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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Heinrich N, de Jager V, Dreisbach J, et al. Safety, bactericidal activity, and pharmacokinetics of the antituberculosis drug candidate BTZ-043 in South Africa (PanACEA-BTZ-043–02): an open-label, dose-expansion, randomised, controlled, phase 1b/2a trial. *Lancet Microbe* 2025. https://doi.org/10.1016/j.lanmic.2024.07.015

PanACEA - BTZ-043-02 online supplementary material

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The PanACEA consortium – list of contributors

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Supplemental Methods: Full In- and Exclusion Criteria

Supplemental Methods: Inclusion Criteria

Participants are required to meet **all** of the following criteria in order to be included in the trial:

<u>General inclusion criteria:</u>

1. Provide written, informed consent prior to all trial-related procedures including HIV testing.
2. Understand and willing to comply with the study procedures.
3. Male or female adults aged 18 up to and including 64 years.
4. Body weight (in light clothing and with no shoes) ≥ 40 kg.
5. Participants are either unable to conceive/father children AND/OR they will be using effective methods of contraception, as defined below:

Non-childbearing condition:

- Female participant/sexual partner of male participant: bilateral oophorectomy and/or hysterectomy or bilateral tubal ligation ≥ 12 months ago and/or has been postmenopausal with a history of no menses for ≥ 12 consecutive months as per medical history
- Male participant/sexual partner of female participant: vasectomised and/or bilateral orchiectomy ≥ 3 months prior to screening as per medial history
- Female pregnant sexual partner of male participant: agree to use protective method specified below
- Male sexual partner of male participant: agree to use protective method specified below
- Abstaining from sexual intercourse, but agreeing to use effective methods of contraception/protection as described below, should this situation change

Effective contraception methods:

- Female participants: two methods, including methods used by the patient's sexual partner(s). At least one to be a barrier method. Contraception must be practised for at least until 12 weeks after the last dose of BTZ-043.
  (Note: hormone-based contraception alone may not be reliable when taking RIF during continuation Phase; therefore, hormone-based contraceptives alone cannot be used by female participants/female partners of male participants to prevent pregnancy).
- Male participants: must ensure effective contraception (two methods) for at least 12 weeks after the last dose of BTZ-043, including at least one barrier method.

Effective protective methods:

- Male participants with female pregnant sexual partner: are required to use at least one barrier method for at least until 12 weeks after the last dose of BTZ-043 for protection of the pregnant partner and the pregnancy.
- Male participants with male sexual partner: are required to use at least one barrier method for at least until 12 weeks after the last dose of BTZ-043 for protection of the partner.

Disease-specific inclusion criteria:

6. Newly diagnosed, previously untreated current episode of drug-susceptible pulmonary TB (presence of MTB complex with rapid molecular test result confirming susceptibility to RIF and INH such as "GeneXpert" and/or "HAIN MTBDR plus")
7. Chest X-ray (no older than 2 weeks) which, in the opinion of the Investigator, is consistent with TB
8. Ability to produce an adequate volume of sputum (approximately 10ml estimated overnight production)
9. ≥ 1 sputum sample from concentrated sputum positive for acid-fast bacilli on microscopy (at least 1+ on the IUATLD/WHO scale) from either a spot sputum or overnight sputum sample.

Supplemental Methods: Exclusion Criteria

Participants for whom **one** of the following criteria is met will be excluded from participating in the trial:

General exclusion criteria:

1. Poor general condition, where delay in treatment cannot be tolerated or death within three months is likely, as assessed by the investigator.
2. The patient is pregnant or breast-feeding.

