of Pharmacovigilance Madagascar |

### 3.1.5 Data banks and programs

*Table 10 Used data banks and programs*

| Data bank / program | Producer | Version |
|---|---|---|
| Microsoft Excel | Microsoft, Redmond, USA | 16.66.1 |
| R® | R Foundation for statistical computing, Vienna, Austria | R 4.1.2 GUI 1.77 |
| R® Studio | R Foundation for statistical computing, Vienna, Austria | 2022.07.0+548 |
| REDCap® (Research Electronic Data Capture) | Vanderbilt University, Nashville, USA | 8.11.6 |
| REDCap® data bank with servers located in Hamburg at Bernhard-Nocht-Institut für Tropenmedizin (BNITM) | IT Department of BNITM | NA |
| MedDRA® | Maintenance and Support Services Organization (MSSO), Intellectual Property Rights belong to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) | 25.1 |

## 3.2 Methods

### 3.2.1 freeBILy study organigram and study design

The freeBILy study organigram is organized as depicted in Figure 1:

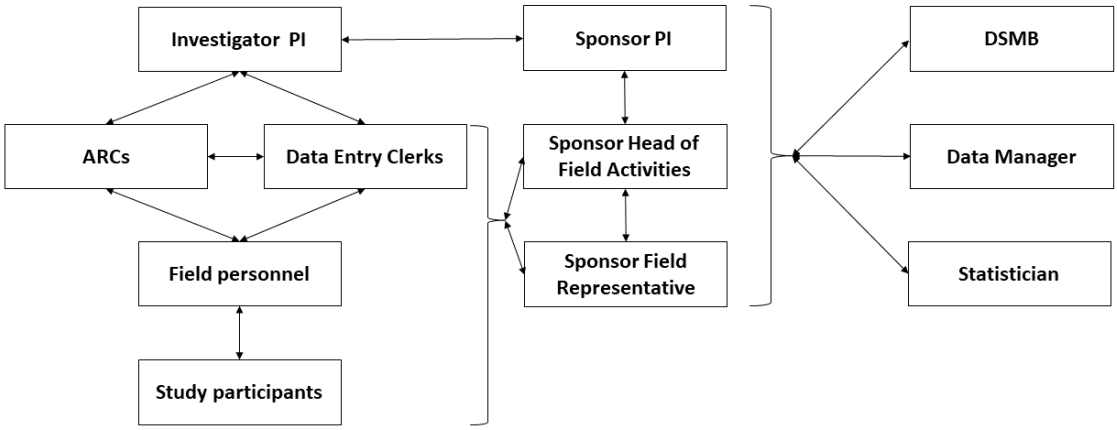


*Figure 7 freeBILy study organigram*

- Investigator Principal Investigator (PI) and sponsor PI are responsible for the orderly conduct of the trial. The Investigator PI is a Madagascan professor and physician. The sponsor PI is a Hamburg-based scientist and physician.
- Clinical Research Associates (ARCs) are Madagascan trained physicians. Data entry clerks is Madagascan trained technical staff responsible for production of CRFs and double data entry of filled CRFs
- Field personnel consists of Madagascan trained nurses and midwives with repeated Good Clinical Practice (GCP) trainings.
- Study participants are recruited at CSBs with antenatal care.
- Sponsor head of field activities is a European trained physician or scientist, but stationed in Madagascar and in charge of monitoring of key study elements.
- Sponsor field representatives are consisting of doctoral students in the medical field or with a background of natural sciences. Their task is to monitor certain aspects of the study in the field and lab in Madagascar.
- The DSMB, data manager and statistician are, except one member of DSMB, based at BNITM in Hamburg and informed about relevant general activities and reporting of safety data.

Pregnant women in the intervention CSBs were offered a test-based treatment for schistosomiasis. The participants were recruited in 42 different CSBs, 21 for each study arm. During recruitment, participants were encouraged to give birth with professional assistance, free of charge, at the allocated study CSBs. The children were then registered to the study and followed up together with their mothers until 24 months of age of the child.

### 3.2.2 Data collection

After the informed consent was accepted and inclusion/exclusion criteria were evaluated, the participant received a pseudonymized, personal identifier (PID; Figure 2) to pseudonymize participants for all future visits and data acquisition in order to respect confidentiality. The study data was then collected on paper CRFs (Appendix Figure 9 and 10) by field staff which consisted of locally trained nurses

and midwifes. The CRFs were later transported to the respective data centres in Fianarantsoa or Antananarivo for double data entry with an online REDCap® interface of which the servers were located at BNITM in Hamburg. The data centres consist of two designated offices with data entry personnel, who deal with the administrative side of CRF printing, double data entry with the REDCap® software and folder storage of CRFs. The ARCs, Madagascan locally trained physicians, also work in the data centres for administrative tasks and query solving. The queries were created by a data manager in Hamburg at BNITM on a monthly basis based on inconsistencies in the REDCap® database.

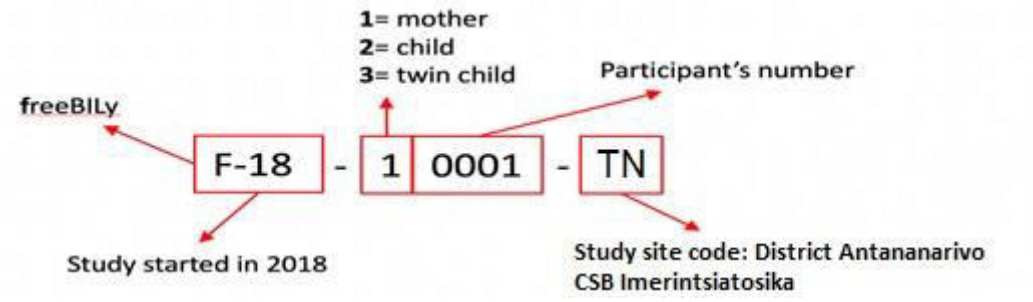


*Figure 8 Creation and Meaning of Personal Identifier (PID)*

### 3.2.3 Praziquantel treatment

Mothers with a positive POC-CCA test result received 40 mg praziquantel per kilogram bodyweight as single and oral treatment dose as defined by the freeBILy study protocol. The individual dose is calculated in 300 mg increments, which represents a separated 600 mg tablet.

### 3.2.4 Adverse and serious adverse events reporting and management

The information and workflow regarding the Adverse Event (AE)/ Serious Adverse Event (SAE) reporting and its management is presented in the following paragraph and is visualized in Figure 3. AEs/SAEs were reported according to the following schematic steps:

1. Reporting of AE/SAE verbally to field personnel (trained project nurses/midwives) by participant or person close to participant (e.g. mother of pregnant participant)
2. Field personnel fills out CRFs and reports case to ARC also by mobile phone.
3. ARCs create standardized clinical report in case of SAE. AE and SAE CRFs are entered in database by data entry clerks.
4. Quality check of clinical report for SAE is conducted by field sponsor representative.
5. Clinical report is shared with country principal investigator (PI) and sponsor PI.
6. Clinical report and cumulative report on AEs/SAEs distributed to the Data and Safety Monitoring Board (DSMB) on a monthly basis. The DSMB is a board consisting of experienced research experts that independently gives feedback to sponsor and investigator. There are five members in the DSMB: A paediatrician, a pharmacovigilance expert, two epidemiologists based in Germany and a physician from Madagascar.

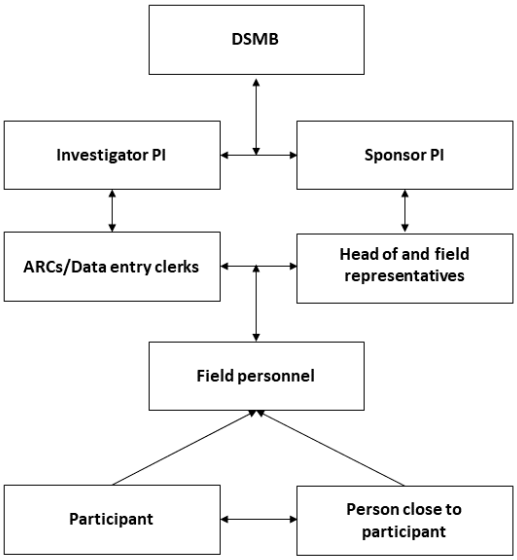


*Figure 9 AE/SAE Reporting Information Flow*

In case of an AE/SAE, the trial participant was generally advised to approach the trial staff for communication of the medical condition largely by means of passive follow-up. Passive follow-up defined that the initiative of reporting a medical condition lied in the hands of the participant and not actively asked and checked by study personnel. It was, however, also possible to receive information about AEs/SAEs by a person close to the participant, such as a community worker or

relative of a participant. This is crucial and the only possible way for receiving information of deceased participants that were not under immediate care of the personnel when the SAE occurred. Specific conditions were, however, also actively followed-up. Active follow up in the trial was defined as a check of only specific and typical pregnancy-related questions during visits including the symptoms haemorrhage, vomiting, pelvic pain, icterus, anaemia or none of the previous. Also, after the delivery of the child, medical conditions such as respiratory symptoms, diarrhoea and vomiting, malaria or other diseases are checked during follow-up visits.

Next step was under the responsibility of the field personnel (trained project nurses/midwives) to take further action. This included the reference to a medical doctor, typically the head of CSB where recruiting takes place, if the condition cannot be adequately handled by the field personnel and requires treatment. An AE requires the filling of a specified AE CRF (Appendix Figure 11) and also the CRF of an unscheduled visit (Appendix Figure 12), if this applies. Additionally, an SAE must be communicated by the staff in the field to the corresponding ARC, who is a trained Malagasy doctor of the respective study province Antananarivo and Fianarantsoa. The communication from field staff to ARCs is conducted via mobile phone. Further, it is the responsibility of the ARC to gather all the relevant and available medical information regarding a serious adverse event and compose a written report of the case with the freeBILy SAE clinical report form (Appendix Figure 13) in French. The staff notifying the ARCs in the field must then be available for further questions concerning the case and possibly ask the participant and/or other implicated medical staff further questions to complete the report of the adverse event. AE CRFs and a potential unscheduled visit CRF are entered into the database by data entry clerks.

In the process, a field sponsor representative is also involved in the information flow in order to perform quality checks and monitor clinical reports. The clinical report is then shared with the investigator and sponsor PIs.

Subsequently, the report is printed to be signed by the local principal investigator or co-principal investigator and stored in the investigator site files in the data centres (Fianarantsoa and Antananarivo) and an additional digital, unsigned version is stored on the BNITM cloud server. In case of problems appearing the adverse event reporting procedure, the cause of it is to be identified, documented and, if possible, resolved (e.g. lack of information and delays in communication). Additionally, information concerning the adverse events is shared with the DSMB on a monthly basis that also include overall statistics of the trial with the overall SAE and AE report. SAEs that are unexpected and the field staff gets notified of are subject to expedite reporting, which implies a planned reporting timeline to the DSMB within 24 hours.

### 3.2.5 AE/SAE inclusions and classification for analysis

The analysis of safety data comprises all reported AEs and SAEs starting with the recruitment of the first participant (T0) from April 2019 and ends with the termination of the study phase and all follow-up visits including the last study visit two years after birth of the child of all recruited participants in September 2022. This includes

all reported adverse events regardless of their actual time point of occurrence. According to the freeBILy study, the AEs and SAEs are classified in the following manner:

- Grade 1 – defined as weak and/or is easily tolerated
- Grade 2 – defined as moderate and/or interferes with habitual activity
- Grade 3 – defined as severe, associated with an incapacity to work or to conduct a habitual activity and can necessitate a hospitalization
- Grade 4 – defined as life-threatening

Safety will be assessed by quantifying the number of AEs/SAEs and mortality rates. This includes endpoints such as foetal death, child death and maternal mortality. Tolerability will be determined by withdrawal from trial after a registered AE or SAE.

Technical details of the AE/SAE process are presented in the following section: For each AE and SAE CRFs are completed for the database. Additionally, and exclusively for SAEs, standardized clinical reports are also filed for the trial master file and backup on the cloud server. Additional and exceptional SAEs from the database with missing clinical report will be considered as well with the limited, available information from the database. Furthermore, lower graded adverse events (Grade 1 – 3) that were exclusively collected in the REDCap® database and without clinical report will be considered part of this analysis.

Concerning administrative aspects and requirements, there is a notification sheet available to inform the Madagascan ministry of health and Madagascan national centre of pharmacovigilance in case of ADRs (Appendix Figure 14 and 15).

### 3.2.6 Distribution of AEs/SAEs across sites and study regions

The distribution of AEs was stratified by the two study provinces Antananarivo and Fianarantsoa and furthermore also the individual recruitment sites, the health care centres (CSBs) of which 21 were selected per study province. The rationale behind the display of separated data of the two study provinces is that they were also separately managed by two data centres, attributed ARCs and data entry clerks, which could generate variability in the results. The study regions in Madagascar, where participants were recruited, are Bongolava, Itasy (both Antananarivo province) and Amoron'i Mania (Fianarantsoa province). Concerning another aspect of stratification, sociodemographic and medical data from the population were additionally summarized in order to associate possible risk factors to adverse events.

