Population Pharmacokinetics of Benznidazole in Children with Chagas' Disease

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INTRODUCTION

There is an unmet medical need for new paediatric formulations for Chagas' disease (CD). Also, there is an absolute lack of information on benznidazole (BZ) pharmacokinetic (PK) data for paediatric population and its relationship with treatment safety and efficacy.

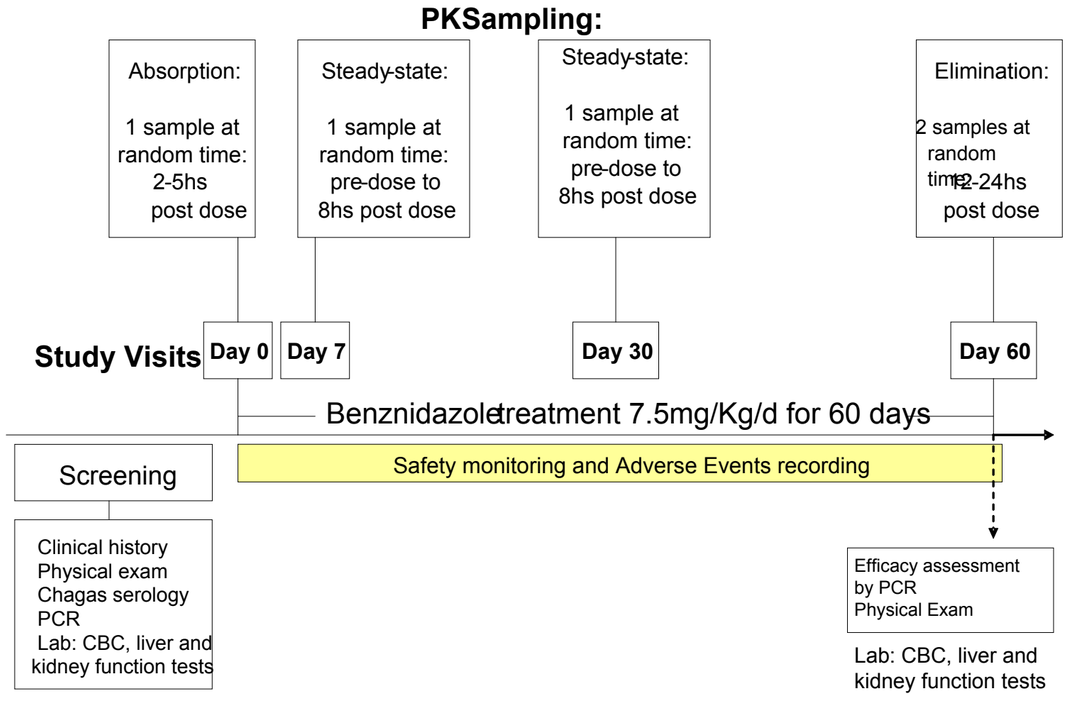
OBJECTIVES

Primary Objective: To describe the population pharmacokinetics parameters of BZ in children with acute or early chronic indeterminate form of CD. **Secondary Objectives:** 1) To evaluate if pharmacokinetics parameters are associated with parasitological cure (negative PCR) at the end of treatment; 2) to evaluate if benznidazole pharmacokinetics parameters are associated with the occurrence and severity of adverse events; 3) to evaluate the efficacy of BZ treatment at Day 60 (the end of treatment) through the assessment of parasitological cure by PCR; 4) to evaluate the incidence of Serious Adverse Events, and/or adverse events leading to discontinuation of treatment in children

METHODOLOGY

- 80 patients with CD will be recruited, including congenital cases, children with early chronic indeterminate form of disease as well as vector-borne acute cases. Diagnosis will be confirmed at entry by direct microscopic examination or at least 2 positive conventional serologies (ELISA, IIF or HAI).
- Subject enrolment will be stratified by age: 40 patients in the group of newborns to 2 years (minimum of 10 newborns) and 40 patients in the group of ≥ 2-12 years.
- PK sampling will occur at Day 0 (at randomly selected time-point 2-5hs after first dose), at steady state phase [two samples to be collected at Day 7 (pre-dose and 1-3hs post dose); and two samples to be collected at Day 30 (at randomly selected time-points 4-8hs post dose), and at the end of treatment (one sample to be collected at a randomly selected time-point 18-24hs after last dose at Day 60).
- Total study duration will be of approximately 10 weeks.

