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First-in-human study of the benzothiazinone and DprE1 inhibitor BTZ-043, a novel drug candidate for the treatment of Tuberculosis

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Objectives: This first-in-human, single ascending dose study evaluated the safety, tolerability and pharmacokinetics (PK) of the decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1) inhibitor BTZ-043.

Methods: BTZ-043 was administered as an oral suspension at doses of 125, 250 and 500 mg along with placebo to healthy participants. Safety assessments included evaluation of laboratory parameters, vital signs, physical and neurological examination, and 12-lead ECG. Blood samples for PK assessment in plasma were collected over a 36 h post-dose period. PK parameters were calculated using non-compartmental analysis for parent BTZ-043, metabolites M1 and M2, and BTZ-043$_{total}$ (sum of BTZ-043 and M2) in plasma.

Results: Thirty participants completed the study. All administered BTZ-043 doses were safe and well tolerated. Nervous system disorders (dizziness and headache) and vascular disorders (hypertension and hot flush) were the most frequently reported adverse events (AEs). All AEs were mild or moderate. The parent compound BTZ-043 was rapidly metabolized to metabolite M2 (unknown activity), with median time to maximum concentration in plasma (t_{max}) of 1.5 h (1–2 h). BTZ-043 and M2 had a short half-life. The second main inactive metabolite M1 showed a median t_{max} of 7–8.5 h and a geometric mean half-life of 8.4–9.0 h. The increases in AUC and maximum concentration of drug in plasma (C_{max}) of BTZ-043 were more than dose-proportional, and those of BTZ-043$_{total}$ were almost dose-proportional. No relevant differences in systemic exposures between males and females were observed.

Conclusions: BTZ-043 was safe, well tolerated and underwent rapid absorption, metabolism and elimination, supporting further clinical development.

Background

Tuberculosis (TB) is the leading cause of death from a single infectious disease worldwide, recently surpassing coronavirus disease (COVID-19). Despite being a curable disease, an estimated 10.6 million people developed TB in 2022, resulting in 1.3 million deaths.[1]

The emergence of MDR-TB has triggered renewed anti-TB drug development, with novel drugs such as bedaquiline, delamanid and pretomanid receiving authorizations by the EMA and FDA in the last decade, and a 6 month regimen against MDR-TB recommended by the WHO in 2022.[2,3] However, increasing resistance to bedaquiline requires the development of new drugs for patients with XDR-TB,[4] in addition to the continued need to develop new and effective regimens for both drug-sensitive TB and MDR-TB that are shorter, better tolerated and easier to administer. BTZ-043 is a novel benzothiazinone that inhibits decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1), a key enzyme involved in mycobacterial cell wall synthesis. DprE1 is required for the biosynthesis

of decaprenylphosphoryl-β-D-arabinose, an essential component for cell wall assembly in mycobacteria. Formation of the covalent adduct between BTZ-043 and DprE1 results in inhibition of cell wall biosynthesis and loss of viability of *Mycobacterium tuberculosis* (Mtb).[5] Currently, three other novel candidate drugs in clinical development (quabodepistat, macozinone and TBA-7371) exhibit the same mechanism of action.[6]

BTZ-043 is highly active against a variety of mycobacterial species *in vitro* (including Mtb) with MIC values in the range of 0.001–0.008 mg/L.[5] BTZ-043 is also active *in vitro* against Mtb-infected macrophages, and moderately active against dormant cells of Mtb. Among primary isolates of Mtb, no baseline rate of BTZ-043 resistance has been identified so far.

In vivo, BTZ-043 efficiently kills Mtb in BALB/c mice at oral doses from 50 mg/kg upwards, with activity increasing up to dose levels of 250 mg/kg, after which a plateau is reached.[7] In IL-13 transgenic mice that form human-like necrotic granuloma, BTZ-043 was shown to penetrate well into the foamy macrophage layer and the necrotic core of the lesion.[7] A molecular bacterial load assay performed on necrotic core dissections showed a decrease in viable mycobacteria after 2 weeks of treatment, and an approximate 2 log reduction after 4–6 weeks. In Kramnik (C3HeB/FeJ) mice, BTZ-043 was strongly bactericidal, mainly during the second month of administration, and between-experiment comparisons suggest a higher activity than other DprE1 inhibitors currently in development.[7,8] Two systemically relevant major metabolites of BTZ-043 are formed in all species tested so far. The first metabolite, M1, an amino derivative of BTZ-043, is 500 times less active against Mtb than the parent BTZ-043. The second metabolite, M2, represents an unstable hydride Meisenheimer complex.[9] Exposures of M2 are higher than of the parent BTZ-043 in plasma of rats and minipigs. It is presently not known whether metabolite M2 has an antibiotic activity, since its pronounced instability makes traditional testing of mycobacterial killing difficult.

In an *in vitro* cytochrome P450 (CYP) inhibition study, BTZ-043 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 or CYP3A4 over the concentration range tested. CYP2C9 was inhibited by BTZ-043 to 23.5% (average of two experiments) at 10 μM. Preclinical animal studies have shown differences in the pharmacokinetics (PK) of BTZ-043 between animal sexes. Interestingly, there was no consistency in sex-dependent exposures. In rates females had higher BTZ-043 plasma levels, whereas male mini pigs had higher BTZ-043 concentrations. In this first-in-human (FIH) study, we assessed the safety, tolerability and PK of single escalating doses of BTZ-043.

Methods

Ethics

The protocol, subject information and informed consent form received approval from the Ethical Committee of the Bavarian State Medical Council. The protocol was also approved by the Federal Institute for Drugs and Medical Devices (BfArM). This study was registered in the EU Drug Regulating Authorities Clinical Trials Database (EudraCT) prior to commencement of recruitment (EudraCT number: 2017-003488-37).

