Appendix 16.1.1 List of Protocols and Protocol Amendments

Protocol Version 1.0, 09 January 2020

Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase I, open-label, randomized, four-period, crossover, fully replicated, reference-scaled, single center study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers
Study Number:	MS200585_0004
Amendment Number	Not applicable
Merck Compound Number:	MSC1028703
Study Phase:	Phase I
Short Title:	Bioequivalence study of coated Cesol tablet formulation vs Biltricide
Principal Investigator:	PPD Nuvisan GmbH, PPD Germany
Sponsor Name and Legal Registered Address:	Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany
Regulatory Agency Identifying Numbers:	EudraCT: 2019-002868-27
Protocol Version:	09 January 2020/ Version 1.0
Replaces Version:	Not applicable
Approval Date:	09 January 2020
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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase I, open-label, randomized, four-period, crossover, fully replicated, reference-scaled, single center study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers

Short Title: Bioequivalence study of coated Cesol tablet formulation vs Biltricide

Rationale: As a requirement for the praziquantel donation program by Merck KGaA, the WHO requested the development of an improved formulation of praziquantel 600 mg tablets. This study is planned to investigate the bioequivalence (BE) of the test product, Merck's new praziquantel 600 mg coated tablet formulation (herein coated Cesol tablet) versus the reference product praziquantel 600 mg tablet from Bayer (Biltricide). Biltricide is the comparator product recognized by the WHO Prequalification Team Medicines.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Primary	
To assess the BE of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg with regard to rac-PZQ	• PK parameters C_{max} and area under the plasma concentration-time curve from time zero to last measurable concentration (AUC_{0-t}) of rac-PZQ after single dose administration
Secondary	
To evaluate the safety and tolerability of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg	• Occurrence of TEAEs and treatment related AEs per Qualitative Toxicity Scale • Standard laboratory hematology and biochemical parameters, vital signs (body temperature, systolic and diastolic blood pressure, and pulse rate) and ECG parameters.
To assess the BE of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg with regard to PZQ enantiomers	• PK parameters C_{max} and area under the plasma concentration-time curve from time zero to last measurable concentration (AUC_{0-t}) of R-(-)-PZQ and S-(+)-PZQ after single dose administration
To further characterize the PK profile of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg	• PK parameters of rac-PZQ, R-(-)-PZQ and S-(+)-PZQ after single dosing: $AUC_{0-\infty}$, time to reach maximum plasma concentration (t_{max}), t_{lag}, $t_{½}$, λ_z, $CL/_f$ and $V_{Z/f}$

Overall Design: This is a Phase I, crossover, open-label, single dose, fully replicated, reference-scaled, randomized 4-period clinical pharmacology study to assess the relative bioavailability of coated Cesol tablets versus (vs) Biltricide in healthy male volunteers.

Number of Participants: 36 participants are planned to be randomized (18 participants per sequence). If 5 or more participants drop out of the study before completing period 4, additional participants may be randomized to meet the required minimal number of evaluable participants (N = 32).

Study Intervention Groups and Duration: Participants will be randomized to one of two sequences: T1-R1-T2-R2 or R1-T1-R2-T2, where T is Test product and R is Reference product, with a washout period of at least 1 week in between. In accordance with the fully replicated study design, the number after T and R refers to the first or second administration of the test or reference product, respectively, within the assigned sequence.

Involvement of Special Committee(s): No

1.2 Schema

<table>
<tr><th></th><th>Period 1</th><th></th><th>Period 2</th><th></th><th>Period 3</th><th></th><th>Period 4</th></tr>
<tr><td>Sequence 1 (18 participants)</td><td>Test 1</td><td rowspan="2">Washout at least 7 days</td><td>Reference 1</td><td rowspan="2">Washout at least 7 days</td><td>Test 2</td><td rowspan="2">Washout at least 7 days</td><td>Reference 2</td></tr>
<tr><td>Sequence 2 (18 participants)</td><td>Reference 1</td><td>Test 1</td><td>Reference 2</td><td>Test 2</td></tr>
</table>

Test = coated Cesol tablet, 2 tablets of praziquantel 600 mg;
Reference = Biltricide, 2 tablets of praziquantel 600 mg.

1.3 Schedule of Activities

Activity/Assessment	Screening (Baseline)	Treatment Period 1, 2, 3 and 4					End of Treatment / Safety Follow-up	Comments
Study Day	**Day -28 to -1**	**Day -1/7/14/21**	**Day 1/8/15/22[a]**			**Day 2/9/16/23**	**Day 27 (± 3 days)**	[a] Assuming 7 days for washout between the 4 treatment periods.
Period Day		**-1**	**1**			**2**		
Study Day timepoints			**-1 h**	**-0.5 h**	**0 h**	**24 h**		
ICF signature available	X							
Demographics (incl. BW and BMI), medical history and history of medication	X							
Smoking history, alcohol intake, use of caffeine or xanthine-containing beverages	X							
Serology test	X							
Physical examination[b]	X	X					X	[b] According to the CRO procedure.
Vital signs[c] (BP, HR, body temperature)	X	X	X			X	X	[c] At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs and ECG assessments within 15 min before the specific time point and PK blood sampling on time.
12-Lead-ECG[c]	X		X			X	X	[c] At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs and ECG assessments within 15 min before the specific time point and PK blood sampling on time.
Safety lab tests	X	X				X	X	
Drug screening urine	X	X						

Activity/Assessment	Screening (Baseline)	Treatment Period 1, 2, 3 and 4					End of Treatment / Safety Follow-up	Comments
Study Day	**Day -28 to -1**	**Day -1/7/14/21**	**Day 1/8/15/22[a]**			**Day 2/9/16/23**	**Day 27 (± 3 days)**	[a] Assuming 7 days for washout between the 4 treatment periods.
Period Day		**-1**	**1**			**2**		
Study Day timepoints			**-1 h**	**-0.5 h**	**0 h**	**24 h**		
Alcohol breath test	X	X						
Confinement[d]		[----------X----------]						[d] Confinement from the morning of Day -1/7/14/21 (about 20-24 hours prior to each IMP administration) until the morning of Day 2/9/16/23.
Standardized breakfast				X				
In/exclusion criteria check/recheck	X	X	X					
Randomization			X[f]					[f] Randomization will be performed in eligible participants on Day 1 only.
Administration of IMP					X			
PK sampling[c,e]			[-------X----]					[c] At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs and ECG assessments within 15 min before the specific time point and PK blood sampling on time. [e] PK sampling at predose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0 and 12 hours.
AE and concomitant medication	X	[----------X----------]						

AE=adverse events; BP=blood pressure; CRO=Contract Research Organization; ECG=electrocardiogram; HR=heartrate; ICF=informed consent form; IMP=investigational medicinal product; PK=pharmacokinetics.

2 Introduction

Schistosomiasis, also called Bilharzia, belongs to one of the most neglected tropical diseases caused by flatworms. It remains one of the most prevalent parasitic diseases in developing countries. After malaria, schistosomiasis is the most important tropical disease in terms of human morbidity with significant economic and public health consequences. The disease is a severe chronic inflammatory disease and is endemic in about 78 developing countries, affecting more than 220 million people, with more than 90% of them living in Africa. Infected individuals live in rural agricultural and peri-urban areas. In those areas more than 700 million people are at risk. Of the infected patients, 20 million suffer severe consequences from the disease. The WHO estimate that there are approximately 20,000 deaths related to schistosomiasis yearly. In many areas, a large proportion of children under the age of 14 years are infected.

The control strategy of schistosomiasis as recommended by the WHO is based on preventive chemotherapy interventions targeting the majority of the at-risk population. The current gold standard treatment employs an annual single oral dose of praziquantel (rac-PZQ) in tablet form. Rac-PZQ was jointly developed by Bayer AG and Merck KGaA in the 1970s and commercialized for human use in 1980 as Biltricide® (Bayer) and Cisticid/Cysticide® (Merck KGaA). Note that Cesol™ (herein Cesol) is the tradename for the WHO donation program. Cesol and Cisticid are identical 600 mg final tablet presentations. Since 2007, Merck is donating praziquantel 600 mg tablets, manufactured at Merck's manufacturing site in Mexico, to the WHO under the tradename Cesol.

As a requirement for the praziquantel donation program, the WHO requested the development of an improved formulation of Cesol to address complaints of broken tablets of the current formulation and to consider a tablet coating to decrease the bitter tasting of the tablets (herein coated Cesol tablet). For WHO this improved coated Cesol tablet is seen as a new generic PZQ formulation and should be compared with the current WHO standard PZQ being Biltricide.

Rac-PZQ tablets consist of a racemic mixture of the two enantiomers R-PZQ (L-PZQ; MSC2499550A) and S-PZQ (D-PZQ; MSC2499551A) in a 1 to 1 ratio. The R-PZQ enantiomer is associated with the anti-helminthic activity, whereas the S-PZQ has no cidal activity against worms and was reported to be responsible for the extreme bitterness of the product.

Complete information on the pharmacology, efficacy, and safety of rac-PZQ is in the German Summary of Product Characteristics for Biltricide.

Table 1 gives an overview of the generic and alternate names used. The generic name "Praziquantel" is used for IMP labeling, see Section 6.1.

Table 1 Praziquantel enantiomers

Generic Name	Abbreviations	Alternate names	MSC# (Refers only to drug substance synthesized by the Sponsor)
Praziquantel	rac-PZQ	Generic: racemic Praziquantel Trade: Biltricide, Cisticid, Cysticide, Cesol, Cestox	MSC1028703A
Enantiomers			
Levo-Praziquantel	L-PZQ, R-(−)-praziquantel	R-(-)-Praziquantel, R-Praziquantel, L-Praziquantel, R Enantiomer, L Enantiomer	MSC2499550A
Dextro-Praziquantel	D-PZQ, S-PZQ	D Praziquantel, S-(+)-Praziquantel, D Enantiomer, S Enantiomer	MSC2499551A

D-PZQ = Dextro-praziquantel, S-PZQ, MSC2499551A; PZQ = praziquantel; rac-PZQ = racemic praziquantel (mixture of L-PZQ and D-PZQ in a 1 to 1 ratio); L-PZQ = levo-praziquantel, R-(−)-praziquantel, MSC2499550A; S-PZQ = S-(+)-praziquantel, dextro-praziquantel, D-PZQ, MSC2499551A.

2.2 Background

See Section 2.

2.3 Benefit/Risk Assessment

Healthy participants in this Phase I trial will not derive any clinical benefit from the treatment. However, the planned trial is thought to have a beneficial impact for future patients. The clinical trial protocol has been designed to minimize the risk to participants in this trial by an adequate selection of eligibility criteria, schedule of clinical monitoring, in-house observation, and administration and treatment duration.

Rac-PZQ is very well tolerated. Side effects are usually mild and transient and do not require treatment.

Side effects reported after use of Biltricide as specified in the Summary of Product Characteristics (dated Oct 2017) are presented in Table 2, and based on data from the literature and spontaneous reports. It is frequently not clear whether the complaints reported by patients or adverse effects determined by the physician have been caused directly by praziquantel (direct relationship), whether these are to be regarded as a physical reaction to the killing off of the parasites by praziquantel (indirect relationship) or else represent signs and symptoms of the parasitic infection (no relationship).

Table 2 Side effects reported after use of Biltricide

	Frequencies		
System Organ Class	**Very Common ≥1/10**	**Frequently ≥ 1/100 to < 1/10**	**Very Rare <1/10,000**
Immune system disorders			Allergic reactions Eosinophilia
Nervous system disorders	Headache Lightheadedness	Dizziness Somnolence	Convulsions
Cardiac disorders			Unspecific arrhythmias
Gastrointestinal disorders	Gastrointestinal and abdominal pain Nausea Vomiting	Anorexia Diarrhea (bloody diarrhea is very rare)	
Skin and subcutaneous tissue disorders	Urticaria	Skin rash	Pruritus
Musculoskeletal and connective tissue and bone disorders		Myalgia	
General disorders and administration site conditions	Fatigue	General discomfort Fever	

The side effects vary depending on the dose and duration of praziquantel use. In addition, they depend on the parasite species, the extent and duration of the infections, as well as the localization of the parasites in the body.

A justification of the dose used is provided in Section 4.3.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of rac-PZQ may be found in the Participant Information and Sections 15-18 of the current Periodic Benefit-Risk Evaluation Report for Praziquantel (01 May 2015 to 30 April 2018, PPD

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
To assess the BE of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg with regard to rac-PZQ	PK parameters C_{max} and area under the plasma concentration-time curve from time zero to last measurable concentration-(AUC_{0-t}) of rac-PZQ after single dose administration
Secondary	
To evaluate the safety and tolerability of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg	Occurrence of TEAEs and treatment related AEs per Qualitative Toxicity Scale Standard laboratory hematology and biochemical parameters, vital signs (body temperature, systolic and diastolic blood pressure, and pulse rate) and ECG parameters.
To assess the BE of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg with regard to PZQ enantiomers	PK parameters C_{max} and area under the plasma concentration-time curve from time zero to last measurable concentration (AUC_{0-t}) of R-(-)-PZQ and S-(+)-PZQ after single dose administration
To further characterize the PK profile of the 600 mg coated Cesol tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg	PK parameters of rac-PZQ, R-(-)-PZQ and S-(+)-PZQ after single dosing: $AUC_{0-\infty}$, time to reach maximum plasma concentration (t_{max}), t_{lag}, $t_{½}$, λ_z, $CL/_f$ and $V_{Z/f}$

4 Study Design

4.1 Overall Design

The purpose of the current clinical pharmacology study is to assess the relative bioavailability of the coated Cesol tablets vs Biltricide, in healthy male participants. The study is a Phase I, crossover, open-label, single dose, fully replicated, reference-scaled, randomized 4-period study.

Participants will be randomized to one of 2 sequences: T1-R1-T2-R2 and R1-T1-R2-T2, where T is Test product and R is Reference product, with a washout period of at least 1 week in between. The number after T and R refers to the first or second administration of the test or reference product, respectively, within the assigned sequence. An overview of the treatment sequences for the fully replicated crossover design is given in Section 1.2.

