Clinical Trial Protocol

Clinical Trial Protocol Number	MS 200585-0002 BD1604-12CEC
International non-proprietary name	Praziquantel
Title	A phase I, open-label, randomized, three-period, crossover, partial replicated, reference-scaled, single center trial to assess the bioequivalence of a single oral dose of 1200 mg of the new Cisticid® (herein Cisticid) 600 mg tablet formulation versus comparator Biltricide® (herein Biltricide) in healthy male volunteers
Phase	I (Bioequivalence)
IND Number	Not applicable
EudraCT Number	Not applicable
Principal Investigator	PPD
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Medical Responsible	PPD Merck,S.A. de C.V. Calle 5, No. 7, Frac. Industrial Alce Blanco, Nuacalpan de Juárez., México, C.P. 53370
Clinical Trial Protocol Version	27 October 2017/ Version 1.0

[redacted]

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List of Abbreviations

A	Absorption
AE	Adverse Event
AUC	Area Under the Curve
BE	Bioequivalence
BMI	Body Mass Index
C_{max}	Maximum Concentration
CRF	Case Report Form
CYP	Cytochrome
ECG	Electrocardiogram
EOT	End of Trial
FDA	Food and Drug Administration
GI	Gastrointestinal
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention To Treat
IUPAC	International Union of Pure and Applied Chemistry
IUD	Intra-Uterine Device
IVRS	Interactive Voice Response System
MOP	Manual of Operations
ODT	Orally Disintegrating Tablet
PD	Pharmacodynamics
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
PQP	Prequalification of Medicines Programme
PZQ	Praziquantel
RNEC	National Registry of Clinical Trials
SAE	Serious Adverse Event
SPC	Summary Product Characteristics
WHO	World Health Organization

1 Synopsis

Clinical Trial Protocol Number	MS 200585-0002
Title	A phase I, open-label, randomized, three-period, crossover, partial replicated, reference-scaled, single center trial to assess the bioequivalence of a single oral dose of 1200 mg of the new Cisticid 600 mg tablet formulation versus comparator Biltricide in healthy male volunteers
Trial Phase	I (Bioequivalence)
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	Not applicable
Principal Investigator	PPD
Sponsor	Merck KGaA Darmstadt, Germany
Sponsor Legal Representative in the European Union	Merck KGaA
Trial centers/countries	Mexico
Planned trial period (first subject in-last subject out)	Dec 2017-Jan 2018
Trial Registry	RNEC (National Registry of Clinical Trials)

Objectives:

Primary objectives: To assess the bioequivalence (BE) of the new 600 mg Cisticid tablet (Test) versus the comparator 600 mg tablet of Biltricide (Reference) at a dose of 1200 mg, administered as single dose in fed condition to healthy male volunteers.

Secondary objectives:

To assess the safety and tolerability of the new 600 mg Cisticid tablet formulation at a single dose of 1200 mg.

General pharmacokinetic evaluation of the new 600 mg Cisticid tablet formulation at a single dose of 1200 mg in comparison to the current reference of 600 mg Biltricide tablet

Methodology: A randomized, open label, single dose, crossover design will be used with 60 subjects in fed conditions, 3 periods, and with a 7-day washout period between 3 study stages.

Planned number of subjects: Sixty subjects will be randomized

Primary endpoints: The primary pharmacokinetic (PK) parameters are the area under the serum concentration-time curve from 0 to the time of the last quantifiable concentration (AUC_{0-t}) and the maximum serum concentration (C_{max}) for L-PZQ.

Secondary endpoints:

- Recording, reporting and analysis adverse events (AEs), physical examination findings including vital signs (body temperature, systolic / diastolic blood pressure, and pulse rate), standard laboratory parameters hematology, biochemistry, urinalysis, and coagulation) and 12-lead electrocardiogram (ECG).
- Additional pharmacokinetic parameters will be estimated: t_{max}, t_{lag}, $AUC_{0-\infty}$, AUC_{extra}, t ½ , λZ, CL/f and Vz/f of L-PZQ and t_{max}, t_{lag}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{extra}, C_{max}, t ½ , λZ, CL/f and Vz/f parameters for rac-PZQ.

Diagnosis and key inclusion and exclusion criteria:

Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Healthy males aged 18-55 years of age (inclusive at screening).
2. A male participant must agree to use and to have their female partners willing to use additional non-hormonal contraception (e.g., condoms or occlusive cap [diaphragm or cervical/vault cap] with spermicide, non-hormonal intra-uterine device [IUD], previous sterilization of subject or his partner, being sexually inactive) from Day of randomization up to final EOT visit.
3. Gave written informed consent prior to any trial related procedure.
4. Have a body weight (BW) of > 55.0 kg to < 95 kg and a body mass index (BMI) between 18.0 and 27.0 kg/m^2.
5. Able to communicate well with the Investigator, understanding the protocol requirements and restrictions, and willing to comply with the requirements of the entire trial.
6. Non-smoker (= 0 cigarettes, pipes, cigars or others) since at least three months.
7. Electrocardiogram recording (12-lead) without signs of clinically relevant pathology in particular QTc (Bazett) <450 ms
8. Vital signs in the following normal range (after 10 minutes in supine position):
   - systolic blood pressure: 90 to 140 mmHg
   - diastolic blood pressure: 50 to 90 mmHg
   - pulse rate: 45 to 90 bpm
   - oral body temperature between 35.0°C to 37.5°C
9. All values for biochemistry, liver function test and hematology tests of blood and urine within the normal range or showing no clinically relevant deviation as judged by the Investigator. Hematocrit and hemoglobin must be above the lower limit; upper limit may range up to 15 %. Remaining results, including white blood cells may range ± 15 %, if subject is asymptomatic
10. Negative screen for alcohol and drugs of abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants) at screening and on each admission.
11. Negative screen for Hepatitis B surface (HBs) antigens, Hepatitis C Virus (HCV) antibodies, Hepatitis A Virus (HAV) antibodies and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies.

Exclusion criteria:

1. Any surgical or medical condition, including findings in the medical history or in the pre-study assessments, or any other significant disease, that in the opinion of the Investigator, constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation.
2. History of surgery of the gastrointestinal tract, history of other GI tract diseases, or acute GI tract infections in the last 2 weeks, which could influence the gastrointestinal

absorption and/or motility according to the Investigator's opinion.

3. Any clinically relevant abnormality in the safety laboratory parameters as judged by the Investigator.
4. Have positive results from serology examination for Hepatitis B surface (HBs) antigen, Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV.
5. Allergy: ascertained or presumptive 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 outcome of the trial.
6. History or presence of drug abuse (opiate class, barbiturates, cocaine and its main metabolite, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants) or alcohol abuse at screening and on each admission. Alcohol abuse is defined by the assessment of the Investigator.
7. Loss or donation of more than 400 mL of blood within 90 days prior to first PZQ administration.
8. Administration of any investigational product or use of any investigational device in any clinical study within 30 days prior to first PZQ administration. Subjects who have used drugs that may affect the pharmacokinetics of PZQ from 14 days before dosing until the last PK sample, e.g., phenytoin, barbiturates, primidone, carbamazapine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin, oral ketoconazole.
9. Consumption of substances known to be potent inhibitors or inducers of CYP P450s such as grapefruit, orange, cranberry or juices of these fruits, herbal remedies or dietary supplements containing St. John's Wort, poppy seeds, cruciferic vegetables, in the two weeks before dosing until last PK sample.
10. Unlikely to comply with the protocol requirements, instructions and trial-related restrictions, e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial.
11. Non-acceptance or non-compliance with the study breakfast (e.g. vegetarians, vegans and subjects who follow special diets).
12. Excessive consumption of beverages containing xanthine (>5 cups of coffee a day or equivalent) or inability to stop consuming caffeine from 48 hours prior to drug administration until discharge from the clinic.
13. Subject is the Investigator or any Sub-Investigator, research assistant, pharmacist, trial coordinator, other staff or relative thereof directly involved in the conduct of the trial.
14. Vulnerable subjects (e.g., persons kept in detention).
15. Legal incapacity or limited legal capacity.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule

Test: 1200 mg of Cisticid new formulation (two 600 mg tablets), single dose administered orally in fed condition

Reference: 1200 mg of Biltricide (two 600 mg tablets), single dose administered orally in fed condition in two periods.

Planned trial and treatment duration per subject: Screening period of maximal 28 days,

Three weeks dosing period including washout followed by one week of clinical follow-up.
Statistical methods: Statistical analysis will be performed using the computer program package SAS® System PPD . If not stated otherwise, the level of statistical significance will be alpha=0.05. PK data evaluation will be performed based on standard non-compartmental methods using the validated software tool PPD . Details on the statistical analysis and PK data analysis will be presented in the statistical 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. The analysis of the primary endpoints AUC_{0-t} and C_{max} of L-PZQ will be performed using the PK population. Both parameters will be log-transformed before analysis. For the demonstration of bioequivalence different approaches will be applied for AUC_{0-t} and C_{max}. For AUC_{0-t} the standard approach will be followed, i.e. the point estimate and the 90% CI of the Test/Reference geometric mean ratio must fall within [0.80, 1.25]. A linear mixed-effects model will be applied for the analysis of AUC_{0-t}. The treatment difference TEST – REFERENCE will be estimated, and the 90% CIs for the difference will be calculated. The difference and 90% CIs will be back-transformed to the original scale. If the 90% CI for the ratio (test/reference) lies entirely within the interval [80.00 – 125.00], then the BE criterion is fulfilled for AUC_{0-t}. For the analysis of C_{max}, a reference-scaled bioequivalence approach will be applied.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

Merck KGaA Frankfurter Strasse 250, 64293 Darmstadt, Germany

Committees

Ethics and Investigation Committee :	PPD Phone: PPD Filing at PPD PPD
Investigation Committee:	PPD Phone: PPD Filing at PPD

Clinical Laboratory

Clinical Laboratory and Corporate Health Representative:	PPD Tel. PPD

The study will be conducted in one single site, PPD . Responsible for the clinical part of the trial including trial set-up, coordination, safety and analytical lab, monitoring, data capture, data management, statistical analysis, and clinical trial reporting. The bioanalytics will be performed at PPD , under the responsibility of the Sponsor. The Sponsor will supervise all outsourced activities.

The Principal Investigator PPD , represents all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP) (17). The Principal Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

This protocol meets requirements of current clinical research regulations, including: ICH GCP, ethical principles for clinical research in human beings from the Declaration of Helsinki issued in the 64th General Assembly from the World Medical Association, Fortaleza, Brazil, October 2013; General Health Act and General Health Act Regulations in the field of Health Research and the provisions stated in NOM 177-SSA1-2013 which states that “tests and procedures to prove that the drug is interchangeable as well as the requirements which authorized third parties, performing tests, should adhere”.

The study will be listed in the following registries for clinical trials: National Registry for Clinical Trials (RNEC) from the Mexican Ministry of Health through the Federal Commission for the Protection against Sanitary Risks.

Study Monitor: Monitoring will be performed by PPD

This study will be conducted according to the provisions stated in NOM 177-SSA1-2013 which states that "tests and procedures to prove that the drug is interchangeable as well as the requirements which authorized third parties, performing tests, should adhere", including the Good Clinical Practice (GCPs), ICH and all other applicable regulations.

According to the General Health Act Regulations in the field of health research, second title, chapter I, article 17, section III which was published on the Official Gazette on April 2nd, 2014 this study is considered an investigational study with risk higher than minimum.

Based on the non-clinical and clinical data available so far, the conduct of the trial specified in this clinical protocol is justified.

The investigational medicinal product (IMP) will be provided to the trial site under the responsibility of the Sponsor’s Clinical Trial Supply department.

Details of structures and associated procedures (e.g. PK sampling) will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

3 Background Information

Schistosomiasis, also called Bilharzia, belongs to one of the most neglected tropical diseases caused by flatworms which remain 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, infecting more than 220 million people, with more than 90% of them living in Africa. They live in rural agricultural and peri-urban areas, and placing more than 700 million people at risk. Of the infected patients, 20 million suffer severe consequences from the disease. Some estimate that there are approximately 20,000 deaths related to schistosomiasis yearly. In many areas, schistosomiasis infects a large proportion of children under the age of 14 years.

The WHO recommended control strategy of schistosomiasis is based on preventive chemotherapy interventions targeting the majority of the at-risk population. The current gold standard treatment employs annual single oral dose of Praziquantel (PZQ) tablets, jointly developed by Bayer AG and Merck KGaA in the 1970's, and commercialized in 1980 as Biltricide (Bayer) and Cisticid (Merck KGaA) for human use. Note that Cesol® (herein Cesol) is the tradename for the donation program, but for the purposes of this document the product is hereby referred to Cisticid, Praziquantel, or PZQ. Note also that Cisticid is the product that is approved for the Mexican market CCI [redacted]. Cesol and Cisticid are the identical 600 mg final tablet presentation.

PZQ tablets consist of a racemic mixture of the two enantiomers L-PZQ and D-PZQ in a 1 to 1 ratio. The L-PZQ enantiomer is associated with the anti-helminthic activity, whereas the D-PZQ has no cidal activity against worms and was reported to be responsible for the extreme bitterness of the product. The L-4-OH-PZQ metabolite also possesses anti-helminthic activity but only at much higher concentrations (the IC50 of L-trans-4-OH-PZQ was approximately 335 fold higher than of L-PZQ at 4 hours of incubation).

Merck KGaA is donating PZQ tablets to the World Health Organization (WHO). As a requirement for this Praziquantel donation program, WHO requested the development of a new formulation of Praziquantel tablets to address complaints of broken tablets of the current formulation. In addition, the request included the necessity that this formulation considers the development of a tablet coating to decrease the bitter tasting. This new formulation complies with the dissolution profile similarity, comparing with the reference selected by the WHO that in this case corresponds to Biltricide tablets manufactured by Bayer and sold in the US. However, as PZQ is a Biopharmaceutics Classification System class II (= High Permeability, Low Solubility) compound, a biowaiver cannot be granted, and WHO Prequalification of Medicines Programme (PQP) requested a bioequivalence study against the original tablet. Since PZQ is known to be a highly variable product within blood concentration, the sponsor prefers to employ a replicated study design.

WHO PQP, opposed to FDA, does not allow scaling the acceptance range for AUC but they do allow scaling for C_{max}, which leads to a higher sample size than if scaling for both parameters would be incorporated.