Study objectives

The primary objective was to evaluate the safety and tolerability of a single dose of BTZ-043 administered orally in a dose range around an anticipated therapeutic dose, as measured by clinical observations, vital signs, safety laboratory and ECG assessments.

Secondary objectives were to describe the PK of BTZ-043, to evaluate the effect of sex on systemic exposure of BTZ-043, and to assess potential cardiac effects of BTZ-043 using triplicate 12-lead ECG monitoring.

Study design

This was a prospective, randomized, double-blind, placebo-controlled, single ascending dose (SAD) study evaluating the safety, tolerability and PK of single doses of BTZ-043 in healthy adult participants (clinicaltrials.gov identifier: NCT03590600). This study was conducted at the Center for Human Pharmacology, in Neu-Ulm, Germany, between June and August 2018. Participants were hospitalized from Day −1 until discharge in the morning of Day 3. After completion of all Day 3 assessments of a cohort, safety and PK data were reviewed and the next dose increment was decided by the Trial Steering Committee. There was a time interval of at least 1 week between two consecutive dosing groups to allow a careful analysis of the safety parameters of the previous dose group. The study was to be interrupted in case of serious adverse drug reactions in at least one participant. Further stopping rules for the study and within a cohort were defined in the protocol.

Drug formulation

The starting dose of BTZ-043 was selected at 125 mg, based on allometric scaling from the no observed adverse effect level (NOAEL) in rat toxicity studies, accounting for a safety factor of 10. The investigational drug product for this study was an amorphous oral suspension containing 25 mg/mL of the active compound to be reconstituted before administration. Hot melt extrusion of BTZ-043 in Soluplus™ resulted in a glass formulation that was milled to an amorphous granulate (coarse powder). The oral suspension was prepared directly before administration by dispersing the granulate in an aqueous solution of polysorbate 80 and carmellose sodium. The final oral suspension contained 2.5% BTZ-043. In order to obtain the different planned strengths of 125/250/500/1000/2000 mg, different amounts of the oral suspension were to be administered. An oral suspension was selected for this study as it was closest to the formulations used in preclinical development. Bioavailability was considered to be similar and allometric scaling could be used to determine the starting dose.

Study population

Healthy adult males or females of non-childbearing potential aged 18–55 years, with a BMI of 18–30 kg/m^2, body weight ≥55 and ≤90 kg, and no clinically significant abnormalities in vital signs, ECGs or in chemistry, haematology or liver function tests were included. Key exclusion criteria included a positive HIV, hepatitis B and C virus status, presence of a QT interval corrected for heart rate according to Fridericia's formula (QTcF) of >450 ms on ECG, history or current use of alcohol or illicit drugs, and concomitant use of prescription drugs.

Up to 50 male and female participants were planned for inclusion in this study in up to five cohorts, each cohort consisting of 10 participants, with 8 participants assigned to BTZ-043 and 2 to placebo per cohort. In the first two cohorts, an equal number of male and female participants were included without relevant differences in baseline criteria (age and BMI). As interim analyses showed no apparent differences in exposure between the two sexes, the restriction on equal number of male and female participants was relaxed in all following cohorts as planned in the protocol.

Safety and tolerability assessments

Safety was assessed by physical examination (general appearance, respiratory, cardiovascular, gastrointestinal, vascular and neurological

systems), vital signs (blood pressure, heart rate, respiratory rate and tympanic body temperature), and 12-lead ECGs at predefined timepoints. On Day 1 all ECGs were recorded in triplicate. Heart rate, PR, QRS duration, QRS axis, QT interval and QTcF were measured.

Blood samples for haematology, biochemistry and coagulation, and urine samples for urinalysis were collected at screening visit, and on Day −1, Day 2 and Day 3 prior to discharge. Laboratory abnormalities considered clinically relevant by the investigator were reported as an adverse event (AE).

Information on AEs was derived by interviewing the participants in general terms, by participants' spontaneous reports, or by observation. AEs were documented on special source data sheets and the following information was given for each: description of the AE, start date, start time, stop date, stop time, severity, action taken, outcome, seriousness, and possible relationship to the study drugs (rating of AEs was performed by the investigator using the 'Common Terminology Criteria for Adverse Events' as a guideline).

Pharmacokinetic assessments

PK blood sampling was performed pre-dose and 0.25, 0.5, 1, 2, 3, 4, 5, 7, 10, 15, 24 and 36 h after dosing. The plasma was analysed for BTZ-043 and metabolites M1 and M2 concentrations using two different validated LC-MS/MS methods. BTZ-043$_{total}$ was the concentration of BTZ-043 measured after complete back-conversion of the M2 metabolite to BTZ-043 by acidification. The bioanalytical methods used have been validated according to both the FDA and EMA guidelines on bioanalytical method validation.[10,11]

Incurred sample reanalysis revealed that 18 of 24 samples for BTZ-043 (75%) and 23 of 24 samples (95.8%) for M1 were within the defined acceptance criteria. The acceptance criterion, −20% < difference (% mean) < +20% for at least 2/3 of the samples, was met.

Twenty-three of 24 samples (95.8%) for BTZ-043$_{total}$ were within the defined acceptance criteria. The acceptance criterion, −20% < difference (% mean) < +20% for at least 2/3 of the samples, was met.

PK parameters were calculated by non-compartmental analysis, using Phoenix WinNonlin 7.0, and applied linear up log down trapezoidal rule for AUC, and log-linear regression for the apparent terminal rate constant (λz), etc. Actual sampling times were used in the calculations. Concentrations below the lower limit of quantification (LLOQ) were treated as zero. PK parameters such as the AUC from 0 h to the last measurable concentration, to time infinity, and over 24 h dosing interval (AUC_{0-t}, AUC_{0-inf}, and AUC_{0-24h}, respectively), the highest drug concentration in plasma (C_{max}), the time to reach the highest drug concentration in plasma (t_{max}) and half-life ($t_{½}$) were computed. Linear regressions for determination of λz was performed using at least three data points of the terminal elimination phase. λz was not assigned if the terminal elimination phase was not apparent (i.e. concentrations not decreasing consistently), or if the coefficient of determination r^2 value was less than 0.8. In cases where the λz rate was not assigned, the values of AUC_{0-inf}, CL/F (total clearance), Vz/f (apparent volume of distribution) and $t_{½}$ were not calculable and were not reported.