In each treatment period participants are institutionalized in the morning of the day before dosing until 24 hours after dosing. The total time in the study for a participant is up to 8 weeks, including

the screening period of maximum 4 weeks, and 4 weeks from first to 4th dose and including the safety follow-up period of approximately one week after the last dose.

The detailed Schedule of Activities (SoA) is provided in Section 1.3

4.2 Scientific Rationale for Study Design

4.2.1 General

For the design of this BE study the following documents were taken into account: the WHO PQTm Guidance Document 13 October 2015 regarding the design of BE studies for rac-PZQ “Notes on the Design of Bioequivalence Study: Praziquantel"; the new WHO PQTm Guidance Document 22 November 2018 “Application of reference-scaled criteria for AUC in BE studies conducted for submission to PQTm”, which allows scaling of the acceptance criteria for AUC for highly variable active pharmaceutical ingredients if scientifically justified. In addition, the Protocol of this BE study will be reviewed by WHO PQP before finalization.

Replicate crossover designs are used to allow estimation of (1) within-subject variance for the reference product, or for both the test and reference products, and (2) the participant by formulation interaction variance component. This design accounts for the inter-occasion variability that may confound the interpretation of a BE study as compared to a nonreplicate crossover approach. In contrast to the previous study (EMR200585-0002), which had a 3-period design, the currently planned study will have a 4-period, fully replicated crossover design. Due to the high variability known for rac-PZQ, in the first BE study a reference scaled approach for C_{max} was used. To be able to accommodate this, a partial replicated design was adopted where the Reference formulation was given twice. The new WHO PQTm guidance document “Application of reference-scaled criteria for AUC in BE studies conducted for submission to PQTm” allows also scaling of the acceptance criteria for AUC for highly variable active pharmaceutical ingredients if scientifically justified. Therefore, in the current study, it is proposed to use the reference scaled approach for both C_{max} and AUC (see Section 9.4.3 for details). To be able to do such a scaled approach for both PK parameters a full 4-way replicate design needs to be adopted.

Only male participants will be included as no information on variability of rac-PZQ in adult women was found. It is known that increased levels of estrogen and progesterone can alter hepatic enzyme activity (Choi 2013); this might lead to fluctuations in metabolism over the 4-week study period and thus increase the within-subject variability in women. In addition, the use of contraceptives can also lead to fluctuations in estrogen and progesterone activity over a 4-week period, with concomitant changes in hepatic enzyme activity and the risk for increased variability and confounding the PK data. For this reason, only male participants will be included.

Food effect

A significant positive food effect is well known for PZQ and was also shown for the orally dissolving tablet formulation (Bagchus 2019). The WHO guideline for rac-PZQ states the following: “the bioequivalence study should be conducted in the fed state as praziquantel is recommended to be taken with food. While specific requirements regarding the type of meal are not necessary, the variability is increased if the tablets are taken with a high-fat, high-calorie meal

and hence, administration with a standard breakfast, not a high-fat, high-calorie meal, is recommended."

The breakfast administered in the first BE study had about a total of 550 kilocalories with 302.5 kilocalories (76 g) carbohydrates, 82.5 kilocalories (21 g) proteins and 165 kilocalories (18 g) lipids. A similar composition will be adopted for the current study. All meals and timing of meals on the dosing day in each period should be similar.

4.2.2 Justification for using the reference scaled approach

When using a reference scaled approach to establish bioequivalence, the acceptance region of (0.80-1.25) for the confidence interval of the ratio of geometric means may be widened depending on the within-subject variability of the reference product. If the observed within-subject coefficient of variation is less than 30%, no scaling will be applied. For a coefficient of variation (CV) above 30%, scaled acceptance criteria will be applied. Details are described in Section 9.4.3. To support the request to apply a reference scaled approach also for AUC, the known variability as well as the effect for the therapeutic window/safety effect need to be taken into account.

a) Magnitude of observed variability for rac-PZQ.

The guidance document of 2015 issued by PQTm states the following: Information on rac-PZQ currently available to the PQTm indicates that the intrasubject variability for rac-PZQ is around 50−60% for C_{max} and 35% for AUC_{0-t}.

The data from the first BE study showed that the observed intrasubject variability for rac-PZQ for C_{max} and AUC for the reference formulation was respectively 47.08% and 33.4% while the overall CV% was above 60% for both C_{max} and AUC for all 3 administrations.

b) Impact of widened acceptance criteria on safety and efficacy.

As of now, no clinical data are available that show a convincing correlation between exposure to rac-PZQ or R-(-)-PZQ and efficacy (characterized by cure rate as assessed by Kato-Katz method), neither in adults nor in children. At the time of registration in the seventies no proper dose-finding and efficacy studies were performed and the available PK data was obtained in a few healthy volunteers. Most data on efficacious doses have been gathered later from meta-analysis studies.

Recently, several meta-analyses have been performed showing quite an extensive overlap in efficacy in schistosomiasis treatment between a dose of 30, 40 and 60 mg/kg of rac-PZQ indicating a wide therapeutic range (Olliaro 2011, Zwang 2014). From these data, combined with the overall acceptable safety of the compound even at high doses, it is expected that accepting a wider CI for showing BE will not affect the overall efficacy or the safety of the upgraded formulation.

4.2.3 Washout Period

The minimum washout period between each investigational medicinal product (IMP) administration is set to 7 days in accordance with the WHO Guidance. It is expected that for logistic reasons a washout period of 7 days is convenient. From a scientific point of view a shorter

period could be envisaged as the mean half-life of rac-PZQ is 2.5 hours while the half-life of the main trans-OH-rac-PZQ metabolite is approximately 4.5 hours (Geomean; min-max 2.8 to 6.3 hours; data on file). In addition, for individual cases a longer washout period could be allowed.

4.3 Justification for Dose

The WHO PQTm advises the use of one oral tablet of rac-PZQ 600 mg for a BE study, which corresponds to a dose of just below 10 mg/kg for an adult of 70 kg, but in the first BE (EMR200585-0002) study a dose of 1200 mg was used and agreed with WHO. For this study also a dose of 1200 mg will be used.

From a safety perspective, the dose of 1200 mg rac-PZQ is below the therapeutic dose range and remains within 12.6 mg/kg up to 21.8 mg/kg according to the body weight limits of 55.0 - 95.0 kg in this study. In a previous 4-way crossover PK and food effect study (EMR200585-001) in healthy participants (N=32), single doses of other PZQ formulations of 40 mg/kg as well as 60 mg/kg administered during the 4 periods were shown to be well tolerated and without any serious adverse events (SAEs) or withdrawals due to treatment-emergent adverse events (TEAEs) (https://clinicaltrials.gov/ct2/show/NCT02325713?term=200585-001&rank=1). Nausea (7 of 24 TEAEs) and headache (7 of 24 TEAEs) were the most commonly reported TEAEs. The majority of TEAEs reported in a total of 12 participants (37.5%) was mild (91.7% [22/24]) and 2 TEAEs were moderate (8.3% [2/24]; both were headache), and all were transient and resolved during the study. Taken together, the proposed single dose of 1200 mg rac-PZQ to be administered in the 4 periods with a washout time of at least 7 days is considered safe and appropriate to address the study objectives.

4.4 End of Study Definition

A participant has completed the study if he has completed all study parts, including the last visit shown in Section 1.3 (SoA).

The end of the study is defined as the date of the last visit of the last participant.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are 18 to 55 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Are overtly healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, and cardiac monitoring. Rescreening will be allowed for laboratory tests and cardiac monitoring to exclude false-positive/negative findings.
3. Nonsmoker (=0 cigarettes, pipes, cigars or others) since at least 3 months.
4. Electrocardiogram (ECG) recording (12-lead) without signs of clinically relevant pathology in particular QTc (Fredericia) < 450 ms.
5. Vital signs in the following normal range (after 5 minutes in supine position):

   Systolic blood pressure 90 to 140 mmHg,

   Diastolic blood pressure 50 to 90 mmHg,

   pulse rate 50 to 90 bpm

   auricular body temperature between 35.9°C and 37.6°C

Weight

6. Have a body weight within 55.0 to 95.0 kg and body mass index within the range of 18.5 to 29.9 kg/m^2 (inclusive).

Sex

7. Are males. Agree to the following during the study intervention period and for at least 120 days starting on the day of the first IMP dose (covering a full sperm cycle of 90 days starting after 5 half-lives of last dose of IMP):
   - Refrain from donating sperm
   - Use a male condom when having sexual intercourse with a woman of child-bearing potential, who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.

Informed Consent

8. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any condition, including any clinically relevant abnormality in the safety laboratory parameters as judged by the Investigator, that in the Investigator's opinion constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
2. Allergy: ascertained or presumed hypersensitivity to the active drug substance and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the study outcome.
3. Have positive results from serology examination for Hepatitis B surface antigen (indicative of active Hepatitis B), Hepatitis C Virus or Human Immunodeficiency Virus (Human Immunodeficiency Virus 1/2 antibodies).
4. Nonacceptance or noncompliance with the study breakfast (e.g. vegetarians, vegans and participants who follow special diets).
5. Any condition that according to the Investigator's opinion could influence the gastrointestinal (GI) absorption and/or motility, e.g. history of surgery of the GI tract, history of other GI tract diseases, or acute recent GI tract infections (in the last 2 weeks).
6. Vomiting within 6 hours after dosing.

Prior/Concomitant Therapy

7. Participants who have used drugs that may affect the pharmacokinetics of rac-PZQ from 15 days before dosing until the last PK sample, e.g., phenytoin, barbiturates, primidone, carbamazapine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin, oral ketoconazole.

Prior/Concurrent Clinical Study Experience

8. Participation in any clinical study within 1 month or 5 half-lives of the IMP, whatever is longer, prior to first planned dose of IMP or during participation in this study, confirmed by a negative Verified Clinical Trials check (with the check to be completed before randomization).
9. Loss or donation of more than 400 mL of blood within 90 days prior to first rac-PZQ administration.
10. Consumption of substances known to be potent inhibitors or inducers of CYP P450 enzymes such as grapefruit juice, grapefruit juice containing products, Seville oranges, herbal remedies or dietary supplements containing St. John's Wort, broccoli, and Brussel sprouts, in the two weeks before dosing.

Diagnostic Assessments

11. History or presence of drug or alcohol abuse. Alcohol abuse is defined as: an average daily intake of more than 3 units or a weekly intake of more than 21 units where 1 unit equals 340 mL of beer, 115 mL of wine or 43 mL of spirits.
12. Positive test for drugs of abuse (including alcohol) at Screening and prior to each dosing.

Other Exclusions

13. Unlikely to comply with the protocol requirements, instructions and study-related restrictions; e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study.
14. Subject is the Principal Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
15. Inability to communicate or cooperate with the Investigator (e.g. language problem, illiterates, poor mental status) or to comply with the requirements of the entire study, including dietary restrictions.
16. Vulnerable subjects (e.g., persons kept in detention).
17. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit, grapefruit juice or grapefruit juice containing products, cranberry containing food or beverages, herbal remedies or dietary supplements containing St. John's Wort, broccoli, and Brussel sprouts from 2 weeks before the start of study intervention until Day 2 after the final dose.

Poppy seeds may not be consumed within 48 hours before dosing and throughout the treatment periods.

The study participants will receive a standardized breakfast at the time specified in the SoA (Section 1.3).

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoids

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for at least 48 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

- Use of cannabinoids is not allowed during the whole study. Subjects must have a negative test for drugs of abuse at Screening and prior to each dosing and subjects with a history or presence of drug abuse will be excluded from the study (exclusion criteria 11 and 12).
- Use of any tobacco or nicotine-containing products (including nicotine patches) will not be permitted until completion of all study assessments.

5.3.3 Activity

Participants will abstain from strenuous exercise for at least 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

For all treatments, participants will stay in a semirecumbent position for 2 hours postdose.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Study Intervention Name	Coated Cesol tablet	Biltricide
Drug Name on IMP Label	Test product: Praziquantel	Reference product: Praziquantel
Dose Formulation	Film-coated tablet	Film-coated tablet
Unit Dose Strength(s) /Dosage Level(s)	600 mg	600 mg
Route of Administration	Oral	Oral
Dosing Instructions	2 tablets of 600 mg with 240 mL of water after a standardized breakfast.	2 tablets of 600 mg with 240 mL of water after a standardized breakfast.
Supplier/ Manufacturer	Supplied by Merck Healthcare KGaA as labelled IMP in a bottle of 1000 tablets (sourced from Merck Mexico)	Supplied as labelled IMP by Merck Healthcare KGaA (sourced from Germany)
Packaging and Labeling	Each bottle will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. • For the **Reference product: Praziquantel** 600 mg (Biltricide), QP released IMP is one labelled bottle, containing six tablets. Each bottle is labelled individualized per participant (one bottle per participant for two administrations). - For Good Clinical Practice (GCP) dispensing, individual doses (of 2 tablets) will be administered directly from the bottle per participant (containing six tablets) • For the **Test product: Praziquantel** 600 mg (coated Cesol tablet), QP released IMP is one labelled bottle of 1000 tablets imported from Merck Mexico. - For GCP dispensing, participant individual containers with dispensing labels will be prepared at the trial site. On each dosing day shortly prior to the administration, trained and delegated staff of the Phase I unit will prepare individual doses of the test product under GCP requirements using a "4 eyes principle". For each participant 2 tablets from the QP released IMP (bottle of 1000 tablets) will be dispensed into labeled, participant- and drug-specific containers. More details will be described in the IMP Handling Manual.	

6.1.1 Medical Device(s) Use

Not applicable.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the IMP handling manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study and prepared at the site.
    - The dose(s) each participant used during the study.
    - The disposition (including return, if applicable) of any unused study intervention(s).
    - Dates, quantities, batch numbers, container numbers, if applicable, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the IMP handling manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

On Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the 2 sequences of the study, per the randomization schedule generated prior to the study by Nuvisan GmbH PPD.