3.1 Pharmacology

3.1.1 Chemical Structure

Chemical Name: (11b*R*)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one

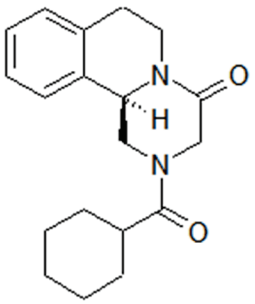
Recommended International

Nonproprietary name (rINN): R-(-)-Praziquantel

Chemical Abstracts Service

Registry Number (CAS-RN): 57452-98-9

Structural Formula



Molecular Formula: $C_{19}H_{24}N_2O_2$

Relative Molecular Mass (L-PZQ 2.1)**:** 312.4 g/mol

3.1.2 Absorption

Praziquantel is rapidly absorbed (80%) following oral administration with a T_{max} of approximately 1 - 3 hours. When administered with food, the C_{max} and AUC of Praziquantel are higher relative to the fasting state, although the variability is also increased. Praziquantel should always be taken with food. (36).

The bioavailability of Praziquantel increases with concomitant food administration. Castro et al, 2000(6), showed that following the administration of a dose of 1800 mg (~25 mg/kg for a 70 kg body weight) to healthy adults, the AUC_{0-8h} was 2.7-fold higher with a fatty diet (eggs, ham, orange juice, milk; ~ 30% lipid; ~ 50% carbohydrate), and ~ 4-fold higher with a high-carbohydrate content diet (tortillas, tomato, chicken, bread, orange juice; ~ 10% lipid; ~ 75% carbohydrate) than without food.

Similarly, the administration to Sudanese adult males of Praziquantel at a dose of 40 mg/kg with food (cooked beans/10% cotton seed oil/bread) resulted in a 2.6-fold increase in the $AUC_{0-\infty}$.

3.1.3 Distribution

The volume of distribution is not known. Praziquantel crosses the blood–brain barrier, explaining its effectiveness in neurocysticercosis (18). Concentrations in breast milk are approximately one-fourth of the plasma concentration. (32).

Praziquantel is highly protein-bound (~ 80%, nearly exclusive to albumin), (8;11) which makes the levels of free drug subject to factors such as nutrition and inflammation (4).

3.1.4 Metabolism

Praziquantel undergoes an extensive first-pass metabolism in the liver by the CYP system (CYP1A2, CYP3A4, CYP2B1, CYP3A5 and CYP2C19). (1;8). This makes its pharmacokinetics susceptible to variability due to:

- Possible Interindividual pharmacogenetics differences (no data available).
- Interactions with drugs or substances taken concomitantly that induce or inhibit specific isoenzymes of the CYP system [e.g. increased exposure with cimetidine or grapefruit juice (5) and decreased exposure with the anti-epileptic CYP inducers carbamazepine and phenytoin (3) or rifampicin (33)].
- The condition of the liver function (exposure increases with the severity of hepatic impairment) (20)

The main metabolite in man is trans-4-hydroxypraziquantel. D-PZQ also produces additional monohydroxypraziquantel metabolites (22).

3.1.5 Elimination

Elimination of Praziquantel is essentially renal (80% within 4 days, of which 90% occurs within 24 h); as the product is extensively metabolized, 0.01% is found in the urine as the parent compound (1). The terminal elimination half-life of Praziquantel is approximately 0.8 - 3 hours when administered with food (36).

3.1.6 Mechanism of action

Although the exact mechanism of killing of the parasites is unknown, Praziquantel disrupts Ca^{2+} homeostasis in adult worms, which induces a spasmodic muscular contraction and immobilization of the worm's body (7).

Worms treated with 1 mg/mL Praziquantel stop moving immediately, as demonstrated by microcalorimetric studies (21). Adult worms are slightly more susceptible to Praziquantel (LC_{50} 0.03 mg/mL at 72 h) than schistosomula (0.68 mg/mL at 72 h) (16).

3.1.7 Pharmacological Properties

Praziquantel is widely used for the treatment and control of all Schistosoma species infecting humans and causing the intestinal (mainly Schistosoma mansoni and Schistosoma japonicum) and urinary (Schistosoma haematobium) forms of schistosomiasis (34; 12). Adult male–female pairs reside in the mesenteric veins and lay eggs, which sustain both the transmission and the pathology. Schistosomiasis develops over many years and is characterized by immunogenic inflammatory, granulomatous and fibrotic reactions, which are provoked by trapped schistosome eggs in the tissues (12). Whereas treatment is directed against the adult worms, the effects of treatment are customarily assessed by counting the eggs in the excreta (stools or urine).

3.1.8 Adverse Reactions

For Praziquantel, the expected occurrence of adverse reactions depends on the quantity and duration of Praziquantel use, the type, extent and location of parasite infestation as well as on the duration of infection.

The adverse reactions listed in the below occur independently from the above factors. There are mostly transient complaints not generally requiring any special treatment. Adverse reactions may partly represent endogenous reactions to the killing off of the parasites by Praziquantel

Table 1 **Undesirable Effects**

System organ class	Common ≥1/100 to <1/10	Very rare < 1/10.000	Not known
Cardiac disorders		arrhythmia, bradycardia, ventricular fibrillation, auricular-ventricular locks	
Ear and labyrinth disorders		vertigo	

Gastrointestinal disorders	abdominal pain, nausea, vomiting, diarrhea, blood in stool, urgency to defecate		
General disorders and administration site conditions	fever, malaise	fatigue	
Metabolism and nutrition disorders	loss of appetite		hyperglycemia*
Nervous system disorders	Headache, dizziness, drowsiness	seizures	
Skin and subcutaneous tissue disorders		erythema, pruritus	

* *in patients treated with praziquantel for neurocysticercosis*

Patients with neurocysticercosis after completing treatment with praziquantel may have fever, nausea, vomiting, meningitis and increased intracranial pressure; symptoms associated with the inflammatory response induced by the destruction of cysticercoid.

4 Trial Objectives

4.1 Primary Objectives

To assess the BE of the new 600 mg Cisticid tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg, administered as single dose in fed condition to healthy male volunteers (AUC_{0-t} and C_{max} of L-PZQ).

4.2 Secondary Objectives

To evaluate the safety and tolerability of the new 600 mg Cisticid tablet at a single dose of 1200 mg.

General pharmacokinetic evaluation of the new 600 mg Cisticid tablet formulation at a single dose of 1200 mg in comparison to the current reference of 600 mg Biltricide tablet Pharmacokinetic parameters will be determined: t_{max}, t_{lag}, $AUC_{0-\infty}$, AUC_{extra}, t ½, λZ, CL/f and Vz/f of L-PZQ and t_{max}, t_{lag}, $AUC_{0-\infty}$, AUC_{extra}, t ½, λZ, CL/f and Vz/f parameters of rac-PZQ).

4.3 Statistical Hypothesis

H_0: Drug R and drug T are not bioequivalent.

H_1: Drug R and drug T are bioequivalent.

Test, T: New 600 mg Cisticid tablet

Reference, R: 600 mg Biltricide tablet

5 Investigational Plan

5.1 Overall Trial Design and Plan

The purpose of the current relative bioavailability trial is to assess the bioequivalence (BE) of the the new 600 mg Cisticid tablet (Test) versus Biltricide (Reference) in healthy male volunteers under fed conditions.

This is a phase I, crossover, open-label, single dose, randomized, three period trial where subjects will be randomized to one of three sequences: T-R-R, R-T-R and R-R-T where T is test product and R is Reference product, with a washout period of at least 1 week in between.

The study will investigate the BE of the new 600 mg Cisticid tablet versus the comparator 600 mg tablet of Biltricide at a dose of 1200 mg (primary endpoints AUC_{0-t} and C_{max} of L-PZQ), administered in fed condition in 60 healthy male volunteers. Finally safety and tolerability will be also investigated.

In each treatment period subjects are institutionalized the evening before dosing until 24 hours after dosing with a washout period of 7 days. Total duration of the study for a subject is up to 7 weeks, including a Screening period of maximal 28 days, and 3 weeks dosing period including washout, and safety follow-up (EoT visit) at 7 days after third dose (period).

The subjects will be randomized to one of the 3 treatment sequences (see Table 2 below).

Table 2 Treatment Sequences of the Study.

Sequence	Period 1		Period 2		Period 3	
1	Test	Wash-out 7 days	Reference	Wash-out 7 days	Reference	Wash-out 7 days and EOT visit
2	Reference		Test		Reference	
3	Reference		Reference		Test	

5.2 Discussion of Trial Design

For the design of this BE study the following documents were taken into account: the recommendation from WHO PQP group regarding the design of BE studies for PZQ (WHO PQP Guidance Document 13 October 2015[36]) as well as the EMA Bioequivalence Guideline and NOM-177-SSA1-2013(10).

A cross-over study is a standard design for a bioequivalence study; a replicate design is a necessary prerequisite for the reference scaled approach applicable for C_{max} CVs greater than 30%. Sixty healthy male subjects who meet all inclusion and none of the exclusion criteria will

be randomized and dosed to have at least 48 evaluable subjects with all assessments performed. The use of only male subjects is acceptable since no gender effect on the PK has been described for PZQ. Moreover, although there are well known differences in the response of males and females to drug treatment, this should not necessarily increase the within subject variability and thus be the reason for excluding females from a BE study. On the other hand, women have fluctuating hormone levels during a normal cycle. As it is known that increased levels of estrogen and progesterone can alter hepatic enzyme activity this might lead to fluctuations in metabolism over the study period and thus increase the within subject variability in women. Use of contraceptives also 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. Moreover women often have more problems with the obligatory breakfast prescribed for this study. For this reason only male subjects have been included.

Due to the different form and color of the tablets blinding is difficult. However, the PK will be measured at an independent laboratory, where the analyst is not aware of the treatment given. In addition, the PK is an independent variable that cannot be influenced by the subjects. Therefore, it is felt that a non-blinded study is acceptable for the defined objective.

Following the WHO guidance, the variability of AUC rather than the CV of C_{max} is the driver for the sample size of this trial.

A cross-over study is the optimal design for a bioequivalence study since each subject serves as its own control. The application of the reference scaled BE approach to C_{max} requires a repeated administration of the reference drug. A BE study with a 3 period cross-over design is proposed.

Justification for Dose

The WHO PQP advises the use of one oral tablet of PZQ 600 mg, which corresponds to a dose of just below 10 mg/kg for an adult of 70 kg, in case of a BE study for Praziquantel. This dose is well below the therapeutic dose of 40 mg/kg, recommended by WHO (23), and the use of therapeutic doses in BE studies is recommended by EMA. Since it is also known that PZQ PK are not linear for both the commercial (36) and the new (ODT) formulations (own observations), and the exposure at a dose of ~ 10 mg/kg is currently unknown, it is felt that a higher dose might be more appropriate.

Therefore, it is recommended that in view of the fact that 1) the individual enantiomers will be measured and the L-PZQ will be used for BE evaluation and 2) that the recommendation by WHO PQP is a (minimum) 600 mg dose but should take into account the LOQ of the method, and 3) the LLOQ for L-PZQ is 5 ng/mL and 4) mean C_{max} and the range of C_{max} after administration of 1200 mg is expected to be around 156.6 (range 38.0– 566) ng/mL and 5) 20 mg/kg is the lowest recommended therapeutic dose, to use a dose of 1200 mg.

Mean C_{max} and AUC for L-PZQ and rac-PZQ after administration of 40 mg/kg of the current Cisticid tablet is shown in Table 3. Mean C_{max} and AUC as recently observed in an exploratory

phase I study with an ODT formulation of PZQ at doses of 20, 40 and 60 mg/kg is also shown in the table and clearly confirmed the non-dose proportionality, already mentioned in the literature (WHO, 2015). When the dose is decreased by a factor 2 from 40 to 20 mg/kg, C_{max} and AUC decreased non-dose proportional by a factor 3 to 4.

The non-dose-proportionality observed after doubling the dose is a factor ~4 for L-PZQ and a factor ~3 for rac-PZQ. Assuming similar non-dose-proportionality at lower doses of 10 mg/kg, the expected C_{max} for L-PZQ analyte after a dose of 10 mg/kg is around 40 ng/mL for L-PZQ (range 9.5 to 144 ng/mL) and ~ 300 ng/mL (range of ~180-700) for rac-PZQ. As the current LLOQ for the L-PZQ is 5 ng/mL, a mean C_{max} of 40 ng/mL is only 8 times higher than the LLOQ and does not comply with the LLOQ being < 5% of C_{max}. For the racemate PZQ the LLOQ of 10 ng/mL is for most subjects expected to be within the pre-specified range of less than 5% of C_{max}. Since the BE comparison is to be based on L-PZQ levels for the BE endpoint, a dose of 1200 mg (2 tablets) is recommended, if rac-PZQ had been used for the BE endpoint, a dose of 600 mg might have been compliant.

Choice of analyte.

Although the WHO recommendation states that the parent compound is considered to best reflect the biopharmaceutical quality of the product and should be used to assess bioequivalence, the EMA guideline states for compounds consisting of enantiomers the following:

Enantiomers
The use of achiral bioanalytical methods is generally acceptable. However, the individual enantiomers should be measured when all the following conditions are met:

(1) the enantiomers exhibit different pharmacokinetics

(2) the enantiomers exhibit pronounced difference in pharmacodynamics

(3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

The individual enantiomers should also be measured if the above conditions are fulfilled or are unknown. If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer.

It is known that the PK and PD of the individual enantiomers of PZQ is clearly different (30; 35). Whether the exposure ratio of the enantiomers is modified by a difference in the rate of absorption or a difference related to differential metabolism is currently unknown. However this would point to the measurement of both individual enantiomers. In addition the current consensus is that the L-PZQ is the active enantiomer against S. mansoni and japonicum (23).

All in all, after having received feedback from WHO PQP pinpointing the fact that a nonchiral method is only acceptable if it is known that the exposure ratio is not modified by a difference in the rate of absorption, combined with the different ratios in enantiomers seen after administration of 20 and 40 mg/kg to humans, it was decided to use an enantioselective method for this registration study and the PK parameters of L-PZQ as the primary endpoint. As the CV% for L-PZQ were observed as being much higher than for rac-PZQ this had consequences for the sample size determinations.

5.3 Selection of Trial Population

Only those subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized. Before performing any study specific assessment which is not part of the subject's routine health care, the Principal Investigator will make sure that the subject has provided his written consent form according to the procedure described in section 9.2 Subject's Information and Informed Consent Form.

