Title: Population pharmacokinetics of macozinone (PBTZ-169) and active metabolites in healthy volunteers after different oral formulations

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Introduction:

Macozinone (PBTZ-169) is a new benzothiazinone anti-tuberculosis drug candidate that selectively and irreversibly inhibits the DprE1 enzyme of *Mycobacterium tuberculosis*. The compound was discovered through the FP6 "NM4TB" and FP7 "MM4TB" programs of the European Commission and optimized by medicinal chemistry from the lead BTZ043. With this novel mechanism of action, macozinone is intended for the treatment of drug-susceptible and drug-resistant tuberculosis. Due to low solubility of the compound, several formulations have been developed. Macozinone is also known to form several active metabolites where H2-PBTZ and 3OH-PBTZ show the highest abundance. We aimed to characterize the population pharmacokinetics (PK) of macozinone and main active metabolites in healthy volunteers. In addition, we also evaluated the impact of different formulations on the PK of macozinone.

Methods:

Macozinone was given as a salt form (PBTZ-169 HCl) in different formulations in phase 1a and phase 1b studies (NCT03423030). In total, 1761 plasma concentration samples from 54 healthy volunteers were included in the analysis. In the phase 1a trial, a spray-dried dispersion (SDD) formulation (10, 20, 40, 80, 160 and 320 mg) and a native crystal powder (NCP) formulation (160 and 320 mg), both given as water suspension were evaluated as single doses using a cross-over study design. In the phase 1b trial, NCP formulation suspended in water (300 mg once daily and 300 mg twice daily) and NCP formulation suspended in syrup (150 mg twice daily, 300 mg twice daily and 600 mg once daily) were evaluated for 14 days. Log transform-both-sides of the data was used and the modelling was performed using NONMEM version 7.4.3. Allometric scaling using body weight was applied to all clearance and volume parameters of parent drug and metabolites. Stepwise covariate model was also performed on age, ethnicity. The M3 method was applied to handle the data below limit of quantification. Once the PK model for the parent was developed, the PK parameters of the parent drug were fixed and the PK parameters of the metabolites were estimated.

Results:

The disposition of macozinone, H2-macozinone and 3OH-macozinone were best described by a 2-compartment model with linear elimination. The absorption of macozinone was described by dual parallel first order absorption with lag time on the fast absorption (ALAG2). The fraction metabolite could not be estimated therefore fixed to 1. Different parameters for relative bioavailability (Frel), fraction of slow absorption (Frc1), fast absorption rate (ka2) and ALAG2 were estimated for different formulations. Trial differences were identified in Frc1 and ka2 parameters for NCP formulation. Relative to NCP formulation, SDD formulation showed almost twice higher bioavailability while syrup formulation showed almost 3 times lower bioavailability. Age and ethnicity were not identified as significant covariates.

Conclusions:

A population PK model for macozinone and its major active metabolites in different oral formulations in healthy volunteers was successfully developed. Different formulations of macozinone impacted significantly the absorption process and relative bioavailability of the compound.

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