Participants will be randomized in a 1:1 ratio to 1 of 2 sequences: T1-R1-T2-R2 or R1-T1-R2-T2.

6.3.2 Blinding

Blinding Method

This is an open-label study.

Assignment Method Retention

As the study is a crossover study using administration of active (either Test or Reference) at each administration, there is no blinding, although the coated Cesol tablet and Biltricide differ only slightly in their appearance. However, the bioanalytical monitors and analytical laboratory for measurement of rac-PZQ concentrations will be blinded since obtaining the result will not reveal the study intervention arm for the participant.

Unblinding Clinical Studies for Sample Analysis of Special Data

Not applicable.

6.3.3 Emergency Unblinding

Not applicable.

6.4 Study Intervention Compliance

During the treatment periods, study interventions will be administered by a Nuvisan GmbH staff member in accordance with the specifications of the Investigator. This includes checking the oral and buccal cavity with the aid of a flashlight and tongue depressor. The proper administration of the study intervention will be documented on the source data (paper workbook) and then transferred into the electronic case report form (CRF).

6.5 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any

changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Permitted Medicines

The only permitted medications are the following: paracetamol/(acetaminophen) respective ibuprofen, at doses of ≤ 2 grams/24 hours for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the CRF, noting the name, dose, duration and indication of each drug.

If the administration of a nonpermitted concomitant drug becomes necessary during the study, e.g., because of AEs, the participant will have to discontinue his/her participation in the study if in the opinion of the Investigator and Sponsor, the medication will interfere with the study. Use of any investigational agent is not permitted within 30 days, or 5 half-lives of the IMP, whichever is longer, prior to the first planned dose of IMP and during the whole study duration.

Use of any prescription or nonprescription medication (with paracetamol and ibuprofen being the only exemption), including multivitamins, nutritional supplements and herbal products (e.g. St. John's wort), is not allowed within 2 weeks or 5 half-lives, whichever is longer, prior to dosing and during the PK sampling period, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

6.5.4 Other Interventions

A standardized breakfast will be provided on Day 1 of each period as described in the Manual of Operations. Breakfast will be started 30 minutes before dosing and should be completed within 25 minutes. Participants will fast for at least 10 hours before consumption of the standardized breakfast and subsequent dosing and will again fast until 5 hours after dosing with water only allowed up to one hour before (except for any fluids provided during the standardized breakfast) and after the first hour of IMP intake. All other meals will be provided at the usual meal times of the study center.

Before and throughout the PK profiling days (until Day 2 of each treatment period) the following restrictions should be met:

- No alcohol, caffeine- and xanthine-containing food and beverages (e.g., coffee, black or green tea, chocolate or chocolate containing food or beverages) 48 hours before each application until Day 2 of each treatment period.
- No intake of recreational drugs from Screening until final examination.
- No exhausting physical activities (body building, sports) during the hospitalization period starting at least 48 hours before dosing until Day 2 after final dose.

6.6 Dose Selection and Modification

No dose modification is allowed.

6.7 Study Intervention after the End of the Study

Because the study population consists of healthy participants, no further treatment or medical care is planned or required after the follow-up visit. In case of the occurrence of a pregnancy see Section 8.3.5.

6.8 Special Precautions

Not applicable.

6.9 Management of Adverse Events of Interest

Not applicable.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

The participant must be withdrawn in the event of any of the following:

- Occurrence of a SAE related to IMP
- Occurrence of an exclusion criterion which is clinically relevant and may affect the participant's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Occurrence of AEs, if discontinuation of study drug is desired or considered necessary by the Investigator and/or the participant
- Use of a nonpermitted concomitant drug (after discussion with and approval by the Sponsor to discontinue)
- Noncompliance.

The SoA specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Not applicable.

7.1.2 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator must document this in the site study records.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.

- Vomiting within the first 6 hours after study drug administration, as vomiting interferes with the PK assessments in this study.
- Not consuming the whole breakfast before drug administration.

In case of premature withdrawal from the study, the investigations scheduled for the last visit (End of Treatment/ Safety Follow-up Visit) should be performed as soon as possible, but at least 7 days after last dosing. In any case, the appropriate section in the CRF must be completed.

The WHO guideline regarding drop-outs states the following: "Sponsors should select a sufficient number of study participants to allow for possible drop-outs or withdrawals. Because replacement of participants during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced."

After discussion with the contract research organization (CRO), the nonevaluable rate (including drop-out) was set at 10%. Therefore, the number of participants to be included in the study is set to 36 to cover a minimum of 32 evaluable participants (see Section 9.2). If 5 or more participants drop out of the study before completing period 4, additional participants may be randomized to meet the required minimal number of evaluable participants (N = 32).

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 310 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments and Procedures

Not applicable.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, abdomen, as well as neurological, peripheral vascular, musculoskeletal, cardiovascular and pulmonary system.
- Height (at Screen) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Tympanic temperature, pulse rate, and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed semisupine with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the SoA. All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the Nuvisan laboratory. Reference ranges of the laboratory parameters for the Nuvisan laboratory are provided in Appendix 8.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to Sponsor.
- The Investigator must review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- A Laboratory Manual will be prepared which contains the following information: sampling methods (e.g. whole blood, plasma, serum, urine), processing and storage of samples through to the analysis, and any special analysis methods.

8.2.5 Suicidal Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in Appendix 4.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the end of the Safety Follow-up.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome at the Safety Follow-up Visit. All SAEs ongoing at the Safety Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) that approved the study.

In accordance with International Council for Harmonization Good Clinical Practice (ICH GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The

Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 must be recorded in the AE page/section of the CRF for pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting Serious Adverse Events.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

8.4 Treatment of Overdose

For this study, any dose of rac-PZQ greater than 1200 mg will be considered an overdose.

There have been no reports to date of acute intoxication caused by PZQ. Treatment is directed to symptoms as applicable.

Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events.

8.5 Pharmacokinetics

- Twenty-one venous blood samples of approximately 2 mL each collected in K_3-EDTA tubes will be taken for measurement of plasma concentrations of R-(-)-PZQ and S-(+)-PZQ, as specified in the SoA in Section 1.3. Concentrations of both enantiomers will be added to calculate the rac-PZQ concentrations and these will be used to evaluate the PK parameters of the study intervention as primary objective. Plasma concentrations and PK parameters of the enantiomers will be evaluated as secondary endpoints.
- Samples will be taken per period with a catheter or by venipuncture for the measurement of drug's plasma concentration: Predose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0 and 12.0 h following dosing. The quantification of R-(-)-PZQ and S-(+)-PZQ in K_3-EDTA plasma will be performed using a validated assay method.
- The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration and recorded in the CRF.
- Except for the predose sample, all PK samples will be taken after dosing.
- The following noncompartmental PK parameters (Table 3) will be calculated from the individual plasma rac-PZQ, R-(-)-PZQ and S-(+)-PZQ concentration-time data obtained on Days 1, 8, 15 and 22 respectively, using commercial software Phoenix®/WinNonlin®, Version 6.3 or higher (Certara, L.P., Princeton, New Jersey), when appropriate. C_{max} and AUC_{0-t} are the main parameters for further statistical analysis.

Table 3 Pharmacokinetic Parameters Derived from rac-PZQ Concentrations

C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration.
t_{lag}	Time prior to the first measurable (non-zero) concentration; calculated as last time point at which the concentration is <LLOQ before the occurrence of the first quantifiable concentration
λ_z	Terminal rate constant.
$t_{1/2}$	Terminal elimination half-life.
AUC_{0-t}	Area under the drug concentration-time curve from time zero to the time of last measurable concentration using the linear-log trapezoidal method (linear up log down).
$AUC_{0-\infty}$	Area under the drug concentration-time curve from time zero extrapolated to infinity.
$\%AUC_{extra}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
$CL_{/f}$	Apparent clearance
$V_{Z/f}$	Apparent volume of distribution during terminal phase

- Remaining samples collected for analyses of rac-PZQ concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- The bioanalytical assessment will be outsourced to Nuvisan under the responsibility of Merck. PK parameter estimation and generation of PK TLFs will also be outsourced to Nuvisan.
- Primary and back up samples will be shipped separately. It is planned that pooled samples for concentration range estimation and enantiomer detection as well as metabolite identification will be prepared according to CRO's SOPs. These specificity samples originate from some of the blood samples collected for drug assays and may be used by the analytical laboratory to

determine suitable quantification ranges, enantiomer identification and exploratory metabolite identification.

- Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.6 Pharmacodynamics

Not applicable.

8.7 Pharmacogenetics

Not applicable.

8.8 Biomarkers

Not applicable.

8.9 Immunogenicity Assessments

Not applicable.

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock without the information of treatment allocation.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. The PK population will include all participants: • Who have completed at least one study period without any relevant protocol deviations and factors likely to affect the comparability of PK results • With adequate study intervention compliance • With evaluable PK data, i.e., nonmissing values for primary endpoints in each study period. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.5, they will be excluded from the PK population. Relevant decisions will be made before database lock. All PK analyses will be based on this analysis set.

9.4 Statistical Analyses

Statistical analysis will be performed using the computer program package SAS® System (release 9.2 or later version; SAS Institute, Cary NC, USA). Details on the statistical analysis will be presented in the integrated analysis plan prior to database lock.

The statistical analysis will not be started until all data have been corrected and checked for plausibility, and until all necessary coding and assessments have been completed.

Medical history and AE terms will be coded with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA; version 22.0 or later); concomitant medication will be coded with WHO Drug Dictionary, WHO Drug Reference List and Anatomical Therapeutic Chemical Classification System, latest version. Versions of dictionaries used for coding will be defined in the Data Management Plan (DMP).

All data recorded during the study will be presented in individual data listings.

All data will be evaluated as observed, no imputation method for missing values will be used except for missing dates/times in AE data which will be performed for the classification of treatment-emergence, assigning AEs to treatment periods and for calculation of duration. The handling of concentration values below the limit of quantification will be described in the statistical analysis plan.

Summary statistics will be provided for all endpoints.

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

In general, for the evaluation of safety parameters, the numerical values will be summarized descriptively (N, arithmetic mean, median, standard deviation, minimum and maximum values). Categorical variables will be presented in frequency tables by the number of observations and percentages.

Adverse event counts and participants with AEs will be summarized for each treatment by system organ class and preferred term. In addition, AEs will be tabulated and listed per participant and analyzed by severity and relationship to study drug.

Participants who prematurely withdrew from the study or from treatment will be displayed in a by-participant listing and summarized by primary withdrawal reason for each treatment sequence.

Safety laboratory parameters will be listed for each participant including changes from baseline and flags for measurements outside the reference ranges, where applicable. Laboratory parameters (hematology and clinical chemistry) will be summarized by time point including both absolute values and changes from baseline.

Vital signs and ECG parameters will be listed by participant including changes from baseline and summarized by treatment and time point using descriptive statistics. Physical examination assessments will be listed for each participant.

All safety analyses will be performed on the Safety Analysis population.

9.4.3 Other Analyses

The analysis of the primary endpoints AUC_{0-t} and C_{max} of rac-PZQ will be performed using the PK population. The analysis of the secondary endpoints AUC_{0-t} and C_{max} of R-(-)-PZQ and S-(+)-PZQ will use a similar approach.

For the analysis of AUC_{0-t} and C_{max}, a reference-scaled BE approach will be applied as follows:

The within-subject variability of the reference product will be calculated from a linear model fitted to the log-transformed PK parameters C_{max} and AUC_{0-t}, with sequence, subject within sequence, period included as fixed effects, described in Section 3.4 of Question 8 in EMA/618604/2008 Rev. 13: Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP). In this analysis, only participants with evaluable data from both administrations of the reference product will be included. If the within-subject coefficient of variation for the reference treatment (CV_{WR}) ≤ 30% for C_{max} or AUC_{0-t} (i.e. the within-subject CV for the reference drug is ≤ 30%), then the common acceptance range (80.00% to 125.00%) for BE will apply for the respective PK parameter. For 30% < CV_{WR} ≤ 50% the acceptance interval will be widened according to $[L, U] = exp(\mp k\, s_{WR})$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and s_{WR} is the intrasubject standard deviation of the log-transformed values of C_{max} or AUC_{0-t} of the reference product, and $CV_{WR} = \sqrt{\exp(s_{WR}^2) - 1}$. s_{WR} will be calculated using the data under reference treatment only. For all values of CV_{WR} greater than 50% the acceptance range is fixed to [69.84% to 143.19%].

An analysis of variance with treatment, period, sequence and subject within sequence as effects, will be fitted to log-transformed PK parameters AUC_{0-t} and C_{max} according to Method A in Question 8 in EMA/618604/2008 Rev. 13. Only participants with at least one valid PK parameter under both reference and test treatment will be included in this model. Least-squares mean differences between treatments will be derived on the log-scale together with 90% confidence intervals.

Estimates and confidence intervals will be back-transformed to the natural scale. Bioequivalence will be accepted if, firstly, the back-transformed 90% confidence intervals are included in the acceptance range, and, secondly, the geometric mean ratios are contained in the conventional acceptance range 80.00% to 125.00%.

The estimated within-subject variability CV_{WR} may be inflated in the presence of outliers. In order to exclude such inflation, sensitivity analyses will be performed. In these analyses, outliers will be identified using graphical methods (such as plotting the PK parameter after the first administration against the corresponding value after the second administration) and/or statistical methods (such as identifying subjects whose studentized residuals fall outside the interquartile range), and the acceptance range will be based on CV_{WR} calculated with outliers removed from the dataset.

Descriptive statistics and boxplots for PK parameters of all analytes will be provided by treatment. Additional exploratory analyses will be described in the integrated analysis plan.

PK analyses will be specified in the Integrated Analysis Plan finalized before database lock.

9.4.4 Sequence of Analyses

All final, planned analyses identified in the Clinical Study Protocol will be performed only after the last participant has completed the last visit, i.e. follow-up/end of study visit with all study data in-house, all data queries resolved, and the database locked.