- Recruitment by invitation by means of an open announcement.
- Inclusion of 60 subjects in study as per protocol's criteria.
- Male subjects to decrease overall variability (see section 5.2)

5.3.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Healthy males aged 18-55 years of age (inclusive at screening)

2. A male participant must agree to use and to have their female partners willing to use additional non-hormonal contraception (e.g., condoms or occlusive cap [diaphragm or cervical/vault cap] with spermicide, non-hormonal intra-uterine device [IUD], previous sterilization of subject or his partner, being sexually inactive) from Day of randomization up to final EOT visit
3. Gave written informed consent prior to any trial related procedure.
4. Have a body weight (BW) of > 55.0 kg to < 95 kg and a body mass index (BMI) between 18.0 and 27.0 kg/m^2.
5. Able to communicate well with the Investigator, understanding the protocol requirements and restrictions, and willing to comply with the requirements of the entire trial.
6. Non-smoker (= 0 cigarettes, pipes, cigars or others) since at least three months.
7. Electrocardiogram recording (12-lead) without signs of clinically relevant pathology in particular QTc (Bazett) <450 ms
8. Vital signs in the following normal range (after 10 minutes in supine position):

- systolic blood pressure: 90 to 140 mmHg
- diastolic blood pressure: 50 to 90 mmHg
- pulse rate: 45 to 90 bpm
- oral body temperature between 35.0°C to 37.5°C

9. All values for biochemistry, liver function test and hematology tests of blood and urine within the normal range or showing no clinically relevant deviation as judged by the Investigator. Hematocrit and hemoglobin must be above the lower limit; upper limit may range up to 15 %. Remaining results, including white blood cells may range ± 15 %, if subject is asymptomatic.
10. Negative screen for alcohol and drugs of abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants) at screening and on each admission.
11. Negative screen for Hepatitis B surface (HBs) antigens, Hepatitis C Virus (HCV) antibodies, Hepatitis A Virus (HAV) antibodies and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies

5.3.2 Exclusion Criteria

1. Any surgical or medical condition, including findings in the medical history or in the pre-study assessments, or any other significant disease, that in the opinion of the Investigator, constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation.
2. History of surgery of the gastrointestinal tract, history of other GI tract diseases, or acute GI tract infections in the last 2 weeks, which could influence the gastrointestinal absorption and/or motility according to the Investigator's opinion.

3. Any clinically relevant abnormality in the safety laboratory parameters as judged by the Investigator.
4. Have positive results from serology examination for Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV), Hepatitis A Virus (HAV), or Human Immunodeficiency Virus (HIV.
5. Allergy: ascertained or presumptive 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 outcome of the trial.
6. History or presence of drug abuse (opiate class, barbiturates, cocaine and its main metabolite, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants) or alcohol abuse at screening and on each admission. Alcohol abuse is defined by the assessment of the Investigator.
7. Loss or donation of more than 400 mL of blood within 90 days prior to first PZQ administration.
8. Administration of any investigational product or use of any investigational device in any clinical study within 30 days prior to first PZQ administration. Subjects who have used drugs that may affect the pharmacokinetics of PZQ from 14 days before dosing until the last PK sample, e.g., phenytoin, barbiturates, primidone, carbamazapine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin, oral ketoconazole.
9. Consumption of substances known to be potent inhibitors or inducers of CYP P450s such as grapefruit, orange, cranberry or juices of these fruits, herbal remedies or dietary supplements containing St. John's Wort, poppy seeds, cruciferic vegetables, in the two weeks before dosing until last PK sample.
10. Unlikely to comply with the protocol requirements, instructions and trial-related restrictions, e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial.
11. Non-acceptance or non-compliance with the study breakfast (e.g. vegetarians, vegans and subjects who follow special diets).
12. Excessive consumption of beverages containing xanthine (>5 cups of coffee a day or equivalent) or inability to stop consuming caffeine from 48 hours prior to drug administration until discharge from the clinic.
13. Subject is the Investigator or any Sub-Investigator, research assistant, pharmacist, trial coordinator, other staff or relative thereof directly involved in the conduct of the trial.
14. Vulnerable subjects (e.g., persons kept in detention).
15. Legal incapacity or limited legal capacity.

5.4 Criteria for Initiation of Trial Treatment

Eligible subjects will continue screening at the time of admission to the study center (Day -1). Results of screening procedures performed on Day -1 as detailed Section 7.1.1, must be available prior to randomization. All inclusion and exclusion criteria will undergo a final verification before randomization.

All subjects should have negative result for oral alcohol screening at the beginning of each visit (day -1 for treatment period) and drugs of abuse (opioids, barbiturates, cocaine and its metabolites, amphetamines, methamphetamines, morphine, cannabinoids, benzodiazepines and tricyclic antidepressants), throughout the screening period and start of each one of the visits (day -1 for each treatment period).

All relevant inclusion and exclusion criteria will be rechecked on admission to the clinic in Period 1, 2 and 3 and before IMP administration on each dosing day.

5.5 Criteria for Subject Withdrawal

Participant subjects in the study are free to withdraw from the study at any time and they will only be asked to give the reason of their withdrawal. End of study examination must be performed if the subject has received at least one active drug as described in section 6.7. Withdrawal reason should be documented in the medical chart in the case report form, if known. Study drug assigned to the withdrawn subject cannot be assigned to another subject. Subjects who withdraw will not be replaced.

5.5.1 Withdrawal from Trial Treatment

Not applicable since only single doses will be administered.

5.5.2 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent.
- Non-compliance that jeopardizes subject safety or the validity of the trial data, including lost to follow-up.
- Participation in any other trial during the duration of this trial.
- Use of a non-permitted concomitant drug as defined in section 6.5.2 Prohibited medicines, where the predefined consequence is withdrawal from treatment with investigational medicinal product (IMP).

- Occurrence of AEs, if discontinuation from the trial due to drug effects is desired or considered necessary by the Investigator and/or the subject (if applicable), e.g. severe unacceptable gastrointestinal side effects or inter-current illness.
- Signs of liver injury, as defined by:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 x upper limit of normal (ULN).
  - ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5 x ULN.
  - ALT or AST > 3 x ULN with clinical symptoms of hepatitis such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
- 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/during drug administration

Subjects may withdraw consent to participation in the clinical trial at any time without penalty and for any reason without prejudice to future medical care. Withdrawal of consent will be considered withdrawal from the trial.

If a subject failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. If a subject is withdrawn, or chooses to withdraw, from the clinical study for any reason, the Investigator must make every possible effort to perform the evaluations described for the EOT visit (see Appendix 2). If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned. In all cases, the reason(s) for withdrawal must be recorded in the case report form (CRF).

If the Investigator withdraws a subject for an IMP-related reason (e.g vomiting), the subject is considered a dropout. In this event, the Sponsor will be provided with a reasonable medical justification of such a decision.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

The end of trial date will be the Last Subject Last Visit (LSLV) date. The trial will end when all treated subjects in the trial have completed/discontinued from the trial as per protocol.

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving any IMP.
- Visits specified by the protocol are still taking place.
- Procedures or interventions according to the protocol are still being undertaken in any subject.
- The post-treatment follow-up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference treatment or therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

All IMPs are manufactured in compliance with Good Manufacturing Practices. Study Sponsor will provide drugs to be administered to the subjects in each of the study visits.

- International non-proprietary name: Praziquantel.
  - Test drug: New Cisticid®.
    - Dosage form: Tablet
    - Qualitative-Quantitative Formula: Each tablet contains 600 mg of Praziquantel.
    - Manufacturer: Merck, Mexico S. A. de C. V.
    - Batch: M73271-LP
    - Expiry date: 31-May-2019.
  - Reference drug: Biltricide®

- Dosage form: Tablet
- Qualitative-Quantitative Formula: each tablet contains 600 mg of Praziquantel.
- Manufacturer: Bayer HealthCare Pharmaceuticals Inc.
- Marketing Authorization Holder: Bayer HealthCare Pharmaceuticals Inc.
- Batch: BXA6VKC
- Expiry date: 06-Oct-2018

Reference drug should be imported as per the following quantities and specifications:

Description: Biltricide® praziquantel tablet 600 mg.

Batch number: **BXA6VKC**

CCI [redacted]

Quantity required for each stage of the research: 60 tablets.

200 tablets for the study.

152 tablets for the finished product analysis and dissolution profile (if apply)

200 tablets as retention sample.

Manufacturer:

PPD [redacted]

[redacted]

Products importer:

PPD [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Dosage and Administration

Single dose, oral administration of 1200 mg Praziquantel (two 600 mg tablets) with 250 ml water, in each period, after the breakfast. A mouth check will be performed after each administration. The subject will take investigational medical product between 08:00 till 08:09 h, in 4 groups of 5 subjects each, with a 3-minute gap among each group for dosing

Subjects will enter the clinic the day before dosing (in 3 groups of 20 participants) and must fast overnight before IMP administration.

Dosing in the non-fasted state should be done at 30 minutes after the start of a standardized normal breakfast. The breakfast should be eaten within a period of 20 minutes and time should be recorded. Compliance with breakfast consummation will be recorded. All subjects will fast for 5 hours after dosing/completion of breakfast. At 5 hours after dosing, subjects will receive a light lunch.

The start of dosing between the three groups listed below will be separated by approximately three days, e.g. Group 2 dosing will start approximately three days after Group 1 has started.

During each period one of the three treatments will be dosed from 08:00 till 08:09 h, in 4 groups of 5 subjects each, with a 3-minute gap among each group for dosing. Group's distribution and timing can be changed due to operational reasons, as long as there is no impact in the study results.

Group's distribution, subjects and dose schedules are shown in the Table 4:

Table 4 Dosing Scheme

	Subgroups	No. of subjects	Dosing schedule
Group 1	A	01, 02, 03, 04 and 05	08:00 h
	B	06, 07, 08, 09 and 10	08:03 h
	C	11, 12, 13, 14 and 15	08:06 h
	D	16, 17, 18, 19 and 20	08:09 h
Group 2	E	21, 22, 23, 24, and 25	08:00 h
	F	26, 27, 28, 29, and 30	08:03 h
	G	31, 32, 33, 34, and 35	08:06 h
	H	36, 37, 38, 39, and 40	08:09 h

	Subgroups	No. of subjects	Dosing schedule
Group 3	I	41, 42, 43, 44 and 45	08:00 h
	J	46, 47, 48, 49 and 50	08:03 h
	K	51, 52, 53, 54 and 55	08:06 h
	L	56, 57, 58, 59 and 60	08:09 h

Water is not allowed until lunch. At 3 hours after treatment administration 250 ml water will be offered. The time and amount of water consumed at that time will be recorded. Subjects will leave the clinic 24 hours after dosing.

Subjects will be instructed not to consume alcohol, caffeine or xanthine-containing products (chocolate, tea, coffee, cola, energy drinks, etc.) from 48 hours prior to dosing until 24 hours after each IMP administration.

6.3 Assignment to Treatment Groups

Once it is confirmed that all inclusion criteria and none exclusion criteria have been met, subjects will be randomized to one of three treatment sequences in a 1:1:1 ratio.

Randomization of each subject to a treatment sequence will occur prior to dosing on Day 1. The Principal Investigator or delegate will allocate from the treatment kit stock (numbered 101-160 the next available treatment kit in a sequential, chronological order starting with the lowest number. Randomization will be based on a unique randomization list.

6.4 Non-investigational Medicinal Products to be used

Not applicable.

6.5 Concomitant Medications and Therapies

All concomitant drugs taken by the subjects during the study, starting as per informed consent signature should be appropriately recorded in the CRF, stating the name, dose and indication for each drug. Non-pharmacological interventions or any other intervention should be recorded in the CRF.

6.5.1 Permitted Medicines

The occasional use of paracetamol (maximum 1000 mg per day) or ibuprofen (1200 mg to 3200 mg daily) is allowed only after approval of the Principal Investigator.

Any medications that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Rescue medications may be administered to address anticipated adverse reactions or anticipated emergency situations.

6.5.2 Prohibited Medicines

Administration of any investigational product or use of any investigational device within 30 days prior to first administration of the IMP and during the entire clinical trial is not permitted.

No medication from screening until the last PK sample is allowed without prior approval from the Investigator (except for occasional use of paracetamol or ibuprofen). Attention should be paid to any drugs that may affect CYP450 enzyme status, e.g. phenytoin, barbiturates, primidone, carbamazapine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin and oral ketoconazole.

Subjects who two weeks prior to dosing have consumed substances known to be potent inhibitors or inducers of CYP P450s such as grapefruit, orange, cranberry or juices of these fruits, herbal remedies or dietary supplements containing St. John's Wort, poppy seeds, cruciferous vegetables are not allowed to participate in the study.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, e.g. because of AEs, the subject should be discontinued from the trial but only after consultation with the Sponsor.

6.5.3 Other Interventions

Subjects who have been exposed to agents known as inducers or inhibitors of liver enzymatic systems, who have taken drugs potentially toxic within 30 days prior to the study start-up, who require any drug throughout the study, who have history of gastrointestinal tract surgery which might affect gastrointestinal absorption and/or motility are not allowed to participate in the study.

6.5.4 Special Precautions

Subjects who have excessive consumption of beverages containing xanthine (>5 cups of coffee a day or equivalent) or inability to stop consuming caffeine from 48 hours prior to drug administration until discharge from the clinic are not allowed to participate in the study.

Subjects who have history or presence of drug abuse (opiate class, barbiturates, cocaine and its main metabolite, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants) or alcohol abuse at screening and on each admission are not allowed to participate in the study.

<u>Standardization of Physical Activity</u>

While resident in the trial site, the subjects will be confined to bed during the first 1 hour after the IMP administration. Thereafter, they may get out of bed, however restricting their activity to a minimum. Subjects should avoid excessive physical exercise throughout the trial until collection of the last PK sample.

Smoking Restrictions
Only non-smoking subjects or subjects who have refrained from smoking for at least 3 months prior to Screening.

In case of adverse events, medical staff will provide medical care required depending on the adverse event occurred. In case of severe eventuality, which requires hospital admission, the Principal Investigator or medical staff on due will request the transfer of the subject to the agreed hospital and will contact the external ambulance service, according to the standard operating procedure, code: IC-PNO-033, Management of Clinical Eventualities.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

In case of adverse events, medical staff will provide immediate medical care required depending on the adverse event occurred. The Principal Investigator will decide the subsequent management, according to the standard operating procedure, code: PPD , Management of Clinical Eventualities.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Cisticid® Merck, Mexico S. A. de C. V.

CCI [redacted]

[redacted]

Test product will be given orally as a single dose of 1200 mg (two tablets) of Cisticid with 250 mL of water during a breakfast.