Disease-specific exclusion criteria:

3. The patient is infected with HIV.
4. The patient has a known intolerance to any of the study drugs or concomitant disorders or conditions for which study drugs or standard TB treatment are contraindicated.
5. Treatment with any other investigational drug within 1 month prior to enrolment or enrolment into other clinical (intervention) trials during participation.
6. The patient has a history of or current evidence of clinically relevant cardiovascular, metabolic, gastrointestinal, neurological, ophthalmological, psychiatric or endocrine diseases, malignancy or any other condition, that will influence treatment response, study adherence or survival in the judgement of the investigator, especially:
    a. Clinically significant evidence of severe TB (e.g. miliary TB, TB meningitis, excluding limited lymph node involvement)
    b. Serious lung conditions other than TB or significant respiratory impairment in the discretion of the investigator
    c. Neuropathy, epilepsy or significant psychiatric disorder

d. Any diabetes mellitus
e. Cardiovascular disease, such as myocardial infarction, heart failure, coronary heart disease, arrhythmia, tachyarrhythmia, or pulmonary hypertension
f. Current (as measured on two occasions during screening) or history of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) AND/OR ever received antihypertensive treatment
g. Long QT syndrome or family history of long QT syndrome or sudden death of unknown or cardiac-related cause
h. Alcohol or other drug abuse, that is sufficient to significantly compromise the safety or cooperation of the patient, includes substances prohibited by the protocol, or has led to significant organ damage, at the discretion of the investigator
i. Condition that makes ophthalmologic assessment difficult or render results unreliable

<u>Laboratory exclusion criteria at screening:</u>

7. Serum amino aspartate transferase (AST) and/or alanine aminotransferase (ALT) activity >2.5x the ULN
8. serum alkaline phosphatase (ALP)> 2.5x the ULN
9. serum total bilirubin level >1.5 times the ULN
10. estimated creatinine clearance (eCrCl) using the Cockcroft and Gault formula level lower than 60 mls/min
11. haemoglobin level <8.0 g/dL
12. platelet count <100,000/mm3
13. serum potassium below the lower level of normal (LLN) for the laboratory

<u>ECG-specific exclusion criteria:</u>

14. QTcF of > 450 milliseconds (ms)
15. Atrioventricular (AV) block with PR interval > 200 ms
16. QRS complex > 120 ms
17. any other changes in the ECG that are clinically relevant as per discretion of the investigator

<u>Restricted medication:</u>

18. Treatment with drugs active against MTB within the last 3 months prior to screening
19. Requires medication as included in the following drug classes within 2 weeks prior to the first dose of study treatment:
    - medication that prolongs the QTc interval
    - CYP 450 inhibitors or inducers, including grapefruit containing foods / beverages and St. John's Wort
20. Requires medication as included in the following drug class within 2 days prior to the first dose of study treatment
    - antacids or antipeptic drugs (antacids, H2 blockers, proton pump inhibitors)

Supplemental Methods: Patient Stopping Criteria

Stopping criteria for individual patient dosing of IMP:

Blood pressure Stopping Criteria:

- A medium systolic blood pressure >180 mm Hg or <80 mm Hg, and/or a medium diastolic blood pressure >110 mm Hg as measured by triplicate measurements
- A medium systolic blood pressure >160 mm Hg or <85 mm Hg for more than 12 hours, and/or a medium diastolic blood pressure >100 mm Hg for more than 12 hours as measured by triplicate measurements with control measurements after 4, 8 and 12 hours
  (in this case, study drugs will be discontinued for 24 hours and the patient's blood pressure regularly re-assessed before a decision on continuation of study drugs is made)

ECG Stopping Criteria:
A patient that meets either bulleted criterion below will be withdrawn from the study. Withdrawal of patients is to be based on an average QTcF value of triplicate ECGs during treatment phase.

- QTcF >500 msec,
- Change from baseline: increase in QTcF >60 msec

Hepatotoxicity stopping criteria:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN and/or alkaline phosphatase (ALP) >5×ULN for >7 days.
- ALT or AST >8× ULN and/or alkaline phosphatase (ALP) >8× ULN
- ALT or AST >3x ULN and (total bilirubin (TBL) >2xULN or INR >1.5

Other:
Severe signs or symptoms, or significant changes in any of the safety assessments that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests etc.), in consultation with the sponsor medical expert.