### 3.2.7 MedDRA coding of Adverse events

For the present study AEs and SAEs were classified according to standardized MedDRA® coding procedures (49). The subscription-based dictionary is used in order to appropriately code the adverse events System Organ Classes (SOC) and Preferred Terms (PT) according to instructions. The approach used for the adverse event analysis is determined by ICH guidelines (50).

ICH developed a subscription-based clinically validated and regularly updated international dictionary MedDRA® for communication and standardized presentation of clinical safety information (34, 36). It represents a hierarchical classification model with five levels of item categories and number of items that are available to classify practically any sign or symptom of a clinical investigation:

System Organ Class (SOC): 27

High-Level Group Term (HLGT): 337

High-Level Term (HLT): 1737

Preferred Term (PT): 25,592

Lowest Level Term (LLT): 85,668

The numbers of each category display the amount of possibilities to classify a sign or symptom by selecting one of each hierarchical level with standardized instructions. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the ICH. MedDRA® trademark is registered by ICH.

One reported AE or SAE may code for multiple PTs according the available information concerning reported signs or symptoms. The question whether a symptom is related or not should be included in a clinical report according to EMA, but due to its extensive nature, is not part of this work and therefore only timely associations are investigated (50).

The time of interest for the start of a related AE was typically within the time frame of clinically relevant drug concentration in the participant. Data suggests, that even with severe hepatic impairment (Child-Pugh C), half-life of praziquantel may increase to up to 8.45±2.46 hours (35). A drug is typically considered below a clinically relevant concentrations and effectively eliminated after five half-lives (51). The AEs of interest that are possibly related are likely starting within the time of biological effect in the first 55h (for this analysis a cut-off ≤7 days) after administration (52). Adverse events that are suspected to be related, but appear later than the effective time of the drug, will be investigated and discussed, if needed.

For the freeBILy trial, withdrawal lists that were filled out by field personnel for each CSB on the field level from both study provinces were collected and investigated with regards to a potential reason for withdrawal mentioned in the comment section of the form. Furthermore, the list of MedDRA® codes of all collected adverse events will be searched for PIDs of subjects that decided to withdraw from the trial to

potentially find a connection with AEs that may not be reflected in the comment section of the CRF.

### 3.2.8 Data analysis

The study data was described using methods as suggested by ICH and European Medicines Agency (EMA) guideline (30). Univariate analyses were conducted to show the distribution of all results and explanatory variables (AE and SAE rates, mortality rates and sociodemographic variables) for the overall sample. For categorical variables, numbers and percentages were presented, continuous variables were described using median and interquartile range (IQR). Sociodemographic factors of mothers (Level of education, status of employment, pregnancy, clinical history and diagnostics) who experience foetal death were evaluated according to data that was collected in the CRF during recruitment (T0). (Appendix Figure 9 and 10).

Safety will be assessed by quantifying the number of AEs/SAEs and mortality rates. This includes endpoints such as foetal death, child death and maternal mortality. Tolerability will be determined by withdrawal from trial after a registered AE or SAE. For this, withdrawals and discontinuations that were accounted in logs on the level of the individual CSBs are screened for previously known AEs or SAEs. The overall data concerning missing the last follow-up visit (T4) is considered loss to follow-up according to consensus in evaluation of clinical trials (53). This results in a sum of no information on visit and visit not done as an account for lost to follow-up (LFU). Withdrawals and discontinuations are also considered as LFU. Due to limitation of data, only an association of AEs or SAEs with a withdrawal or discontinuation can be tracked, which does not necessarily imply causality.

#### 3.2.8.1 Death rates

The calculation of foetal rates is based on the number of 5114 total births in relation to 1000 births, whereas the neonatal death is based on the number of 5022 live births in relation to 1000 live births births as used by WHO (54). In addition, stratified foetal death rates will be estimated related to gestational age, i.e., “early” (20 – 27 weeks’ gestation) and “late” (≥28 weeks’ gestation) separately. The term ‘stillbirth’ is also used to describe fetal deaths at 20 weeks’ gestation or later. Stillbirth is not specifically divided into early and late gestations, but for international comparisons the WHO defines stillbirth as at or after 28 weeks’ gestation. In this analysis, stillbirths are considered as late gestations. The maternal death rates are defined as the number of deaths in relation to 5022 live births. Overall maternal death rates as well as stratified death rates will be estimated. Stratification will be based on days after delivery, of which maternal death occurring before the end of the 42-day reference period are standard for calculation according to ICD and WHO (54). Accordingly, maternal mortality is stratified by occurrence of death up to 42 days after delivery. A maternal mortality rate that is independent of the day of the delivery will also be calculated.

The death rates in percent are displayed from all currently available AE and SAE reports. The displayed data includes death rates from control sites, intervention sites, combined sites (total) and corresponding 95% binomial confidence intervals (95% CI) for reported deaths per 1000 births. The 95% binomial confidence intervals were calculated with BETAINV function in Excel (55):

$$\boldsymbol{p = BETAINV\left(1 - \frac{\alpha}{2}; k + 1; n - k\right)}$$

$$\boldsymbol{\alpha = 1 - \gamma}$$

$$\boldsymbol{p = point\ estimate}$$

$$\boldsymbol{k = number\ of\ successes\ (deaths)}$$

$$\boldsymbol{n = sample\ (mothers\ or\ children)}$$

$$\boldsymbol{\gamma = confidence\ interval}$$

The reported foetal death rate per 1000 births (FDR) was calculated with available data and grouped according to age groups of five years from 15 to 40 or older (40+). The Clopper-Pearson binomial 95% confidence intervals were added.

### 3.2.9 Analysis of time dependency of SAEs after PZQ administration

According to the definition of time-dependency of SAEs following drug administration, cases are identified which require further investigations. So, all cases occurred in intervention CSBs no later than seven days after praziquantel intake. In order to evaluate a possible association with praziquantel, more background information about the individual cases is displayed. The data was obtained through the in-depth analysis of the available clinical reports and available information from the database.

### 3.2.10 Ethical considerations and Good Clinical Practice

The freeBILy study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) - GCP guidelines (56). The study was approved both by the National Ethics Committee of Madagascar (ref. no 022-SANP/CERBM of 05/03/ 2018) and the Ethics Committee of the Hamburg State Medical Chamber in Germany (ref. no PV5966 of 18/03/2019). All participants received information about the aims of the study and its procedures in the local language Malagasy. The participation was voluntary and on basis of written informed consent. Informed consent for the participation of mother and child was obtained from the participating mother by signature or in case of illiteracy through a thumbprint in the presence of an independent witness. In the event of the death of either the mother or the child, the other could remain in the study; for the child, a new signature of a custodial family member was required. Participants were free to refuse participation and withdraw the informed consent at any time, without giving reasons. The signed informed consent and carbon copies of all documents including CRFs stayed in a locked cabinet on the CSB site.

# 4 Results

## 4.1 Study population and summary of adverse event reporting

All AEs/SAEs described in this thesis were retrieved following the recruitment of 5114 pregnant women between April 2019 and September 2022. The control arm contained 2768 pregnant women and the intervention arm contained 2346 pregnant women.

The AEs/SAEs were collected for the complete study period, starting on April 11th 2019 with recruitment and ending with the last follow-up visit on September 1st 2022. Descriptive characteristics of the adverse events are displayed in Table 11. In total, there were 287 AEs of any grade reported of which 131 were reported in the control arm and 156 in the intervention arm. Overall, 5.5% (n=280) of all mother-child couples reported at least one adverse event of any severity (Grade 1 – 4) in all CSBs and both study arms, split to 4.7% (n=130) of all mothers in the control arm and 6.4% (n=150) of all mothers in the intervention arm. All AEs and SAEs are always referring to a specific mother-child couple, otherwise the number of participants and the denominator would double. In the control arm, there were 0.4% (n=11) of mothers that reported lower-graded AEs (Grade 1 – 3) and 4.3% (n=119) of mothers that reported SAEs (Grade 4) reported. In the intervention arm, there were 2.4% (n=57) of mothers that reported lower-graded AEs (Grade 1-3) and 4.0% (n=93) of mothers that reported SAEs (Grade 4) (Table 11).

*Table 11 AE and SAE counts and percentages per study arm*

| Parameter | Control (N=2768) (%) | Intervention (N=2346) (%) |
|---|---|---|
| Number of AEs (Grade 1-3) | [11] 11 (0.4) | [58] 57 (2.4) |
| Number of patients with at least one AE | 11 (0.4) | 57 (2.4) |
| Number of patients with one AE | 11 (0.4) | 55 (2.3) |
| Number of patients with two AEs | 0 (0.0) | 1 (0.0) |
| Number of patients with at least one AE and following SAE | 0 (0.0) | 1 (0.0) |
| Number of SAEs (Grade 4) | [120] 119 (4.3) | [98] 93 (4.0) |
| Number of patients with at least one SAE | 119 (4.3) | 93 (4.0) |
| Number of patients with one SAE | 118 (4.3) | 91 (3.9) |
| Number of patients with two SAEs | 1 (0.0) | 1 (0.0) |
| Number of patients with three or more SAEs | 0 (0.0) | 1 (0.0) |

*in [] total number of AEs/SAEs, without brackets number of affected mother-child pairs

In total, 76% (n=218) of all reported AEs/SAEs of any grade were classified as serious (Grade 4), so deadly or life-threatening with need of hospitalization. The SAEs were mainly limited to a single mother-child pair and single event. This affected 4.3% (n=118) of woman-child pairs with a single SAE in the control arm and 3.9% (n=91) of woman-child pairs with a single SAE in the intervention arm. With regards to lower graded AEs (Grade 1 – 3), 69 were reported in total of which 15.9% (n=11) were reported in the control arm, whereas 84.1% (n=58) were reported in the intervention arm.

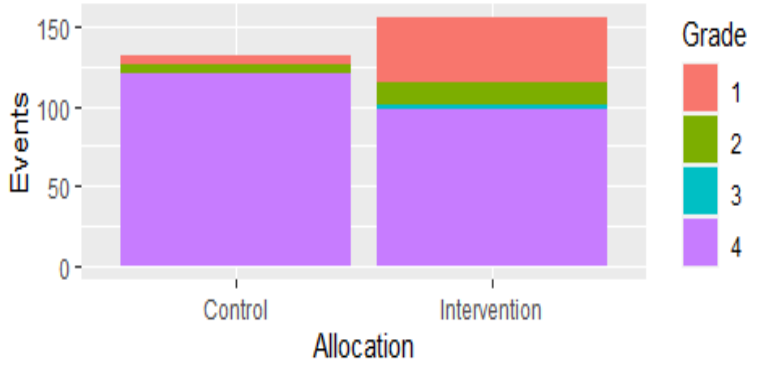


*Figure 6 Reported adverse events by study arm*

The distribution of reported AEs and its according grades are displayed in bar charts (Figure 6).

### 4.1.1 AEs and SAEs per site in Antananarivo province

In the study province Antananarivo, where 2785 pregnant women were enrolled in the trial, 178 AEs/SAEs occurred during the freeBILy trial of which 61 were classified as lower graded AEs (Grade 1-3) and 117 as SAEs (Grade 4). This corresponds to a mean rate of 2.2 lower graded AEs (Grade 1-3) and 6.4 SAEs (Grade 4) per 100 recruited mothers. Among all 21 sites in Antananarivo province, 38% (n=8) did not report any AEs. These eight sites recruited 1127 pregnant women, which corresponds to a mean of 140.9 participants per site. Moreover, among the 21 sites in the Antananarivo province, 14% (n=3) did not report any SAEs including a control site that reported neither an AE nor an SAE. These three sites recruited 308 pregnant women, which corresponds to a mean of 102.7 participants per site.