10 References

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11 Appendices

Appendix 1 Abbreviations

AE	Adverse Event
AUC	Area under the concentration-time curve
AUC_{0-t}	Area under the concentration-time curve from time zero to the last sampling time
BE	Bioequivalence
C_{max}	Maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of variation
CV_{WR}	Within-subject coefficient of variation for the reference treatment
ECG	Electrocardiogram
GCP	Good Clinical Practice
GI	Gastrointestinal
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational-medicinal product
IRB	Institutional Review Board
PK	Pharmacokinetics
PQTm	Prequalification Team Medicines
PZQ	Praziquantel
SAE	Serious Adverse Event
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
VCT	Verified Clinical Trials
vs	Versus

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- A participant who is rescreened is not required to sign another ICF if the ICF version has not changed.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries: EudraCT (2019-002868-27) and www.ClinicalTrial.gov.

Details of structures and associated procedures will be defined in a separate Operations Manual.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
- Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator and other relevant study-appointed experts of the Sponsor and Nuvisan.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

A summary of data will be provided to ClinicalTrials.gov as well as to the European Clinical Trial Database, as applicable, and will occur 12 months after the last clinic visit of the final trial participant or another appropriate date to meet applicable requirements. Healthy participants might be provided with the results of the medical examinations at request. After finalization of the study, healthy participants might be provided with the information published on ClinicalTrials.gov and/or the European Clinical Trial database at request.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Operations Manual.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the

following demographic and medical information for the participant, and should be as complete as possible:

- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e., the Sponsor's study number) and participant's study number.
- Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the Source Data Location Form.

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development of the Sponsor's compound

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not:**

1. Premenarchal
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion applies to determine study entry.
3. A postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency • Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation
  ○ Oral
  ○ Injectable
• Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes: Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants. Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the rac-PZQ include, but may not be limited to, temporal relationship between the AE and the rac-PZQ, known side effects of rac-PZQ, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically /clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of **24 HOURS** after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Appendix 5 Clinical Laboratory Tests

Table 4: Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count Reticulocytes Hemoglobin Hematocrit Red Blood Cell Counts		Mean Corpuscular Volume MCH	WBC Count with Differentials and Absolute Counts [a]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Biochemistry	Blood Urea Nitrogen Creatinine Glucose; CK [b]	Potassium Sodium Calcium Uric acid	Aspartate Aminotransferase Alanine Aminotransferase Alkaline phosphatase γ-Glutamyltransferase	Bilirubin [c] Total Protein Triglycerides Cholesterol
Routine Urinalysis	• pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination [d].			
Other Tests	Urine drug screen: amphetamines, methamphetamines, barbiturates, cocaine, opiates, cannabinoids, benzodiazepines, methadone, tricyclic antidepressants, 3,4-methylenedioxymethamphetamine, and cotinine Serology: Hepatitis B surface antigen Hepatitis C antibody HIV1/HIV2 antibodies Alcohol breath test Thyroid-stimulating hormone (TSH)			

CK = creatine phosphokinase; CK-MB = CK- myocardium/brain type; HIV = human immunodeficiency virus, MCH = Mean Cell Hemoglobin; WBC = white blood cell.

a In case of abnormal findings, manual differential blood count can be requested by the Investigator.

b In case of an increased CK, CK-MB will be determined; if the ratio of CK-MB/CK is above 6%, troponin will be determined as well.

c In case of an increased bilirubin (total) the direct bilirubin will be determined

d Only if blood, protein, nitrite, or leukocytes are positive on the dipstick.

Reference ranges of the laboratory parameters are provided in Appendix 8.

Appendix 6 Protocol Amendment History

Not applicable.

Appendix 7 Periodic Benefit-Risk Evaluation Report for Praziquantel (01 May 2015 to 30 April 2018; Sections 15-18)

The first subject would have been categorized as “moderately infected” (defined as 100 to 399 epg) at baseline and stayed that way after treatment. The other two subjects started as “light infected” (defined as 1 to 99 epg) at baseline and stayed light infected after treatment. These 3 subjects had no related AEs/TEAEs.

14 Late-breaking Information

No relevant new safety information or information with potential impact on the benefit-risk balance of praziquantel has been received after the DLP of the PBRER.

15 Overview of Signals: New, Ongoing, or Closed

No safety signals were newly identified, or closed for PZQ during the reporting period of this PBRER.

15.1 Ongoing signals

The following events are being closely monitored by the Company during the period covered by this PBRER:

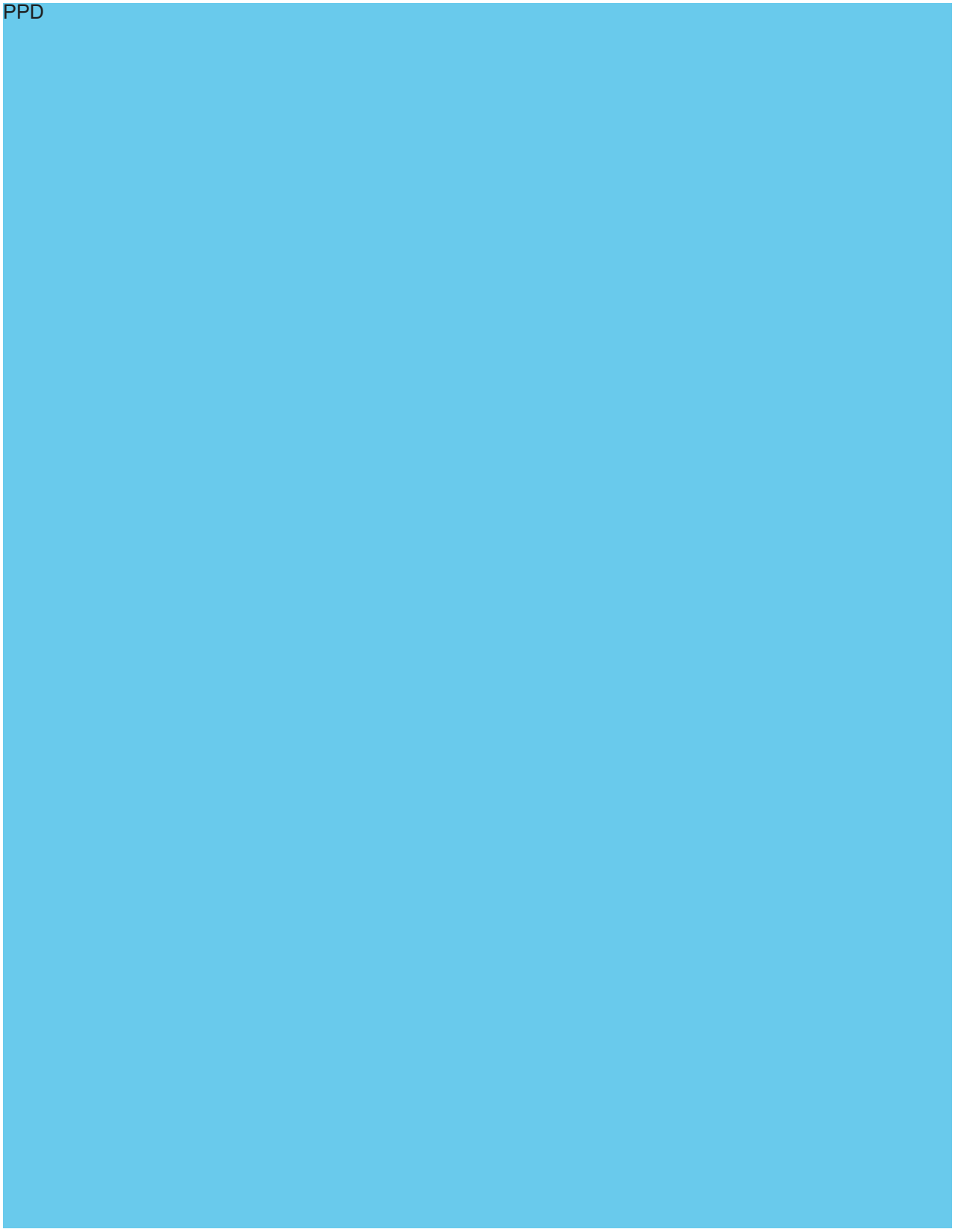
- Diarrhoea,
- Increase in liver enzymes.

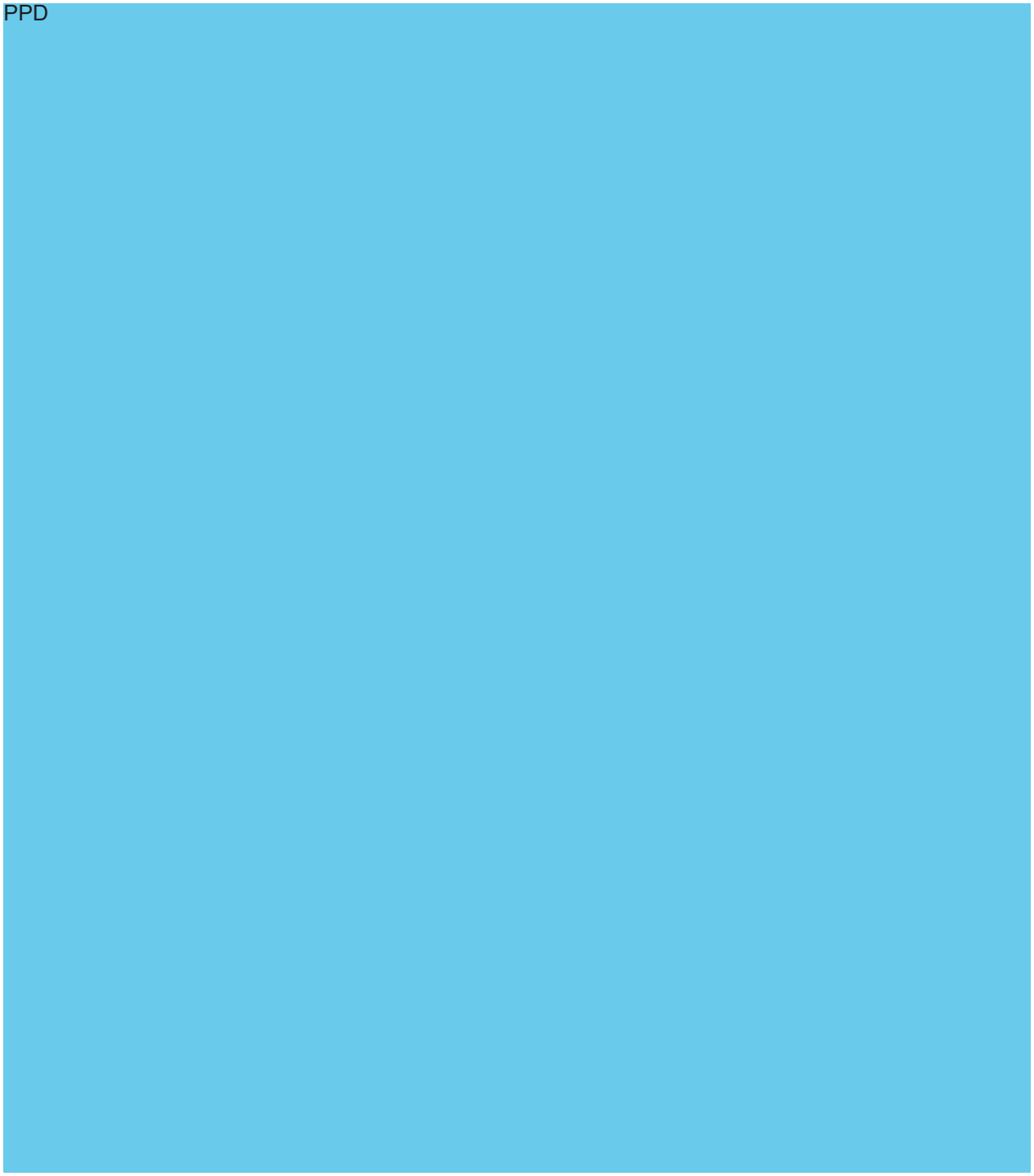
15.1.1 Diarrhoea

The Company has been closely monitoring the event of diarrhoea since the previous PBRER with reporting period 01 May 2012 to 30 Apr 2015.

For the global analysis for diarrhoea, a cumulative search was performed in the Company Safety database (ARISg) from the beginning of the safety database until the DLP of this PBRER, using MedDRA version 21 for the standardized MedDRA query (SMQ) “Noninfectious diarrhoea (SMQ)” (broad scope). A total of 14 ICSRs were revealed. No ICSR reporting the SMQ “Noninfectious diarrhoea” was received during the reporting period of this PBRER.

PPD


PPD



No new significant safety information changing the overall benefit-risk profile of praziquantel has emerged from the review of these ICSRs.

Following the literature review, no evidence could be identified of an increased risk of diarrhea with the use of praziquantel. In case of intestinal schistosomiasis, diarrhea has been linked to worm death in the mesenteric veins (Cupit Pauline M), and to the release of antigens and other metabolites by dying worms (Nuno Vale).

To conclude, from the Company's cumulative experience, there is no evidence of an increased risk of "Diarrhoea" with the use of praziquantel. However, beyond routine pharmacovigilance activities, further close monitoring of this event will be continued, since the event "Diarrhoea" was subject of a request from the German Health Authority Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) for praziquantel 500 mg.

15.1.2 Increase in Liver Enzymes

A search was performed in the Company Safety database (ARISg), using MedDRA version 21 for the following PTs: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Gamma-glutamyltransferase abnormal, Gamma-glutamyltransferase increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hypertransaminasaemia, Liver function test abnormal, Liver function test decreased, Liver function test increased, Transaminases abnormal, Transaminases increased, Blood alkaline phosphatase abnormal, Blood alkaline phosphatase increased. The search revealed one ICSR PPD reported during the period covered by this PBRER, and 2 cumulatively PPD Both cases are presented below.