Supplemental Methods: Pharmacokinetic assessment

The PK assessments in stage 1 and 2 of the study aimed to describe the PK of BTZ-043 (Parent compound, and total including M2), and its major metabolites (M1 and M2), after a single dose (day 1 in both stages) or at steady state (day 12 stage 1 and day 14 in stage 2) for different doses of BTZ-043. In stage 1, BTZ-043 was ingested without food, and the effect of food on BTZ-043 steady state exposure was evaluated on day 14 by providing a high-fat high-calorie breakfast before intake BTZ-043. In stage 2, BTZ-043 was taken with food in the form of a standard breakfast (timing ranging from prior to 30 minutes after breakfast). Finally, in stage 2 the drug interaction potential of BTZ-043 was assessed by giving a pre-defined single dose probe drug cocktail or dolutegravir when BTZ-043 was not yet started (day 0) and on steady state (day 14) (stage 2).

The time points for intensive PK sampling were at 0.0h (pre-dose) and post-dose at 15min, 30min, 1.0h, 1.5h, 2.0h, 3.0h, 4.0h, 6.0h, 8.0h, 10.0h, 12.0h, 24.0h (pre-dose of the following day). The sampling period of 24h was sufficient to achieve peak concentrations (Cmax) within the sampling time and an appropriate estimate of the half-life.

On day 14 in stage 2, BTZ-043 was administered 2 hours after the probe-drugs. Simultaneous administration was not possible as the probe drugs and dolutegravir need to be administered in fasted state but BTZ-043 was administered with food. Probe drug PK sampling (Day 0 and Day 14) followed the same time points as PK sampling for BTZ. For practical reasons, sampling was not extended beyond 24 hours to more accurately assess elimination of the probe drug digoxin (AUC0-24h reported instead of AUC0-inf). The wash-out period of 14 days in the second stage was considered to be adequate to avoid any carry-over between days of single dose administration of the probe drugs or dolutegravir. This was also the maximal possible wash-out phase as the study treatment phase was restricted to 14 days.

The bioanalysis of BTZ-043 (parent), M1, BTZ-043$_{total}$ (BTZ-043 + M2)$_{(}$, dolutegravir and probe drug-cocktail (caffeine, digoxine, dextromethorphan, midazolam, tolbutamide) was conducted by GLP-accredited Nuvisan (Neu Ulm, Germany). For BTZ-043 and M1 analysis sampling tubes were prepared with ascorbic acid to stabilize M2 to avoid back-conversion to the parent BTZ-043.

PK-parameters were estimated at each PK sampling day and for each analyte from subjects' individual plasma concentrations with noncompartimental analysis (NCA) using Phoenix Winnonlin® software v8.3. For this, the maximum concentration of drug in plasma was defined as the Cmax, and the time to this maximum concentration as the Tmax. The Cmax and Tmax were determined directly from the plasma concentration-time data. The rate constant of the elimination phase (λz) was calculated by log-linear regression of the terminal portion of the concentration-time profile where there were sufficient data (i.e. at least 3 time points and the correlation coefficients for the terminal slope [R2] ≥ 0.8). If these criteria were not fulfilled, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24h}$, λz and t1/2 were not calculated.

During the derivation of individual subject PK parameters plasma concentrations:

- Any values below the lower limit of quantification (LLOQ) that occur before the first quantifiable concentration were replaced with zero.
- Any values that fall below the LLOQ between 2 measurable values will were treated as missing.

When the concentrations at x h post dose (all after the last measurable concentration) were below the LLOQ they were calculated using the formula Cx= Clast*e-Kel*(x-Tlast), in which Clast is the last measurable concentration and Tlast is the time to reach Clast. These extrapolated concentrations were used together with other measured concentrations to assess the Area under the drug concentration - time curves (AUC) using 'Linear up' and 'Log down' from time zero to the end of the dosing interval (24h for once daily dosing).

Descriptive statistics including mean, standard deviation, geometric mean, coefficient of variation, geometric coefficient of variation, median, minimum and maximum were computed for each PK parameter by dose group in each stage in WinNonlin.