Biltricide Bayer HealthCare Pharmaceuticals Inc.

CCI [redacted]

CCI [redacted]

Reference product will be given orally as a single dose of 1200 mg (two tablets) of Praziquantel, given with 250 mL of water during a breakfast.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

IMPs will be received at the PPD [redacted], S. C. by the Pharmacy Responsible or by the designated staff, as per the standard operating procedures, code: PPD [redacted]: Receipt, use, balance and final disposition of the study drug. Once drugs have been identified, they will be kept by the clinical unit until they are administered to the subjects.

Acceptance criteria for test and reference drugs:

- Complete documentation:
  - Certificate of Analysis.
  - Dosage units.
  - Content assessment.
  - For test drug, letter of Good Manufacturing Practice compliance.
  - For reference drug, confirmation from Bayer that material was donated and belongs to a batch that has been released as commercial material.
  - For reference drug, copy of the zero-charge invoice from the packaging site (Merck Spittal).
- Test drug with label compliant with the minimum requirements from NOM-072-SSA1-2012, Labelling of Drugs and Herbal Remedies (25).
- Enough quantity of test and reference drug for the trial and for retention medication.
- Expiry date not due at the moment of use in the clinical study.
- Test and reference drug in good physical conditions.

Rejection criteria for test and reference drugs:

- Evidence of tampering of primary packaging.

- Drug received out of the storage or transportation specifications.
- Evidence of damage to primary packaging (physical damage from any source e.g. impact, moisture, insects and rodents, etc.)

CCI [redacted]

[redacted]

6.8 Investigational Medicinal Product Accountability

The Principal Investigator, Pharmacy Responsible or designated staff at the PPD [redacted], S. C. will be in charge for ensuring IMP accountability, including reconciliation of drugs and maintenance of records, according to the standard operating procedure, code: PPD : Preparation and administration of drugs in clinical trials of interchangeability and PPD : receipt, use, balance and final disposition of the study drug.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial and prepared at the site.
  - The use of each dose by each subject.
  - The disposition (including return, if applicable) of any unused IMP.
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject trial numbers.

The Pharmacy Responsible site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial.

A Trial Monitor will periodically collect the IMP accountability forms according to the standard operating procedure, code: PPD Receipt, use, balance and final disposition of the study drug.

The Sponsor will ship enough quantities of the test and reference product to conduct the study and keep enough as "retention samples" to the Clínica de PPD

6.9 Assessment of Investigational Medicinal Product Compliance

Throughout dosing period, dose, full intake and time will be checked and recorded in the appropriate forms and CRF, according to the standard operating procedure, code: PPD : Preparation and administration of drugs in clinical trials of interchangeability and biocomparability; PPD , randomization in an interchangeability and biocomparability clinical study

A subject is compliant with the treatment only if he completes all study periods.

6.10 Blinding

Not applicable, this is an open-label trial for subjects but analysts will be blinded.

6.11 Emergency Unblinding

Not applicable, this is an open-label trial.

6.12 Treatment of Overdose

Overdose is defined as any dose higher than the highest daily dose included in the clinical protocol or foreseen for a subject recruited in the study. Even though this does not meet criteria for serious adverse event, any overdose should be recorded in the study drug section of the CRF and medical chart.

It should be reported to the *National Center of Pharmacovigilance* (CNFV) from the *Federal Commission for the Protection Against Sanitary Risks* (PPD), according to the standard operating procedures, code: PPD , Adverse event reporting in clinical and bioavailability studies and the Mexican Official Standard for Setting-up and Operations of Pharmacovigilance in Mexico, PPD (29) and following procedure listed in section 7.4.1.9.

Information on overdose of PZQ in humans is not available. Treatment should be supportive and provide symptomatic care.

6.13 Medical Care of Subjects after End of Trial

Subjects will sign a consent, which states that they will receive an economical compensation for their participation in the study. The Sponsor will pay treatment (or compensation, if applicable) resulting from injuries or diseases caused by their participation in the study until their resolution as per the clinical criteria. The Sponsor will not pay injuries caused by subject's negligence, irresponsible behavior or medical reasons no related to the study.

External follow-up will be given to all subjects recruited in the study. As per the last dose of the drug, free appointment or telephone contact will be available as per the Principal Investigator's judgment, for a period equivalent to the established wash-out period.

7 Trial Procedures and Assessments

At the beginning of each period, on day -1 and one hour prior to initial dosing, a physical examination will be done (including general appearance, skin, head, neck (including thyroid), ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system, oral cavity examination) as well as vital signs measurement, ECG and follow-up of adverse events. Blood and urine samples will be taken (day -1 only, following a 10-h fasting period) for safety laboratory tests such as hematology; blood chemistry, and urinalysis as well as urine sample for drug screening and alcohol breath test will also be performed in order to check if the subject remains eligible for the study.

Subjects should inform the medical staff in charge of the study conduct about any symptom they might have. Likewise, medical staff will question the subjects in every study period about symptoms occurred since recruitment in the first period, prior and following dosing. In case they report any, they will be provided with care and notes will made in the appropriate documents.

During each period, the vital signs (3, 7, 11h post dose) and the PK samples (see Table 4) will be taken.

During each period, safety laboratories test will be performed such as hematology, blood chemistry and urinalysis. Samples will be taken pre-dose (day -1 only, following a 10-h fasting period) and at discharge (24 h post-dose).

At the end of each period, at discharge (24 h post-dose) a clinical assessment consisting of an interview, physical examination (including general appearance, skin, head, neck (including thyroid), ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system, oral cavity examination), vital signs measurement, ECG and follow-up of adverse events, will be done. Blood and urine samples will be taken for safety laboratory tests such as hematology; blood chemistry, and urinalysis.

At the last visit a clinical assessment consisting of an interview, physical examination (see above) will be performed. Weight, ECG, vital signs and adverse events follow-up will be carried out. Blood and urine samples will be taken for safety laboratory tests such as hematology; blood

chemistry, and urinalysis, this visit will be performed around seven days after the last administration of the IMP, day 22.

Due to operational issues, the Principal Investigator may modify start of the study (starting as per the dosing of study drug) for one hour, as long as there is no impact on the study results.

7.1 Schedule of Assessments

Detailed schedule of study procedures/assessments is provided in Section 12.2 Appendix 2 Schedule of Assessments.

Prior to performing any trial assessments, the Investigator will obtain written informed consent as described in Section 9.2

In case of several assessments planned at the same time point, the PK samples will be taken at the predefined time point. The ECG recordings, followed by vital signs measurements, will be performed before PK sampling. Any ECG and vital signs taken within 60 minutes predose will be considered to have been taken at the scheduled time point. Safety laboratory samples collected within 15 minutes of the scheduled time point will be considered to have been taken at the scheduled time point. Sampling for safety laboratory will be assessed after PK blood sampling. All actual times need to be recorded in the eCRF.

The allowed deviation from the prespecified assessment time will be:

Predose samples:

- Within 1 hour before IMP administration

Postdose samples and assessments:

- Up to and including 24 hours: ± 5% of scheduled time point in minutes
- After 24 hours up to and including 96 hours: ± 1 hour
- After 96 hours: ± 4 hours

7.1.1 Screening of Subjects

Screening of the subjects will take place within 28 days prior to the first administration of the trial medication, according to the standard operating procedures, code: PPD Recruitment subjects, and comprises the following:

- Informed consent for participation in the trial,
- Inclusion/exclusion criteria checked.
- Demographics including body height and body weight and BMI, nicotine consumption, smoking history, alcohol consumption, intake of caffeine or xanthine-containing beverages, intake of grapefruit, orange, cranberry or juices of these three fruits and other things as described in Section 6.5.2)

- Medical history and history of medications
- Vital signs (body temperature, as well as blood pressure (BP) and pulse rate after at least 5 minutes rest in supine position),
- Physical examination
- Safety laboratory: biochemistry tests, hematological tests, urinalysis and Serology test,
- An urine drug screen test,
- 12-lead standard ECG (after 5 minutes rest in supine position),

Concomitant medications, AEs and procedures will be continuously assessed from signature of informed consent to the end-of-trial examination.

If no clinically relevant finding is made at screening and the subject satisfies all of the protocol inclusion criteria and none of the exclusion criteria, the subject will be considered as eligible and will be enrolled into the clinical trial.

Subjects who fail to meet the protocol specified criteria for dosing or who withdraw their consent in the screening period are considered screening failures. The following data will be recorded for these subjects: demographics (including age, weight and height), AEs, concomitant medications and reason for screening failure.

7.1.2 Treatment periods 1, 2, and 3

Day -1/7/14:

- Admission the day prior to the visit for assuring 10-h fasting period.
- Blood and urine samples will be taken (day -1 only, following a 10-h fasting period) for safety laboratory tests such as hematology; blood chemistry, and urinalysis
- Subject's eligibility will be checked again
- Dinner at least 10 h before the dosing.

Day 1/ 8 / 15:

- At 5:00 h, grooming and intake of 250 mL of water.
- Between 05:20 and 06:30 h, electrocardiogram will be performed.
- Post electrocardiogram the following activities will be done:
    - Catheter insertion (pre-dose sample).
    - Vital signs will be measured at 3, 7, and 11 h after dosing.
    - Adverse events and previous medication

- Randomization for the first period of treatment only
- At 07:30 h, breakfast. They will be given 20 minutes as maximum for having food, time should be recorded.
- At 08:00 h, oral administration of IMP with 250 mL of water at room temperature p.o., according to the standard operating procedure, code: BE-PNO-012: Preparation and administration of drugs in interchangeability and biocomparability clinical studies.
- From 08:15 to 20:00 h, PK sampling as per the schedule of assessments.
- At 11.00 h, 250 mL of water
- At 13:00 h, light lunch
- As from 16:00 h, lunch.
- As from 21:00 h, dinner.

Day 2/ 9 / 16:

- At 07:00 h, electrocardiogram will be performed.
- At 08:00 h, safety laboratory tests (hematology, blood chemistry and urinalysis) and catheter removal.
- At 08:30 h, vital signs will be measured
- Physical examination.
- Approximately at 10:00 h, discharge (temporarily on Day 2 and 9) from the clinical unit.

7.1.3 End of Trial (EoT)

- Physical examination and weight measurement for each subject.
- Vital signs measurement.
- Electrocardiogram.
- Safety laboratory tests (hematology, blood chemistry and urinalysis)

Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

7.2 Demographic and Other Baseline Characteristics

At screening (within 28 days before first administration), the following demographic data will be collected: date of birth, sex (gender), race and ethnicity. Specify any additional critical variables to be assessed such as:

- Information about previous and concomitant medications, medical history data including medication history within the last 5 years consisting of all previous diseases as considered relevant by the Investigator and all previous hospital stays, previous medication consisting of all previous medications within the last 5 years as considered relevant by the Investigator, and all regularly taken medications within the last year,
- No efficacy in this study Weight, height and BMI
- Special diets
- Month prior to drug administration, nicotine consumption
- Smoking history
- Alcohol consumption
- Consumption of caffeine or xanthine-containing beverages, intake of grapefruit, orange, cranberry or juices of these three fruits, intake of food containing xanthine and usual diet, physical examination, and serum virology
- Safety laboratory
- ECG
- Vital signs

7.3 Efficacy Assessments

Not applicable.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events (AEs), physical examination findings including vital signs (body temperature, blood pressure, and pulse rate), 12-lead electrocardiogram (ECG), and laboratory tests (hematology, biochemistry, urinalysis, and coagulation).

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.7). The reporting period for AEs is described in Section 7.4.1.8.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation of the subject administered a pharmaceutical product which does not necessarily have a causal relationship with the study drug. Therefore, an adverse event can be any unfavorable and unintended sign (including any abnormal laboratory finding), symptom or condition/disease temporarily associated with the use of the investigational drug, whether or not considered related to that product.

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

7.4.1.2 Adverse Event's Causality with the Investigational Product

Investigators must systematically assess the causal relationship of AEs to IMP(s) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, trial procedures.

Causality will be assessed using both NOM-220-SA1-2016 (29) and Merck standard. Adverse event records and reporting by PPD should include causality assessment per both the NOM and Merck standard scale described above as follows:

Per Merck standard:

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

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

Per the regulation in Mexico, NOM-220-SA1-2016 (29):

Certain. It consists of an event (clinical onset or an abnormal result of laboratory test) which occurs within a reasonable period of time following the drug's administration and which cannot be explained by the natural condition's evolution, by any concomitant pathology or by other drugs dosing. Response to drug's stop should be clearly evident.

Probable. It consists of an event (clinical onset or an abnormal result of laboratory test) which follows a reasonable period of time following the drug's administration and which can hardly be related to the natural condition's evolution, concomitant pathologies or to other drugs dosing. A clinically reasonable response is obtained upon stop of other(s) drug(s).

Possible. It consists of an event (clinical onset or an abnormal result of laboratory test) which follows a reasonable period of time following the drug's administration and which can hardly be related to the natural condition's evolution, concomitant pathologies or to other drugs dosing. There is no information available related to the suspect drug's dosing or this is not clear.

Suspect. It consists of an event (clinical onset or abnormal laboratory test) which follows a reasonable sequence of time following the drug's dosing which makes causality unlikely (but not impossible). It might be explained in a reasonable way since it is part of the natural evolution of the condition, or it is due to the presence of concomitant pathologies or other drugs dosing.

Conditional - Unclassifiable It consists of an event (clinical onset or abnormal laboratory test result) which cannot be properly assessed since more data are required or because additional data are still being analyzed.

Not evaluable - Unclassifiable It consists of a report which suggest that there is an adverse reaction which cannot be assessed since collected information is not enough or inconsistent. The report cannot be completed or checked

Other factors to be considered for adverse event's causality assessment with the study drug are:

- Recovery or discontinuation, relapse or rechallenge: Subject's response following stopping the drug or subject's response following rechallenge should be considered based on the usual clinical course of the corresponding event.
- Response pattern known for this type of drug: Clinical/Pre-clinical
- Exposure to physical and/or mental stress: Exposure to stress may produce adverse changes in the receptor and provide a rationale and a better explanation for the event.

Test drug's pharmacology and pharmacokinetics: Test drug's pharmacokinetic properties (absorption, distribution, metabolism and excretion) as well as the subject's individual pharmacodynamics should be considered.