PPD

PPD

Schistosoma infection is one of the most important causes of noncirrhotic portal hypertension in Latin America, Africa, and Asia. Despite some species-specific variations in inflammatory/fibrotic responses, *Schistosoma*-induced liver injury results from a granulomatous inflammatory reaction around trapped *Schistosoma* eggs in the presinusoidal periportal spaces. In early phases of infection, a predominantly hypercellular nonfibrotic granuloma response produces liver dysfunction that is not clinically detectable. Development of chronicity results in collagen deposition in the periportal spaces, which is the basis of the pathognomonic pathological feature of schistosomal-associated liver fibrosis known as "Symmers' pipestem fibrosis".

In chronic hepatosplenic forms of *S. mansoni* infection, liver and spleen size may achieve around 80% reduction after PZQ use in a period of 1 to 5 years. However, persistence of the inflammatory process also occurs for prolonged periods (several years) in some cases (Cavalcanti et al).

The pharmacokinetics and therapeutic efficacy of praziquantel were studied in 40 patients with *S.mansoni* and various degrees of hepatic dysfunction. The patients were allocated into four groups: the first included 10 patients with simple active schistosomiasis; the other three were made up of patients with schistosomiasis associated with liver cirrhosis and splenomegaly according to Child's classification of hepatocellular function. Every patient was treated with 40 mg/kg of praziquantel as a single oral dose. The efficacy of the drug was evaluated after two months by rectal snip examination. The pharmacokinetic parameters did not differ significantly between patients with simple active schistosomiasis (group 1) and those with hepatosplenomegaly with liver involvement but without ascites and jaundice (group 2). However, as liver cell dysfunction became more evident (groups 3 and 4), pharmacokinetic parameters of praziquantel such as the half-life of elimination, the half-life of absorption, the maximum concentration, the time to maximum concentration, and the area under the concentration-time curve increased proportional to the degree of hepatic insufficiency. Linear correlations were found between each of these parameters on the one hand and hepatic function test results (total bilirubin, direct bilirubin, and serum albumin) on the other. In spite of these pharmacokinetic differences, the cure rates were 70%, 80%, 90%, and 90% in the four groups, respectively. Although the incidence of side effects was high (53%), such effects were transient and mild (el Guiniady et al).

There was no evidence of an increased risk of "Increase in liver enzymes" with the use of praziquantel. However, beyond routine pharmacovigilance activities, further close monitoring of this event will be continued.

16 Signal and Risk Evaluation

16.1 Summary of Safety Concerns

No Risk Management Plan exists for this product.

Two important identified risks and one important potential risk are addressed within the current report:

Important identified risks:

- cardiac arrhythmias,
- convulsions in patients with co-existing neurocysticercosis.

Important potential risk:

- increases of the liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis.

During the period covered by this report, no additional potential or identified risks for praziquantel were identified.

16.1.1 Important Identified Risks

16.1.1.1 Cardiac Arrhythmias

Within the Company`s safety information, a warning has already been implemented that patients with cardiac arrhythmias should be monitored during therapy. The same applies to patients with heart failure requiring digitalis therapy, since a digitalis-antagonistic effect has been demonstrated in animal studies.

Reflecting the literature search, there is a lack of evidence-based data proving a biological plausibility of an association of praziquantel and the development of (unspecific) cardiac arrhythmias in healthy volunteers or in patients.

16.1.1.2 Convulsions in Patients with Co-existing Neurocysticercosis

After the administration of praziquantel for treating tapeworm infection, convulsions have occurred in rare individual cases, which have proved to be a reaction to co-existing neurocysticercosis. Such cases, which may occur especially in endemic regions of *Taenia solium* (*Cysticercus cellulosae*), should be clarified as quickly as possible.

16.1.2 Important Potential Risks

16.1.2.1 Increases of the Liver Transaminases in Patients with Decompensated Hepatic Insufficiency or in Patients with Hepatosplenic Schistosomiasis

Caution is warranted in decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis since, due to reduced drug metabolisation in the liver and/or collateral circulations, appreciably higher serum concentrations are reached and the half-life may be prolonged. In such cases, treatment should be carried out on an inpatient basis.

Since these increases of the liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis can be linked to the underlying schistosomiasis rather than the treatment, no significant impact on public health is foreseen with this potential risk.

16.2 Signal Evaluation

No safety signals were newly identified or closed for PZQ during the period covered by this PBRER.

16.3 Evaluation of Risks and New Information

16.3.1 Important Identified Risks

16.3.1.1 Cardiac Arrhythmias

A search performed in the Company Safety database (ARISg), using MedDRA version 21 for the SMQ "Cardiac arrhythmias" (broad scope) revealed a total of 2 ICSRs cumulatively, with a total of 2 non-serious, not-medically confirmed events pertaining to cardiac arrhythmias. Both ICSRs are presented in Table 12 and events pertaining to cardiac arrhythmias are in **bold**.

PPD

As an overall assessment for cardiac arrhythmias, 2 ICSRs with tachycardia have been reported to the Company. Therein, alternative explanations such as underlying intestinal parasitosis and/or concomitant medication exist, explaining the reported event. In addition, an evidence-based causal relationship between the intake of praziquantel and the development of cardiac arrhythmias could not be provided by a literature search.

16.3.1.2 Convulsions in Patients with Co-existing Neurocysticercosis

A search was performed in the Company Safety database (ARISg), using MedDRA version 21 for the SMQ "Convulsions" (broad scope) and PT "Neurocysticercosis". The search did not reveal any cases.

16.3.2 Important Potential Risks

16.3.2.1 Increases of the Liver Transaminases in Patients with Decompensated Hepatic Insufficiency or in Patients with Hepatosplenic Schistosomiasis

A search performed in the Company Safety database (ARISg), using MedDRA version 21 for the PTs "Alanine aminotransferase abnormal", "Alanine aminotransferase increased", "Aspartate aminotransferase abnormal", "Aspartate aminotransferase increased", "Gamma-glutamyl-transferase abnormal", "Gamma-glutamyltransferase increased", "Hepatic enzyme abnormal", "Hepatic enzyme increased", "Hepatic function abnormal", "Hypertransaminasaemia", "Liver function test abnormal", "Liver function test decreased", "Liver function test increased", "Transaminases abnormal", "Transaminases increased", SMQ "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions" (broad scope) and PT "Schistosomiasis liver" did not reveal any cases.

16.4 Characterization of Risks

16.4.1 Important Identified Risks

16.4.1.1 Cardiac Arrhythmias

Frequency:

In clinical trials with PZQ, no serious/non-serious events, considered as related to PZQ, have been reported.

A search performed in the Company Safety database (ARISg), using MedDRA version 21 for the SMQ "Cardiac arrhythmias" (broad scope) revealed a total of 2 ICSRs cumulatively with a total of 2 non-serious, not-medically confirmed events pertaining to cardiac arrhythmias.

Seriousness:

Some arrhythmias truly are asymptomatic and these are usually discovered during a routine physical examination. These arrhythmias can be considered non-serious. Some symptomatic arrhythmias may be serious or life-threatening. Both ICSRs reported cumulatively non-serious.

Severity and nature of risk:

In general, supraventricular arrhythmias are not serious or life-threatening. In contrast, ventricular arrhythmias may be life-threatening. Non-life-threatening arrhythmias may, however, have serious long-term consequences. For example, atrial arrhythmias that are present for at least 90% of the day and resulting in an average daily heart rate of at least 130 beats per minute may lead to left ventricular cardiomyopathy and congestive heart failure.

Background incidence/prevalence:

The most common types of cardiac arrhythmias among the general population include atrial fibrillation (AFib), atrial flutter, supraventricular tachycardia and ventricular tachycardia. AFib is the most common sustained arrhythmia, with an estimated prevalence of 6 million among all Europeans, which places a huge public health burden in terms of morbidity and mortality [Pillarisetti J, Lakkireddy D. (2014)]. In 2010, the estimated numbers of men and women with AFib worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries [Kirchhof P et al (2016)]. Atrial flutter is less common than AFib, and more prevalent in patients with organic heart disease. According to an epidemiological study in the United States, the estimated prevalence of atrial flutter (including patients complicated with AFib) was 0.3%, and that of atrial flutter alone (without AFib) was 0.13%. The prevalence of paroxysmal supraventricular tachycardia is approximately 2 to 3 per 1,000 persons and the incidence is 35 per 100,000 person-years in the general population [Murakoshi N, Aonuma K. (2013)].

Risk groups or risk factors:

Arrhythmias are very common in older adults. Most serious arrhythmias affect people older than 60 years of age, because older adults are more likely to have heart disease and other health problems that can lead to arrhythmias. Older adults also tend to be more sensitive to the side effects of medicines, some of which can cause arrhythmias. Some medicines used to treat arrhythmias can even cause arrhythmias as a side effect. Some types of arrhythmia happen more often in children and young adults. Paroxysmal supraventricular tachycardia, including Wolff-Parkinson-White syndrome, is more common in young people. Arrhythmias are more common in people who have diseases or conditions that weaken the heart, such as: heart attack, heart failure or cardiomyopathy, heart tissue that's too thick or stiff or that hasn't formed normally, leaking or narrowed heart valves, which make the heart work too hard and can lead to heart failure, congenital heart defects that affect the heart's structure or function and other conditions also can raise the risk for arrhythmias, such as high blood pressure, infections that damage the heart muscle or the sac around the heart, diabetes, sleep apnea, an overactive or underactive thyroid gland, heart surgery, certain drugs (such as cocaine or amphetamines), or an imbalance of chemicals or other substances (such as potassium) in the bloodstream. (https://www.nhlbi.nih.gov/node/3790.). Scarring or abnormal tissue deposits can cause bradycardia by interfering with the work of the sinus node or overall atrioventricular conduction. Likewise, they can cause tachycardia (originating in either the atria or ventricles) by causing cells to fire abnormally or by creating islands of electrically inert tissue. (http://www.heart.org/HEARTORG/Conditions/Arrhythmia/UnderstandYourRiskforArrhythmia/Understand-Your-Risk-for-Arrhythmia_UCM_002024_Article.jsp#.WzSMW1Uza00.)

Potential mechanisms:

Praziquantel is a racemic mixture of L-PZQ and D-PZQ. The L-PZQ enantiomer has a better toxicological profile than D-PZQ or rac-PZQ. For example, in rabbits that were administered a single 45 mg/kg intravenous dose of D-PZQ, rac-PZQ, or L-PZQ, the frequencies of ectopic rhythms were 100%, 80% and 20%, respectively. When rabbits were injected with a single 45 mg/kg intravenous dose of praziquantel, arrhythmia and bradycardia appeared in most of them. The severity of arrhythmia and bradycardia induced by D-PZQ was higher than that induced by L-PZQ. Arrhythmogenic effects of praziquantel may partly be mediated via the central nervous system, and the arrhythmogenic effects of praziquantel may be caused mainly by D-PZQ. [Xiao et al. (2010)].

Additionally, there are rare reports of convulsions and cardiac arrhythmias following treatment of schistosomiasis [Bartley P. (2010)]. *Schistosoma*-induced pulmonary hypertension carries a grave prognosis, since it usually denotes an advanced stage of hepatosplenic schistosomiasis. Thrombosis in situ, particularly of the right pulmonary artery, as well as cardiac arrhythmias and sudden cardiac death syndromes, may occur. [Hidron A et al. (2010)].

Preventability:

Patients with cardiac arrhythmias should be monitored regularly during therapy. Routine electrocardiogram monitoring could be considered for early detection.

Impact on individual patient:

Depending on the seriousness, patients may be slightly or severely affected. Some patients truly are asymptomatic, and the arrhythmia can be discovered only during a routine physical examination. However, most patients are symptomatic in some way when an arrhythmia occurs. Patients having paroxysms of arrhythmia may have symptoms of palpitations or outright heart racing. Other symptoms may include chest pain, pulsations in the neck, dyspnea, lightheadedness, fatigue, sweating, etc. After a spell of arrhythmia, the patient may have frequent urination (due to release of atrial natriuretic factor, a polypeptide released from the atria that stimulates diuresis) or feel fatigued for hours to days. Other arrhythmias may cause syncope, with the attendant risk of injury. More serious arrhythmias may result in cardiac arrest or death.

Potential public health impact of safety concern:

Cardiac arrhythmias should resolve with appropriate treatment. In addition, given the uncommon frequency (based on the cumulative reporting rate), there is no relevant impact on public health.

Evidence source:

Post-marketing experience (cumulative review of cases) and literature review.

16.4.1.2 Convulsions in Patients with Co-existing Neurocysticercosis

Praziquantel should be used with caution because there is a risk, although rare, that the administration of antiparasitic drugs to an individual who has silent neurocysticercosis could trigger seizures [Del Brutto OH and Garcia HH (2014)] and [Fogang YF et al (2015)]

Frequency:

In clinical trials with PZQ, no event of convulsions in patients with co-existing neurocysticercosis, considered as related to PZQ, have been reported.

A search performed in the Company Safety database (ARISg), using MedDRA version 21 for the SMQ “Convulsions” (broad scope) and PT “Neurocysticercosis” did not reveal any cases.

Seriousness:

Convulsions in a patient with co-existing neurocysticercosis is serious but is usually reversible with adequate treatment.

Severity and nature of risk:

The convulsions can be serious or life-threatening, and in the absence of potent corticosteroid treatment, may be fatal.

Background incidence/prevalence:

Neurocysticercosis is the most common helminthic infection of the central nervous system and a major cause of acquired epilepsy worldwide. Cysticercosis is considered by the WHO to be the most common preventable cause of epilepsy in the developing world, with an estimated 2 million people having epilepsy caused by *Taenia solium* infection [Fogang YF et al (2015)]. Symptomatic neurocysticercosis accounts for approximately one-third of seizure disorders in developing countries in sub-Saharan Africa, Asia, and Latin America.