In-stream population PK modelling was used to halt dose escalation before exposures (AUC_{0-24h}) of BTZ-043$_{total}$ were expected to exceed certain set maximum limits (translated from animal toxicology data). Dose and demographic information plus PK data (observed concentrations of BTZ-043$_{total}$) from the first and second dose group (receiving doses expected to yield exposures substantially lower than the maximum limits) were used to develop a compartmental population PK model of parent and metabolite M2 with non-linear mixed-effects methodology (including inter-individual variability). A proportional dose–exposure relationship was assumed if the data were not indicating otherwise.

The gold standard software NONMEM 7.4 was employed and the model was evaluated according to best practice standards from the International Society of Pharmacometrics.[12] The model was then used to predict individual exposures for the next planned dose level. The median and the 95th percentile of these exposures were compared with the maximum limits. If limits were not expected to be exceeded (and there were no other safety reasons to stop the dose escalation), the following group was dosed, data collected and the model updated by adding the new data before the prediction procedure was repeated.

Results

Overall, 30 healthy male and female participants were included in this study. Single doses of 125, 250 and 500 mg BTZ-043 were administered to eight participants each, whereas six participants received placebo. No further dose increase was performed because extrapolation of the exposure data from Cohort 1 to 3 resulted in a predicted typical AUC_{0-24h} of more than 43.850 µg h/L BTZ-043$_{total}$ for Cohort 4 (1000 mg BTZ-043), which had been predetermined as the ceiling exposure based on rat NOAEL exposure.

Safety and tolerability

BTZ-043 was well tolerated, with no reports of serious AEs and no discontinuation of the study as a result of AEs.

The most frequently reported treatment-emergent adverse events (TEAEs) were nervous system disorders (dizziness and headache) reported by 11 participants, followed by vascular disorders (hypertension and hot flush), reported by 7 participants. Nearly all TEAEs were considered drug-related by the investigator; only four TEAEs (one TEAE in each treatment group) were judged as unlikely related. All TEAEs were of mild or moderate intensity and resolved without any sequelae (see Table 1).

Hypertension, of maximum grade 2, was reported as an AE for five participants: one participant receiving 125 mg, three participants receiving 250 mg, and one participant receiving 500 mg BTZ-043. A mild increase in mean systolic blood pressure was observed after administration of 250 and 500 mg at 0.5 and 1 h after dosing (increase of 10.0 and 12.1 mmHg, respectively, compared with pre-dose). After 500 mg BTZ-043, systolic blood pressure remained on this level until 3 h post-dose, then decreased to a minimum at 8 h after dosing and returned to pre-dose level at 24 h after dosing (see Figure 1). A similar but lower increase was observed for diastolic blood pressure: the maximal increase was observed at 0.5 and 1 h, respectively, after dosing (increase of 5.3 and 5.8 mmHg, respectively, compared with pre-dose), corresponding to t_{max}. Mean diastolic blood pressure returned to pre-dose level at 24 h after dosing (see Figure 1).

Mean heart rate decreased in all treatment groups after dosing compared with pre-dose except for the 500 mg group, which showed an increase of 7.2 and 11.0 bpm at 0.5 and 1 h post-dose, respectively. The most marked decrease from pre-dose was observed after placebo dosing (−10.6 bpm at 3 h post-dose, compared with −5.5, −7.6 and −3 bpm after 125, 250 and 500 mg BTZ-043 at the same timepoint) (Figure 2).

Mean QTcF showed a maximum increase of 4.55 ms at 4 h after dosing of 125 mg BTZ-043, of 3.08 ms at 2 h after dosing of 250 mg, and of 4.84 ms at 1 h after dosing of 500 mg BTZ-043. The highest increase after placebo dosing within this time period was 0.16 ms at 4 h post-dose. At 12 h post-dose mean QTcF was again 4.5 and 4.12 ms higher than pre-dose in the 125 and 250 mg groups and at pre-dose level (change of

Table 1. Summary of treatment-emergent adverse events in each dosing group[a]