7.4.1.3 Adverse Event's Severity

Investigators must assess the severity/intensity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild

The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

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

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

7.4.1.4 Abnormal Laboratory Findings

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

7.4.1.5 Unexpected Adverse Event

An unexpected adverse event is any adverse event which specificity or severity is not mentioned in the most recent product's information (Investigator's Brochure). Likewise, reports which provide important information about specificity or severity of a known adverse event, already documented, constitute unexpected adverse events. For instance, any event which is more specific or more severe than those described in the Investigator's Brochure should be considered "unexpected".

7.4.1.6 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence which at any dose:

- Results in death.
- It is life-threatening.
- Requires hospitalization or prolongs the existing hospitalization.
- Results in persistent or significant disability or incapacity.
- It is a congenital anomaly or birth defect.
- It is considered as medically important event.

Some medically important events, that do not lead to death, are not life-threatening or require hospitalization, may be considered serious adverse events based on the appropriate medical judgment and may require medical or surgical intervention to prevent one of the outcomes previously mentioned in this definition. Examples of those medical events include: allergic bronchospasm which require intensive care in the emergency room or at home, blood dyscrasias or seizures which require hospitalization, or the development of drug's dependence or abuse.

Life-threatening means an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

Disability means a physical or mental disorder that significantly limits a person's motor, sensory or cognitive abilities.

For reporting purposes, any suspected transmission of an infectious agent by any of the study drugs is considered a serious adverse reaction and all such cases should be reported in an expedited manner as described in section 7.4.1.9.

7.4.1.7 Recording Methods and Adverse Events Assessment

Complete, accurate and consistent data on all adverse events occurring during the study period should be recorded in the appropriate section of the medical chart as well as in the eCRF of each subject. Among these AEs, all SAEs must be additionally documented and reported using an Adverse Event Safety Report Form (Clinical Trial) as described in Section 7.4.1.9.

This information will be obtained from the subject of the study, which will be asked directly about the adverse event.

Documentation should be supported by a record in the subject's medical chart. Any abnormality in laboratory tests, considered clinically relevant, for instance, those which lead to the subject's withdrawal from the study, require treatment, causing evident clinical onset in the subject, considered relevant by the Investigator, should be reported as an adverse event.

All adverse events should be described in detail, including subject's identity (name, age and gender), a description of the adverse event, its duration (onset and resolution dates and times (to be completed when it is important to assess the time of the AE onset, relative to the time of treatment administration), its severity, its relationship with the study drug, any other potential causal factors, any treatment given or other action taken and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented. This information must be consistent with the CRF, the SAE and AESI Report Forms (as applicable).

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.4.1.8 Definition of Reporting Period for Adverse Events

The adverse event reporting period begins when the subject is included into the trial and until EoT.

7.4.1.9 Procedure for Reporting Adverse Events and Serious Adverse Events

Report of adverse events will be the responsibility of the PPD and it will be made according to the drug safety manual and the

standard operating procedure, code: IC-PNO-039, Report of clinical and bioavailability studies adverse events.

Report of adverse events will be made according to the standard operating procedure, code: IC-PNO-039, Report of clinical and bioavailability studies adverse events and the Mexican Official Standard for the Setting-up and Operations of Pharmacovigilance in Mexico, NOM-220-SA1-2016 (29). Therefore, any serious adverse event or suspect serious adverse reaction should be notified to the National Center of Pharmacovigilance (CNFV) from the Federal Commission for the Protection against Sanitary Risks PPD as well as to the Sponsor within the first 24 h following the Investigator is aware of it. A supplemental report, as detailed as possible which include all information collected, should be sent within 15 days. Report to the CNFV will be made by the Pharmacovigilance Officer at the PPD To comply with NOM-220-SSA1-2016 (29), mild or moderate, expected and unexpected adverse reactions should be reported by the study Principal Investigator at the PPD along with the clinical stage report to the CNFV.

Means to notify the Sponsor are the following:
Fax: PPD
Telephone: PPD
Mobile: PPD
E-mail: PPD

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.

The following minimum information is required for new SAEs in the initial notification of the Sponsor:

- Clear identification of the Investigator/Reporter, with full contact information;
- Subject identification details (trial number, site number, subject's initials, and date of birth);
- Trial Treatment administration details;
- Diagnosis of the event, with the description (or a brief description of signs/symptoms/clinical course, if the diagnosis is not available) and the date of onset;
- Reason(s) for considering the event serious; and
- Relationship of the event to the study drug (i.e., the causality according to the Investigator).

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 trial-specific SAE Report Form and the Drug Safety Manual.

Relevant pages from the CRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report and 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 (for example, 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 responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

The reports to Merck shall be sent in English using the Merck SAE form via fax or email within 24 hours.

Fax No.: PPD , email address: PPD .

7.4.1.10 Report of Safety Information to the Health Authorities, Ethics and Investigation Committee and Investigational Committee

According to local law and regulation, all serious and non-serious adverse events should be reported to the appropriate Ethics and Investigation Committee, Investigational Committee and to the Health Authorities. This will be carried out according to the drug safety manual and the standard operating procedure, code: PPD , Report of clinical and bioavailability studies adverse events.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of these Safety reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

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 trials 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.

7.4.1.11 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed on an ongoing basis throughout the study, and they will be assessed for the final outcome in the 7 day follow-up following the last dose of the drug.

Any AE that occurs during the course of a clinical trial and is considered to be possibly related to the IMP must be monitored and followed-up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". All reasonable efforts should be made to collect information and these should be documented. It is also the Investigator responsibility to ensure that all additional and necessary therapeutic measures are taken as well as the follow-up procedures.

The outcome of an adverse event should be entered in the eCRF, with the terms provided below:

- Recovered without sequelae;
- Recovered with sequelae;
- Ongoing;
- Worsening;
- Improving;
- Died;
- Unknown.

In case of a fatality, the cause of death is considered as the SAE, and the death is considered as its outcome.

7.4.1.12 Pregnancy and In Utero drug exposure

All pregnancies observed during the trial period will be recorded in the appropriate eCRF page/section for female partners of subjects' as AE or SAE depending on the outcome of the pregnancy. The Principal Investigator should inform immediately the Sponsor or designated person about any pregnancy using a Pregnancy Report Form which should be completed and submitted according to the same procedure for SAE referred in section 7.4.1.9.

The Investigator or designated person should follow-up, document and report all pregnancies outcomes, even if subjects were withdrawn from the study.

The Investigator should inform the Sponsor or designated person about the outcome using the Pregnancy Report Form. In case of an abnormal outcome, the SAE Report Form will be used. In case subject child/fetus experienced an event, the Parent-Child/Fetus Adverse Event Report Form will be used.

Any abnormal outcome should be reported immediately as described in section 7.4.1.9. All outcomes should be reported within 45 days following the delivery. The first 6 months of life of the newborn should be reported only if an adverse event occurs.

In case of female partners pregnancy during the study, the subject should be withdrawn and study drug should be immediately withdrawn. Sponsor or designated person should be immediately informed and follow-up should be made as aforementioned.

Reproduction studies performed so far in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to Praziquantel.

7.4.2 Clinical Laboratory Assessments

The safety laboratory parameters (hematology, chemistry, serology, urinalysis, drugs of abuse) are presented in Appendix 2 and will be performed in accordance with the clinical unit's standard operating procedures (SOPs).
Analyses of safety laboratory will be performed under responsibility of PPD, according to their SOPs. Detailed description of the procedures and methods will be given in separate laboratory manuals.
Additional clinical laboratory tests may be performed after abnormal findings, if judged appropriate by the Investigator. All samples should be clearly identified. All clinical laboratory samples will be analyzed by the laboratory at the trial site.

The total volume of blood to be withdrawn for these clinical laboratory assessments will be around 72 mL.

The Sponsor should receive a list of laboratory normal ranges before shipment of the IMP. Any change in laboratory normal ranges during the trial will additionally be forwarded to the Sponsor.

7.4.3 Vital Signs, Physical Examinations, and Other Assessments

At Screening, EOT and prior to each dosing, blood pressure, pulse, respiratory rate and body temperature (subjects should be in rest and in supine position at least 5 minutes before vital signs measurement; and they should be in rest and in supine position during the vital signs measurements) will be measured.

These values should be within the normal range (SBP between 80 and 129 mmHg and DBP between 50 and 89 mmHg) in order the subject is allowed to keep on participating in the study. Same measurements will be made during all shifts following dosing at each one of the visits. Vital signs will be measured during the 3 periods as shown in the following Table 5:

Table 5 Record of Vital Signs

First Visit	Second Visit	Third visit
Admission	Admission	Admission
Pre-dose	Pre-dose	Pre-dose
Morning (3 hours post-dose approximately)	Morning (3 hours post-dose approximately)	Morning (3 hours post-dose approximately)
Evening (7 hours post-dose approximately)	Evening (7 hours post-dose approximately)	Evening (7 hours post-dose approximately)
Night (11 hours post-dose approximately)	Night (11 hours post-dose approximately)	Night (11 hours post-dose approximately)
24 hours post-dose approximately	24 hours post-dose approximately	24 hours post-dose approximately
NA	NA	EOT

In the event any subject has clinically significant changes out of normal ranges for blood pressure and pulse during confinement post-dose, he/she will be closely observed by the medical staff. Supportive measures, as appropriate, will be taken according to the current subject's condition until they are resolved. If change persists, continuation in the study will be considered by the Principal Investigator.

At Screening, EOT and prior to each dosing and 24 hours after each IMP administration, electrocardiograms will be taken.

7.5 Pharmacokinetics

7.5.1 Pharmacokinetics Blood Samples

Twenty-one venous blood samples of 5 mL will be taken per period with catheter or venipuncture for the measurement of drug's plasma concentration: Pre-dose, 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. Actual date and time of blood sampling for PK will be recorded in the CRF. Primary and back up samples will be shipped separately. It is planned that pooled samples for concentration range estimation and enantiomer detection will be prepared according to CROs 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 and enantiomer identification (See Table 6).

7.5.1.1 Pharmacokinetics Blood Sampling Procedures

- One blood sample will be collected per period at times established in the schedule. Test tubes with K3EDTA, specifically designed for venipuncture, will be used.
- Each sample will be 5 mL. Blood withdrawn to clean catheter should be disposed prior to the blood sample collection (purge). Blood volume to be withdrawn by visit will be of 105 mL approximately, 315 mL of blood in total at the end of the study.
- The allowed deviation from the pre-specified assessment time will be:
    - Pre-dose samples:
        - Within 1 hour before IMP administration
    - Post-dose samples and assessments:
        - Up to and including 24 hours: ± 5% of scheduled time point in minutes
        - After 24 hours up to and including 96 hours: ± 1 hour
        - After 96 hours: ± 4 hours.
- Each sample will be centrifuged at 1500 x g for 10minutes at 4 °C [39.2 °F] (± 2 °C [35.6 °F – 42.8°F]).
- Resulting plasma volume will be transferred into 1.5 or 2 mL cryotubes. One tube serves as back-up sample.

Plasma tubes will be identified with Study No. (##), Case No. (C##), Sample No. (S##) and Visit No. (V#). They will be kept frozen at a temperature lower than or equal to - 20 °C, according to the standard operating procedures, code: PPD , Early organization for the conduct of an interchangeability and biocomparability study; and PPD : Processing and packaging of biological samples for interchangeability and biocomparability studies, PPD : Samples transportation from the clinical unit to the analytical unit; until their delivery at the analytical unit.

Table 6 Blood Sampling Schedule

Clinical Phase

NUMBER OF SUBJECTS:	60	GENDER:	Male
BIOLOGICAL MATRIX:	Plasma	DOSAGE FORM:	Tablet
FORMULATION:	600 mg Praziquantel	DOSE AND DOSAGE UNITS:	1200 mg Praziquantel
WASH-OUT TIME:	07 days	ANTI-COAGULANT:	K3EDTA
BLOOD VOLUME WITHDRAWN BY SAMPLE:	5 mL	TOTAL OF SAMPLES BY SUBJECT IN EACH PERIOD:	21

Sampling Interval

Phase	Sample	Time	Unit
--	0	-1.5	h
A	1	0.25	h
A	2	0.50	h
A	3	0.75	h
~ $C_{máx}$	4	1.00	h
~ $C_{máx}$	5	1.50	h
~ $C_{máx}$	6	2.00	h
~ $C_{máx}$	7	2.50	h
~ $C_{máx}$	8	3.00	h
~ $C_{máx}$	9	3.50	h
~ $C_{máx}$	10	4.00	h
E	11	4.50	h
E	12	5.00	h
E	13	5.50	h
E	14	6.00	h
E	15	6.50	h
E	16	7.00	h
E	17	8.00	h
E	18	9.00	h
E	19	10.00	h
E	20	12.00	h

Total Number of Samples			
No. of Cases	Samples	Periods	Total
60	21	3	3780

Diet
Standardized by the clinic

Each subject will participate for around 40 h confined for each of the periods within the 7-days wash-out period. The wash-out period starts per the time of drug's intake in the first period and

thus includes the 12 h period for sampling and the approx. 14 h period on day -1 to day 1 of the second period (until second administration)

7.5.1.2 Samples Shipment

To ensure transportation conditions of biological samples from the laboratory, where they were processed for freezing and storage, to the analytical unit do not affect samples' stability, it is essential to comply with the following guidelines:

1. The Study Principal Investigator or the Sub-Investigator will define shipment's date and time in accordance with the analytical unit, as well as the transportation to be used and approximate time for itinerary.
2. Mechanism of control and security for samples shipment will be defined by the person in charge of transportation in agreement with the Principal Investigator or Sub-Investigator.
3. The Samples Processing and Pharmacy Coordinator or a designated person will sign a list of material to be shipped, with a detailed description by subject for tubes quantity and codes.
4. An internal temperature reading system will be available in the freezer. A reading will be made at least every 15 minutes with its appropriate record.
5. In addition, reading at the moment of departure of the material from the samples processing area, as well as a reading at the reception at the analytical unit will be made.
6. Samples transportation is the responsibility of the clinical unit where samples collection and processing took place.
7. Transportation and delivery shall be performed by a specialized courier company which will be contracted by the Principal Investigator in agreement with the Sponsor. Samples will be delivered directly to the PPD per pre-established instructions.
8. All samples should arrive deep frozen (- 20 °C [- 4.0 °F] as maximum).

7.5.1.3 Samples Receipt, Check and Storage by the Analytical Unit

1. The Person responsible for the study or designated person from the analytical area will receive samples (along with documentation) and check 100 % with the assistance from analysts and Quality Assurance. They will record any remarks on the appropriate form (with a focus on the temperature at the time of receipt and a remark observation if any dry ice is still left in the shipment box/container). Once review is finished the person responsible for the study or designated person will store samples frozen (- 20 °C [- 4.0 °F] as maximum) in controlled storage.