A meta-analysis that only included African studies showed a significant association between epilepsy and cysticercosis, with an OR of 3.4. Prevalence rates of 144/1,000 for neurocysticercosis were reported in rural settings in Ecuador. The total number of all people suffering from neurocysticercosis, including symptomatic and asymptomatic cases, is estimated somewhere between 2.56 and 8.30 million, based on the range of epilepsy prevalence data available, which is between 4 and 13/1,000 for sub-Saharan Africa. In non-endemic areas, the prevalence of neurocysticercosis is 0.2 to 0.6 per 100,000 inhabitants in some western states of the United States, and it is diagnosed in more than 2% of patients attending emergency rooms because of seizures. [Fogang YF et al (2015)].

Risk groups or risk factors:

Neurocysticercosis is a major cause of acquired epilepsy in most of the developing world and has been considered as the single cause explaining the increased incidence and prevalence of epilepsy in these regions (Blocher et al, 2011; Carabin et al, 2011; Del Brutto et all, 2005; Medina et al, 2005; Preux and Druet-Cabanac 2005; Villaran et al. 2009) [Del Brutto OH and Garcia HH (2014)]. Seizures may occur at any stage of Cysticerci involution within the brain parenchyma, from viable cysts to calcifications. Unhygienic practices resulting in ingestion of *Taenia solium* eggs directly from a *Taenia* carrier, or less often by contaminated food, are causal factors for cysticercosis. Neurocysticercosis is common where there is clustering of conditions favoring the transmission of *Taenia solium*, including low level of education, poverty, deficient disposal of human feces, slaughtering of pigs without veterinary control, and presence of free-roaming pigs around households.

Therapy with the cysticidal drug albendazole, disrupting the stable neurocysticercosis disease due to secondary inflammation, is an additional risk factor. [(Nash TE et al (2011)]

Potential mechanisms:

The anthelminthic treatment may disrupt the usual stable, non-inflammatory host–parasite relationship, initiating an acute immune response, which has been attributed to inflammation secondary to killing of the cysticerci. As all parasites are affected at the same time, clinical deterioration is frequent.

Preventability:

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

Impact on individual patient:

Between the 2nd and 5th day of treatment with an antiparasitic agent, there may be an exacerbation of neurologic symptoms (such as convulsions, headache, nausea and vomiting) and seizures with generalization may also be noted. As all parasites are affected at the same time, clinical deterioration is frequent and, in the absence of potent anti-inflammatory therapy and symptomatic treatment, may be lethal.

Potential public health impact of safety concern:

If treated appropriately, the convulsions in patients with co-existing neurocysticercosis should resolve. If untreated, the convulsions may progress to a life-threatening condition and the underlying neurocysticercosis may further deteriorate. The prognosis of epilepsy depends on multiple factors related to degree of infection and host response to parasite. Nearly 85% of patients with a solitary cerebral cysticercus granuloma have a good seizure outcome following resolution of the lesion, but the prognosis of epilepsy in patients with multiple cysts and residual calcifications is not as benign. However, given the very rare frequency, there is no relevant impact on public health.

Evidence source:

Literature review.

16.4.2 Important Potential Risks

16.4.2.1 Increases of the Liver Transaminases in Patients with Decompensated Hepatic Insufficiency or in Patients with Hepatosplenic Schistosomiasis

Frequency:

No ICSRs were retrieved following a cumulative review of the Company safety database up to 30 Apr 2018, pertaining to the risk of increase of the liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis.

Seriousness:

Increase of the liver transaminases is frequently non-serious but may be serious, depending on the liver enzyme values.

Severity and nature of risk:

The increase of the liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis should be monitored with caution since, due to the reduced drug metabolism in the liver and/or collateral circulations, appreciably higher serum concentrations of praziquantel are reached and the half-life may be prolonged. In such cases, treatment should be carried out on an inpatient basis.

Background incidence/prevalence:

Praziquantel therapy has been associated with elevations in serum aminotransferase levels in up to 27% of patients, but these abnormalities were self-limiting. Praziquantel has not been associated with clinically apparent liver injury. In a large retrospective survey from China, 2 of 25,000 treated patients were reported to have developed jaundice, but no specific information about the two cases was provided. There have been few studies of long-term therapy with praziquantel, and most controlled trials of this agent have used one-day courses without serum aminotransferase monitoring. However, millions of people have been treated with praziquantel as a part of large-scale control strategies in China, where *S. japonicum* was endemic. The combination of praziquantel preventive therapy and snail control has resulted in marked decreases in the prevalence of infection in the population, with no evidence of significant toxicity (https://livertox.nih.gov/Praziquantel.htm.).

Risk groups or risk factors:

Parasitic infection can itself result in hepatic impairment. Praziquantel is significantly metabolized by the liver and thus, concomitant administration of praziquantel with a strong inducer of hepatic CYP450 enzymes, such as rifampin, is an additional risk factor.

Potential mechanisms:

Praziquantel is extensively metabolized by the liver via the cytochrome P450 system and might cause hepatic injury as a result of a toxic intermediate of its metabolism. Plasma levels of praziquantel are affected by inducers (rifampin decreases drug levels) and inhibitors of P450 activity (cimetidine, ketoconazole and erythromycin can reduce drug levels). (https://livertox.nih.gov/Praziquantel.htm.)

Preventability:

Praziquantel should be used with caution in patients with hepatic disease. Cessation of treatment should be undertaken at onset of symptoms or following detection of increase in transaminase levels. Additionally, treatment in such conditions should be carried out on an inpatient basis.

Impact on individual patient:

In uncompensated hepatic insufficiency and in patients with hepatosplenic schistosomiasis, there is reduced hepatic metabolism of praziquantel, which can result in significantly higher and longer-lasting plasma concentrations of unmetabolized praziquantel. Minimal increases in hepatic enzymes have been reported in some patients.

Potential public health impact of safety concern:

Praziquantel is usually well tolerated and clinically apparent liver injury due to its use would be very rare, if it occurs at all. (https://livertox.nih.gov/Praziquantel.htm.)

Evidence source:

Literature review.

16.5 Effectiveness of Risk Minimization

16.5.1 Important Identified Risks

16.5.1.1 Cardiac Arrhythmias

Safety concern	**Cardiac arrhythmias**
Objective(s) of the risk minimization measures	To inform of risk of cardiac arrhythmias
Routine risk minimization measures	Section 4.4 of the Merck Master SmPC *Special warnings and precautions for use:* *Patients with cardiac arrhythmias should be monitored during therapy. The same applies to patients with heart failure requiring digitalis therapy, since a digitalis-antagonistic effect has been demonstrated in animal studies.*
	Prescription-only medicine
	Treatment with PZQ must be initiated and supervised by an experienced physician
Additional risk minimization measure(s)	No need for additional risk minimization measures
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	AE reporting rates from spontaneous reports and from safety studies
Criteria for judging the success of the proposed risk minimization measures	No increase in reporting rate / incidence of event
Planned dates for assessment	Periodic review of aggregated AE reports in future PBRERs, Study report: MS200661-0005
Results of effectiveness measurement	EMR200585-001, EMR200661-001, and EMR200661-002: no case reporting of cardiac arrhythmias was detected during the reporting period MS200661-0005: no case reporting of cardiac arrhythmias was detected during the reporting period
Impact of risk minimization	no increase in the reporting rate of cardiac arrhythmias was observed
Comment	none

16.5.1.2 Convulsions in Patients with Co-existing Neurocysticercosis

Safety concern	**Convulsions in patients with co-existing neurocysticercosis**
Objective(s) of the risk minimization measures	To inform of risk of convulsions in patients with co-existing neurocysticercosis
Routine risk minimization measures	Section 4.2 of the Merck Master SmPC *Posology and method of administration*: The usefulness of additional corticosteroid administration is to be decided from case to case; 4 to 16 mg dexamethasone daily, for example, can be considered. The same applies to the necessity of using drugs to prevent or alleviate convulsions. Section 4.4 of the Merck Master SmPC *Special warnings and precautions for use*: After the administration of praziquantel for treating tapeworm infection, convulsions have occurred in rare individual cases, which have proved to be a reaction to co-existing neurocysticercosis. Such cases, which may occur especially in endemic regions of *Taenia solium* (*Cysticercus cellulosae*), should be clarified as quickly as possible. Section 4.8 of the Merck Master SmPC *Undesirable effects:* applies only to tablets containing 150 mg praziquantel: Not known: Convulsions (see section 4.4)
	additional corticosteroid administration
	Treatment with PZQ must be initiated and supervised by an experienced physician
Additional risk minimization measure(s)	No need for additional risk minimization measures
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	AE reporting rates from spontaneous reports and from safety studies
Criteria for judging the success of the proposed risk minimization measures	No increase in reporting rate / incidence of event
Planned dates for assessment	Periodic review of aggregated AE reports in future PBRERs, Study report: MS200661-0005
Results of effectiveness measurement	EMR200585-001, EMR200661-001, and EMR200661-002: no case reporting of convulsions in patients with co-existing neurocysticercosis was detected during the reporting period MS200661-0005: no case reporting of convulsions in patients with co-existing neurocysticercosis was detected during the reporting period
Impact of risk minimization	no increase in the reporting rate of convulsions in patients with co-existing neurocysticercosis was observed
Comment	none

16.5.2 Important Potential Risks

16.5.2.1 Increases of the Liver Transaminases in Patients with Decompensated Hepatic Insufficiency or in Patients with Hepatosplenic Schistosomiasis

Safety concern	**Increases of the liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis**
Objective(s) of the risk minimization measures	To inform of risk of increases of liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis
Routine risk minimization measures	Section 4.4 of the Merck Master SmPC *Special warnings and precautions for use:* *Caution is warranted in decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis since, due to reduced drug metabolisation in the liver and/or collateral circulations, appreciably higher serum concentrations are reached and the half-life may be prolonged. In such cases, treatment should be carried out on an inpatient basis.*
	Prescription-only medicine
	Treatment with PZQ must be initiated and supervised by an experienced physician
Additional risk minimization measure(s)	No need for additional risk minimization measures
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	AE reporting rates from spontaneous reports and from safety studies
Criteria for judging the success of the proposed risk minimization measures	No increase in reporting rate / incidence of event
Planned dates for assessment	Periodic review of aggregated AE reports in future PBRERs, Study report: MS200661-0005
Results of effectiveness measurement	EMR200585-001, EMR200661-001, and EMR200661-002: no case reporting of increases of liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis was detected during the reporting period MS200661-0005: one case reporting increases of liver transaminases in a patient with decompensated hepatic insufficiency or in a patient with hepatosplenic schistosomiasis was detected during the reporting period - 8120255(5)
Impact of risk minimization	no increase in the reporting rate of increases of liver transaminases in patients with decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis was observed
Comment	none

17 Benefit Evaluation

17.1 Important Baseline Efficacy /Effectiveness Information

In 1975, among a large number of related compounds, praziquantel, 2-cyclohexylcarbonyl (1,2,3,6,7,11b) hexahydro-4H-pyrazino (2,1-a) isoquinolin-4- one, was developed as a new broad-spectrum anthelminthic agent (Chai 2013). The IBD is 23 May 1980.

After rapid and reversible uptake, praziquantel has two major anthelminthic effects. At the lowest effective concentrations, praziquantel causes increased muscular activity, followed by contraction and spastic paralysis. At higher concentrations, praziquantel causes tegumental damage and exposes a number of tegumental antigens (McCarthy et al. 2011).

The major asset of praziquantel is its broad antihelminthic spectrum of activity.

Praziquantel is indicated for:

150-mg tablets: Treatment of infections caused by *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Hymenolepis nana* (dwarf tapeworm), *Diphyllobothrium pacificum* (South American fish tapeworm)

500-mg tablets: Treatment of infections caused by the larvae of pork tapeworm (*Cysticercus cellulosae*) in the central nervous system (neurocysticercosis).

600-mg tablets:

- Treatment of *Schistosoma* infections (due to *S. haematobium*, *S. mansoni, S.intercalatum*, *S.japonicum, S. mekongi*)
- Treatment of infections with liver flukes (e. g. *Clonorchis sinensis, Opisthorchis viverrini*) and lung flukes (e. g. *Paragonimus westermani* and other species).
- Treatment of cysticercosis (neurocysticercosis, parenchymal and subarachnoid, and visceral and cutaneous cysticercosis) and infections with intestinal nematodes liver (clonorchiasis, opisthorchiasis and fascioliasis) and pulmonary (paragonimiasis).

17.1.1 Infections caused by Taenia saginata, Taenia solium, Hymenolepis nana, Diphyllobothrium pacificum and caused by the larvae of pork tapeworm in the Central Nervous System (praziquantel 150 and 500 mg)

According to the review elaborated by Chai 2013, since praziquantel was first introduced as a broad-spectrum anthelmintic in clinical development in 1975, numerous chemotherapeutic trials have been performed to evaluate the clinical use of praziquantel in the treatment of human cestode (human tapeworm) infections, and multiple papers reporting successful results have been published. It has been revealed that most of the human-infecting cestodes, except larval *Echinococcus granulosus* or *Echinococcus multilocularis* infection and sparganosis (caused by the larva of *Spirometra erinacei*), are treated successfully with recommended drug dosages and regimens, which differ by different types of trematodes and cestodes, in particular, according to

the habitat in the host. All of the human-infecting adult tapeworm infections are successfully treated with 10 to 25 mg/kg praziquantel in a single dose. *T. solium* or *T. saginata* infections are highly susceptible to a low dose (10 mg/kg) of praziquantel, with 96 to 100% cure rates (e.g. Rim et al 1979). In *Diphyllobothrium pacificum* infections, doses of 10 mg/kg are also recommended (e.g. Groll 1980). However, *H. nana* infections generally need a higher dose (15 to 25 mg/kg) to obtain a satisfactory cure rate (e.g. Rim et al 1978). To avoid recurrence of hymenolepiasis, a repeated treatment after 10 to 14 days is recommended. Also, Bouree (1991) stated that human cestodes, *Hymenolepis* species; *Taenia saginata* and *Diphyllobothrium* are easily eradicated with a single low dose of praziquantel.