*Table 12 AEs and SAEs per site in province Antananarivo*

| Site Name | Code | Allocation | AEs | SAEs | Recruited Mothers | All AEs (SAEs) per 100 mothers* |
|---|---|---|---|---|---|---|
| Analavory | TA | Intervention | 7 | 3 | 110 | 9.1 (2.7) |
| Mianarivo | TB | Control | 4 | 11 | 105 | 14.3 (10.5) |
| Manazary | TC | Control | 0 | 8 | 202 | 4.0 (4.0) |
| Antoby Est | TD | Control | 0 | 7 | 135 | 5.2 (5.2) |
| Ampary | TE | Control | 1 | 5 | 104 | 5.8 (4.8) |
| Ampefy | TF | Intervention | 4 | 9 | 129 | 10.1 (7.0) |
| Mananasy | TG | Control | 0 | 7 | 60 | 11.7 (11.7) |
| Soavinandriana | TH | Control | 0 | 5 | 90 | 5.6 (5.6) |
| Antanetibe | TI | Control | 1 | 8 | 132 | 6.8 (6.1) |
| Ampahimanga | TJ | Control | 0 | 8 | 220 | 3.6 (3.6) |
| Arivonimamo I | TK | Control | 0 | 2 | 172 | 1.2 (1.2) |
| Arivonimamo II | TL | Intervention | 7 | 2 | 82 | 11 (2.4) |
| Ambatomirahavavy | TM | Intervention | 6 | 8 | 134 | 10.4 (6.0) |
| Imerintsiatosika | TN | Control | 2 | 8 | 295 | 3.4 (2.7) |
| Tsiroanomandidy Ville | TO | Intervention | 6 | 14 | 179 | 11.2 (7.8) |
| Ambararatabe | TP | Intervention | 4 | 4 | 82 | 9.8 (4.9) |
| Ambatolampy / Ambohitrakely | TQ | Intervention | 10 | 6 | 102 | 15.7 (5.9) |
| Mahasolo | TR | Control | 0 | 0 | 104 | 0 |
| Ankadinondry | TS | Intervention | 0 | 2 | 144 | 1.4 (1.4) |
| Soamahamanina | TT | Intervention | 7 | 0 | 102 | 6.9 (0) |
| Tsinjoarivo | TU | Intervention | 2 | 0 | 102 | 2 (0) |

*All AEs include SAEs, with SAEs in parentheses, total recruited, pregnant mothers: 2785 in Antananarivo province

### 4.1.2 AEs and SAEs per site in Fianarantsoa province

In the study province of Fianarantsoa, where 2329 pregnant women were enrolled in the trial, 109 AEs/SAEs were collected during the freeBILy trial of which eight were classified as lower graded (Grade 1 – 3) and 101 as SAEs (Grade 4). This corresponds to a mean rate of 0.3 lower graded AEs (Grade 1-3) and 4.7 SAEs (Grade 4) per 100 recruited pregnant women in the Fianarantsoa study province. Among all 21 sites in Fianarantsoa province, 67% (n=14) did not report any AEs. These fourteen sites recruited 1423 pregnant women, which corresponds to a mean of 101.6 participants per site. Moreover, among the 21 sites in the Fianarantsoa province, 10% (n=2) of sites did not report any SAEs including a control site and intervention site that both reported neither an AE nor an SAE. These two sites recruited 184 pregnant women, which corresponds to a mean of 92 participants per site.

*Table 13 AEs and SAEs per site in province Fianarantsoa*

| Site Name | Code | Allocation | AEs | SAEs | Subjects | All AEs (SAEs) per 100 participants* |
|---|---|---|---|---|---|---|
| Andina | FA | Intervention | 1 | 16 | 206 | 8.3 (7.8) |
| Ilaka | FB | Control | 0 | 10 | 134 | 7.5 (7.5) |
| Ivony | FC | Intervention | 1 | 1 | 56 | 3.6 (1.8) |
| Vatovory | FD | Intervention | 1 | 6 | 164 | 4.3 (3.7) |
| Tsarasaotra | FE | Intervention | 1 | 9 | 153 | 6.5 (5.9) |
| Ankazoambo | FF | Intervention | 0 | 2 | 88 | 2.3 (2.3) |
| Marasoa | FG | Intervention | 0 | 2 | 75 | 2.7 (2.7) |
| Fahizay | FH | Control | 0 | 0 | 68 | 0 |
| Ivato Centre | FI | Intervention | 1 | 3 | 118 | 3.4 (2.5) |
| Volafotsy | FJ | Control | 1 | 12 | 143 | 9.1 (8.4) |
| Fandriana | FK | Intervention | 0 | 0 | 116 | 0 |
| Mahazoarivo | FL | Intervention | 0 | 4 | 80 | 5.0 (5.0) |
| Sahamadio | FM | Control | 2 | 1 | 66 | 4.5 (1.5) |
| Alakamisy Ambohazao | FN | Control | 0 | 3 | 91 | 3.3 (3.3) |
| Milamaina | FO | Control | 0 | 2 | 37 | 5.4 (5.4) |
| Sandrandahy | FP | Intervention | 0 | 3 | 70 | 4.3 (4.3) |
| Ambovombe Centre | FQ | Control | 0 | 4 | 234 | 1.7 (1.7) |
| Anjoman Akona | FR | Control | 0 | 5 | 157 | 3.2 (3.2) |
| Ambatomarina | FS | Control | 0 | 12 | 157 | 7.6 (7.6) |
| Vinany Andakatanikely | FT | Intervention | 0 | 4 | 54 | 7.4 (7.4) |
| Andakatanibe/Andakatany | FU | Control | 0 | 2 | 62 | 3.2 (3.2) |

*All AEs include SAEs, with SAEs in parentheses, total recruited, pregnant mothers: 2329 in Fianarantsoa province

## 4.2 Reported death rates of foetuses, children and mothers

The data concerning death rates of foetuses, children and mothers is visualized in Table 14.

*Table 14 Death rates according to groups and 95% binomial confidence interval of total per 1000 births*

| | Control [N=2768] (%) | Intervention [N=2346] (%) | Total [N=5114] (%) | 95% CI of total (per 1000 births) |
|---|---|---|---|---|
| **Foetal death** | | | | |
| Early foetal death (Gestational age ≥ 22 0/7 - < 28 0/7) (%) | 3 (0.1) | 1 (0.0) | 4 (0.1) | 0.2 – 2.0 |
| Late foetal death (Gestational age ≥ 28 0/7) (%) | 54 (2.0) | 34 (1.4) | 88 (1.7) | 13.8 – 21.1 |
| Overall foetal death | 57 (2.1) | 35 (1.5) | 92 (1.8) | 14.5 – 22.0 |
| **Child death** | | | | |
| Neonatal death (age ≤ 28d) (%) | 31 (1.1) | 23 (1.0) | 54 (1.1) | 8.1 – 14.0* |
| Adjusted infant death (age 29 d – 1 year) (%) | 7 (0.3) | 12 (0.5) | 19 (0.4) | 2.3 – 5.9* |
| Overall Infant mortality (age: 1d – 1 year) (%) | 38 (1.4) | 35 (1.5) | 73 (1.4) | 11.4 – 18.2* |
| Child death (age 12 – 24 months) (%) | 5 (0.2) | 3 (0.1) | 8 (0.2) | 0.7 – 3.1* |
| Child death (age unknown) (%) | 3 (0.1) | 1 (0) | 4 (0.1) | 0.2 – 2.0* |
| **Maternal death** | | | | |
| prenatal – 42d postpartum (%) | 1 (0.0) | 6 (0.3) | 7 (0.1) | 0.6 – 2.9* |
| > 42d postpartum | 5 (0.2) | 3 (0.1) | 8 (0.2) | 0.7 – 3.1* |
| Overall maternal death | 6 (0.2) | 9 (0.4) | 15 (0.3) | 1.7 – 4.9* |

*reference value is “per 1000 live births” (5022) and not “total births” (5114)

### 4.2.1 Foetal death rates

Summarized over both study arms, a total of 1.8% (n=92) of pregnant women reported foetal deaths, of which 95.7% (n=88) can be classified late foetal deaths and 4.3% (n=4) early foetal deaths. Overall, 57 foetal deaths were reported in the control arm and 35 in the intervention arm. In the control arm, 94.7% (n=54) of foetal deaths were classified as late and 5.3% (n=3) as early. In the intervention arm, 97.1% (n=34) of foetal deaths were classified as late and 2.9% (n=1) as early. Overall, the total foetal death rate is 18.0 (95% CI:14.5-22.0) per 1000 births. Additionally, the late foetal death rate is 17.2 (95% CI:13.8-21.1) and early foetal death rate is 0.8 (95% CI:0.2-2.0) per 1000 births across study arms.

### 4.2.2 Death rate of neonates, infants and children of unknown age

A total of 1.1% (n=54) of mothers reported neonatal deaths (age of child ≤ 28d). Of this total, 57.4% (n=31) were reported in the control arm and 42.6% (n=23) in the intervention arm. The total neonatal mortality rate is at 10.8 (95% CI:8.1-14.0) per 1000 reported live births.

Over both study arms, a total infant mortality (age of child: 1d – 1y) of 1.4% (n=73) was reported. Of the total, 38 were reported in the control arm and 35 were reported in the intervention arm. The overall infant mortality rate is at 14.5 (95% CI:11.4-18.2) per 1000 reported live births.

Also, over both study arms, total child deaths from 12 – 24 months age were reported to be 0.2% (n=8). Of the total, 62.5% (n=5) were reported in the control arm and 37.5% (n=3) in the intervention arm. The overall child mortality rate (aged 12 – 24 months) is at 1.6 (95% CI:0.7-3.1) per 1000 reported live births.

Child deaths of unknown age were attributed to be 0.1% (n=4). Of the total, 75% (n=3) of cases were reported in the control arm and 25% (n=1) in the intervention arm. This corresponds to 0.8 (95% CI:0.2-2.0) child deaths of unknown age per 1000 reported live births.

### 4.2.3 Maternal death rates

An overall maternal death of 0.3% (n=15) was reported across study arms. Of this total, 40% (n=6) were reported in the control arm and 60% (n=9) in the intervention arm. The total maternal mortality rate corresponds to 3.0 (95% CI:1.7-4.9) per 1000 reported live births.

In total, 0.1% (n=7) maternal deaths were reported up to 42 days postpartum. The maternal deaths up to 42 days postpartum represent 14.3% (n=1) of the reported cases in the control arm, whereas 85.7% (n=6) of maternal deaths were reported in the intervention arm. Overall, this corresponds to a rate of 1.4 (95% CI:0.6-2.9) per 1000 reported live births.

Maternal deaths occurring later than 42 days postpartum affected 0.2% (n=8) of all mothers across the study arms. Maternal deaths later than 42 days postpartum represent 62.5% (n=5) of reported cases in the control arm, whereas 37.5% (n=3) of maternal deaths were reported in the intervention arm. This corresponds to an overall rate of 1.6 (95% CI: 0.7-3.1) per 1000 reported live births.

## 4.3 Sociodemographic characteristics and medical history of participants reporting foetal death and respective study allocation in freeBILy

In Table 16, sociodemographic characteristics of mothers with or without a foetal death are depicted in order to describe factors potentially associated with foetal death. Overall and independent from sociodemographic factors, 57 foetal deaths were reported in control CSBs, 35 in intervention CSBs.

*Table 16 Sociodemographic characteristics and medical history of participants experiencing foetal death and no foetal death in freeBILy*

| **Subgroup** | Control with foetal death (%), IQR (Q1, Q3) | Intervention with foetal death (%), IQR (Q1, Q3) | No foetal death in intervention and control (%), IQR (Q1, Q3) |
|---|---|---|---|
| **Total** | 57 (100) | 35 (100) | 5022 (100) |
| **Level of education** | | | |
| never went to school | 1 (1.8) | 1 (2.9) | 193 (3.8) |
| primary school | 28 (49.1) | 14 (40) | 2531 (50.4) |
| secondary school and more | 28 (49.1) | 20 (57.1) | 2298 (45.8) |
| **Status of employment** | | | |
| independent | 51 (89.5) | 30 (85.7) | 4363 (86.9) |
| unemployed, student/apprentice, employed or other | 6 (10.5) | 5 (14.3) | 659 (13.1) |
| months of work per year the past three years | 11 (10,12), n=54 | 10 (10, 12); n=33 | 11 (10, 12); n=4610 |
| If employed or independent, profession | n=52 | n=33 | n=4583* |
| farmer | 41 (78.8) | 16 (48.5) | 3485 (76.0) |
| housewife, driver, artisan, worker, vendor, merchant or other | 11 (21.2) | 17 (51.5) | 1098 (24.0) |
| **Pregnancy** | | | |
| primigravida | 20 (35.1) | 13 (37.1) | 1678 (33.4) |
| pregnancy week at recruitment | 24 (22, 25.5), n=47 | 25 (23.25, 26), n=34 | 24 (23, 26); n=4150 |
| since beginning of the pregnancy: | | | |
| haemorrhage | 0 (0) | 0 (0) | 12 (0.2) |
| pelvic pain | 0 (0) | 2 (5.7) | 134 (2.7) |
| anaemia | 0 (0) | 0 (0) | 5 (0.1) |
| vomiting | 17 (29.8) | 12 (34.3) | 1325 (26.4) |
| icterus | 0 (0) | 0 (0) | 2 (0.0) |
| nothing of the previous | 40 (70.2) | 22 (62.9) | 3610 (71.9) |
| | | | |
| **Clinical history** | | | |
| previous praziquantel treatment | 6 (10.5), unknown 2 (3.5) | 6 (17.1) | 557 (11.1), unknown 66 (1.3) |
| previous albendazole treatment | 17 (29.8) | 14 (40.0) | 1756 (35.0), unknown 12 (0.2) |
| iron supplement | 22 (38.6) | 20 (57.1) | 2172 (43.2) |
| folic acid supplement | 22 (38.6) | 20 (57.1) | 2177 (43.3) |
| malaria prevention drug | 19 (33.3) | 10 (28.6) | 1476 (29.4), unknown 1 |
| **Diagnostics** | | | |
| age, median | 26 (20, 33), n=57 | 26 (19.5, 31.5), n=35 | 23 (20, 29), n=5021 |
| weight [kg] | 50 (46, 56.5), n=46 | 55 (48.5, 58), n=32 | 51 (47, 55), n=4260 |
| blood pressure [mmHg], median | Systolic: 100 (100, 110); Diastolic: 60 (60, 70), n=42 | Systolic: 100 (100, 110); Diastolic: 60 (60, 70), n=31 | Systolic: 100 (100, 110) Diastolic: 60 (60, 70), n= 4508 |

*two employed participants without corresponding profession data omitted (F18-10111-FD, F18-10132-TM), dataset not reconciled

Overall, the median (IQR) age was 23 (20 - 29) years with the youngest mother 15 years of age and the oldest 48 years of age during recruitment. In the control arm with a reported foetal death, the median (IQR) was 26 (20 – 33) years, in the intervention arm 26 (19.5 – 31.5) years and in the group of participants without a reported foetal death 23 (20 – 29) years. Overall, the mean age of a mother during recruitment was 25 years. The age group with most participants was within the range of 20 to 24 years and represents 33.7% (n=1723) of all recruited mothers (Figure 3).