System organ class	Preferred term	125 mg BTZ-043 *N* = 8 *n* (%) e	250 mg BTZ-043 *N* = 8 *n* (%) e	500 mg BTZ-043 *N* = 8 *n* (%) e	Placebo *N* = 6 *n* (%) e
Overall summary data		3 (37.5) 10	8 (100.0) 17	7 (87.5) 16	2 (33.3) 3
Nervous system disorders	Summary data	1 (12.5) 1	5 (62.5) 5	4 (50.0) 6	1 (16.7) 1
	Dizziness	—	5 (62.5) 5	3 (37.5) 4	—
	Headache	1 (12.5) 1	—	2 (25.0) 2	1 (16.7) 1
Vascular disorders	Summary data	1 (12.5) 1	3 (37.5) 3	3 (37.5) 3	—
	Hot flush	—	—	*2 (25.0) 2*[b]	—
	Hypertension	1 (12.5) 1	3 (37.5) 3	1 (12.5) 1	—
Gastrointestinal disorders	Summary data	2 (25.0) 6	1 (12.5) 1	2 (25.0) 2	—
	Abdominal pain	1 (12.5) 1	—	—	—
	Abnormal faeces	1 (12.5) 1	—	—	—
	Nausea	1 (12.5) 3	1 (12.5) 1	2 (25.0) 2	—
	Vomiting	1 (12.5) 1	—	—	—
Skin and subcutaneous tissue disorders	Summary data	—	2 (25.0) 3	3 (37.5) 3	—
	Hyperhidrosis	—	1 (12.5) 2	3 (37.5) 3	—
	Rash	—	1 (12.5) 1	—	—
Cardiac investigations	Summary data	1 (12.5) 1	1 (12.5) 1	1 (12.5) 1	1 (16.7) 1
	ECG PR prolongation	1 (12.5) 1	1 (12.5) 1	1 (12.5) 1	1 (16.7) 1
General disorders and administration site conditions	Summary data	—	1 (12.5) 2	1 (12.5) 1	—
	Asthenia	—	1 (12.5) 1	—	—
	Feeling hot	—	1 (12.5) 1	—	—
	Malaise	—	—	1 (12.5) 1	—
Eye disorders	Summary data	—	1 (12.5) 1	—	—
	Blurry vision	—	1 (12.5) 1	—	—
Infections and infestations	Summary data	—	1 (12.5) 1	—	—
	Rhinitis	—	*1 (12.5) 1*	—	—
Musculoskeletal and connective tissue disorder	Summary data	—	—	—	1 (16.7) 1
	Back pain	—	—	—	*1 (16.7) 1*
Reproductive system disorders	Summary data	1 (12.5) 1	—	—	—
	Dysmenorrhoea	*1 (12.5) 1*	—	—	—

[a]*n* = number of subjects having the event; % = proportion of exposed subjects experiencing the event; e = number of events (all treatment-emergent events considered). A dash (—) means no TEAE; italic values mean unlikely related.
[b]Judged unlikely related to one subject.

0.25 and 0.66 ms) in the 500 mg BTZ-043 and placebo groups. No participants had a QTcF or QTcB value >450 ms, or increases of >30 ms (Figure 3).

Pharmacokinetics

BTZ-043 was rapidly absorbed, metabolized and eliminated. T_{max} occurred 0.5–0.75 h after dosing, and geometric mean half-life was short (approximately 1.1–2.0 h). AUC_{0-t} of BTZ-043 showed a more than dose-proportional increase across the three doses tested (slope of about 1.4, range of geometric mean AUC_{0-t}: 358.9 to 2623.5 h μg/L) (Table 2).

The concentrations of parent BTZ-043 for lower doses were not measurable at later timepoints, but the LLOQ used was the lowest technically achievable with the selected methodology. However, the extrapolated area was low, with the highest individual %extrapolated AUC for parent BTZ-043 being 33.4%, 14.6% and 10.3% in the 125, 250 and 500 mg groups, respectively.

The increase in C_{max} was lower (slope of 1.1, range of the geometric mean: 308.6–1466.0 μg/L). Concentration–time profiles showed a second smaller peak at about 2 h post-dose, mainly after administration of 500 mg (Figure 4).

BTZ-043 was rapidly metabolized to M2, which showed a median t_{max} of 1–2 h after dosing, and a short geometric mean half-life (2.8–3.7 h). Geometric mean AUC_{0-t} of metabolite M2 increased from 6654.6 to 30 854.3 h μg/L, and geometric mean C_{max} increased from 1637.8 to 5329.1 μg/L after administration of 125–500 mg BTZ-043 (Table 3). This indicates rapid transformation of BTZ-043 into M2, and both metabolites appear to reach a relatively constant ratio. The highest individual %extrapolated AUC for M2 was 3.4%, 3.3% and 3.5% in the 125, 250 and 500 mg dose groups, respectively.

Median t_{max} of M1, the second main metabolite, occurred later, 7–8.5 h after dosing; geometric mean half-life was about 8.4–9.0 h. Geometric mean AUC_{0-t} of M1 increased from 661.1 to 6046.9 h μg/L, and geometric mean C_{max} increased from