For the treatment of human central nervous system infections (neurocysticercosis) caused by the larve of pork tapeworm (*Cysticercus cellulosae*) a 15-day treatment course with a daily dose of 50 mg/kg praziquantel in 3 divided doses is effective (e.g. Sotelo et al 1984), usually in combination with corticosteroids (Bale 2000). Concurrent administration of dexamethasone in standard doses is usually required to minimize the inflammation and cerebral edema associated with death of the parasites. Administration of corticosteroids such as dexamethasone should accompany the anthelminthic treatment, in order to reduce adverse reactions such as headache, vomiting, and neurological symptoms, which can occur due to elevated intracranial pressure resulting from inflammatory reactions against antigens liberated from dying Cysticerci worms.

According to Consensus Guidelines (Garcia et al. 2002), therapeutic measures of neurocysticercosis include antiparasitic drugs (e.g., praziquantel), surgery, and symptomatic medication (e.g., corticosteroids). A dosage of 50 mg/kg/day for 2 weeks was adopted by most clinical studies.

17.1.2 Treatment of Schistosoma Infections and Infections with Liver Flukes and Lung Flukes (praziquantel 600 mg)

Praziquantel is a drug for all forms of schistosomiasis. Since the early animal studies, it was apparent that praziquantel is about equally effective against *S. mansoni, S. haematobium, S. japonicum, S. intercalatum and S. mattheei* (Webbe and James 1977).

This finding has been repeatedly confirmed by a large amount of human data collected in endemic areas around the world. The recommended dose is 40 to 60 mg/kg body weight, the lower amount being generally used for *S. mansoni* and *S. haematobium*, whereas the higher dose (generally split into two administrations a few hours apart) is especially recommended for Asian schistosomes (*S. japonicum* and *S. mekongi*). It has been reported repeatedly that the bioavailability of praziquantel increases with the concomitant administration of food, a procedure that should be considered whenever possible (Cioli and Pica-Mattocia 2003).

Using the recommended dosages, cure rates recorded in a review by Wegner (1984) were: 75 to 85% for *S. haematobium*; 63 to 85% for *S. mansoni*; 80 to 90% for *S. japonicum*; 89% for *S. intercalatum,* and 60 to 80% for mixed infections with *S. mansoni* and *S. haematobium*.

The efficacy of praziquantel at a dose of 40 mg/kg was also confirmed in school children (n=592) infected with *S. haematobium,* as stated by Tchuem Tchuente et al (2004). The results of their

study indicated that a single treatment with praziquantel has high efficacy, since at six and nine weeks post-treatment the cure rate was 83 to 88.6% and the ERR was >98%.

Praziquantel is effective in patients of all ages and in the different clinical forms of schistosomiasis, also including advanced hepatosplenic cases (Bassily et al. 1985). Cerebral schistosomiasis caused by *S. japonicum* and *S. mansoni* can be treated successfully with praziquantel (Watt et al. 1986, Vale et al 2012) and neurological syndromes caused by *S. mansoni* and *S. haematobium* also respond well (Scrimgeour and Gadjusek 1985) to this medicinal product.

The fact that no clinically relevant resistance has appeared over the thirty-plus years after its introduction is also strong testimony to the qualities of praziquantel (Cioli et al 2014).

According to review elaborated by Keiser and Utzinger (2004), praziquantel is not only effective against all 3 major species of *Schistosoma* (*S. mansoni, S. haematobium* and *S. japonicum*), but also it is the standard treatment against *Clonorchis sinensis* and *Opisthorchis viverrini*. The cure rates in infected patients were up to 100% with the dose 25 mg/kg given three times a day.

17.2 Newly Identified Information on Efficacy and Effectiveness

A literature research in MEDLINE and EMBASE for the period of the current PBRER from 01 May 2015 to 30 Apr 2018 did not reveal any newly identified information on efficacy of praziquantel in the claimed indications.

One relevant study supporting and confirming use of praziquantel in pregnancy was found.

The objectives of this study, elaborated by Olveda et al (2016), were to assess whether treatment of pregnant women infected with schistosomiasis at 12 to 16 weeks' gestation leads to improved maternal and newborn outcomes, and to collect maternal and newborn safety data. This Phase II, randomized, double-blind, placebo-controlled trial was done in 72 barangays (villages) serviced by six municipal health centers in a schistosomiasis-endemic region of northeastern Leyte, Philippines. Pregnant women (at 12 to 16 weeks' gestation) who were otherwise healthy but infected with *S. japonicum* were enrolled and randomly assigned (1:1) to receive either over-encapsulated praziquantel (total dose 60 mg/kg given as two split doses) or placebo. The primary outcome was birthweight. Safety data were collected, including immediate reactogenicity, post-dosing toxicology ascertained 24 hours after study drug administration, and maternal and newborn SAEs. Between Aug 13, 2007 and Dec 3, 2012, a total of 370 pregnant women were enrolled and randomly assigned to a treatment group (184 to the placebo group, 186 to the praziquantel group). Most women had low-intensity infections (n=334, 90%). Treatment with praziquantel did not have a significant effect on median birthweight (2.85 kg in both groups, p=0.962). Treatment was well tolerated, with reactogenicity rates similar to those seen in non-pregnant participants (severe reactions occurred in five patients in the praziquantel group and two in the placebo group, and included headache, fever, and malaise). There were no significant differences in key safety outcomes including abortion, fetal death in utero, and congenital anomalies. In conclusion, results from this study provide important data from a controlled trial in support of the expansion of treatment policies to include pregnant women, as recommended by WHO.

17.3 Characterization of Benefits

Extensive evidence of efficacy of praziquantel as demonstrated in clinical studies, complemented by comprehensive post-marketing experience since its first approval in 1980, gained in multiple countries worldwide, supports the use of praziquantel in the labeled indications.

Results of several well-designed trials and meta-analyses have established that praziquantel is suitable for treating the majority of human-infecting cestodes (human tapeworms), including the larvae of pork tapeworm (*Cysticercus cellulosae*), *Schistosoma* species, and liver and lung flukes.

Based on its spectrum of activity, praziquantel is also included in WHO Model List of Essential Medicines (2015) in Section Anthelminthics.

18 Integrated Benefit-Risk Analysis for Authorized Indications

18.1 Benefit-risk Context - Medical Need and Important Alternatives

Infections with helminths (parasitic worms) affect more than two billion people worldwide. In regions of rural poverty in the tropics, where prevalence is greatest, simultaneous infection with more than one type of helminth is common. The relative incidence of tapeworm infections in humans is about 3% of the world population; incidence of schistosomes is 7% of the world population (McCarthy et al. 2011).

Human tapeworm (cestode) infections continue to be an important cause of morbidity worldwide. Infection with most adult tapeworms causes nonspecific abdominal symptoms, e.g., abdominal pain, nausea, weakness, loss of appetite, increased appetite, headache, constipation, dizziness, diarrhea, pruritus ani, or hyperexcitability. Children may have more severe symptoms than adults. Unlike adult cestode infections, larval cestode infections such as cysticercosis have substantial morbidity, and often require surgical intervention (Tanowitz et al. 2001). Cysticercosis, the infection caused by the larval stage of the tapeworm *Taenia solium*, is the most common parasitic disease of the nervous system in humans and the single most common cause of acquired epileptic seizures in the developing world. Therapeutic measures include antiparasitic drugs (e.g., praziquantel, albendazole), surgery, and symptomatic medication (corticosteroids, mannitol, antiepileptic drugs, analgesics) (Garcia et al. 2002) Newer techniques, both invasive and non-invasive (serological and molecular), have enhanced the diagnosis of these infections. The use of praziquantel and albendazole have greatly improved the medical treatment of both adult and larval tapeworm infections (Tanowitz et al. 2001).

Schistosomiasis, or bilharzia, is a tropical disease caused by worms of the genus *Schistosoma*. The main disease-causing species are *S. haematobium, S. mansoni*, and *S. japonicum* (Cioli et al 2014).

Schistosomiasis is characterized by focal epidemiology and overdispersed population distribution, with higher infection rates in children than in adults. Complex immune mechanisms lead to the slow acquisition of immune resistance, although innate factors also play a part. Acute

schistosomiasis, a feverish syndrome, is mostly seen in travelers after primary infection. Chronic schistosomal disease affects mainly individuals with longstanding infections in poor rural areas. Immunopathological reactions against schistosome eggs trapped in the tissues lead to inflammatory and obstructive disease in the urinary system (*S. haematobium*) or intestinal disease, hepatosplenic inflammation, and liver fibrosis (*S. mansoni, S. japonicum*) (Gryseels et al. 2006). Mortality has been estimated at 280,000 deaths/year in Sub-Saharan Africa, while the over-all level of disability caused by schistosomiasis has been recently re-evaluated and extended to include previously neglected effects of chronic infection like anemia, growth stunting and diminished physical and mental fitness. Among parasitic diseases, schistosomiasis ranks second only to malaria for the number of people infected and for its health impact. Since no vaccine exists against schistosomiasis and the mollusks acting as intermediate hosts are not easy to attack, chemotherapy is the main approach for schistosomiasis control. Praziquantel is currently the only available antischistosomal drug (Cioli et al 2014).

18.2 Benefit-Risk Analysis Evaluation

Praziquantel was the first anthelminthic drug to fulfill WHO's requirements for treatment of a broad range of parasitic infections. [Reich MR et al (1998)]

The efficacy of praziquantel in the approved indications, treatment of infections due to trematodes and cestodes, as well as infections caused by larvae of *Taenia solium* in the central nervous system (neurocysticercosis) is well-established. Praziquantel damages the syncytial tegument of the tapeworm at a sensitive site (this is a proliferation zone in the neck), resulting in disturbed permeability. In addition, praziquantel leads to contraction of the parasite musculature, with subsequent spastic paralysis.

As stated above, schistosomiasis remains one of the most prevalent parasitic diseases in developing countries, causing not just human morbidity, but also significant economic and public health consequences. Schistosomiasis is a severe chronic inflammatory disease, which is endemic in 78 developing countries and infecting more than 240 million people, with more than 90% of them living in Africa. The prevalence of schistosomiasis in children is very high, accounting for about 50% of the total infected population, and many more are at risk from the disease. At the World Health Assembly in 2001, Resolution A 54.19 was put forward, which urged endemic countries to start seriously tackling worms, specifically schistosomiasis and soil-transmitted helminths, with a global target to treat at least 75% of all school-age children who are at risk of morbidity from schistosomiasis and soil-transmitted helminths by the year 2010.

The current gold standard treatment that is recommended for schistosomiasis, praziquantel, is available for adults and school-age children. These tablets are not suitable for use in younger children due to their size and bitter taste. In addition, they are not registered for pediatric use in preschool-age children and adequate clinical data are lacking in this population. A pediatric formulation of praziquantel, appropriate for children at the age of 3 months to 6 years, would permit accurate dosing and enhanced compliance in these patients, and is highly needed. In order to tackle this important public health problem, a Pediatric Praziquantel Consortium was formed in 2012 under the leadership of Merck KGaA, with the goal of developing a suitable pediatric formulation for preschool-age children and register its use in schistosomiasis. This project is part of Merck's corporate responsibility initiatives and demonstrates the company's strong

commitment to Global Health, in particular to support the 2020 WHO commitment in the fight against schistosomiasis in Africa.

A recent systematic review and meta-analysis considered all comparative and noncomparative trials of PZQ at any dose for any *Schistosoma* species, so long as assessments occurred within 2 months of treatment (Zwang J et al (2014)). A total of 55 studies provided data for 19,499 eligible subjects treated with PZQ (14,047), control treatment or placebo. The largest groups were school-age children (64%), *S. mansoni* infection (58%), and the 40 mg/kg dose (56%); 68% of subjects were in the WHO African region. Efficacy was assessed in more than 17,000 subjects. Cure rates with 40 mg/kg were 94.7% (95% CI: 92.2, 98.0) for *S. japonicum*, 77.1% (95% CI: 68.4, 85.1) for *S. haematobium*, 76.7% (95% CI: 71.9, 81.2) for *S. mansoni*, and 63.5% (95% CI: 48.2, 77.0) for mixed *S. haematobium* and *S. mansoni* infections. Using a random-effect meta-analysis regression model, the cure rate for 40 mg/kg was significantly higher than for 20 and 30 mg/kg, and not different from 50 and 60 mg/kg for *S. mansoni*; for *S. haematobium,* it was higher than 20 mg/kg only; and higher or not different from other PZQ schedules and comparators, but lower than oxamniquine 40 and 50 mg/kg for *S. mansoni.* The mean ERR was assessed in more than 13,000 subjects. The mean ERR with 40 mg/kg was 95% for *S. japonicum*, 94.1% for *S. haematobium*, and 86.3% for *S. mansoni*. No significant relationship between dose and ERR was detected. In preschool-age children, 29.1% and 8.6% experienced drowsiness and itching/rash, respectively (503 subjects), and 2.4% experienced dizziness, 13.3% experienced fatigue, 7.8% experienced nausea, 7.2% experienced abdominal pain, 6.8% experienced vomiting, 4.4% experienced headache and 4.3% experienced diarrhoea (737 subjects). In school-age children, 42.4% experienced drowsiness (1,342 subjects), 9.3% experienced dizziness (285 subjects), 13.2% experienced fatigue (781 subjects), 5.5% experienced itching/rash (1,504 subjects), 12.9% experienced nausea (3,058 subjects), 33.4% experienced abdominal pain (3,495 subjects), 7.9% experienced vomiting (2,911 subjects), 16.6% experienced headache (3,314 subjects), and 12.1% experienced diarrhoea (3,106 subjects). Praziquantel was reportedly safe at all ages, with only mild reported AEs, which cleared rapidly after treatment. The authors concluded that praziquantel 40 mg/kg was effective at reducing infection intensity in all *Schistosoma* species, without differences between preschool- and school-age children.

