Population pharmacokinetics of benznidazole as monotherapy and in combination with fosravuconazole in adult patients with chronic Chagas disease (BENDITA study)

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Background

Chagas disease (American trypanosomiasis) is a neglected tropical disease caused by the protozoan parasite *Trypanosoma cruzi* and can lead to potentially fatal cardiac and gastrointestinal complications [1].

Fig 1. Triatome bug, *T. cruzi* trypomastigote and geographic distribution of Chagas disease [2,3]

Benznidazole (BZN) is the first-line therapy, but has severe limitations such as long treatment duration (30-60 days), poor tolerability (especially in adult patients), poor compliance and questionable efficiency in the chronic stage of Chagas disease [4]. New treatment regimens are therefore currently investigated following two strategies [5,6,7,8]:

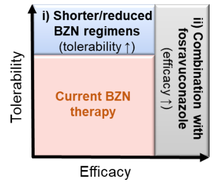

Fig 2. Strategies for improving treatment

Objectives

- To characterize the population pharmacokinetic properties of BZN in adult patients with chronic Chagas disease receiving new treatment regimens.
- To investigate potential drug–drug interactions with fosravuconazole.
- To explore BZN exposure - parasitological recrudescence relationships.

Methods

- 180 adults (18 – 50 years) with chronic indeterminate Chagas disease enrolled in the BENDITA study [5] were included in the pharmacokinetic (PK) analysis.
- Sparse whole blood BZN concentration-time data was pooled and analyzed using nonlinear mixed-effects modeling (NONMEM 7.4).
- PK data was censored at 120h time after dose. Following an evaluation of the M1 and M3 BQL method [9], the M1 BQL method was used for handling LLOQ data (2.3%) .
- The simeval and quality assurance tools in PsN 5.2.6 were used for outlier identification (NPDE and influential outliers (n=3) excluded from the final PK model).
- The relationship between BZN exposure and parasitological recrudescence (qPCR positivity rate after end of treatment) was explored by binomial regression in R (4.0).

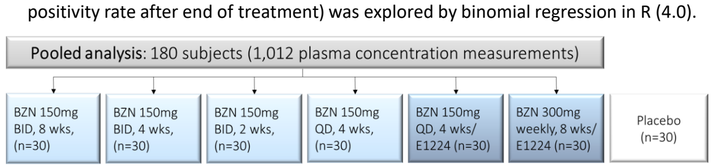

Fig. 3. Study design of the BENDITA study: a double-blind, double-dummy, phase 2, multicenter, randomized trial in three outpatient units in Bolivia (ClinicalTrials.gov, NCT03378661).

Results & Discussion (Pharmacokinetics)

- BZN pharmacokinetics was dose-linear and well described by a transit-absorption model, followed by a 1-compartment disposition model.

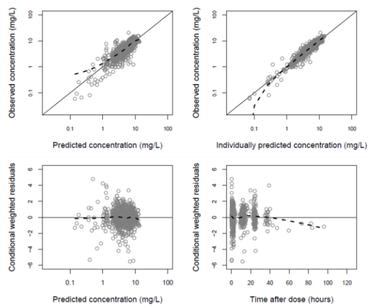

Fig 4. Goodness-of-fit diagnostic for the final population pharmacokinetic model.

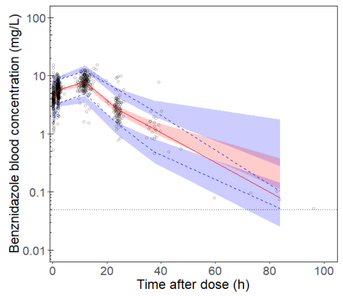

Fig 5. Visual predictive check for the final population pharmacokinetic model.

- Clearance/F, volume of distribution/F and elimination half-life (17.1h) of BZN were in reasonable agreement with literature [10].
- Coadministration of fosravuconazole increased BZN clearance by 14.5% ($P \leq 0.001$) with a corresponding decrease in BZN exposure. However, this effect is probably not clinically relevant (< 20%).

Table1. Parameter estimates of the final population PK model of BZN.

Covariate effects (%)	Population estimate[a], (RSE,%)[b]	Interindividual variability, %CV[a] (RSE,%)[b]
Clearance/F (L/h)	1.43 (2.8%)	21.8 (15.2%)
Volume/F (L)	35.3 (2.8%)	-
Mean transit time (h)	0.78 (10.7%)	61.7 (12.3%)
Relative bioavailability	1 (fixed)	13.4 (17.3%)
Effect of azole co-administration on CL/F (%)	14.5 (38.6%)	-

[a]NONMEM estimate; [b]assessed by sampling NONMEM bootstrap (n=1000)

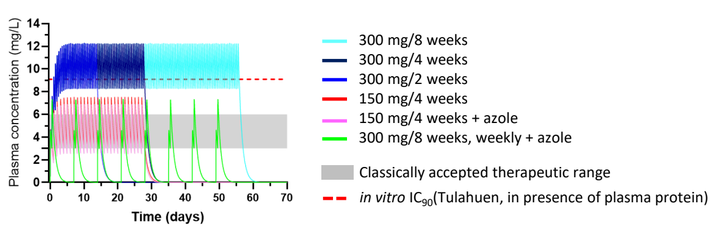

Fig 6. Simulations of BZN plasma concentration – time profiles for different treatment arms (Fig.3)

Results & Discussion (Pharmacodynamics)

- There was a trend towards higher probability of parasitological recrudescence with lower BZN exposure. This trend was sensitive to exclusion of subjects with BZN treatment duration < 7 days or outliers[a])

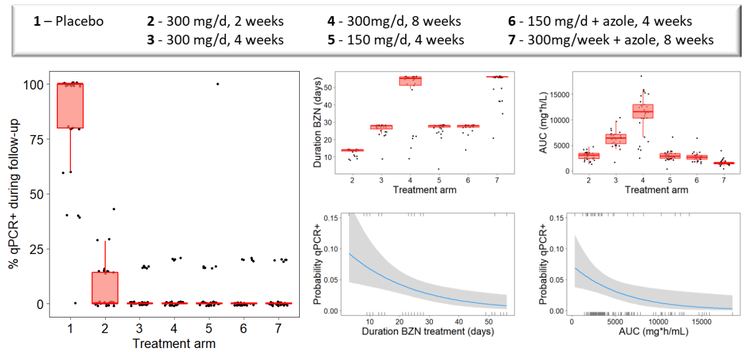

Fig 7. Quantitative PCR positivity rate after end of treatment up to 12 month follow-up for different treatment arms in the BENDITA study (n= 206 subjects with follow-up), along with BZN exposures. Binomial regression shown for daily BZN dosing only (n=146 subjects).

[a] Outliers (PK/PD) defined as: subjects with BZN conc.>LLOQ at TAD>120h, Simeval outliers, unexplainable PK profiles

Conclusions

- Population PK properties of BZN following different treatment regimens in adult chronic Chagas disease patients were successfully described. To the best of our knowledge, this is the largest PopPK analysis of BZN to date.
- No clinically relevant drug-drug interactions were identified between BZN and fosravuconazole.
- Our results provide the basis for the further exploration of BZN exposure - parasitological response relationships. Studies in larger populations are urgently required for the selection of optimized BZN dosing regimens for the treatment of chronic Chagas disease.

Referenes

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Acknowledgements

We sincerely thank all volunteers for their participation in this study as well as all clinical personnel. This research was funded by the Wellcome Trust [220211] and the Bill and Melinda Gates Foundation.