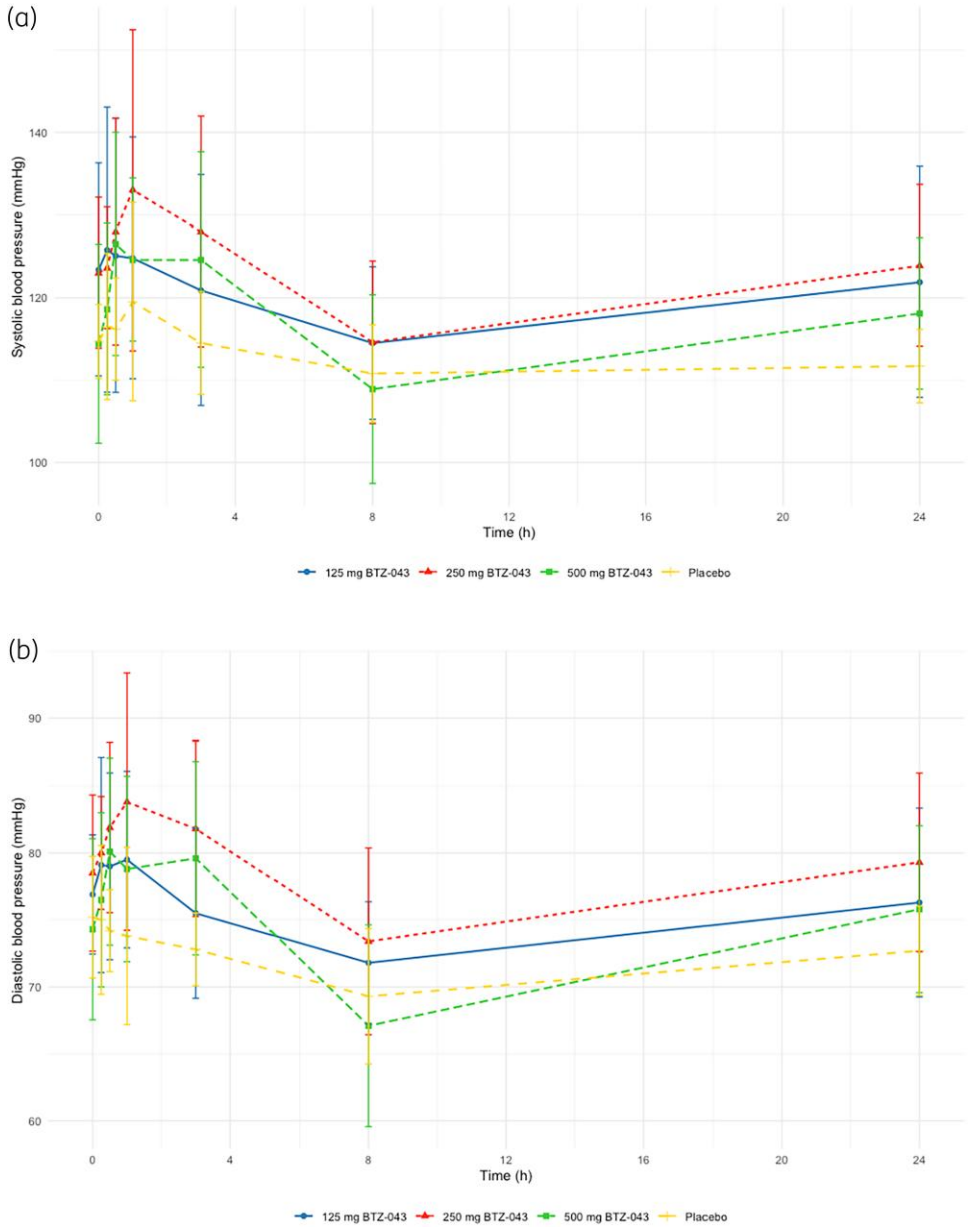

Figure 1. Changes in mean systolic (above) and diastolic (below) blood pressure over time.

61.4 to 295.2 µg/L after administration of 125–500 mg BTZ-043 (Table 4). The highest individual %extrapolated AUC for M1 was 18.9%, 24.1% and 24.4% in the 125, 250 and 500 mg dose groups, respectively.

Median t_{max} of BTZ-043$_{total}$ (parent compound + M2) occurred 1.0–1.75 h after dosing; geometric mean half-life was short (about 2.9–3.6 h). AUC and C_{max} of BTZ-043$_{total}$ increased nearly dose-proportionately (slope of AUC about 1.1; range of geometric mean AUC_{0-t} = 7067.6 to 33 774.2 h µg/L; slope of C_{max} = 0.9; range of geometric mean C_{max} = 1756.0 to 5856.5 µg/L) (Table 5). The highest individual %extrapolated AUC for BTZ-043$_{total}$ was 3.3%, 3.1% and 3.1% in the 125, 250 and 500 mg dose groups, respectively.

Figures 4–7 show mean plasma concentration time profiles of BTZ-043, metabolite M1, M2 and BTZ-043$_{total}$.

Discussion

This FIH study evaluated the safety, tolerability and PK of single ascending oral doses of BTZ-043 in healthy adult volunteers. BTZ-043 was safe and well tolerated. There were no SAEs and no participant discontinued the study due to AEs; all AEs were of mild or moderate intensity. There were no safety findings related to laboratory parameters and ECG. The most frequently reported AEs were dizziness and headache, followed by hypertension and hot flush.

The transient increase of blood pressure of grade 2 or less after doses of 125, 250 and 500 mg, and slight increase in heart rate after doses of 500 mg, may be linked to an antagonistic interaction of BTZ-043 with the muscarinic acetylcholine receptor

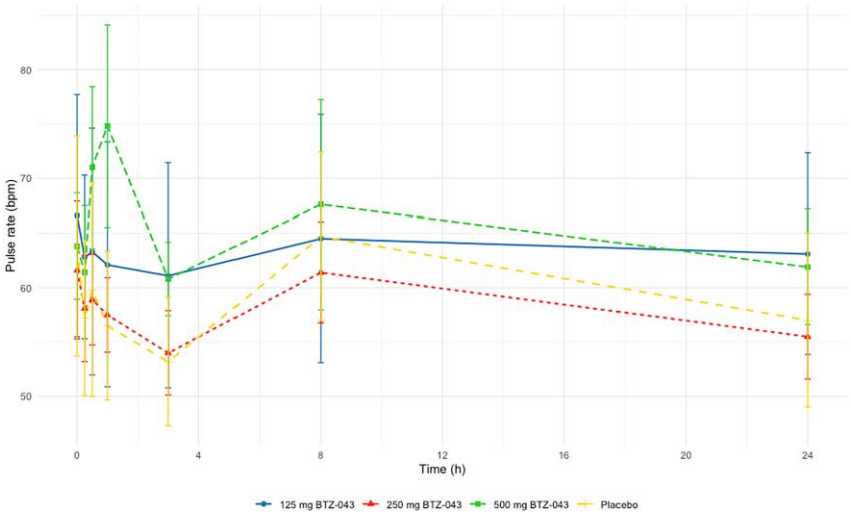

Figure 2. Mean time courses of heart rate in each dosing group.