2. Quality Assurance will confirm accuracy and reliability of operations.

Samples which do not meet acceptance criteria will be rejected (refer to Manual of Operations (MOP). In addition to those which don't have documentation along with them. In such instances, the clinical unit should be informed about the reason why samples were rejected. Rejected biological specimens will be kept at the analytical unit until the analytical unit and the clinical unit makes an agreement about their disposition.

Further details e.g. on the collection, processing, labeling, and shipping of the samples will be detailed in the trial MOP.

Back up samples will be kept in the Clinical Unit, they should not be sent at the same time as the primary samples.

7.5.1.4 Handling of Biological Specimens by the Analytical Unit

Biological specimens will be handled and processed as described in the appropriate analytical Method description.

7.5.1.5 Biological Specimens Disposition

As agreed with the Sponsor or 30 calendar days following the final report, samples will be removed from the ultra-freezer and will be stored in a transient warehouse for infectious biological hazard residues until they are collected for their final disposition by an authorized designated company.

7.5.1.6 Ultra-frozen Samples Labeling

Cryotubes will be identified with labels according to the standard operating procedure, code: PPD , early organization for the conduct of an interchangeability and biocomparability study. Each cryotube will state the study number, subject's number, period and number of samples specified in the protocol. Labels will be digitally designed and printed using thermal printer. Label and printing type will ensure that that printing and adhesion resist several freezing and thaw cycles.

7.5.2 Calculation of Pharmacokinetics Variables

The following non-compartmental PK parameters will be calculated from the individual plasma L PZQ and rac-PZQ concentration-time data obtained on Days 1,8 and 15, respectively, using commercial software Phoenix®/WinNonlin® (Version 6.3 or higher).

Table 7 Pharmacokinetic Parameters Derived from L PZQ and rac-PZQ Concentrations

C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration.

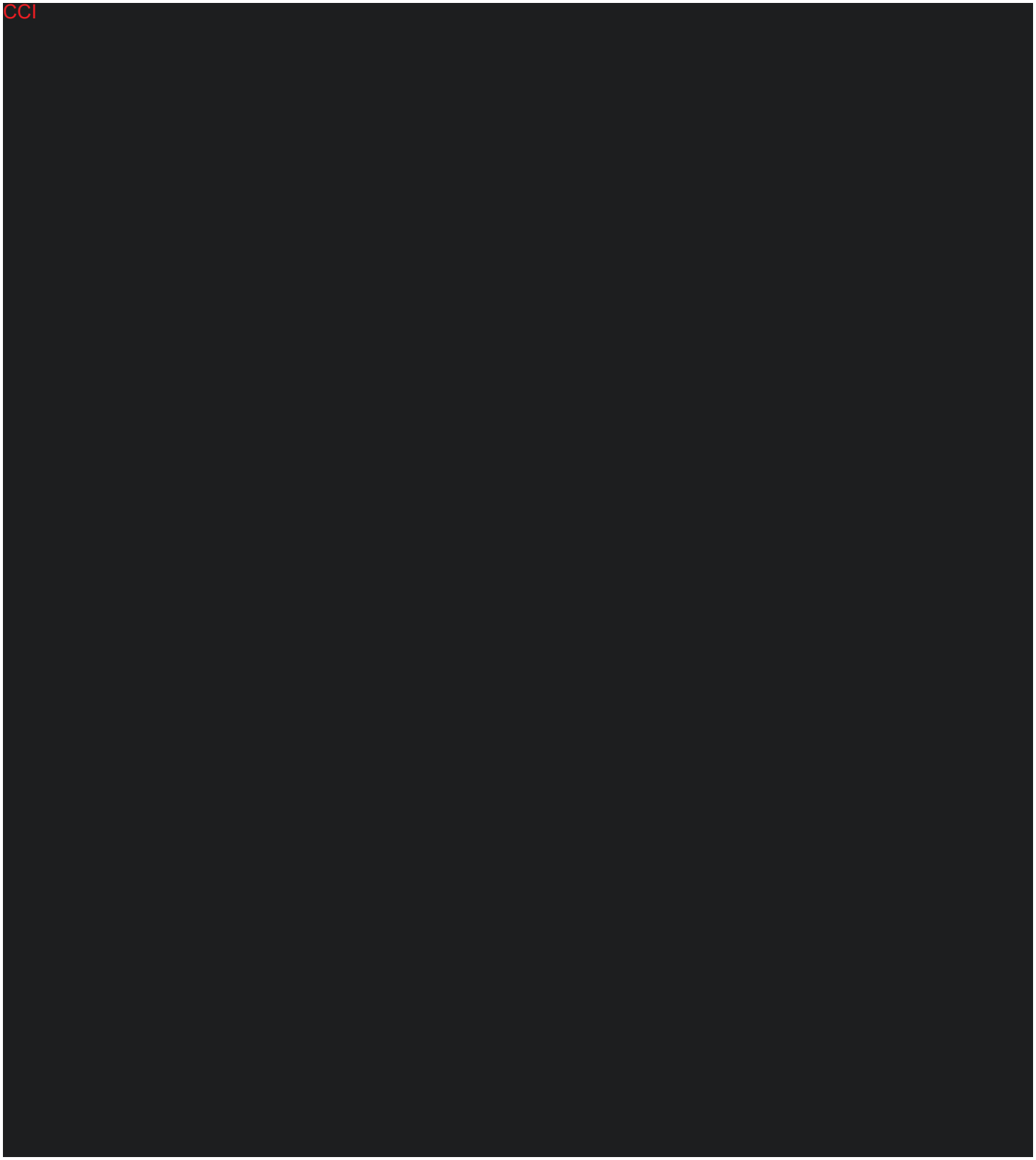
t_{lag}	Time prior to the first measurable (non-zero) concentration; calculated as last time point at which the concentration is <LLOQ before the occurrence of the first quantifiable concentration
λ_z	Terminal rate constant.
$t_{1/2}$	Terminal elimination half-life.
AUC_{0-t}	Area under the drug concentration-time curve from time zero to the time last measurable concentration.
$AUC_{0-\infty}$	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

The bioanalytical assessment will be outsourced to a third party vendor under the responsibility of Merck. PK parameter estimation and generation of PK TLFs will be outsourced to a third party vendor under the responsibility of Merck. Statistical analysis of Praziquantel will be conducted by the PPD , according to their standard operating procedures and in accordance with the NOM-177-SSA1-2013 (28).

CCI [redacted]

[redacted]

CCI



8 Statistics

8.1 Sample Size

Information on Praziquantel currently available to the WHO PQP Group indicated that the intrasubject variability for Praziquantel is around 50-60% for C_{max} and 35% for AUC, placing this compound in the highly variable drug class. The data from the Merck Serono phase I study performed recently, where Cisticid was used as comparator and different doses of PZQ ODT formulations were examined, confirmed this information and indicated for L-PZQ a CV% of 34.5 for AUC in the overall population and of 39.5% in non-whites, and a CV% for C_{max} of 52%.

The sample size calculation was performed using the R-functions sampleN.RSABE and sampleN.TOST of the package PowerTOST, which takes advantage of the reference-scaled approach suggested by the EMA.

Points to consider:

- For this clinical study comparison, the reference scaled approach is only applicable for C_{max}. For AUC conventional BE limits apply [0.80 – 1.25].
- In general, the reference scaled approach is applicable for CV<=50%: For CVs >50% fixed BE margins need to be used [0.70 – 1.43].
- Regulatory constant applied for reference scaled approach (EMA): 0.76

The following assumptions were made:

- Assumed true mean Test/Reference ratio for primary PK: 0.95
- C_{max} Coefficient of variation (Reference): 45 - 55%
- C_{max} Coefficient of variation (Test): 45 - 55%
- AUC Coefficient of variation (Reference): 39.5%
- AUC Coefficient of variation (Test): 39.5%
- One-side alpha: 0.05 (corresponds to 90% confidence level)
- Power: 80%
- Drop-out (DO) rate: 20% (agreed with CRO)

For this comparison the conventional BE margins [0.80 – 1.25] need to be applied for AUC. Therefore the rather high CV for AUC of L-PZQ determines the sample size for this trial. CCI [redacted]
Together with the assumptions above, 48 evaluable subjects will provide 80% power to demonstrate BE. Taking a drop-out rate of 20% into account, 60 subjects should be randomized in this BE trial.

8.2 Randomization

Valid statistical inferences are generally derived by assuming that errors in the observations are distributed independently, in random variables. Randomization generally ensures validity of this hypothesis. Full randomization of subjects to the treatment's sequence will be made according to the design sequences based on the internal procedures from the PPD compliant with the PPD (28) using the PPD.

A total of 60 subjects are to be enrolled in the trial and randomized to one of 3 treatment sequences, such that 20 subjects are assigned to each treatment sequence.

8.3 Endpoints

Statistical analysis for determining bioequivalence will be calculated using the computer program package SAS® System PPD.

8.3.1 Primary Endpoints

The primary endpoints are the PK parameters AUC_{0-t} and C_{max} for L-PZQ.

8.3.2 Secondary Endpoints

- Additional pharmacokinetic parameters will be estimated: t_{max}, t_{lag}, $AUC_{0-\infty}$, AUC_{extra}, t ½, λZ, CL/f and Vz/f of L-PZQ and t_{max}, t_{lag}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{extra}, C_{max}, t ½, λZ, CL/f and Vz/f parameters of rac-PZQ.

- To assess safety and tolerability of 1200 mg of the Cisticid tablets administered in fed condition. Safety will be assessed by AEs, standard laboratory parameters hematology, biochemistry, urinalysis, and coagulation), vital signs (body temperature, systolic blood pressure, diastolic blood pressure, and pulse rate) and 12-lead electrocardiogram (ECG) Analysis Sets

Table 8 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who sign informed consent
Safety	The Safety Analysis Set will include all subjects who receive at least one dose of trial treatment. Subjects will be analyzed according to the actual treatment they receive.
Pharmacokinetic	All subjects that received all administrations of treatment and have PK parameters for AUC_{0-t} and C_{max} in all periods and without any relevant protocol violations and factors likely to affect the comparability of PK results.

8.4 Description of Statistical Analyses

8.4.1 General Considerations

Statistical analysis will be performed using the computer program package SAS® System PPD . If not stated otherwise, the level of statistical significance will be alpha=0.05. PK data evaluation will be performed based on standard non-compartmental methods using the validated software tool PPD . Details on the statistical analysis and PK data analysis will be presented in the statistical 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 Medical Dictionary for Regulatory Activities (MedDRA), version 18.0 or later; concomitant medication will be coded with WHO (World Health Organization) Drug Dictionary, WHO Drug Reference List and Anatomical Therapeutic Chemical Classification System, latest version. Medical History will be coded according to MedDRA, latest version. Versions of dictionaries used for coding will be defined in the Data Management Plan (DMP).

All data recorded during the trial 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 (BLQ) will be described in the statistical analysis plan.

Summary statistics will be provided for all endpoints.

8.4.2 Analysis of Primary Endpoints

The analysis of the primary endpoints AUC_{0-t} and C_{max} of L-PZQ will be performed using the PK population. For the demonstration of bioequivalence different approaches will be applied for AUC_{0-t} and C_{max} For AUC_{0-t} the standard approach will be followed, i.e. the point estimate and the 90% CI of the Test/Reference geometric mean ratio must fall within [0.80, 1.25]. AUC_{0-t} of L-PZQ will be log-transformed and analyzed using a generalized linear model as given by the SAS code below:

```
PROC GLM DATA=PK;
CLASS SEQ SUBJ PER TRT;
MODEL LNPARAM = SEQ PER TRT SUBJ(TRT) / DDFM=SATTERTH;
```

LSMEANS TRT / ADJUST=T PDIFF CL ALPHA=0.10.

TEST H=SEQ E=SUBJ(TRT);

RUN;

QUIT;

The treatment difference TEST – REFERENCE will be estimated, and the 90% CIs for the difference in LS-means will be calculated. The difference and 90% CIs will be back-transformed to the original scale. If the 90% CI for the ratio (test/reference) lies entirely within the interval [80.00 – 125.00], then the BE criterion is fulfilled for AUC_{0-t}.

For the analysis of C_{max}, a reference-scaled bioequivalence approach will be applied as follows:

Point estimate and 90% confidence interval will be computed as described above for AUC. If $CV_{WR} \leq 30\%$ for C_{max} (i.e. the within-subject CV for the reference drug is ≤30%), then the common acceptance range for bioequivalence will apply. For $30\% < CV_{WR} \leq 50\%$ the acceptance interval will be widened according to [U, L] = exp [± k·sWR], 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 sWR is the intrasubject standard deviation of the log-transformed values of Cmax of the reference product. sWR 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 – 143.19].

The geometric mean ratio for Cmax should always lie within [80.00 – 125.00].

a. Descriptive statistics and boxplots will be provided by treatment.

CCI [redacted]

PROC GLM DATA=PK;

CLASS SEQ SUBJ PER TRT GROUP;

MODEL LNPARAM = SEQ PER TRT GROUP GROUP*TRT SUBJ(TRT) / DDFM=SATTERTH;

LSMEANS TRT / ADJUST=T PDIFF CL ALPHA=0.10.

TEST H=SEQ E=SUBJ(TRT);

RUN;

QUIT;

8.4.3 Analysis of Secondary Endpoints

All secondary endpoints will be listed and descriptively analyzed.

There will be no formal statistical comparison of the secondary PK endpoints. Treatment ratio and 90% confidence interval will be presented for $AUC_{0-\infty}$ of L-PZQ and for all the secondary PK endpoints for rac-PZQ (t_{max}, t_{lag}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{extra}, C_{max}, t ½ , λZ, CL/f and Vz/f). For t_{max} the Hodges-Lehmann shift estimate will be calculated together with the 90% confidence interval according to Tukey.

8.4.4 Analysis of Safety and Other Endpoints

8.4.4.1 Safety endpoints

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.

AE counts and subjects with AEs will be summarized for each treatment by system organ class and preferred term. In addition AEs will be tabulated and listed per subject and analyzed by severity and relationship to trial drug.

Subjects who prematurely withdrew from the trial or from treatment will be displayed in a by-subject listing, and summarized by primary withdrawal reason for each treatment sequence.

Safety laboratory parameters will be listed for each subject 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 subject including changes from baseline, and summarized by treatment and time point using descriptive statistics. Physical examination assessments will be listed for each subject.

