Inhaled amorphous drug nano-particle formulations of BTZ043 to improve tuberculosis treatment

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Abstract

8-Nitrobenzothiazinones (BTZ) are a new class of anti-mycobacterial drugs with minimum inhibitory concentrations (MICs) as low as 2.3 nM [1] for drug-resistant *Mycobacterium tuberculosis* strains. However, due to poor solubility and metabolic instability, BTZs generally show poor oral bioavailability [2], which could significantly reduce treatment efficacy. The formulation of BTZ043 into amorphous drug nanoparticles is hypothesized to improve oral bioavailability via enhanced dissolution kinetics and also reduce the side effects.

In this study, amorphous BTZ043 nanoparticles were prepared via a solvent-antisolvent technique with a mean diameter of around 400 nm. The control group was comprised of BTZ043 crystals with a mean particle diameter of around 23 µm, which are representative of the current clinical formulation. Pharmacokinetic studies in healthy Balb/c mice demonstrated that the nanoparticle formulation increased the relative oral bioavailability (F_{ref} %, Equation 1) of 384% in plasma compared to crystalline BTZ043. Inhalation administration of the BTZ043 nanoparticles further increased the relative plasma bioavailability of 862% compared to orally administered crystalline neat drug. Thus, the inhalation of amorphous drug nanoparticles is a promising approach to improve BTZ043 pharmacokinetics, thereby improving tuberculosis treatment with both oral and inhaled products.

References

[1] Makarov V et al. Towards a new combination therapy for tuberculosis with next generation benzothiazinones. EMBO Mol Med. 2014 Mar;6(3):372-83.
[2] Gao C et al. Benzothiazinethione is a potent preclinical candidate for the treatment of drug-resistant tuberculosis. Sci Rep. 2016 Jul 13;6:29717.

Figures

$$F_{rel}\% = \left(\frac{AUC_{nano} / Dose_{nano}}{AUC_{micro} / Dose_{micro}} \right) * 100$$

Equation 1. Calculation of relative bioavailability

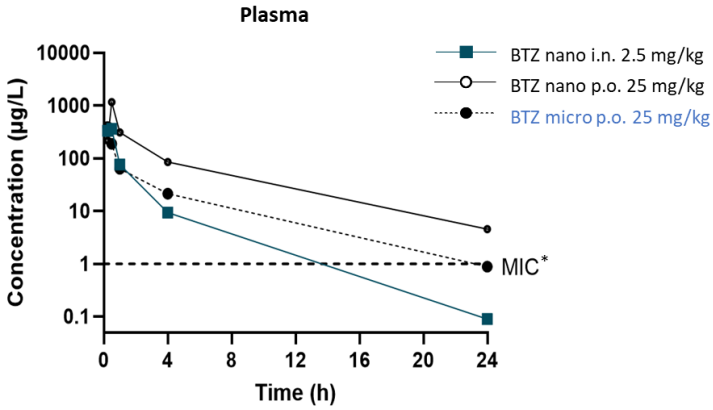

Figure 1. Plasma levels of BTZ043 observed in BALB/c mice

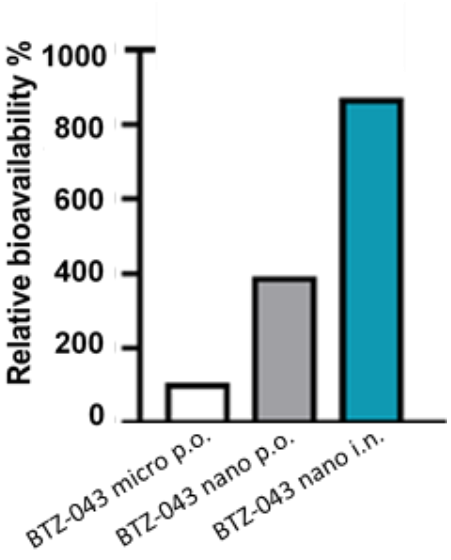

Figure 2. Relative bioavailability of BTZ-043 amorphous drug nanoparticle compared to oral administration in plasma.