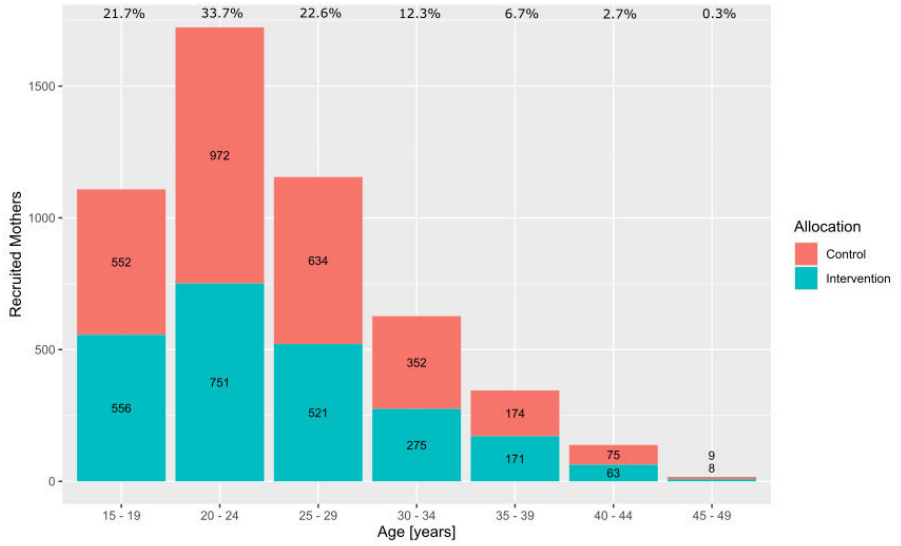


*Figure 3 freeBILy mothers by age group and study allocation; One missing age value in intervention arm (F18-10016-FG) not accounted; Percentages of the total (N=5114) by age group displayed above*

Concerning educational background of mothers with reported foetal death in the control arm, 1.8% (n=1) indicated no schooling, 49.1% (n=28) attended only primary school and 49.1% (n=28) received secondary school education or more. In the intervention arm of mothers with reported foetal death, 2.9% (n=1) indicated no schooling, 40% (n=14) attended only primary school and 57.1% (n=20) received secondary school education or more. In the group of participants without a reported foetal death, 3.8% (n=193) indicated no schooling, 50.4% (n=2531) attended only primary school and 45.8% (n=2298) received secondary school education or more.

Concerning the status of employment, 89.5% (n=51) of participants in the control arm with a reported foetal death indicated a status of employment of independent, the remainder 10.5% (n=6) was either unemployed, a student/apprentice or employed. Of the participants with a reported foetal death in intervention CSBs, 85.7% (n=30) indicated a status of employment of independent, whereas the remaining 14.3% (n=5) indicated either being employed or unemployed. In the group of women not reporting a foetal death in both study arms, 86.9% (n=4363) indicated a work status of independent and the remainder 13.1% (n=659) was either considered unemployed, student/apprentice, employed or other status of employment. If the participant indicated being employed or independent, the most common profession was farmer, which accounted for 78.8% (n=41) in the control arm with foetal death, 48.5% (n=16) in the intervention arm with reported foetal death and 76.1% (n=3485) in the group without a reported foetal death and both study arms.

With regards to clinical history, 35.1% (n=20) in the control arm with foetal death indicated being primigravida, whereas 37.1% (n=13) in the intervention arm with foetal death and 33.4% (n=1678) in the group without reported foetal death indicated being primigravida.

During recruitment, the participants were asked about typical symptoms during pregnancy since its beginning: Haemorrhage, pelvic pain, anaemia, vomiting, icterus or none of the previous. In the control arm with foetal death, 29.8% (n=17) of participants indicated having experienced vomiting since the start of pregnancy and 70.2% (n=40) reported none of the previously mentioned symptoms.

In the intervention arm with foetal death, 34.3% (n=12) reported vomiting, 5.7% (n=2) pelvic pain and 62.9% (n=22) none of the previously mentioned symptoms.

In the arm without reported foetal deaths, 26.4% (n=1325) indicated vomiting, 2.7% (n=134) pelvic pain, 0.2% (n=12) haemorrhage, 0.1% (n=5) anaemia, 0.0% (n=2) icterus and the majority with 71.9% (n=3610) reported none of the previously mentioned symptoms.

Concerning additional details of clinical history, in the control arm with reported foetal death, 10.5% (n=6) reported a previous praziquantel treatment, 29.8% (n=17) a previous albendazole treatment, 38.6% (n=22) reported iron and folic acid treatment and 33.3% (n=19) intake of a malaria prevention drug.

In the intervention arm with reported foetal death, 17.1% (n=6) reported previous praziquantel intake, 40% (n=14) previous albendazole intake and 57.1% (n=20) folic acid and iron supplement intake. Of control participants with foetal death, 28.6% (n=10) indicated a history of malaria prevention drug intake.

In the group without reported foetal deaths, 11.1% (n=557) reported a previous praziquantel intake, 35.0% (n=1756) reported a previous albendazole intake, 43.2% (n=2172) iron supplementation, 43.3% (n=2177) folic acid supplementation and 29.4% (n=1476) reported a previous intake of a malaria prevention drug.

For all participants, 11.1% (n=569) reported a previous praziquantel treatment, for 1.3% (n=68) it was unknown in this regard. Previous albendazole treatment was indicated by 34.9% (n=1787) and for 0.2% (n=12) it was unknown. Of all participants, 43.3% (n=2214) indicated an iron supplementation in the past and with 0.0% (n=0) indicating an unknown previous intake. Folic acid supplementation was indicated by 43.4% (n=2219) of all pregnant participants with 0.0% (n=0) unknown previous intake. A malaria prevention drug was previously taken by 29.4% (n=1505) in the past with 0.0% (n=1) unknown previous intake.

Concerning weight, the participants reporting foetal death in the intervention arm exhibited a median (IQR) of 50 (46 – 56.5) kg (n=46), control group with foetal death median (IQR) 55 (48.5 – 58) kg (n=32) and group without foetal death median (IQR) 51 (47 – 55) kg (n=4260). The blood pressure in all participant groups (intervention, control and no foetal death) was in median (IQR) 100 (100 – 100) mmHg systolic and 60 (60 – 70) mmHg diastolic (n=4581).

## 4.4 Foetal death rate per 1000 births and age groups of mothers

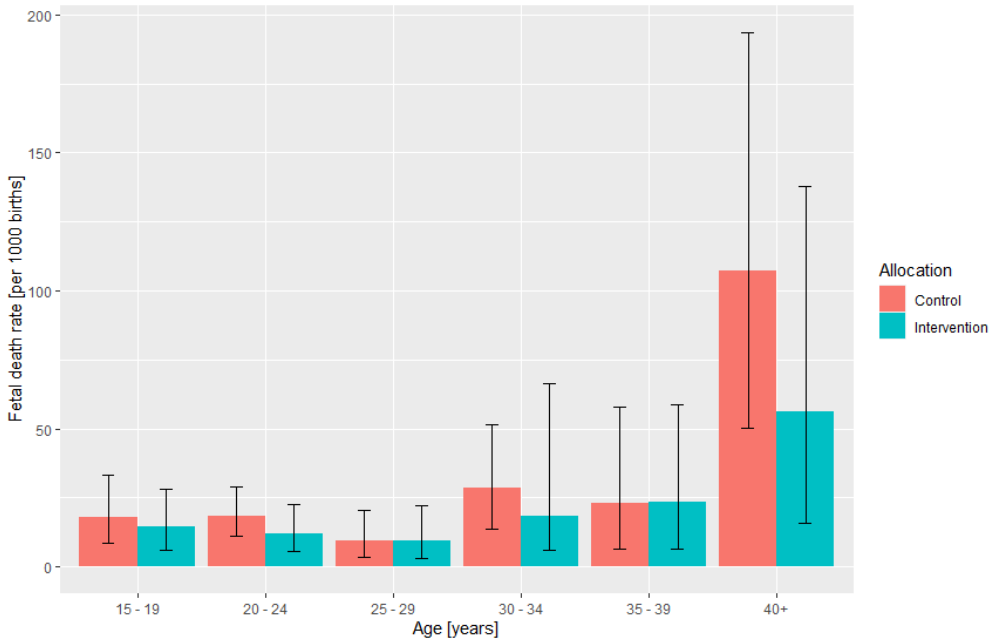


*Figure 10 Reported foetal death rate in freeBILy mothers and binomial 95% CI by age group and study allocation*

In the age group from 15 to 19 years, the FDR in the mothers registered in intervention CSBs was 14.4 (95% CI: 6.2-28.2) whereas the mothers in the control CSBs exhibited a reported foetal death rate of 18.1 (95% CI:8.7-33.1). In the age group 20 to 24 years, intervention FDR was 12.0 (95% CI:5.5-22.6) and the control FDR was 18.5 (95% CI:11.0-29.1). In age group from 25 to 29 years the FDR was 9.6 (95% CI:3.1-22.3) in intervention and 9.5 (95% CI:3.5-20.5) in control CSBs. Then, in the age group from 30 to 34 years, the FDR was 18.2 (95% CI:5.9-66.5) and in control CSBs 28.4 (95% CI:13.7-51.6). In the age group from 35 to 39, mothers recruited in intervention CSBs exhibited an FDR of 23.4 (95% CI:6.4-58.8) and in control CSBs 23.0 (95% CI:6.3-57.8). Ultimately, in the group of maternal age 40 years or older, the mothers recruited in intervention CSBs reported an FDR of 56.3 (95% CI: 15.6-138) and an FDR of 107.1 (95% CI: 50.2-193.7) in the control arm. Over all age groups, the mothers in intervention CSBs reported an FDR of 14.9 (95% CI:10.4-20.7) and 20.6 (95% CI: 15.6-26.6) in the control arm.

## 4.5 Analysis of time-dependency of SAEs following drug administration

In total, we have identified four SAEs that appeared within seven days after praziquantel administration including one case with inconsistencies but start of an AE within hours that likely developed into an SAE:

F18-10055-FD (0 days 3 hours): Timely association of praziquantel intake and following SAE with haematochezia, hypotension including hospital surveillance and no sequelae

A 23-year-old woman (Gravida 1 Para 0 Abortus 0) in week of amenorrhea 26 was enrolled in the study. Schistosome rapid test was positive and the participant received praziquantel treatment. Also, two hours before praziquantel treatment, intake of sulfadoxine/pyrimethamine as antimalarial was reported. The participant then presented emesis which started around three hours after praziquantel intake. The symptoms presented included little discharge of bloody stool and a vertigo with complications, namely hypotension (80/40 mmHg). Multiple episodes of bloody diarrhoea were already previously known for three years with an average of two episodes per year and the last one having appeared about three months before the reported SAE. Then, a hospitalization followed with a treatment, including an oral and intravenous rehydration and an unknown oral dose of aluminium hydroxide. After one hour of treatment, Glasgow Coma Scale (GCS) value of maximum possible 15, conjunctivae well coloured, cardiac frequency 80/min, blood pressure 110/60 mmHg, respiratory frequency 15/min and free lungs, soft abdomen without organomegaly and lymph nodes without pathological was reported. The participant was then discharged from surveillance three hours later without any further sequelae reported.

F18-10128-TS (0 days): Timely association of praziquantel intake and following SAE with premature delivery and neonatal death

A 16-year-old woman (Gravida 1 Para 0 Abortus 0) in week of amenorrhea 24 was enrolled in the study and when the SAE occurred. Schistosome rapid test was positive and the participant received praziquantel treatment. At an unspecified time but shortly after praziquantel intake, the woman indicated lumbopelvic pain and returned to the CSB for a consultation three hours after the beginning of the symptoms. At the CSB, the cervix was detected to be dilated and subsequent premature delivery of a female neonate about four hours after the first symptoms appeared. APGAR score was evaluated to be 10/10 and birth weight 1000g. One hour after delivery, the neonate died, suspected due to dyspnoea. There were no further sequelae of the mother reported.