During the reporting period, 4 interventional clinical trials of praziquantel have been initiated and conducted by Merck KGaA, in conjunction with the Paediatric Praziquantel Consortium. Three of these clinical trials (EMR200585-001, EMR200661-001, and EMR200661-002) have been completed and the corresponding Clinical Study Reports have been written. For the fourth study, MS200661-0005, Part 1 of this Phase II trial has been completed and Part 2 is ongoing. Only TEAEs reported in the Gastrointestinal disorders SOC occurred in >10% of subjects: abdominal pain (n=25), vomiting (n=11), and diarrhoea (n=10)/ diarrhoea haemorrhagic (n=1). Cohort 6 (L-PZQ 45 mg/kg) had the lowest number of participants with IMP-related TEAEs (n=2) and Cohort 4 (rac-PZQ ODT 60 mg/kg) had the highest number (n=16), with the other cohorts in between (Cohort 3, 40 mg/kg rac-PZQ ODT – 6 TEAEs; Cohort 5, 30 mg/kg L-PZQ ODT – 8 TEAEs; Cohort 1, Biltricide® 3x20 mg/kg – 9 TEAEs; Cohort 2, Biltricide® 40 mg/kg – 11 TEAEs, and Cohort 7, 60 mg/kg L-PZQ ODT – 12 TEAEs). The TEAEs were generally transient; 59 of 68 TEAEs resolved within 24 hours post-dosing, and they resolved spontaneously, not requiring any special treatment. Combined with the low overall numbers of TEAEs, these data confirm the good safety profile of PZQ.

This favorable tolerability has been confirmed by post-marketing experience over nearly 40 years. The most common and identified side effects of praziquantel treatment are associated with gastrointestinal disorders: diarrhoea (under close monitoring by the Company), nausea, vomiting and abdominal pain; although transient neurological effects have been also recorded (headache and dizziness). Regarding general disorders, the following AEs have been reported: weakness, fatigue and increased body temperature. All of these symptoms are usually transient, and they resolve spontaneously in most cases. Adverse reactions, including hypersensitivity reactions, may partly represent endogenous reactions to the killing off of the parasites by praziquantel.

Patients with cardiac arrhythmias should be monitored during therapy. The same applies to patients with heart failure requiring digitalis therapy, since a digitalis-antagonistic effect has been demonstrated in animal studies. Praziquantel is contraindicated in proven hypersensitivity to praziquantel or any of the excipients, as well as in intraocular cysticercosis or in combination with rifampicin. Caution is warranted in decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis. In such cases, treatment should be carried out on an inpatient basis. Additionally, after the administration of praziquantel (150 mg) for treating tapeworm infection, convulsions have occurred in rare individual cases, which have proved to be a reaction to co-existing neurocysticercosis. The Company RSI provides a valid and thorough guidance aimed to prevent these undesirable events. Reported cases and literature were reviewed in the current PBRER and no changes to the RSI are warranted. Thus, the post-marketing safety profile of praziquantel remains favorable.

Based on all of the data described above, resulting from numerous clinical studies and from the extensive post-marketing experience with praziquantel worldwide, with nearly 40 years since its first approval and launch, the efficacy of praziquantel is considered to be well-established in the labeled indications.

Regarding the safety profile, the risks in association with praziquantel therapy are equally well established and generally known, and appropriately described in the Company RSI.

Based on this long-time experience and since there is no new relevant information constituting a new safety concern, the use of praziquantel is justified in the labeled indications and the benefit-risk balance of praziquantel remains positive in the approved indications.

Appendix 8 Reference ranges of laboratory parameters

Analyte No.	Analyt	Test Group	Synonym	Sex	>= Age	< Age	Unit	Lower Limit	Upper Limit	Unit	Spezimen	Method (Analyzer)
101	Potassium	Elektrolyte	K	Unisex			year	3,5	5,1	mmol/L	Serum	ISE indirect (cobas c501/Integra 400 Plus)
100	Sodium	Elektrolyte	SODIUM	Unisex			year	136	145	mmol/L	Serum	ISE indirect (cobas c501/Integra 400 Plus)
111	Alanine Aminotransferase	Enzyme	ALT	Male			year	5	50	U/L	Serum	PHO (cobas c501/Integra 400 Plus)
113	Alkaline Phosphatase	Enzyme	ALP	Male			year	40	129	U/L	Serum	PHO (cobas c501/Integra 400 Plus)
110	Aspartate Aminotransferase	Enzyme	AST	Male			year	5	50	U/L	Serum	PHO (cobas c501/Integra 400 Plus)
241	Creatine Kinase	Enzyme	CK	Male			year	7	308	U/L	Serum	PHO (cobas c501/Integra 400 Plus)
600	Creatine Kinase MB	Enzyme	CKMB	Unisex			year	3,0	25,0	U/L	Serum	PHO (cobas c501/Integra 400 Plus)
112	Gamma Glutamyl Transferase	Enzyme	GGT	Male			year	3	71	U/L	Serum	PHO (cobas c501/Integra 400 Plus)
343	Ery. Mean Corpuscu. Hemoglobin	Hematology	MCH	Unisex			year	1,600	2,000	fmol	EDTA	Calculation by formula (Sysmex XN-1000)
344	Ery. Mean Corpuscular Volume	Hematology	MCV	Male			year	79,0	92,2	fL	EDTA	Calculation by formula (Sysmex XN-1000)
347	Erythrocytes	Hematology	RBC	Male			year	4,63	6,08	T/L	EDTA	DC sheath flow detection method (Sysmex XN-1000)
345	Hematocrit	Hematology	HCT	Male			year	0,401	0,510	L/L	EDTA	Cumulative pulse height method (Sysmex XN-1000)
346	Hemoglobin	Hematology	HGB	Male			year	8,50	10,86	mmol/L	EDTA	SLS detection method (Sysmex XN-1000)
348	Leukocytes	Hematology	WBC	Male			year	4,23	9,07	G/L	EDTA	Fluorescence flow cytometry (Sysmex XN-1000)
341	Platelets	Hematology	PLAT	Male			year	163	337	G/L	EDTA	DC sheath flow detection method (Sysmex XN-1000)
529	Reticulocytes	Hematology	RETI	Male			year	26,0	95,0	G/L	EDTA	Fluorescence flow cytometry (Sysmex XN-1000)
523	Basophils/Leukocytes	Hematology %	BASOLE	Male			year	0,2	1,2	%	EDTA	Calculation by formula (Sysmex XN-1000)
522	Eosinophils/Leukocytes	Hematology %	EOSLE	Male			year	0,8	7,0	%	EDTA	Calculation by formula (Sysmex XN-1000)
520	Lymphocytes/Leukocytes	Hematology %	LYMLE	Male			year	21,8	53,1	%	EDTA	Calculation by formula (Sysmex XN-1000)
521	Monocytes/Leukocytes	Hematology %	MONOLE	Male			year	6,0	15,1	%	EDTA	Calculation by formula (Sysmex XN-1000)
349	Neutrophils/Leukocytes	Hematology %	NEUTLE	Male			year	34	67,9	%	EDTA	Calculation by formula (Sysmex XN-1000)
340	Reticulocytes/Erythrocytes	Hematology %	RETIRBC	Male			year	0,51	1,81	%	EDTA	Calculation by formula (Sysmex XN-1000)
707	Hepatitis B Virus Core AB	Serology	HBCAB	Unisex			year	neg	neg		Serum	ECLIA (cobas e601/cobas e411)
702	Hepatitis B Virus Surface AG	Serology	HBSAG	Unisex			year	neg	neg		Serum	ECLIA (cobas e601/cobas e411)
704	Hepatitis C Virus AB	Serology	HCAB	Unisex			year	neg	neg		Serum	ECLIA (cobas e601/cobas e411)
700	HIV-1/2 Antibody/HIV-1 p24 AG	Serology	HIV12P24	Unisex			year	neg	neg		Serum	ECLIA (cobas e601/cobas e411)
477	Troponin I	Special Tests	TROPONI	Unisex			year	neg	neg		Serum	Stick Mölab (manual)
121	Creatine Kinase MB/CK	Calculated Parameter	CKMBCK	Unisex			year	0	6	%	Serum	Calculation by formula
166	Blood Urea Nitrogen	Substrate	UREAN	Unisex	18	60	year	2,14	7,14	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
166	Blood Urea Nitrogen	Substrate	UREAN	Unisex	61	90	year	2,86	8,21	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
171	Bilirubin	Substrate	BILI	Unisex			year	0,0	21,0	µmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
139	Calcium	Substrate	CA	Unisex	61	90	year	2,20	2,55	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
139	Calcium	Substrate	CA	Unisex	18	60	year	2,15	2,50	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
156	Cholesterol	Substrate	CHOL	Unisex			year	0,0	5,2	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
146	Creatinine	Substrate	CREAT	Male			year	59	104	µmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
167	Direct Bilirubin	Substrate	BILDIR	Unisex			year	0,0	5,0	µmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
143	Glucose	Substrate	GLUC	Unisex			year	4,11	5,89	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
154	Protein	Substrate	PROT	Unisex			year	64	83	g/L	Serum	PHO (cobas c501/Integra 400 Plus)

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155	Triglycerides	Substrate	TRIG	Unisex			year	0,0	2,3	mmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
147	Urate	Substrate	URATE	Male			year	202,3	416,5	µmol/L	Serum	PHO (cobas c501/Integra 400 Plus)
383	Amphetamine	Urine Drug Sticks	AMPHET	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
387	Barbiturates	Urine Drug Sticks	BARB	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
388	Benzodiazepines	Urine Drug Sticks	BNZDZPN	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
382	Cannabinoids	Urine Drug Sticks	CANNAB	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
389	Cocaine	Urine Drug Sticks	COCAINE	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
381	Cotinine	Urine Drug Sticks	COTININE	Unisex			year	neg	neg		Spot Urine	Stick Nal von Minden (manual)
390	Methadone	Urine Drug Sticks	METHDN	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
384	Methamphetamine	Urine Drug Sticks	METHAMPH	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
385	Methylenedioxymethamphetamin	Urine Drug Sticks	MDMA	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
391	Opiate	Urine Drug Sticks	OPIATE	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
386	Tricyclic Antidepressants	Urine Drug Sticks	TRCYANDP	Unisex			year	neg	neg		Spot Urine	Cassette SureStep (manual)
366	Bacteria	Urine Sediment	BACT	Unisex			year	0	0	1/HPF	Spot Urine Sediment	Microscopy (manual)
365	Calcium Oxalate Crystals	Urine Sediment	CYCAOXA	Unisex			year	0	0	1/HPF	Spot Urine Sediment	Microscopy (manual)
362	Erythrocytes	Urine Sediment	RBC	Unisex			year	0	2	1/HPF	Spot Urine Sediment	Microscopy (manual)
378	Granular Casts	Urine Sediment	CSGRAN	Unisex			year	0	0	1/HPF	Spot Urine Sediment	Microscopy (manual)
364	Hyaline Casts	Urine Sediment	CSHYAL	Unisex			year	0	0	1/HPF	Spot Urine Sediment	Microscopy (manual)
361	Leukocytes	Urine Sediment	WBC	Unisex			year	0	5	1/HPF	Spot Urine Sediment	Microscopy (manual)
363	Round Epithelial Cells	Urine Sediment	EPIROCE	Unisex			year	0	0	1/HPF	Spot Urine Sediment	Microscopy (manual)
379	Squamous Epithelial Cells	Urine Sediment	EPISQCE	Unisex			year	0	10	1/HPF	Spot Urine Sediment	Microscopy (manual)
393	Uric Acid Crystals	Urine Sediment	CYURIAC	Unisex			year	0	0	1/HPF	Spot Urine Sediment	Microscopy (manual)
358	Bilirubin	Urine Stick Device	BILI	Unisex			year	0	0	µmol/L	Spot Urine	Urine Stick (automated evaluation; cobas u411)
359	Erythrocytes	Urine Stick Device	RBC	Unisex			year	0	0	1/µL	Spot Urine	Urine Stick (automated evaluation; cobas u411)
355	Glucose	Urine Stick Device	GLUC	Unisex			year	0	0	mmol/L	Spot Urine	Urine Stick (automated evaluation; cobas u411)
356	Ketones	Urine Stick Device	KETONES	Unisex			year	0	0	mmol/L	Spot Urine	Urine Stick (automated evaluation; cobas u411)
377	Leukocyte Esterase	Urine Stick Device	LEUKASE	Unisex			year	neg	neg		Spot Urine	Urine Stick (automated evaluation; cobas u411)
353	Nitrite	Urine Stick Device	NITRITE	Unisex			year	neg	neg		Spot Urine	Urine Stick (automated evaluation; cobas u411)
350	pH	Urine Stick Device	PH	Unisex			year	5,0	8,0		Spot Urine	Urine Stick (automated evaluation; cobas u411)
354	Protein	Urine Stick Device	PROT	Unisex			year	0	0	g/L	Spot Urine	Urine Stick (automated evaluation; cobas u411)
357	Urobilinogen	Urine Stick Device	UROBIL	Unisex			year	0	0	µmo/L	Spot Urine	Urine Stick (automated evaluation; cobas u411)

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PHO: Photometric; ECLIA: Elektrochemilumineszenz Immunoassay; EIA: Enzymeimmunoassay; TURB: Turbidimetry,TINIA: Turbidimetric inhibition immunoassay; LIA: Luminescence-Immunoassay; CLIA: Chemiluminnescence Immuno Assay, NEPH: Nephelometry; LFIA Lateral Flow Immunoassay

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Appendix 9 Sponsor Signature Page

Study Title:	A Phase I, open-label, randomized, four-period, crossover, fully replicated, reference-scaled, single center study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers
Regulatory Agency Identifying Numbers:	EudraCT: 2019-002868-27
Clinical Study Protocol Version:	09 January 2020/Version 1.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

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I approve the design of the clinical study:

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Appendix 10 Principal Investigator Signature Page

Study Title:	A Phase I, open-label, randomized, four-period, crossover, fully replicated, reference-scaled, single center study to assess the bioequivalence of a single oral dose of 1200 mg of the coated Cesol tablet formulation versus comparator Biltricide® in healthy male volunteers
Regulatory Agency Identifying Numbers:	EudraCT: 2019-002868-27
Clinical Study Protocol Version:	09 January 2020/Version 1.0

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

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