Figure 1. Overall Study Design



TRIAL ENDPOINTS

Pharmacokinetics endpoints: Plasma level concentrations of BZ determined in children at first day of treatment (Day 0), steady state phase (D7 and Day 30) and at the end of treatment (Day 60); population pharmacokinetics parameters of benznidazole in children, including CL, Vd, and Ka. Individual AUC, Cmax, Cmin, and t1/2 will be estimated using population parameters. **Efficacy endpoint:** Parasitological cure rate as determined by qualitative PCR at the end of treatment (Day 60). **Safety endpoints:** Rate of Serious Adverse Events and/or adverse events leading to treatment discontinuation, rate and severity of adverse events, covariates to be evaluated: age, gender, weight, height, parasite load at baseline and phase of disease (acute vs chronic). Age, weight, height, parasite load at baseline and phase of disease (acute vs chronic) will be assessed as covariates.

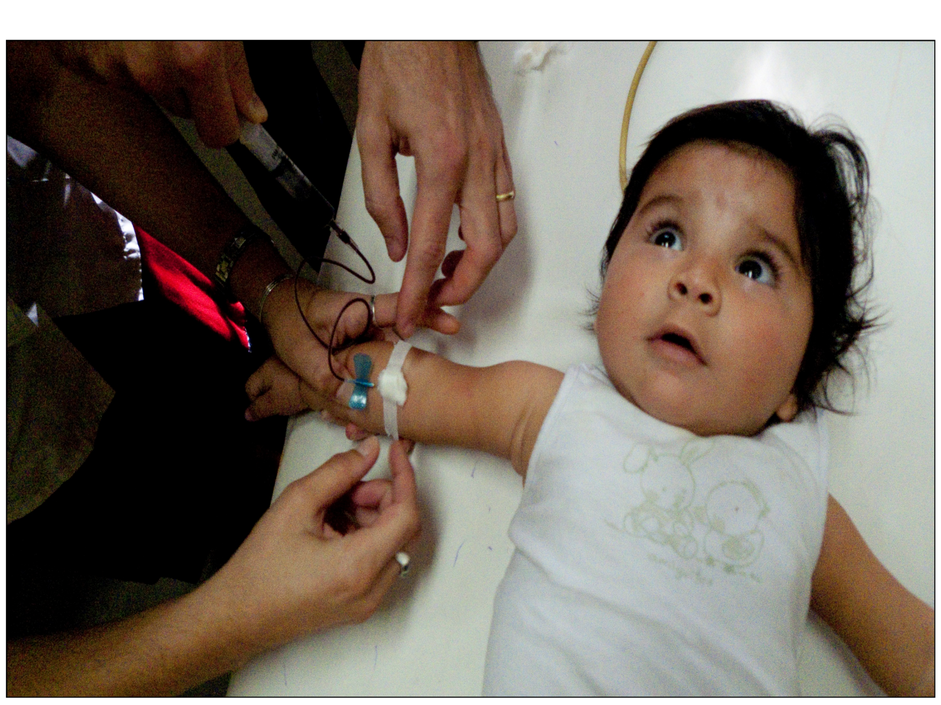
TEST DRUG

All 80 subjects recruited into the study will receive treatment with: Benznidazole (LAFEPE, tablet 12.5mg or 100mg), 7.5 mg/Kg/day PO (actual range of 5.5-8.5 mg/Kg/d), divided in two daily doses, for 60 days

INCLUSION / EXCLUSION

Inclusion Criteria: 1) Age between newborn (1 day) – 12 years; 2) Diagnosis of *T. cruzi* infection by: direct microscopic examination or conventional serology, at least two positive tests (ELISA, IIF or HAI); 3) Written informed consent form by parent/ legal representative; children assent if > 7 years;

Exclusion Criteria: 1) Pre-term (< 37 weeks gestational age) or weight < 2500 g; 2) female subject who has reached menarche; 3) subjects presenting any other acute or chronic health conditions, that in the opinion of the PI, may interfere with the PK, efficacy and/or safety evaluation of the study drug; 4) known history of hypersensitivity or serious adverse reactions to nitro-imidazoles; 5) history of CD treatment with benznidazole or nifurtimox in the past ; 6) immunocompromised patients (clinical history compatible with HIV infection, primary immunodeficiency or prolonged treatment with corticosteroids or other immunosuppressive drugs); 7) abnormal laboratory test values at screening for the following parameters: total WBC count, platelet count, ALT, AST, total bilirubin and creatinine; 8) inability to comply with follow-up and/or not having a permanent address; 9) any condition that prevents the subject from taking oral medication.



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