F18-10034-FC (7 days): Timely association of praziquantel intake and following SAE with stillbirth at home

A 28-year-old woman (Gravida 9 Para 8 Abortus 0) in week of amenorrhea 28 was enrolled in the study. Schistosomiasis rapid test was positive and the participant received praziquantel treatment. Seven days after treatment, the woman presented an episode of diarrhoea, emesis and an unspecified fever (no temperature, duration or suspected cause known). Three hours after initial appearance of aforementioned symptoms, abdominal pain and uterine contractions additionally appeared, which motivated the woman to consult a traditional midwife (*matron*), who declared the woman was in labour. The parturient then delivered a female stillbirth at home. A day after delivery of a stillbirth, a clinical examination (not specified where and by whom conducted) led to the following results: Woman conscious, without particular complaints, maternal impact of stillbirth appears without any pathological findings, hemodynamic state stable with a blood pressure of 100/70 mmHg. There were no further sequelae of the mother reported.

F18-10004-TQ (unknown time): Timely association of praziquantel intake and following SAE with premature delivery and child death

A 20-year-old woman (Gravida 2 Para 1 Abortus 0) in week of amenorrhea 26 was enrolled in the study. Schistosomiasis rapid test was positive and the participant received praziquantel treatment. According to the limited available information from the database, the participant indicated appearance of vomiting and vertigo approximately one hour after intake of praziquantel. In the following, but at an unknown timepoint, pelvic pain and premature delivery at, supposedly, week 24 of amenorrhea occurred and no clinical report with further information is available. Information regarding week of amenorrhea is inconsistent in database with actual dates. Data from the withdrawal lists suggest a child death at an unknown time with missing SAE report. Nevertheless, on this case, there were reconciliation inconsistencies that need to be investigated further. There were no further sequelae of the mother reported.

## 4.6 Overall lost to follow-up and withdrawals/discontinuations of the freeBILy trial by study province

Of all mothers across both study arms, 20.7% (n=1057) did not seek to attend the follow-up visit (T4) planned around the child's age of 24 months. Data for the last visit T4 was missing for 2.0% (n=103) of all participants, corresponding to 50.5% (n=52) in the control arm and 49.5% (n=51) in the intervention arm. Withdrawals and discontinuations are also considered as lost to follow-up (LFU). Therefore, across both study arms, 22.7% (n=1160) of participants are considered loss to follow-up. In the control arm, this represents 20.3% (n=562) LFU, whereas in the intervention this 25.5% (n=598) of participants are considered LFU.

By allocation, 18.4% (n=510) of the control arm did not attend the last follow-up visit (T4), whereas 23.3% (n=547) of the intervention arm did not attend the last visit. By also including the missing data for the last visit, this corresponds to 11.6% (n=65) LFU in the control arm that have indicated a withdrawal/discontinuation. Conversely, 88.4% (n=497) of LFU in the control arm have not indicated a withdrawal/discontinuation previously. For the intervention arm including missing data for the last visit, this corresponds to 13.0% (n=78) LFU that have indicated a withdrawal/discontinuation. Conversely, 87.0% (n=520) of LFU in the intervention arm have not indicated a withdrawal/discontinuation previously. The withdrawals/discontinuations and indicated reasons are reported in Table 15 and 16 for both study provinces, respectively.

*Table 15 Withdrawal / discontinuation counts and reason in study province Fianarantsoa; recruited participants N=2329*

| **Reason for withdrawal/discontinuation** | **Count [N=2329] (%)** |
|---|---|
| Any reason | 32 (1.4) |
| **Withdrawal** | |
| Relocation | 14 (0.6) |
| No time for CSB visits | 3 (0.1) |
| Fear of blood draw | 3 (0.1) |
| Separation and/or husband's decision | 2 (0.1) |
| Negative POC-CCA test | 1 (0.0) |
| **Discontinuation** | |
| Maternal death | 3 (0.1) |
| Neonatal death | 3 (0.1) |
| unknown | 2 (0.1) |
| Staff self-enrolled | 1 (0.0) |

In the Fianarantsoa study province, there were a total of 32 withdrawals/discontinuations collected of which 75.0% (n=24) were allocated to intervention CSBs. The total withdrawals/discontinuations represent 1.4% (n=32) of all 2329 recruited participants in the study province Fianarantsoa. Of these 32 SAEs with discontinuations/withdrawals, 43.8% (n=14) were associated with relocation of the study participants wishing to discontinue the study. Of all discontinuations/withdrawals from Fianarantsoa study province, 18.8% (n=6) were associated with SAEs, of which all six were deadly: 50% (n=3) individual maternal deaths and 50% (n=3) individual neonatal deaths were reported.

*Table 16 Withdrawal / discontinuation counts and reason in study province Antananarivo; recruited participants N=2785*

| **Reason for withdrawal/discontinuation** | **Count [N=2785] (%)** |
|---|---|
| Any reason | 111 (4.0) |
| **Withdrawal** | |
| Relocation | 27 (1.0) |
| Foetal death | 26 (1.0) |
| Separation and/or husband's decision (e.g. because of rumours) | 9 (0.3) |
| Refusal to be followed up | 8 (0.3) |
| CSB far away | 1 (0.0) |
| Work | 1 (0.0) |
| **Discontinuation** | |
| Neonatal death | 19 (0.7) |
| Infant death | 7 (0.3) |
| Maternal death | 5 (0.2) |
| Child death (age > 1 year or unknown) | 4 (0.1) |
| Wrongful inclusion (e.g. double enrolment) | 2 (0.1) |
| unknown | 2 (0.1) |

In the Antananarivo study province, there were 111 withdrawals/discontinuations registered of which 48.6% (n=54) were allocated to intervention CSBs. 55% (n=61) of withdrawals/discontinuation also reported adverse events, of which 53.2% (n=59) were SAEs (Grade 4), which were all associated with deadly events. Additionally, 3.3% (n=2) of withdrawals/discontinuations were associated with non-deadly lower graded AEs (Grade 1 and 3).

In the Antananarivo study province, 61 SAEs were reported that in the course of the trial also followed a withdrawal or discontinuation. The total withdrawals/discontinuations represent 4.0% (n=111) of all 2785 recruited participants in the study province Antananarivo. The 61 SAEs with withdrawal or discontinuation included 42.6% (n=26) foetal deaths, 31.1% (n=19) neonatal deaths, 11.5% (n=7) infant deaths, 8.2% (n=5) maternal deaths and 6.6% (n=4) child deaths (age >1 year or unknown).

# 5 Discussion

The insufficient treatment of schistosomiasis during pregnancy remains a widespread issue as pregnant women are often still excluded from MDA programs despite clear recommendations by the WHO (21-23). The alignment with international guidelines on a national level is urgent to provide better health care for pregnant women in countries where schistosomiasis is endemic. Therefore, any delay or other impairment of including pregnant women in treatment programs will continue to perpetuate the transmission of Schistosome infection so as adverse health outcomes for the vulnerable groups of mothers and children. Nevertheless, additional safety data on praziquantel use during pregnancy can still deliver further valuable insights, particularly about less frequent AEs/SAEs, for which data is still scarce. The data generated in this thesis can corroborate the safety of praziquantel for its use during pregnancy. According to the analysis performed on the adverse events derived from the treatment with praziquantel in the context of the freeBILy clinical trial, the treatment of pregnant women with praziquantel appears to have an overall favourable safety and tolerability profile. There is no evidence of an increased tendency of foetal deaths or congenital anomalies within the intervention compared to the control group. Overall, only three individual cases of congenital anomalies were reported during the trial: One case of congenital hepatobiliary anomaly (control), one congenital hydrocephalus (intervention) and one cleft palate (control). All these three cases were evaluated by the Data Safety Monitoring Board (DSMB) of the trial and no causality or correlation with treatment could be proved to halt the study. According to a systematic review and meta-analysis, it is estimated that in low- and middle-income countries (LMICs) congenital hydrocephalus has an incidence rate of 123 (95% CI: 98-152) per 100 000 births (57). Therefore, a single case of congenital hydrocephalus in the intervention arm should be considered as a natural probable event with no correlation with treatment.

## 5.1 Sociodemographic characteristics of mothers experiencing foetal death following PZQ treatment

The analysis presented in this thesis shows an increased foetal death rate with a higher maternal age (Figure 2), which is in line with literature findings among different populations (58-63). Overall, the risk factors for foetal deaths may vary across populations, for example between high income countries (HIC) and LMICs. In HICs, risk factors for foetal death include maternal overweight and obesity, advanced maternal age (>35 years), maternal smoking, primiparity, pregnancy-related disorders such as small size for gestational age and placental disorders as well as pre-existing conditions such as diabetes or hypertension (58). Additionally, studies in HICs have identified pregnancy-related conditions such as oligohydramnios, polyhydramnios, congenital malformations, previous adverse perinatal outcome, true knot of cord, meconium stained amniotic fluid, hypertensive disorders to be risk factors for foetal death (59, 60). In LMICs, maternal age younger than 20 or older than 35 years, lower maternal education, nulliparity or parity greater than three, and no prenatal care are associated with an all-cause stillbirth based on data of the Global Network's Maternal Newborn Health Registry for resource-limited environments (61, 62, 64). A case-control study from Madagascar also identified with statistical significance risk factors such as multiparity (≥5 births), prematurity, fewer than four prenatal consultations,

previous foetal loss or hypertension and the mother working in agriculture or commerce (63) for foetal death of maternal age of 35 or older. There is an overlap of risk factors across the populations, but for freeBILy it was not studied and analysed in depth for this scope as the trial was not designed to capture all the relevant information through the CRFs.

Also, by looking at the sociodemographic data, the deficiency of folic acid sparked our interest, which is a known risk factor during pregnancy for increased prevalence of spina bifida or other congenital neural tube defects (65). According to review data, spina bifida has a prevalence of 48.4 (95% CI:41.1-57.0) per 100 000 live births in countries without mandatory fortification (65). However, it is unclear how well this strategy was implemented and adhered to over time. Concerning the freeBILy study, 43.3% (n=2214) of all mothers reported an iron supplementation and 43.3% (n=2216) folic acid supplementation without a single case of spina bifida reported during the trial. Even though there is no data suggesting a higher prevalence of spina bifida in the total freeBILy study group, literature findings suggest that mandatory fortification lowers prevalence of this disease and African countries are also beginning to adopt the mandatory fortification strategy (65).The freeBILy data suggests room for improvement with regards to the supplementation strategy in Madagascar. Nevertheless, the absence of reported neural tube defects in the context of the trial and 43.3% (n=2216) of all mothers being supplemented with folic acid can be seen as an encouraging result. Mandatory fortification entails enrichment of cereal products with folic acid for the total population and has been introduced in at least 53 countries and has been introduced in the USA since 1998 (66). In Germany, however, there is no mandatory fortification of the total population, but instead the German society for nutrition recommends 400µg synthetic folic acid supplementation to women who intend to become pregnant four weeks before conception until the end of the first trimester of pregnancy to prevent neural tube defects (67). In Madagascar, it has become a national strategy to supplement pregnant women with iron and folic acid since 2004 (68).

## 5.2 Mortality rates

The overall reported foetal death rate of the freeBILy trial resulted in 18.0 (95% CI: 14.5-22.0) deaths per 1000 births. Late foetal death rate (≥ 28 weeks of gestation) is 17.2 (95% CI: 13.8-21.1) and early foetal deaths 0.8 (95% CI: 0.2-2) per 1000 births. Survey data from 19 879 Madagascan women of 2018 and conducted by *Institut National de la Statistique* (INSTAT) in Madagascar included women aged 15 to 49 years in 23 regions of Madagascar, also incorporating the freeBILy study regions Bongolava, Itasy and Amoron'i mania (69). It reports 16.7 stillbirths per 1000 births (≥ 28 weeks of gestation), which is within the previously mentioned confidence interval of the data of the freeBILy study (69, 70). The stillbirth rate in Sub-Saharan Africa in 2019 was estimated to be 21.7 (90% Uncertainty Interval: 19.9-24.8) per 1000 births (71). The Global stillbirth rate in 2019 was estimated to be 13.9 (90% UI: 13.5-15.4) per 1000 births (71). Therefore, freeBILy data suggests a stillbirth rate (foetal death ≥ 28 weeks of gestation) that is lower than Sub-Sahara Africa, but still higher than the estimated global stillbirth rate.

Our freeBILy dataset has also shown 10.8 (95% CI: 8.1-14.0) neonatal deaths per 1000 live births. The corresponding official data suggests a neonatal mortality rate of

24.0 (CI 90% 20.6-28.3) per 1000 live births in 2018 based on UN Inter-agency Group for Child Mortality Estimation estimates in Madagascar (70). A demographic survey from Madagascar from 2016 to 2021 suggests a neonatal mortality rate of 26 per 1000 live births (69). We can speculate that this may be due to underreporting of neonatal deaths, a generally higher sense for health of the freeBILy participants compared to the overall population or other unknown factors. Estimations for 2017 for all regions worldwide result in a neonatal mortality rate of 18.0 (90% UI: 17.0-19.9) per 1000 livebirths (72). Estimations for 2017 for Sub-Sahara Africa result in 27.2 (90% UI: 24.7-31.6) per 1000 livebirths (72). This suggests that freeBILy data on neonatal deaths is closer and therefore lower compared to the global estimates than for Sub-Saharan Africa.

The maternal mortality (≤42d postpartum) rate results in 1.4 (95% CI: 0.6-2.9) per 1000 live births which corresponds to a reporting standard of 140 (95% CI: 60-290) per 100 000 live births. Our data is below data estimated by WHO based on national data, which estimated 335 (UI 80%: 229-484) per 100 0000 live births in 2017 (73). More recent estimates by WHO from 2020 conclude 392 (UI 80%: 311-517) maternal deaths (≤42d postpartum) per 100 000 live births (74).