8.4.4.2 Further endpoints

Demographic parameters (such as age, height, weight) and other baseline characteristics will be summarized by means of tabulated descriptive statistics for all subjects by sequence group and overall. Subject habits (including alcohol consumption and smoking history), medical history, prior and concomitant medications and exposure to IMP will be listed for each subject.

L-PZQ and rac-PZQ concentrations will be listed by subject, by treatment, by period and time point for each treatment and summarized by treatment and time point. Individual and mean concentration versus time plots will be prepared.

Further details will be described in the statistical analysis plan.

8.5 Interim and Additional Planned Analyses

No interim analysis is planned.

8.6 Deviation and Exclusion to the Statistical Analysis

All deviations should be justified with statistical or scientific data and any change to the original statistical plan should be documented, in the study master file and in the pharmacokinetics statistical report as well as in the final study report. Subjects' data will not be replaced. Any missing data will be considered as non-existent data. Likewise, data cannot be removed from the statistical analysis, except in the following events.

8.6.1 Research Subjects with Pre-dose Concentrations in the Biological Matrix

In the event pre-dose concentration is < 5 % of the C_{max} value for a research subject, subject's data can be included. When pre-dose value is > 5 % of the C_{max}, research subjects data should be removed from all study bioequivalence assessments.

8.6.2 Exclusion of Data Due to Vomit or Diarrhea.

Data from research subjects who experience vomiting and diarrhea throughout the bioequivalence study for immediate release products can be removed from the statistical analysis if vomiting and diarrhea occur after 6 hours post administration.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Principal Investigator is responsible for the study conduct at the site. She will make sure that the study is conducted according to the clinical trial protocol, ethical principles established in the Declaration of Helsinki, ICH, GCP and established regulation NOM-177-SSA1-2013 (28), which states tests and procedures to show that a drug is interchangeable as well as the requirements which Authorized Third-Parties should fulfill to perform the tests. The Investigator should ensure that only subjects who have provided their informed consent are included in the study.

9.2 Subject Information and Informed Consent

An unconditional requirement for each subject before their participation in the study is to have a written informed consent, which should be given before any study-related activity is carried out.

Therefore, the Principal Investigator or designated personnel should provide appropriate information before obtaining informed consent.

Subject's Information Sheet should be elaborated in Spanish, according to the ICH GCP and will be provided by the Sponsor with the purpose to get the informed consent. Besides providing written information to the potential subject, Investigator or designated person will inform them verbally all relevant aspects of the study, using language chosen so that information can be fully and easily understood by the subjects. Subject will be given enough time to read the information and ask questions and request additional information and explanations.

After providing information to the subject, informed consent form should be signed and dated by the subject, the Principal Investigator or designated personnel and two witnesses.

The dated and signed informed consent will be kept in the study site and should be securely filed so that files can be retrieved at any moment for monitoring, auditing and inspection purposes. A copy of the signed and dated informed consent form should be provided to the subject before their participation in the study.

Whenever new relevant information arises for the informed consent, the Investigator will revise subject's information and any other written information to be provided to the subjects, which should be submitted to the Committees for review and approval.

Revised and approved version of the written information will be used. The Principal Investigator or designated personnel will explain each subject all changes made to the previous version and will obtain a new written consent to continue his participation in the study. Subject will be given enough time to read the information and ask questions, and request additional information and explanations about changes.

9.3 Subject Identification and Privacy

A unique number is assigned to each subject that corresponds to their clinical file number, this number will be used as subject's identification in the study, as well as in the clinical study database. Once it is confirmed that all inclusion criteria and none exclusion criteria have been met, a consecutive number in ascendant order will be assigned to subjects. For each one of these numbers, it will correspond one of the three sequences as described in section 6.3.

All data collected from study subjects will be recorded in appropriate charts. Only the Investigator will be able to link the test's data for a subject by means of an identification list which will be located at the site. For each subject, clinical data will be available for verification

purposes by the monitor, audits and regulatory inspections, but subject's confidentiality will be strictly kept.

Data protection and confidentiality will be kept during data entry, processing, submission and storage. Subjects will be informed about it and they will be requested to provide their consent for data management according to the national regulations.

The Ministry of Health, Ethics and Investigation Committee and the Investigational Committee will be the only authorized bodies for reviewing study documentation, (which includes participant subject's identity data) and documents considered confidential by PPD and by the analytical unit from Merck.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide the subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.
The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for the Investigator.
In cases where 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.

9.5 Medical Insurance and Subject Compensation

Subjects will sign a consent which states that they will receive a compensation for their participation in the study.

The Sponsor will pay treatment (or compensation, if applicable) resulting from injuries or diseases caused by their participation in the study until their resolution as per the clinical criteria. The Sponsor will not pay injuries caused by subject's negligence, irresponsible behavior or medical reasons not related to the study.

9.6 Ethics and Investigation Committee or Investigational Committee

Before study start-up, approval from the Ethics and Investigation Committee and from the Investigational Committee has to be obtained. They should provide a list of the members who compose it, as per request from the Study Sponsor or Principal Investigator. If necessary due to amendments to the clinical trial protocol, case report form or informed consent form, a new approval should be got from both Committees.

The IEC will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version, and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.
Amendments to this clinical trial protocol will also be submitted to the concerned IEC, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical study as well as the appropriate documents will be submitted to the health authorities, according to the local and national applicable regulations.

10 Trial Management

10.1 Case Report Form Handling

An Electronic Case Report Forms will be completed by authorized medical staff according to the standard operating procedure, code: PPD : Good Documentation Practices, with legible letter and without amendments.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Principal Investigator should keep a paper or electronic file (medical file, and original medical records) for each subject in the study. It should be possible to identify each subject by means of this file. This file will contain the following subject's demographic and medical information and should be as complete as possible.

- Subject's complete name, date of birth, sex, height and weight.
- Medical history.
- Previous and concomitant medications / therapies (including changes during the study).
- Study identification; that is, subject's number provided by the clinical study Sponsor, and subject's number.
- Study recruitment dates (informed consent) and visits to the site.
- Any medical exam and pre-defined clinical findings in this clinical trial protocol.
- All adverse events.
- Date when the subject abandoned the study, including any reason for study withdrawal.

All documents which contain source data should be shown, including but not limited to, electrocardiograms and laboratory tests results. These documents should have subject's number and date of procedure. If possible, this information should be printed by the equipment used to perform the assessment or measurement. As necessary, medical assessment should be conducted; all assessments should be documented, signed and dated by the Principal Investigator.

10.3 Investigator Site File and Archiving

At the beginning of the study, the Principal Investigator will receive a master file for the site which contains all necessary study documents to be completed throughout the study and which will be updated as necessary. Master file should be available for Monitor's review, Sponsor's audits and Health Authorities' inspection during and following study. It should be securely filed for at least 15 years (or more, according to the local needs or otherwise stated by the Sponsor) following study completion. Documents to be filed include the subject's identification list and the signed informed consent by the subject. In the even the master file cannot be kept at the site anymore, the Principal Investigator should inform the Sponsor/designated person.

All subjects' source documents (medical charts) should be stored at the site as long as possible, as allowed by applicable guidelines and/or according to the ICH GCP guidelines, whatever is

longer. In any case, the Principal Investigator should ensure that no destruction of medical charts is done without written approval from the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

Quality assurance is performed by means of follow-up to the standard operating procedures, codes: PPD , Elaboration of quality assurance report for clinical trials; PPD , First stage of quality control and quality assurance review during clinical studies conduct; PPD , Second stage of quality control and quality assurance review during clinical studies conduct; and PPD , Third stage of quality assurance review during clinical studies conduct.

Quality Management follows up the conduct of the study by means of quality control monitoring for the review of compliance with the clinical trial protocol, internal standard operating procedures, and applicable guidelines according to the GCP (ICH E6R1).

Discrepancies and areas of improvement identified are followed up according to the standard operating procedure, code: PPD , Discrepancies identification and follow-up, and potential causes of discrepancies and continuing improvement. All information collected is analyzed for the preparation and issue of the Quality Assurance report.

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Trial protocol amendments can be issued by the Principal Investigator and agreed with the Sponsor or vice-versa. Substantial changes should be approved by the Ethics and Investigation Committee and by the Investigational Committee.

Administrative changes which do not affect the study will be agreed with and approved by the Sponsor, the analytical unit and by the Principal Investigator. They will also be notified to the Ethics and Investigation Committee and to the Investigational Committee.

When a protocol deviation occurs during the clinical stage, the Principal Investigator should assess it and consider if study subject's continuation may affect protocol's outcome. Sponsor will be informed and jointly they will make a decision about subject's continuation in the study.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After study completion, the Principal Investigator with Sponsor's advice will prepare a clinical trial report and according to the Mexican Official Standard Mexican Official Standard and ICH Topic E3, which states tests and procedures to prove that a drug is interchangeable. Requirements which authorized third parties should fulfill for interchangeability tests. Requirements for performing biocomparability studies and requirements which authorized third parties, investigational sites and hospitals conducting biocomparability tests should fulfill (NOM-177-SSA1-2013) (28) and applicable guidelines.

10.6.2 Publication

All data and results, and all intellectual property rights for data and outcomes from the study will be property of Merck, which may use data for different purposes such as, submission to government health authorities or submission to other investigators.

The Investigator, although is free to use data derived from the study for scientific purposes, should discuss any publication with Merck in advance and obtain Sponsor's written consent for the pursued publication.

The Sponsor acknowledges the Investigator's right to publish outcomes once the study is completed. Anyway, the Investigator should submit a draft of the paper or summary to be published to Merck 30 days before submitting the final version for publication.

It will be reviewed soon and approval will not be unnecessarily delayed. In case of controversies between the Sponsor and the Investigators, publication content will be discussed in order to find a satisfactory solution for both parties.

Posting of data on the results of this bioequivalence trial is planned and may occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements

11 References

1. Andrews P, Thomas H, Pohlke R et al. Praziquantel. Med Res Rev 1983; 3: 147–200.
2. Bayer. Biltricide (Praziquantel) tablets prescribing information. West Haven, CT; 2004.
3. Bittencourt PR, Gracia CM, Martins R et al. Phenytoin and carbamazepine decreased oral bioavailability of praziquantel. Neurology 1992; 42: 492–6.
4. Bohnert T, Gan LS. Plasma protein binding: from discovery to development. J Pharm Sci 2013; 102: 2953–94.
5. Castro N, Jung H, Medina R et al. Interaction between grapefruit juice and praziquantel in humans. Antimicrob Agents Chemother 2002; 46: 1614–6.
6. Castro N, Medina R, Sotelo J et al. Bioavailability of Praziquantel increases with concomitant administration of food. Antimicrob Agents Chemother 2000; 44: 2903–4.
7. Chan JD, Zarowiecki M, Marchant JS. Ca2+ channels and Praziquantel: a view from the free world. Parasitol Int 2013; 62: 619–28.
8. Dollery CT. Praziquantel. In: Therapeutic Drugs. Edinburgh, UK: Churchill Livingstone, 1999; 184–8.
9. Ethical Principles for Medical Research in Humans contained in the Declaration of Helsinki, published on the 64th General Assembly from the Worldwide Medical Association, Fortaleza, Brazil; October 2013.
10. European Medicines Agency. Science Medicines Health. Guideline on the Investigation of Drug Interactions**.** 21 June 2012. Date for coming into effect 1 January 2013.
11. Gonzalez-Esquivel D, Rivera J, Castro N et al. In vitro characterization of some biopharmaceutical properties of Praziquantel. Int J Pharm 2005; 295: 93–9.
12. Gryseels B. Schistosomiasis. Infect Dis Clin North Am 2012; 26: 383–97.
13. Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). December 2002.
14. Guideline on the Investigation of Bioequivalence. CPMP/QWP/EWP/1401/98 Rev.1, 20 Jan 2010.
15. Homeida M, Leahy W, Copeland S et al. Pharmacokinetic interaction between Praziquantel and albendazole in Sudanese men. Ann Trop Med Parasitol 1994; 88: 551–9.
16. Ingram K, Yaremenko IA, Krylov IB et al. Identification of antischistosomal leads by evaluating bridged 1, 2, 4, 5-tetraoxanes, alphaperoxides, and tricyclic monoperoxides. J Med Chem 2012; 55: 8700–11.

17. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH Harmonized Tripartite Guideline - Guideline for Good Clinical Practice E6(R1) - June 10th, 1996.
18. Jung-Cook H. Pharmacokinetic variability of anthelmintics: implications for the treatment of neurocysticercosis. Expert Rev Clin Pharmacol 2012; 5: 21–30.
19. Kearns GL, Abdel-Rahman SM, Alander SW et al. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med 2003; 349: 1157–67.
20. Mandour ME, el Turabi H, Homeida MM et al. Pharmacokinetics of Praziquantel in healthy volunteers and patients with schistosomiasis. Trans R Soc Trop Med Hyg 1990; 84: 389–93.
21. Manneck T, Braissant O, Haggenmu¨ ller Y et al. Isothermal microcalorimetry to study drugs against Schistosoma mansoni. J Clin Microbiol 2011; 49: 1217–25.
22. Meier H, Blaschke G. Investigation of Praziquantel metabolism in isolated rat hepatocytes. J Pharm Biomed Anal 2001; 26: 409–15.
23. Meister I, Ingram-Sieber K, Cowan N, et al. Activity of Praziquantel enantiomers and main metabolites against Schistosoma mansoni. Antimicrob Agents Chemother. 2014; 58 (9):5466-72.
24. Merck, Cisticid (Praziquantel) tablets prescribing information, July 2007.
25. Mexican Official Standard for Drugs and Herbal Remedies Labeling (NOM-072-SSA1-2012).
26. Mexican Official Standard for Medical Charts (NOM-004-SSA3-2012).
27. Mexican Official Standard for the Prevention, Treatment and Control of Hypertension (NOM-030-SSA2-1999).
28. Mexican Official Standard which states tests and procedures to prove that a drug is interchangeable. Requirements which authorized third parties should fulfill for interchangeability tests. Requirements for performing biocomparability studies. Requirements which authorized third parties, investigational sites and hospitals conducting biocomparability tests should fulfill (NOM-177-SSA1-2013).
29. Mexican Official Standard. Setting-up and Operations of Pharmacovigilance (NOM-220-SSA1-2016).
30. Olliario P, Delgado-Romero P, Keiser J. The little we know about the pharmacokinetics and pharmacodynamics of praziquantel (racemate and R-enantiomer). Antimicrob Chemother 2014; 69: 863–870.
31. Piero Olliaro, Petra Delgado-Romero and Jennifer Keiser. The little we know about the pharmacokinetics and pharmacodynamics of praziquantel (racemate and R-enantiomer). J Antimicrob Chemother 2014; 69: 863–870.