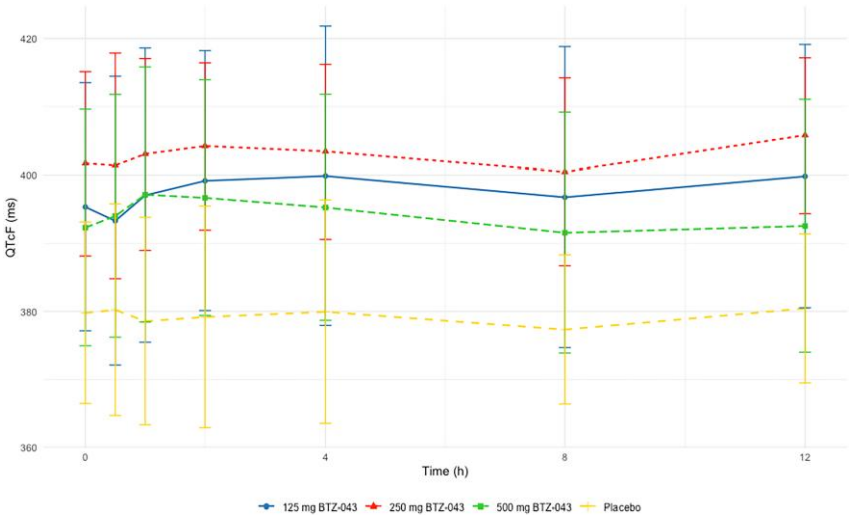

Figure 3. Changes in mean QTcF over time.

Table 2. PK parameters of BTZ-043 after single administration of oral solution[a]

Parameter	125 mg BTZ-043 $N=8$	250 mg BTZ-043 $N=8$	500 mg BTZ-043 $N=8$
AUC_{0-t}, h μg/L	358.9 (51.7)	810.0 (40.4)	2623.5 (39.3)
AUC_{0-24h}, h μg/L	377.2 (49.3)	839.7 (39.4)	2691.0 (38.3)
AUC_{0-inf}, h μg/L	441.2 (58.4)[b]	826.0 (36.2)[c]	2745.1 (36.1)
C_{max}, μg/L	308.6 (84.0)	840.3 (60.1)	1466.0 (77.3)
$t_{½}$, h	1.05 (47.6)	1.44 (17.1)	2.02 (55.0)
t_{max}, h	0.53 (0.5–1.5)	0.52 (0.5–1.0)	0.75 (0.5–4.0)
CL/F, L/h	283.3 (58.4)[b]	302.7 (36.2)[c]	182.1 (36.1)
Vz/f, L	429.9 (107.2)[b]	629.0 (32.9)[c]	530.9 (81.6)

[a]Values are geometric mean (geometric coefficient of variation, %) except for t_{max}, where median (minimum–maximum) are displayed.
[b]$n=4$, [c]$n=7$ due to unreliable λz in four and one subject(s), respectively.

M1. However, *in vitro* receptor occupancy data and IC_{50} data do not imply such an effect during realistic clinical exposure scenarios. BTZ-043 has since been evaluated in an adaptive two-stage Phase 1b/2a dose-finding study evaluating early bactericidal activity (EBA), safety, PK, food effect and drug–drug interaction potential in participants with pulmonary TB.[13] In this 14 day monotherapy study, BTZ-043 administered at doses of 250, 500 and 1000 mg did not result in any relevant increase in blood pressure or heart rate, suggesting that the effect seen in this study is not clinically relevant.

BTZ-043 was rapidly absorbed, metabolized and eliminated. The variability in exposure between individuals was relatively large, and plasma PK of parent BTZ-043 showed a more than dose-proportional increase after single-dose administration. BTZ-043 was rapidly metabolized, mainly to M2, with the second main metabolite M1 appearing later. There was an indication that the increases in AUC and C_{max} of parent BTZ-043 were more than dose-proportional and

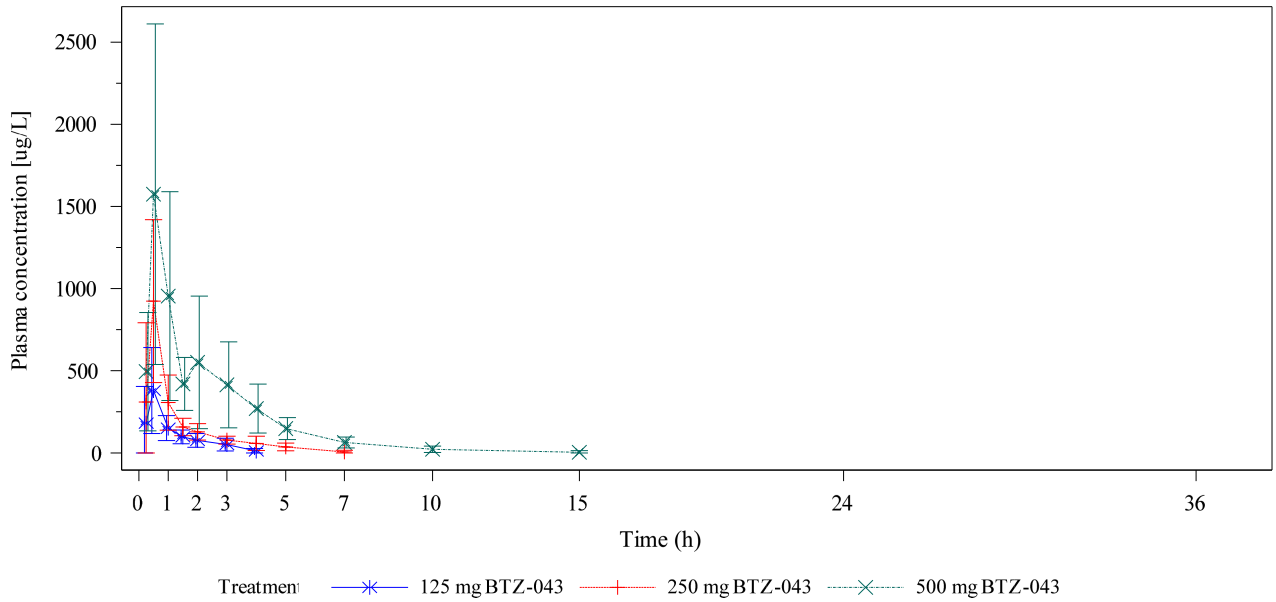

Figure 4. Mean plasma concentration–time profiles of BTZ-043 after single administration of BTZ-043 oral solution.