Generally, clinical trials in resource-limited settings offer great potential to improve health outcomes because these populations are typically under-represented in global clinical research and suffer from great disease burden that can potentially be addressed in these researches (75). In our study population, we can observe the effect of the clinical trial freeBILy on two health outcomes analysed for this thesis: Child and maternal mortality. On one hand, the stillbirth rate is higher than the overall country statistics, but lower compared to Sub-Saharan Africa. The difference might be due to reporting issues in the context of the study, such as a selective reporting bias. While for the maternal mortality, we can speculate that we see lower deaths exactly because of the direct health benefit that they receive from the study program. These include the incentives the participants receive such as the care and small financial compensation for the trip to visit the health care facilities. The incentives to participate in a clinical trial such as financial compensation or special care can influence adherence to the trial (76, 77). Another possible factor with regards to the maternal mortality rate in freeBILy the fact that an unknown amount of maternal deaths is likely not reported and accounted as lost to follow-up.

Also, different collections processes (e.g. retrospective versus prospective) influence the estimated mortality rates that may also be relevant for freeBILy and its data comparison with other published data. Jensen et al. published findings that assuming full information with retrospective studies underestimates stillbirth rates and early neonatal mortality rates compared to prospective studies in analysed births between 2012 to 2020 in Western African Guinea-Bissau (78).

The overall and adjusted maternal mortality rate (irrespective of timepoint postpartum) 3.0 (95% CI: 1.7-4.9) per 1000 live births, which corresponds to 300 (95% CI: 170-490) per 100 000 live births. As this is not a standard rate for reporting, comparing the data with literature findings would provide only limited value.

## 5.3 Challenges for safety and tolerability studies in resource-limited settings

There are challenges associated with safety monitoring in clinical research in resource-limited settings. According to van den Broeck et al. these can generally be categorized into the three main groups (79). First, the scarcer resources and complicated field logistics contribute to a burdensome supply of study material, personnel and data capture. Second, the type and level of healthcare associated with safety-monitoring that is influenced by a wide range of factors, such as cultural, financial, geographical and characteristics of the health care system. Third, the technical, educational and cultural factors affecting communications with study participants and other involved parties as these factors may obfuscate crucial information for safety data reporting. Additionally, known barriers to health care also affect safety and tolerability reporting in resource-limited environments. Under broader definitions, these barriers include availability, accessibility, affordability and acceptability of the healthcare services (80). Any of these can hamper the data collection process and also bias the selection of study participants as potential participants will be excluded by these barriers. The study participants may be less likely to report crucial information about safety and tolerability during the trial. Generally, the information flow is also highly dependent on the relation and trust between the healthcare workers and its local community. In literature, the type of trust can generally be differentiated between interpersonal, public and workplace (77). The interpersonal trust relates to the individual level, such as the trust between healthcare provider and patient, whereas public trust relates to the trust of a person in an institution in general (81-83). The trust in workplace relates to trust in colleagues, supervisors and employers (84, 85).

There are also multiple possibilities regarding the issue of under-/overreporting of safety and tolerability data that are not uniquely associated with the freeBILy trial, but rather a recurring theme in resource-limited settings in general. The type of missing data can be classified according to a systematic guide (86). Data of AEs that are systematically related to the unobserved but not the observed data are considered missing not at random (MNAR). For example, MNAR data that is related to participants with a general distrust of the health care system or its health care workers (not measured, so unobserved) are more likely to deliver their children in their community with a trusted traditional midwife, seek alternative treatment in the form of massages/decoctions and only consult the health centre in case of exacerbation of a condition and/or extreme illness after failed traditional treatment or long inaction. A factor indicating the severity of this aforementioned issue may be the number of participants lost to follow up at the end of the study.

Another factor influencing the AE data which may be considered MNAR is the proximity: A participant that lives far away from a health centre is less likely to report AEs, especially lower graded AEs. Furthermore, MNAR may be the fact that some health centres and project nurses are more crowded and busier with participants than others, which may represent another hurdle to report an adverse event, also particularly the lower graded AEs. Also, the financial situation likely plays a role as on the one hand, a participant may refuse indicated treatment (such as a caesarean section during labour complications at a health centre) in the fear of not being able to pay the treatment, causing exacerbations of a medical issue and put both the mother's

and child's life at risk. On the other hand, a participant may abstain completely from reporting AEs as she may fear of having to pay a treatment.

Additionally, data may be missing completely at random (MCAR). "When data are MCAR, the fact that the data are missing is independent of the observed and unobserved data" (87, 88). This may be due to random factors such as possibly missing study material or circumstances hampering the data collection process.

Data can also be considered missing at random (MAR). "When data are MAR, the fact that the data are missing is systemically related to the observed but not the unobserved data" (87, 88). It is, for example, possible that study participants with a higher degree of education or more financial resources are more likely to be aware of health problems and pay services and therefore consult a medical professional earlier or at all compared to study participants with a lower degree of education and less available financial resources.

With regards to the freeBILy study, some midwives and nurses working for the study may be already under a high workload with general study activities so that details about reporting may be lost easily. The study participants may then be reluctant to wait in line for a consultation, especially when there are only minor effects such as for example headache or nausea to report. This is also particularly relevant when the information is passed along multiple steps and therefore some people along the way, potentially also without a medical professional background, fail to report crucial details about AEs/SAEs. This was frequently the case with SAEs with deadly sequelae that were reported by family members or other members of the participants community. This leaves some AEs and SAEs with very limited information, merely anecdotal and little to no possibility to clarify information. Another challenging aspect is related to CRF data capture and filling out by hand writing. Despite the double data entry of CRF data in the data centres, mistakes still occur.

Underreporting of deadly events such as maternal mortality is an obvious issue as the reporting will rely on a caregiver of the child or another close person to report the mother's death. Following the calculations of death rates, which are based on all pregnancies and are disregarding lacking information of lost-to-follow up subjects. This causes the death rates to likely be underestimated. The possibility arises to adjust rates based on actual follow-up data and participants lost to follow-up.

In freeBILy, maternal deaths were also reported by fieldworkers of the community. These fieldworkers typically aid in transmitting information to and from the community and also helped in recruiting participants. With regards to the reporting of safety and tolerability data in freeBILy, the interpersonal of healthcare provider and public trust in the system are likely most relevant.

The details of SAE reports are based on a qualitative questionnaire (Appendix Figure 13), leaving room for written, individual details described by the participant, who reports it to the field personnel (midwives/nurses) and is then subsequently written down by the ARC. This enables individual writing style of preparing the clinical report which may differ from person to person (e.g. ARCs).

Concerning the treatment, a review on single dose treatment with 40mg PZQ per kg bodyweight on adult and school-aged children suggests 88.7% (n=1079) adverse events of the studied population (28). The reported AEs are described as mild and transient in the review. However, there is a great disparity between the AE data (Grade 1-3) of the freeBILy trial and the conclusion of the review as only 2.4% (n=57) of the intervention arm in freeBILy reported at least one lower-graded AE as opposed to 88.7% (n=1079) of the review. The causes for this disparity can only be speculated, such as lack of active-follow up and different priorities of the studies.

## 5.4 Strengths and Limitations

### 5.4.1 Strengths

The present study reports about AEs and SAEs recorded in the context of a randomized controlled trial where 5114 women were assessed. Main strengths of this thesis are associated to the relatively large sample size and the randomization scheme that with a more in-depth analysis will allow to draw strong conclusions about safety and tolerability of PZQ treatment during pregnancy. Another strength is a relatively large dataset with 2346 pregnant women selected for the test-based treatment strategy. Also, the long follow-up period of 24 months can be seen as strength. Of the intervention arm, 76.7% (n=1799) of 2346 participants attended the last follow-up visit after 24 months. 1799 mother-child pairs successfully followed-up for 24 months in the intervention arm can provide valuable data, particularly about rare AEs and SAEs that are less likely to occur in a smaller sample.

### 5.4.2 Limitations

Despite the previously described strengths, the study is not free of limitations. The first limitation of this thesis is that it is based on the analysis of a non-closed data set hence, despite many cleaning efforts, the data used for this study is not final so that different conclusions can still occur in further analysis efforts. Additionally, the freeBILy trial was not designed to specifically evaluate safety and tolerability of PZQ administration during pregnancy. Factors like passive-follow up may have generated a reporting bias. The extent of the reporting bias is difficult to evaluate with the available data.

Further, the fact that in the Fianarantsoa province, 14 sites did not report any AEs, corresponding to 1423 recruited pregnant women and two sites did not report any SAEs, corresponding to 184 recruited pregnant women. Compared to the Antananarivo province with eight sites without AEs, corresponding to 1127 recruited pregnant women and three sites without SAEs, corresponding to 308 recruited pregnant women. The exact reporting procedures vary across the sites and according to the associated field personnel and ARCs. The imbalance of AEs/SAEs reported between the two provinces might be random, but possibly also due to the proactivity of the staff in identifying or reporting adverse events. The reporting is therefore highly dependent on the staff, hence human variability can only be partially controlled

Also, the the fact that the nature of this analysis is merely descriptive can be seen as a limitation, hence more in-depth analysis will have to be conducted in order to provide stronger conclusions.

Another technical aspect is the language barrier that likely also plays an important role as the level of French language proficiency was highly variable in freeBILy staff, who was responsible for translation of Malagasy conversations in order to collect data and fill out CRFs in French. The level of French proficiency of the study personnel was not objectively assessed.

# 6 Summary / Zusammenfassung

## 6.1 Summary

Schistosomiasis is a parasitic, neglected tropical disease that is particularly associated with poverty and lack of WASH facilities. It poses a significant public health problem in endemic countries, particularly in Sub-Saharan-Africa. The control of the disease requires a multifaceted approach, including preventive measures by education, treatment of the infected population, snail control and hygienic measures. A typical way of treatment of the population at risk includes a yearly MDA program with praziquantel. Despite recommendations by WHO to include women after their first trimester of pregnancy in MDA treatment programs, national policy makers and health care practitioners are still reluctant to follow. The consequences are inefficient control and a higher disease burden in vulnerable populations such as pregnant women. The results of this work show that treatment of pregnant women in their 4$^{th}$ to 5$^{th}$ month of pregnancy with praziquantel is generally safe and tolerable. There are no signs of an increase of foetal deaths, congenital anomalies or other SAEs in the pregnant, test-based treatment population. This corroborates the WHO guideline to include pregnant women after their first trimester in MDA treatment programs. Any delay of its implementation will have a negative impact on health of pregnant women in endemic countries. These results need to be considered as a component of a larger strategy to fight schistosomiasis. The strategy should include education and awareness programs as elements for prevention, regular treatment of affected populations by means of MDA, snail control and building and maintaining of WASH facilities.

## 6.2 Zusammenfassung

Bilharziose ist eine parasitäre, vernachlässigte Tropenkrankheit, die insbesondere mit Armut und fehlenden WASH-Einrichtungen in Verbindung gebracht wird. Sie stellt in endemischen Ländern, insbesondere in Subsahara-Afrika, ein erhebliches Problem für die öffentliche Gesundheit dar. Die Bekämpfung der Krankheit erfordert ein vielschichtiges Konzept, das Präventivmaßnahmen durch Aufklärung, Behandlung der infizierten Bevölkerung, Schneckenbekämpfung und Hygienemaßnahmen umfasst. Ein typischer Weg der Behandlung der Risikobevölkerung umfasst ein jährliches MDA-Programm mit Praziquantel. Trotz der Empfehlungen der WHO, Frauen nach dem ersten Schwangerschaftsdrittel in MDA-Behandlungsprogramme einzubeziehen, halten sich die nationalen politischen Entscheidungsträger und das Gesundheitspersonal immer noch zurück. Die Folgen sind eine ineffiziente Kontrolle und eine höhere Krankheitslast in gefährdeten Bevölkerungsgruppen wie schwangeren Frauen. Die Ergebnisse dieser Arbeit zeigen, dass die Behandlung von Schwangeren im 4. bis 5. Schwangerschaftsmonat mit Praziquantel im Allgemeinen sicher und verträglich ist. Es gibt keine Anzeichen für eine Zunahme fötaler Todesfälle, kongenitaler Anomalien oder anderer SAEs in der schwangeren, testbasierten Behandlungspopulation. Damit wird die WHO-Richtlinie, schwangere Frauen nach dem ersten Trimester in MDA-Behandlungsprogramme einzubeziehen, weiter bekräftigt. Jede Verzögerung bei der Umsetzung wird sich negativ auf die Gesundheit schwangerer Frauen in endemischen Ländern auswirken. Diese Ergebnisse müssen als Bestandteil einer umfassenderen Strategie zur Bekämpfung der Bilharziose betrachtet werden. Zu der Strategie gehören Aufklärungs- und Sensibilisierungsprogramme als Elemente der Prävention, die regelmäßige Behandlung der betroffenen Bevölkerung mittels MDA, die Schneckenbekämpfung sowie der Bau und die Instandhaltung von WASH-Einrichtungen.