32. Putter J, Held F. Quantitative studies on the occurrence of Praziquantel in milk and plasma of lactating women. Eur J Drug Metab Pharmacokinet 1979; 4: 193–8.
33. Ridtitid W, Wongnawa M, Mahatthanatrakul W et al. Rifampin markedly decreases plasma concentrations of Praziquantel in healthy volunteers. Clin. Pharmacol Ther 2002; 72: 505–13.
34. Utzinger J, Keiser J. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. Expert Opin Pharmacother 2004; 5: 263–85.
35. Westhoff F, G. Blaschke G, High-performance liquid chromatographic determination of the stereoselective biotransformation of the chiral drug praziquantel Journal of Chromatography 1992; 578: 265-71.
36. WHO Prequalification Notes on the design of bioequivalence study: Praziquantel. Guidance Document. 13 October 2015.
37. WHO Technical report series 992, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. 2015. Annex 7.
38. WHO. Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions: A Manual for Health Professionals and Programme Managers. Geneva: WHO, 2006.
39. Investigator Brochure MSC1028703A L-PZQ 2.1

12 Appendices

12.1 Appendix 1: Diet to be given to the Participating Subjects

Diet to be given to subjects following dose in each of the periods will be the same in quantity and content to that provided during the previous period.

Study breakfast: Ham sandwich, 240 mL of whole milk, ½ piece of gelatin water and fruit (melon, papaya with maple syrup) containing 302.5 Kilocalories (76 g) carbohydrates, 82.5 Kilocalories (21 g) proteins and 165 Kilocalories (18 g) Lipids for a total of 550 Kilocalories.

The rest of the diet (such as lunch, dinner and snacks) will be as shown in the following Table 9 Below:

Table 9 **Diet Energy Distribution for the Study (Lunch, Dinner and Snacks)**

Energetic Distribution			
Group	**%**	**g**	**Kilocalories**
Carbohydrates	55 g	275 g	1100
Proteins	15 g	75 g	300
Lipids	30 g	67 g	600
Total Kcal	----	----	2000

12.2 Appendix 2: Schedule of Assessments

Activity/Assessment	**Screening (Baseline)**							**End of Treatment / safety FU**
Study Week	Day -21 to -1	-1 D	Day 1/8/15			Day 2/9/16		Day 22 (+ 7 days)
Study Day			-1 h	-0.5 h	0 h	4 h	24 h	
ICF signature	X							
Demographics, medical history and history of medication	X							
Smoking history, alcohol intake, use of caffeine or xanthine-containing beverages	X							
Serology test	X							
Physical examination[3]	X	X						X
Vital signs (BP, HR, Temperature)[5]	X	X	X				X	X
12-Lead-ECG	X		X				X	X[4]
Safety lab tests	X	X					X	X
Drug screening urine	X	X						
Oral alcohol test		X						
Confinement [1]			[---------X----------					]
Breakfast				X				
In/exclusion criteria check/recheck	X	X	X					
Administration of IMP					X			
PK sampling [2]			[----X----------					]
AE and concomitant medication		[---------X----------						]

*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.

1 Confinement from the evening of Day -1 (at least 12 hours prior to each IMP administration on Day 1) until the morning of Day 2.
2 PK sampling at pre-dose, 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
3 According to the CRO procedure.
4 ECG .

5 VS will be measurement predose, 3, 7, 11 and 24 h after IMP administration
Biochemistry (albumin, alanine aminotransferase, aspartate aminotransferase, protein total, total bilirubin, conjugated bilirubin, unconjugated bilirubin, globulin, albumin/ globulin ratio, blood urea nitrogen, glucose, urea, creatinine, uric acid, cholesterol and triglycerides)

12.3 Appendix 3: Normal laboratory parameters

PPD

PPD

CITOMETRIA HEMATICA

ERITROCITOS (millones por mm3)

1D - 7D	A	4.9 a 7.2
8D - 1M	A	4.1 a 6.7
2M - 2A	A	3.6 a 4.8
3A - 12A	A	4.1 a 5.2
13A - 18A	M	4.7 a 5.7
13A - 18A	F	4.3 a 5.3
19A - 110A	M	4.7 a 6.0
19A - 110A	F	4.3 a 5.3

HEMOGLOBINA (g/dL)

1D - 7D	A	15.0 a 22.5
8D - 1M	A	12.5 a 20.0
2M - 2A	A	10.9 a 14.7
3A - 12A	A	12.5 a 15.5
13A - 18A	M	14.0 a 17.0
13A - 18A	F	13.0 a 16.0
19A - 110A	M	14.0 a 18.0
19A - 110A	F	13.0 a 16.0

HEMATOCRITO (%)

1D - 7D	A	44.3 a 65.3
8D - 1M	A	37.5 a 60.0
2M - 2A	A	32.7 a 43.9
3A - 12A	A	36.9 a 46.8
13A - 18A	M	42.0 a 51.0
13A - 18A	F	39.0 a 48.0
19A - 110A	M	42.0 a 54.0
19A - 110A	F	39.0 a 48.0

VOLUMEN GLOBULAR MEDIO fL

1D - 7D	A	94.8 a 121.8
8D -1M	A	85.5 a 123.5
2M - 2A	A	83.0 a 105.8
3A - 110A	A	80.0 a 100.0

HEMOGLOBINA GLOBULAR MEDIA pg

1D - 7D	A	30.0 a 37.8
8D -1M	A	28.0 a 40.0
2M - 6M	A	26.0 a 34.0
7M - 110A	A	28.0 a 32.0

CONCENTRACION MEDIA HEMOGLOBINA GLOBULAR g/dL

1D - 1M	A	31 a 35
1M - 110A	A	32 a 34.5

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PPD

PPD

LEUCOCITOS (Miles por mm3)		
1D - 3D	A	9.4 a 34.0
4D - 2M	A	5.0 a 21.0
3M - 2A	A	6.0 a 17.5
3A - 6A	A	5.0 a 14.5
7A - 12A	A	4.5 a 13.5
13A 18-A	A	4.5 a 13.0
19A - 110A	A	4.5 a 11.0
MONOCITOS		
1A - 100A	A	2 a 9
LINFOCITOS		
1A - 100A	A	20 a 50
EOSINOFILOS		
1A - 100A	A	0 a 6
BASOFILOS		
1A - 100A	A	0 a 4
NEUTROFILOS		
1A - 100A	A	45 a 75
BLASTOS		
1A - 100A	A	0
MIELOCITOS		
1A - 100A	A	0
METAMIELOCITOS		
1A - 100A	A	0
EN BANDA		
1A - 100A	A	0 a 5
SEGMENTADOS		
1A - 100A	A	45 a 75
PLAQUETAS miles por mm3		
1D - 100A	A	150 a 450
VOLUMEN PLAQUETARIO MEDIO fL		
1D - 100A	A	7.2 a 12.0

VIGENCIA ENERO A DICIEMBRE 2017

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VALORES DE REFERENCIA DE LA SEDIMENTACION GLOBULAR
(mm/HORA)

EDAD	EDAD	SEXO	FRASE DE REFERENCIA
1 DIA	3 MESES	AMBOS	0 - 2
3 MESES	10 AÑOS	AMBOS	0 - 7
11 AÑOS	17 AÑOS	AMBOS	0 - 11
18 AÑOS	50 AÑOS	MASCULINO	0 - 10
18 AÑOS	50 AÑOS	FEMENINO	0 - 12
51 AÑOS	60 AÑOS	MASCULINO	0 - 12
51 AÑOS	60 AÑOS	FEMENINO	0 - 19
61 AÑOS	100 AÑOS	AMBOS	0 - 20

METODO UTILIZADO: WESTERNGREN

VIGENCIA ENERO A DICIEMBRE DEL 2017

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VALORES DE REFERENCIA QUIMICA SANGUINEA

GLUCOSA (mg/dL)	
1 mes a 100 años ambos sexos	60 a 100
UREA (mg/dL)	
1 mes a 100 años ambos sexos	10.0 a 50.0
NITROGENO DE LA UREA (mg/dL)	
1 mes a 100 años ambos sexos	5.0 a 23.3
CREATININA (mg/dL)	
1 mes a 15 años ambos sexos	0.5 a 1.0
16 años a 100 años	0.5 a 1.3
ACIDO URICO (mg/dL)	
1 mes a 100 años ambos sexos	2.6 a 7.2
COLESTEROL (mg/dL)	
1 día a 2 meses ambos sexos	53 a 135
3 meses a 19 años ambos sexos	70 a 170
20 años a 100 años ambos sexos	70 a 200
TRIGLICERIOS (mg/dL)	
1 día a 9 años ambos sexos	30 a 104
10 años a 14 años ambos sexos	33 a 135
15 años a 19 años ambos sexos	38 a 152
20 años a 100 años ambos sexos	70 a 170
COLESTEROL HDL (ALTA DENSIDAD) (mg/dL)	
15 años a 99 años ambos sexos	Mayor de 40
SODIO (mEq/L)	
1 día a 100 años ambos sexos	135.0 a 145.0
POTASIO (mEq/L)	
1 día a 100 años ambos sexos	3.5 a 4.8
CLORO (mEq/L)	
1 día a 100 años ambos sexos	96.0 a 109.0
CALCIO (mg/dL)	
1 día a 100 años ambos sexos	8.2 a 10.2

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E-mail:servi-med@servi-med.com.mx

VALORES DE REFERENCIA DE LAS PRUEBAS DE FUNCIONAMIENTO HEPATICO

BILIRRUBINA CONJUGADA (mg/dL)	
1 dia a 100 años ambos sexos	0.0 a 0.3
BILIRRUBINA NO CONJUGADA (mg/dL)	0.0 a 0.7
1 dia a 100 años ambos sexos	
BILIRRUBINA TOTAL (mg/dL)	0.0 a 1.0
1 día a 100 años ambos sexos	
TRANSAMINASA GLUTAMICO PIRUVICA (UI/L)	
1 mes a 100 años Femenino	9 a 32
1 mes a 100 años Masculino	9 a 43
TRANSAMINAS GLUTAMICO OXALACETICA (UI/L)	
1 mes a 100 años Masculino	10 a 37
1 mes a 100 años Femenino	10 a 31
FOSFATASA ALCALINA (U/L	
1 año a 17 años ambos sexos	60 a 250
18 años a 99 años ambos sexos	15 a 69
GAMA GLUTAMIL TRANSPEPTIDASA (UI/L)	
1 mes a 100 años Masculino	11.0 a 61.0
1 mes a 100 años Femenino	9.0 a 39.0
PROTEINAS TOTALES SERICAS TOTALES (g/dL)	
1 mes a 100 años ambos sexos	6.0 a 8.0
ALBUMINA (g/dL)	
1 mes a 100 años ambos sexos	4.0 a 6.0
GLOBULINAS (g/dL)	
1 mes a 100 años ambos sexos	2.0 a 4.0
RELACION ALBUMINA/GLOBULINA	
1 año a 100 años	1.0 a 2.0
FOSFOCINASA DE LA CREATINA TOTAL	
EN SUERO (U/L)	
15 años a 100 años Masculino	24.0 a 190.0
15 años a 100 años Femenino	24.0 a 170.0

VIGENCIA ENERO A DICIEMBRE DEL 2017

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VALORES DE REFERENCIA DEL EXAMEN GENERAL DE ORINA

COLOR DE MUESTRA	AMARILLO CLARO
ASPECTO	TRANSPARENTE
DENSIDAD ESPECIFICA	DE 1.003 a 1.015
PH APROXIMADO	DE 6 a 7
MICRO ALBUMINA	NEGATIVO
ALBUMINA (mg/dL)	NO CONTIENE
HEMOGLOBINA LIBRE	NO CONTIENE
BILIRRUBINA	NO CONTIENE
GLUCOSA (g/L)	NO CONTIENE
CUERPOS CETONICOS	NO CONTIENE
NITRITOS	NEGATIVO
UROBILINOGENO (UE/DI)	0.1
LEUCOCITOS POR CAMPO (400x)	MENOR DE 3
ERITROCITOS POR CAMPO (400x)	NEGATIVO
BACTERIAS	NEGATIVO
CILINDROS	NEGATIVO

VIGENCIA ENERO A DICIEMBRE DEL 2017

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VALORES DE REFERENCIA

FRACCION B DE LA HORMONA GONADOTROPINA CORIONICA (mUI/mL)

1 a 2 semanas	16 a 156
2 a 3 semanas	100 a 4,800
3 a 4 semanas	1,000 a 31,000
4 a 7 semanas	2,500 a 233,000
7 a 11 semanas	20,900 a 291,000
11 a 16 semanas	6,100 a 103,000
17 a 21 semanas	4,700 a 80,100
22 a 39 semanas	2,700 a 78,000

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VALORES DE REFERENCIA

ANTIGENO ESPECIFICO DE LA PROSTATA

MASCULINO (ng/mL)

20 a 120 años 0.3 a 4.5

TESTOSTERONA TOTAL
(ng/dL)

MASCULINO 142.4 a 923.1
FEMENINO 10.8 a 56.9

TESTOSTERONA TOTAL
(nmol/L)

MASCULINO 4.94 a 32.0
FEMENINO 0.38 a 1.97

VIGENCIA ENERO A DICIEMBRE 2017

PPD

12.4 Appendix 4: Signature Pages and Responsible Persons for the Trial

Clinical Unit

Name:	PPD	Signature	
Role:	PPD	Date:	
Name:	PPD	Signature:	
Role:	PPD	Date:	
Name:	PPD	Signature:	
Role:	PPD	Date:	
Name:	PPD	Signature:	
Role:	PPD	Date:	
Address:	PPD		
Telephone:	PPD		

Analytical Unit

Name:	PPD	Signature:	
Role:	PPD	Date:	
Name:	PPD	Signature:	
Role:	PPD	Date:	
Address:	PPD		
Telephone:	PPD		

S p o n s o r

Name	PPD	Signature:	
Role:	PPD	Date:	
Address:	Merck,S.A. de C.V. Calle 5, No. 7, Frac. Industrial Alce Blanco, Nuacalpan de Juárez., México, C.P. 53370		
Telephone:	PPD		
Name	PPD	Signature:	
Role:	PPD	Date:	
Address:	Merck Institute for Pharmacometrics, – Building I, CH-1015 Lausanne, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.		
Telephone:	PPD		