Table 3. PK parameters of M2 after single administration of BTZ-043 solution[a]

Parameter	125 mg BTZ-043 $N=8$	250 mg BTZ-043 $N=8$	500 mg BTZ-043 $N=8$
AUC_{0-t}, h μg/L	6654.6 (17.7)	12171.5 (26.4)	30854 (33.7)
AUC_{0-24h}, h μg/L	6834.0 (18.1)	12431.2 (26.1)	30853.8 (33.7)
AUC_{0-inf}, h μg/L	6830.8 (17.8)	12441.7 (26.1)	31237.0 (33.9)
C_{max}, μg/L	1637.8 (22.7)	2927.6 (18.9)	5329.1 (34.7)
$t_{½}$, h	2.83 (5.7)	3.09 (13.3)	3.72 (15.2)
t_{max}, h	1.5 (1.0–2.0)	1.0 (1.0–1.5)	2.0 (1.0–3.0)

[a]Values are geometric mean (geometric coefficient of variation, %) except for t_{max}, where median (minimum–maximum) are displayed.

Table 4. PK parameters of M1 after single administration of BTZ-043 solution[a]

Parameter	125 mg BTZ-043 $N=8$	250 mg BTZ-043 $N=8$	500 mg BTZ-043[b] $N=8$
AUC_{0-t}, h μg/L	661.1 (76.9)	2725.5 (81.3)	6046.9 (56.9)
AUC_{0-24h}, h μg/L	789.0 (63.3)	2578.6 (69.9)	4863.6 (46.3)
AUC_{0-inf}, h μg/L	2016.3 (17.9)[c]	4165.9 (90.1)[d]	5281.8 (38.8)[d]
C_{max}, μg/L	61.4 (56.1)	185.5 (64.7)	295.2 (43.2)
$t_{½}$, h	8.57 (16.4)[c]	8.35 (38.0)[d]	9.02 (25.9)[d]
t_{max}, h	7.0 (7.0–10.0)	8.50 (1.5–10.0)	8.5 (5.0–24.0)

[a]Values are geometric mean (geometric coefficient of variation, %) except for t_{max}, where median (minimum–maximum) are displayed.
[b]In the 500 mg group, individual AUC_t was smaller than AUC_{inf}.
[c]$n=2$, [d]$n=5$ due to unreliable λz in six and three subjects, respectively.

that those of $BTZ\text{-}043_{total}$ were almost dose-proportional over the evaluated dose range. A population PK model was developed in-stream and used for within-study decision making. Since then, another model has been developed based on the EBA study data, representing the formulation going forward in development (tablet rather than suspension) and a more relevant population (TB patients rather than healthy volunteers).[14] Therefore, the interim population PK model from the SAD study is not presented.

Analysis of the first two cohorts showed no relevant differences in systemic exposure of BTZ-043 between male and female participants (data not shown). These results are in line with preclinical data, aside from the distinct differences in exposure observed between sexes observed in rats.

The study was stopped after 500 mg as the exposure limit (mean AUC at NOEAL in the more sensitive species/2), defined by BfArM, was reached. Since this FIH study, newer studies are evaluating the exposure–response relationship of higher doses of BTZ-043 administered once daily.

In the completed Phase 1a/2b study, daily doses starting from 250 mg improved bactericidal activity, despite the short half-life of the molecule.[13] As BTZ-043 covalently binds to DprE1, resulting in irreversible enzyme inhibition, new enzymes need to be produced by Mtb for further bacterial growth.

Further clinical development include the DECISION study (NCT05926466), a dose-finding Phase 2B study evaluating three doses (500, 1000 and 1500 mg) of BTZ-043 administered once-daily over 4 months in combination with bedaquiline and delamanid. Furthermore, PARADIGM4TB is a platform Phase 2B study that will evaluate BTZ-043, dosed at 1000 mg, in six different drug combinations with bedaquiline and a nitroimidazole (NCT06114628). In addition, the STEP2C trial will evaluate the safety and efficacy of 1000 mg of BTZ-043 replacing ethambutol in the standard of care regimen (NCT05807399).

Table 5. PK parameters of BTZ-043$_{total}$ after single administration of BTZ-043 solution[a]

Parameter	125 mg BTZ-043 $N=8$	250 mg BTZ-043 $N=8$	500 mg BTZ-043 $N=8$
AUC_{0-t}, h µg/L	7067.6 (18.6)	13 113.2 (25.4)	33 774.2 (32.3)
AUC_{0-24h}, h µg/L	7246.7 (18.9)	13 371.0 (25.2)	33 773.8 (32.3)
AUC_{0-inf}, h µg/L	7246.1 (18.7)	13 380.8 (25.2)	34 147.7 (32.4)
C_{max}, µg/L	1756.0 (23.2)	3158.0 (17.4)	5856.5 (34.7)
$t_{½}$, h	2.86 (5.7)	3.08 (13.8)	3.62 (14.2)
t_{max}, h	1.3 (1.0–2.0)	1.0 (1.0–1.5)	1.8 (1.00–3.00)

[a]Values are geometric mean (geometric coefficient of variation, %) except for t_{max}, where median (minimum–maximum) are displayed.