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# 8 Abstract

**Background:** Schistosomiasis is a parasitic neglected tropical disease that is particularly associated with poverty and a lack of water, sanitation and hygiene (WASH) facilities. It poses a significant public health problem in endemic countries, mostly in Sub-Saharan-Africa. The World Health Organization (WHO) guidelines recommend to perform preventive annual chemotherapy as mass drug administrations (MDA) in endemic populations that include over two-year-old children, adults, pregnant women after their first trimester and lactating women. Despite its safe and efficient treatment, pregnant women are still often excluded from treatment programs as national policy makers and healthcare practitioners are reluctant to follow recommendations. This thesis aimed to further elucidate safety and tolerability aspects with regards to chemotherapy of pregnant women with schistosomiasis in Madagascar, where data and resources are scarce. This work also comprises evaluation of sociodemographic factors of foetal death and an evaluation of time-dependent serious adverse events (SAE), including prematurity and foetal death after chemotherapy with praziquantel.

**Methods:** This longitudinal study is based on a cohort of 5114 pregnant women recruited and followed-up in a rural context of Madagascar between April 2019 and September 2022. The intervention arm with test-based treatment of schistosomiasis included 2346 women, whereas the control arm included 2768 women. Recruitment and follow-up were conducted in 42 primary health care centres (CSBs) in the regions Bongolava, Itasy (both Antananarivo province) and Amoron'i Mania (Fianarantsoa province) in Madagascar. Adverse events (AE) were classified in four grades and clinical information coded according to the Medical Dictionary of Regulatory Activities (MedDRA®). Data capture of Case Report Forms (CRF) was done with REDCap®. Descriptive statistics was used to visualize results with R® Studio. Clopper-Pearson interval of death rates and interquartile ranges of sociodemographic data were calculated with Excel®. Lost to follow-up was determined based on data in the REDCap® database and available withdrawal/discontinuation CRFs that were filled out on the CSB level.

**Results:** Within the study population, a total of 287 AEs and SAEs were reported. This includes 131 AEs and SAEs in the control arm and 156 AEs and SAEs in the intervention arm. Foetal death was reported in 2.1% (57) of mothers in the control arm, whereas 1.5% (35) of mothers reported foetal death in the intervention arm. Timely association of chemotherapy with an SAE was found in four SAEs of which none were deemed causal by a data safety monitoring board (DSMB). Additional insights are also gained, such as an undersupply of folic acid/iron during pregnancy, but no cases of spina bifida or anencephaly were reported. Further, sociodemographic factors of fetal death suggest the known association of increased fetal death rates with rising maternal age. Of all participants, 20.7% (n=1057) did not seek to attend the last follow-up visit and data was missing for 2.0% (n=103). Therefore, lost to follow-up was determined to be 22.7% (n=1160) of all participants.

**Conclusion:** The results of this study contribute to further understanding of the safety and tolerability of praziquantel treatment during pregnancy. There are no signs of increased AEs/SAEs within the study population. According to this study, chemotherapy with praziquantel during pregnancy is generally safe and tolerable. In order to successfully control schistosomiasis, pregnant women need to be included in MDA programs. Therefore, national policy makers and healthcare practitioners need to incorporate these results along with WHO guidelines to successfully fight schistosomiasis.

# 9 Acknowledgements

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Lebenslauf aus datenschutzrechtlichen Gründen nicht enthalten

# 11 Appendix

Disclosure note: CRFs are confidential and not meant for distribution

*Figure 9 French Recruitment CRF (T0) Page 1*

Disclosure note: CRFs are confidential and not meant for distribution

*Figure 10 French Recruitment CRF (T0) Page 2*

Disclosure note: CRFs are confidential and not meant for distribution

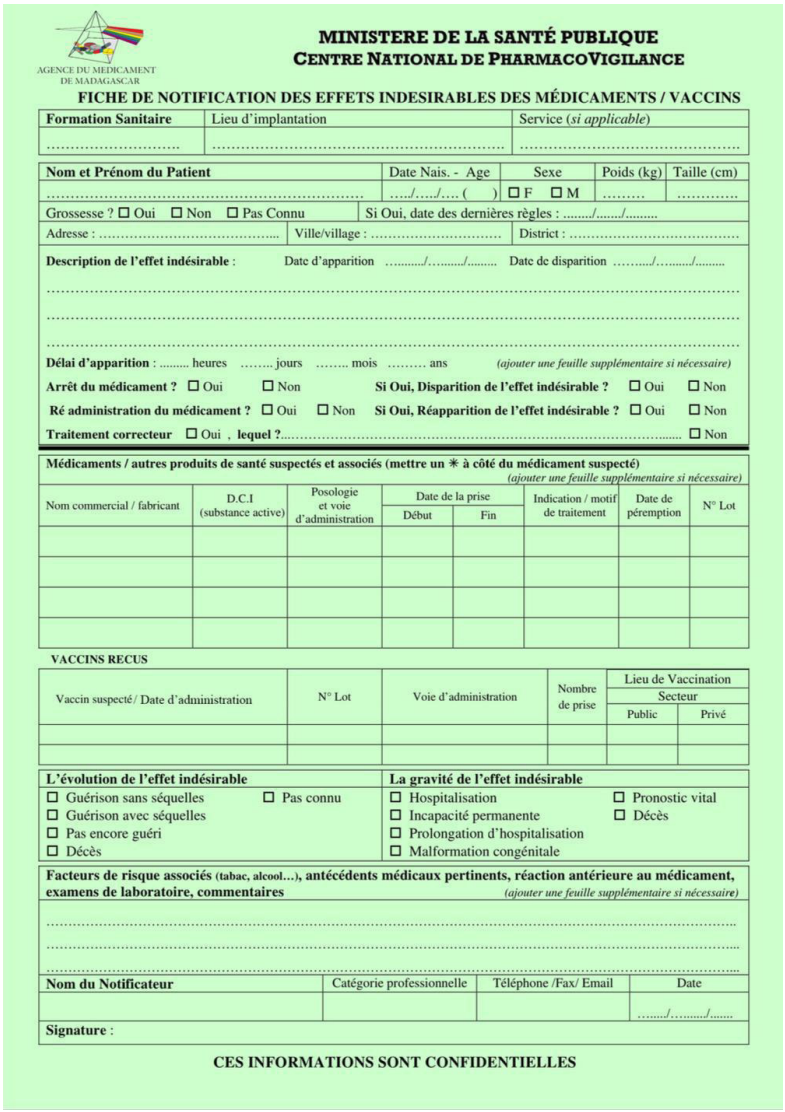
*Figure 11 AE / SAE CRF for freeBILy trial*

Disclosure note: CRFs are confidential and not meant for distribution

*Figure 12 Unscheduled Visit CRF for freeBILy trial*

Disclosure note: CRFs are confidential and not meant for distribution

*Figure 13 SAE Clinical Report CRF (REC_MeC_28_FRA)*



AGENCE DU MEDICAMENT DE MADAGASCAR

**MINISTERE DE LA SANTÉ PUBLIQUE**
**CENTRE NATIONAL DE PHARMACOVIGILANCE**

**FICHE DE NOTIFICATION DES EFFETS INDESIRABLES DES MÉDICAMENTS / VACCINS**

| **Formation Sanitaire** | Lieu d'implantation | Service (*si applicable*) |
|---|---|---|
| …… | …… | …… |

| **Nom et Prénom du Patient** | Date Nais. - Age | Sexe | Poids (kg) | Taille (cm) |
|---|---|---|---|---|
| …… | …./…./… ( ) | ☐ F ☐ M | …… | …… |

Grossesse ? ☐ Oui ☐ Non ☐ Pas Connu — Si Oui, date des dernières règles : ……/……/……

Adresse : …… — Ville/village : …… — District : ……

**Description de l'effet indésirable** : Date d'apparition ……/……/…… Date de disparition ……/……/……

……

……

……

**Délai d'apparition** : …… heures …… jours …… mois …… ans *(ajouter une feuille supplémentaire si nécessaire)*

**Arrêt du médicament ?** ☐ Oui ☐ Non **Si Oui, Disparition de l'effet indésirable ?** ☐ Oui ☐ Non

**Ré administration du médicament ?** ☐ Oui ☐ Non **Si Oui, Réapparition de l'effet indésirable ?** ☐ Oui ☐ Non

**Traitement correcteur** ☐ Oui , **lequel ?**…… ☐ Non

**Médicaments / autres produits de santé suspectés et associés (mettre un ✳ à côté du médicament suspecté)**
*(ajouter une feuille supplémentaire si nécessaire)*

| Nom commercial / fabricant | D.C.I (substance active) | Posologie et voie d'administration | Date de la prise | | Indication / motif de traitement | Date de péremption | N° Lot |
|---|---|---|---|---|---|---|---|
| | | | Début | Fin | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

**VACCINS RECUS**

| Vaccin suspecté / Date d'administration | N° Lot | Voie d'administration | Nombre de prise | Lieu de Vaccination | |
|---|---|---|---|---|---|
| | | | | Secteur | |
| | | | | Public | Privé |
| | | | | | |
| | | | | | |

| **L'évolution de l'effet indésirable** | | **La gravité de l'effet indésirable** | |
|---|---|---|---|
| ☐ Guérison sans séquelles | ☐ Pas connu | ☐ Hospitalisation | ☐ Pronostic vital |
| ☐ Guérison avec séquelles | | ☐ Incapacité permanente | ☐ Décès |
| ☐ Pas encore guéri | | ☐ Prolongation d'hospitalisation | |
| ☐ Décès | | ☐ Malformation congénitale | |

**Facteurs de risque associés (tabac, alcool…), antécédents médicaux pertinents, réaction antérieure au médicament, examens de laboratoire, commentaires** *(ajouter une feuille supplémentaire si nécessaire)*

……

……

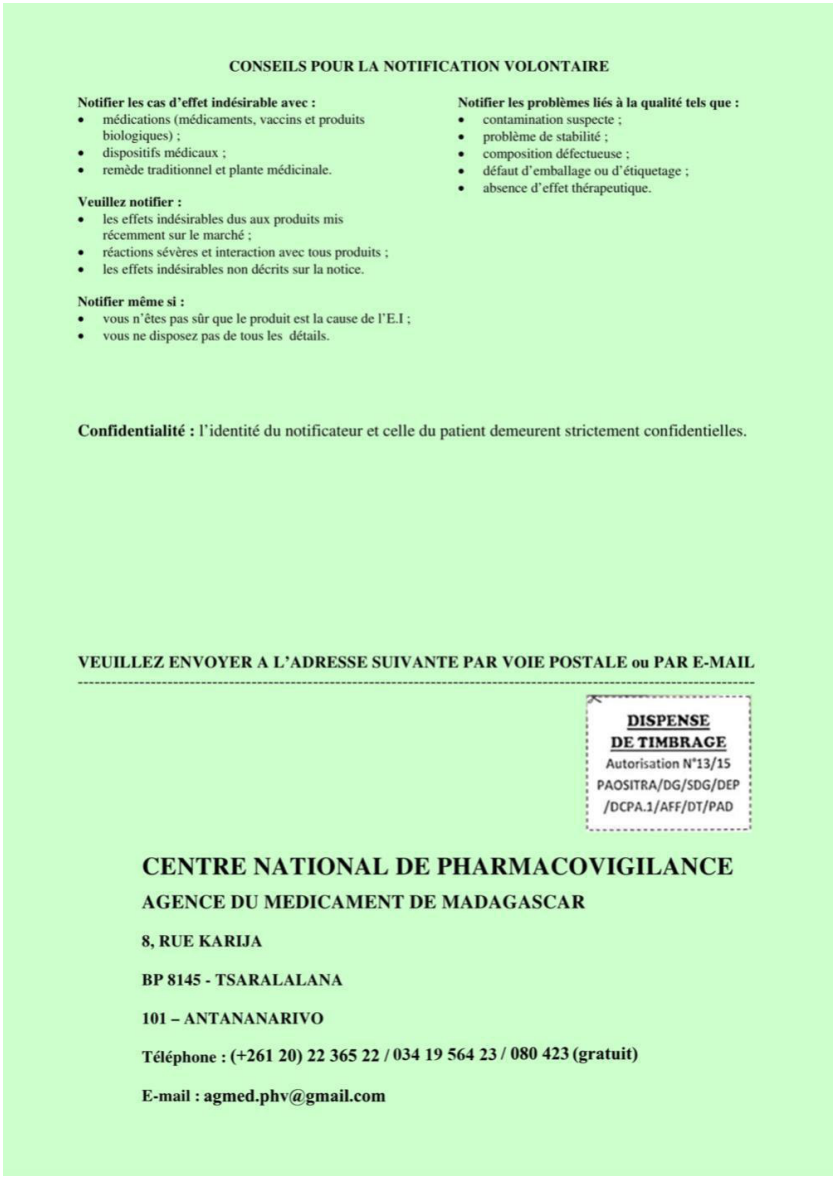
……

| **Nom du Notificateur** | Catégorie professionnelle | Téléphone /Fax/ Email | Date |
|---|---|---|---|
| | | | ……/……/…… |

**Signature** :

**CES INFORMATIONS SONT CONFIDENTIELLES**

*Figure 14 Page 1 of Notification Sheet for ADRs in Madagascar*



**CONSEILS POUR LA NOTIFICATION VOLONTAIRE**

**Notifier les cas d'effet indésirable avec :**

- médications (médicaments, vaccins et produits biologiques) ;
- dispositifs médicaux ;
- remède traditionnel et plante médicinale.