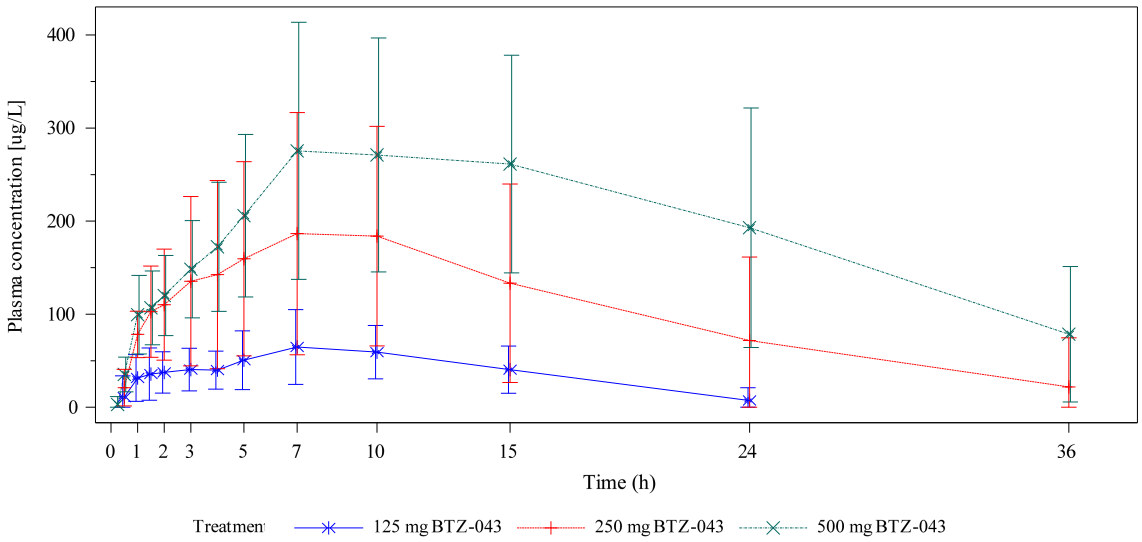

Figure 5. Mean plasma concentration–time profiles of M1 after single administration of BTZ-043 oral solution.

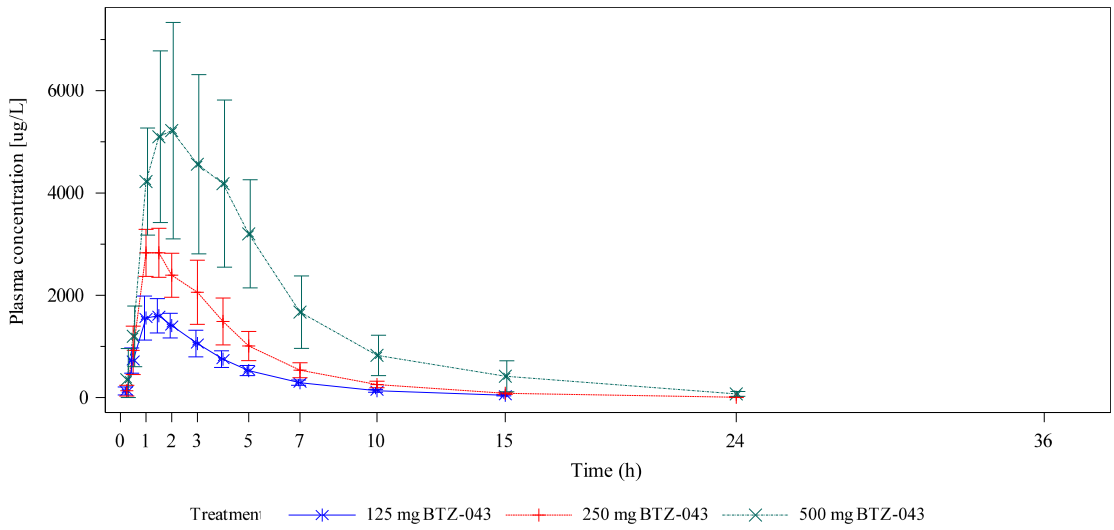

Figure 6. Mean plasma–concentration time profiles of M2 after single administration of BTZ-043 oral solution.

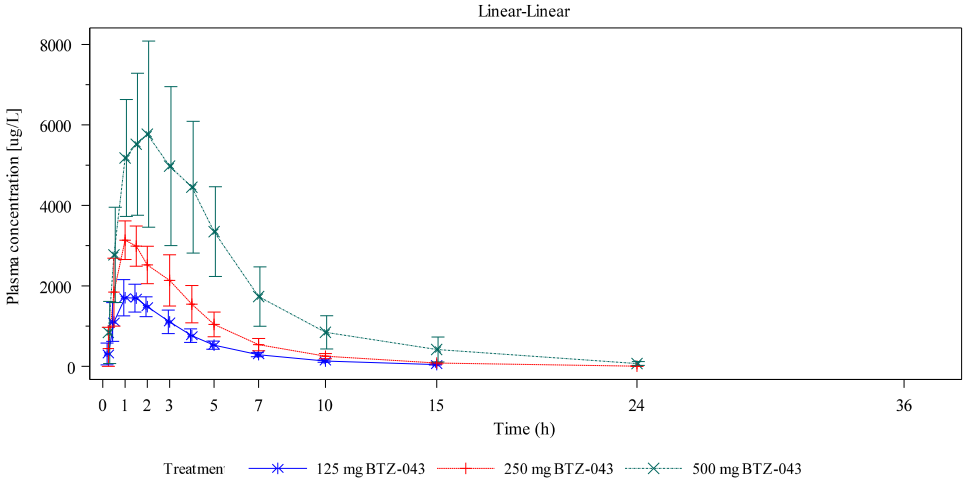

Figure 7. Mean plasma concentration–time profiles of BTZ-043$_{total}$ after single administration of BTZ-043 oral solution.

Conclusion

In this FIH study, BTZ-043 demonstrated an excellent safety profile and good PK properties, warranting further clinical development.

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Author contributions

Funding acquisition: M.H. Study design: M.H., N.H., J.D., F.K. Study conduct and data collection: J.D., S.K. Data analysis and interpretation: M.H., E.M.S., F.K., N.H., J.D., W.L. Writing original draft: W.L., J.D. Review and editing: all authors.

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