**Veuillez notifier :**

- les effets indésirables dus aux produits mis récemment sur le marché ;
- réactions sévères et interaction avec tous produits ;
- les effets indésirables non décrits sur la notice.

**Notifier même si :**

- vous n'êtes pas sûr que le produit est la cause de l'E.I ;
- vous ne disposez pas de tous les détails.

**Notifier les problèmes liés à la qualité tels que :**

- contamination suspecte ;
- problème de stabilité ;
- composition défectueuse ;
- défaut d'emballage ou d'étiquetage ;
- absence d'effet thérapeutique.

**Confidentialité :** l'identité du notificateur et celle du patient demeurent strictement confidentielles.

**VEUILLEZ ENVOYER A L'ADRESSE SUIVANTE PAR VOIE POSTALE ou PAR E-MAIL**

**DISPENSE**
**DE TIMBRAGE**
Autorisation N°13/15
PAOSITRA/DG/SDG/DEP
/DCPA.1/AFF/DT/PAD

**CENTRE NATIONAL DE PHARMACOVIGILANCE**
**AGENCE DU MEDICAMENT DE MADAGASCAR**
**8, RUE KARIJA**
**BP 8145 - TSARALALANA**
**101 – ANTANANARIVO**
**Téléphone : (+261 20) 22 365 22 / 034 19 564 23 / 080 423 (gratuit)**
**E-mail : agmed.phv@gmail.com**

*Figure 15 Page 2 of Notification Sheet for ADRs in Madagascar*

*Table 18 Adverse Event Counts and Sum per study arm*

| | Control | Intervention |
|---|---|---|
| Grade 1 | 5 | 42 |
| Grade 2 | 6 | 13 |
| Grade 3 | 0 | 3 |
| Grade 4 | 120 | 98 |
| Sum | 131 | 156 |

*Table 19 Analysis of foetal death and maternal age with added CI 95% per 1000 pregnancies*

| **Analysis of foetal death and maternal age (Overall)** | | | | |
|---|---|---|---|---|
| | | Foetal deaths | | |
| **Control/Intervention** | Total births* (N=5114) | Number | Rate (per 1000 pregnancies) | CI 95% (per 1000 pregnancies) |
| Maternal age (years) | | | | |
| 15 – 19 | 1108 | 18 | 16.2 | 9.7 – 25.6 |
| 20 – 24 | 1723 | 27 | 15.7 | 10.4 – 22.7 |
| 25 – 29 | 1155 | 11 | 9.5 | 4.8 – 17.0 |
| 30 – 34 | 627 | 15 | 23.9 | 13.45 – 39.2 |
| 35 – 39 | 345 | 8 | 23.2 | 10.1 – 45.2 |
| 40 - 44 | 138 | 10 | 72.5 | 35.3 – 129.2 |
| 45 – 49 | 17 | 3 | 176.5 | 38 – 434.3 |
| All ages | 5114 | 92 | 18.0 | 14.5 – 22.0 |
| **Control** | | | | |
| | | | | |
| | Total births (N=2768) | Foetal deaths | Rate (per 1000 births) | CI 95% (per 1000 births) |
| Maternal age (years) | | | | |
| 15 – 19 | 552 | 10 | 18.1 | 8.7 – 33.1 |
| 20 – 24 | 972 | 18 | 18.5 | 11.0 – 29.1 |
| 25 – 29 | 634 | 6 | 9.5 | 3.5 – 20.5 |
| 30 – 34 | 352 | 10 | 28.4 | 13.7 – 51.6 |
| 35 – 39 | 174 | 4 | 23.0 | 6.3 – 57.8 |
| 40 - 44 | 75 | 6 | 80 | 29.9 – 166.0 |
| 45 – 49 | 9 | 3 | 333.3 | 74.9 – 700.7 |
| All ages | 2768 | 57 | 20.6 | 15.6 – 26.6 |
| **Intervention** | | | | |
| | | | | |
| | Total births* (N=2346) | Foetal deaths | Rate (per 1000 births) | CI 95% (per 1000 births) |
| Maternal age (years) | | | | |
| 15 – 19 | 556 | 8 | 14.4 | 6.2 – 28.2 |
| 20 – 24 | 751 | 9 | 12 | 5.5 – 22.6 |
| 25 – 29 | 521 | 5 | 9.6 | 3.1 – 22.3 |
| 30 – 34 | 275 | 5 | 18.2 | 5.9 – 66.5 |
| 35 – 39 | 171 | 4 | 23.4 | 6.4 – 58.8 |
| 40 - 44 | 63 | 4 | 63.5 | 18.2 – 154.7 |
| 45 – 49 | 8 | 0 | 0 | NA – 369.4 |
| All ages | 2346 | 35 | 14.9 | 10.4 – 20.7 |

*1 missing age value for intervention case F18-10016-FG

*Table 20 Symptoms of all reported AEs/SAEs in freeBILy coded according to MedDRA®*

| System Organ Class (SOC) | Preferred Term (PT) | Intervention (N=2346) | | | | Control (N=2768) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AE Grade | | | | AE Grade | | | |
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| | Any PT | 69 | 34 | 3 | 363 | 5 | 4 | 3 | 389 |
| **Pregnancy, puerperium and perinatal conditions** | | | | | | | | | |
| | Premature baby | 0 | 0 | 0 | 30 | 0 | 0 | 0 | 44 |
| | Labour complication | 0 | 0 | 0 | 18 | 0 | 0 | 0 | 23 |
| | Postmature baby | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 7 |
| | Foetal dystocia | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 4 |
| | Prolonged labour | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 3 |
| | Haemorrhage in pregnancy | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 6 |
| | Placenta praevia | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | Cephalo-pelvic disproportion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| | Breech presentation | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 2 |
| | Gestational hypertension | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| | Meconium in amniotic fluid | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| | Neonatal hypotension | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Placenta accreta | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Placenta praevia haemorrhage | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Premature rupture of membranes | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 |
| | Threatened labour | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| | Foetal distress syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| | Shoulder dystocia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| | Peripartum cardiomyopathy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| | Induced labour | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Maternal death affecting foetus | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Peripartum haemorrhage | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Transverse presentation | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |
| | Umbilical cord around neck | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Umbilical cord occlusion | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Bradycardia foetal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Face presentation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Foetal hypokinesia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Postpartum stress disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Pre-eclampsia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Threatened uterine rupture | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Umbilical cord abnormality | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Umbilical cord prolapses | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

*Table 20 Symptoms of all reported AEs/SAEs in freeBILy coded according to MedDRA®, -Continued*

| System Organ Class (SOC) | Preferred Term (PT) | Intervention (N=2346) | | | | Control (N=2768) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AE Grade | | | | AE Grade | | | |
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **General disorders and administration site conditions** | | | | | | | | | |
| | Foetal death | 0 | 0 | 0 | 35 | 0 | 0 | 0 | 57 |
| | Death neonatal | 0 | 0 | 0 | 23 | 0 | 0 | 0 | 31 |
| | Pyrexia | 1 | 3 | 0 | 20 | 1 | 0 | 0 | 10 |
| | Death | 0 | 0 | 0 | 18 | 0 | 0 | 0 | 13 |
| | Maternal death | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 6 |
| | Fever neonatal | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 7 |
| | Condition aggravated | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Generalised oedema | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| | Chills | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Influenza like illness | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Drowning | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Asthenia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Critical illness | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Fatigue | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Hyperhidrosis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Inflammation | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Pallor | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Gastrointestinal disorders** | | | | | | | | | |
| | Vomiting | 19 | 1 | 0 | 6 | 0 | 0 | 0 | 4 |
| | Diarrhoea | 6 | 1 | 0 | 5 | 0 | 1 | 0 | 3 |
| | Nausea | 10 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Gastroenteritis | 4 | 1 | 0 | 7 | 0 | 0 | 0 | 7 |
| | Infantile vomiting | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 8 |
| | Abdominal distension | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 5 |
| | Diarrhoea neonatal | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 4 |
| | Abdominal discomfort | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Abdominal pain | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| | Abdominal pain upper | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Diarrhoea haemorrhagic | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Haemorrhagic gastroenteritis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Abnormal faeces | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Haematemesis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Aphthous ulcer | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | Inguinal hernia | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Salivary hypersecretion | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

*Table 20 Symptoms of all reported AEs/SAEs in freeBILy coded according to MedDRA®, -Continued*

| System Organ Class (SOC) | Preferred Term (PT) | Intervention (N=2346) | | | | Control (N=2768) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AE Grade | | | | AE Grade | | | |
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | | | | |
| | Cough | 1 | 0 | 1 | 7 | 2 | 0 | 0 | 7 |
| | Dyspnoea | 0 | 1 | 0 | 5 | 0 | 0 | 0 | 9 |
| | Neonatal aspiration | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 5 |
| | Neonatal dyspnoea | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 5 |
| | Cyanosis neonatal | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 |
| | Respiratory distress | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Rhinorrhoea | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 2 |
| | Neonatal pneumonia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Neonatal respiratory distress | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 1 |
| | Neonatal asphyxia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Rhinitis | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| | Neonatal dyspnoea | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 5 |
| | Lower respiratory tract infection | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| | Aspiration | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Neonatal tachypnoea | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Meconium aspiration syndrome | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Bronchial obstruction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Epistaxis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Bronchiolitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Haemoptysis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Cyanosis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Neonatal pneumonia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Cyanosis neonatal | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 |
| | Peritonsillar abscess | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Pneumonia | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 2 |
| | Pleural effusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Productive cough | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | | | | |
| | Vertigo | 12 | 3 | 0 | 2 | 0 | 0 | 0 | 1 |
| | Headache | 6 | 4 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Loss of consciousness | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 6 |
| | Generalised tonic-clonic seizure | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| | Neonatal seizure | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 6 |
| | Somnolence | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Seizure | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 1 |
| | Febrile convulsion | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Haemorrhage intracranial | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Meningitis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Thunderclap headache | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Surgical and medical procedures** | | | | | | | | | |
| | Resuscitation | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 6 |
| | Artificial rupture of membranes | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Caesarean section | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 8 |
| | Ventriculo-peritoneal shunt | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

*Table 20 Symptoms of all reported AEs/SAEs in freeBILy coded according to MedDRA®, -Continued*

| System Organ Class (SOC) | Preferred Term (PT) | Intervention (N=2346) | | | | Control (N=2768) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AE Grade | | | | AE Grade | | | |
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Cardiac disorders** | | | | | | | | | |
| | Oedema peripheral | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 2 |
| | Cardiac failure | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | Ascites | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Peripartum cardiomyopathy | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Cardiomyopathy alcoholic | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Dyspnoea | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Orthopnoea | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Haemoptysis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Reproductive system and breast disorders** | | | | | | | | | |
| | Vaginal discharge | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| | Cervix disorder | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Genital haemorrhage | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Intermenstrual bleeding | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Nipple disorder | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Vulvovaginal pruritus | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Pelvic pain | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Injury, poisoning and procedural complications** | | | | | | | | | |
| | Alcohol poisoning | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Ear haemorrhage | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Fall | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |
| | Accident at work | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Road traffic accident | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Metabolism and nutrition disorders** | | | | | | | | | |
| | Dehydration | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 5 |
| **Skin and subcutaneous tissue disorders** | | | | | | | | | |
| | Pruritus | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Rash | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Hepatobiliary disorders** | | | | | | | | | |
| | Cirrhosis alcoholic | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Congestive hepatopathy | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Jaundice | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| | Jaundice neonatal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Congenital hepatobiliary anomaly | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Psychiatric disorders** | | | | | | | | | |
| | Alcoholism | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | Delirium | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| **Vascular disorders** | | | | | | | | | |
| | Hypotension | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Hypertension | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| **Eye disorders** | | | | | | | | | |
| | Eye injury | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Orbital haematoma | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Eye swelling | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Immune system disorders** | | | | | | | | | |
| | Hypersensitivity | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

*Table 20 Symptoms of all reported AEs/SAEs in freeBILy coded according to MedDRA®, -Continued*

| System Organ Class (SOC) | Preferred Term (PT) | Intervention (N=2346) | | | | Control (N=2768) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AE Grade | | | | AE Grade | | | |
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Musculoskeletal and connective tissue disorders** | | | | | | | | | |
| | Muscle spasms | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Musculoskeletal stiffness | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Myalgia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Abscess limb | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Renal and urinary disorders** | | | | | | | | | |
| | Urinary tract infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| | Leukocyturia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Congenital, familial and genetic disorders** | | | | | | | | | |
| | Congenital hydrocephalus | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Cleft palate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Investigations** | | | | | | | | | |
| | Bleeding time prolonged | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Weight decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Social circumstances** | | | | | | | | | |
| | Parent-child problem | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Victim of crime | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

**Eidesstattliche Versicherung**

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....