The food effect was estimated from stage 1 data by calculating individual ratios of daily exposure (AUC0-last) comparing day 14 (high-fat meal) to day 12 (fasted). A geometric mean was calculated across all doses, after confirming than no obvious trend in the individual ratios with dose was precent.

Table S1: Probe drugs and doses

Substance	Dose	Formulation	Objective of use
Caffeine	150 mg	Tablet 150mg	Probe for CYP1A2
Tolbutamide	125 mg	Tablet 500 mg	Probe for CYP2C9
Midazolam	2 mg	i.v. Solution to be given orally 1mg/1mL	Probe for CYP3A4
Dextromethorphan	30 mg	10mL syrup 15mg/5mL	Probe for CYP2D6
Digoxin	0.5 mg	Tablet 0.25 mg	Probe for P-gp
Dolutegravir	50 mg	Tablet 50 mg	Effect of BTZ-043 on this drug of clinical interest

Table S1: list of probe drugs used in stage 2. CYP: cytochrome p450, P-gp: P-glycoprotein (1).

Figure S1: Systolic Blood Pressure

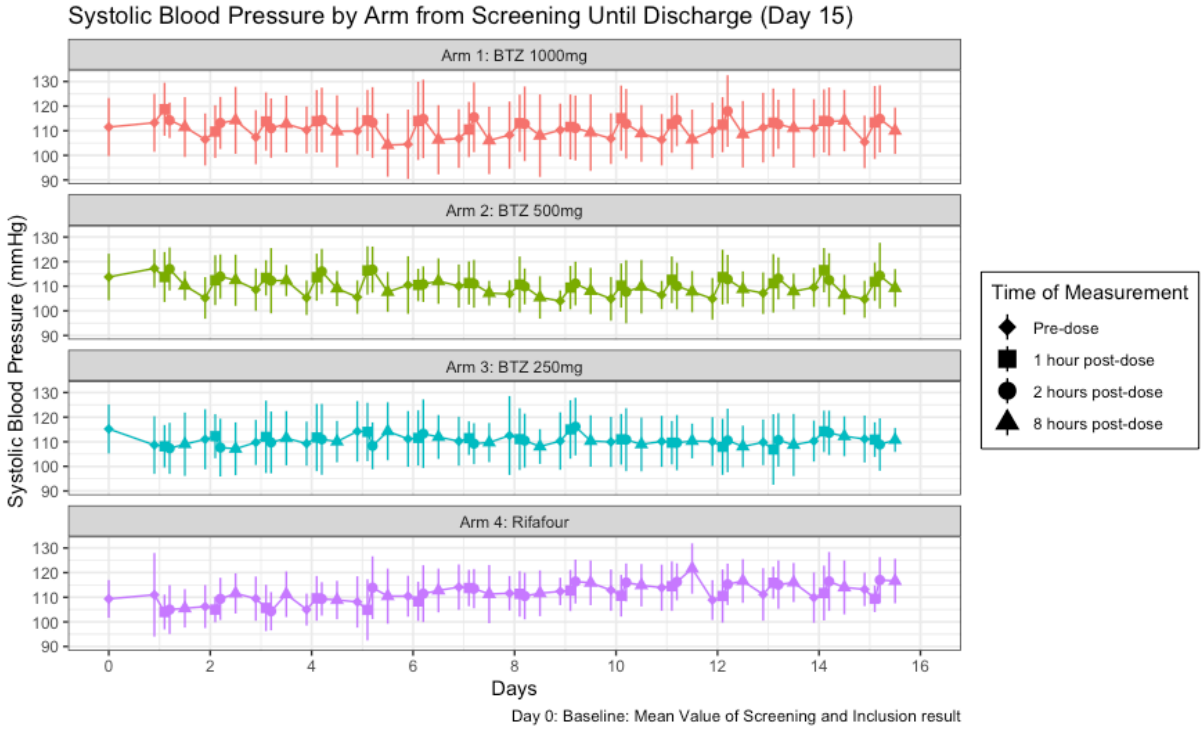

Figure S1: stage 2 group means of systolic blood pressure measurements over time, by treatment arm

Figure S2: ALT over time, stage 2

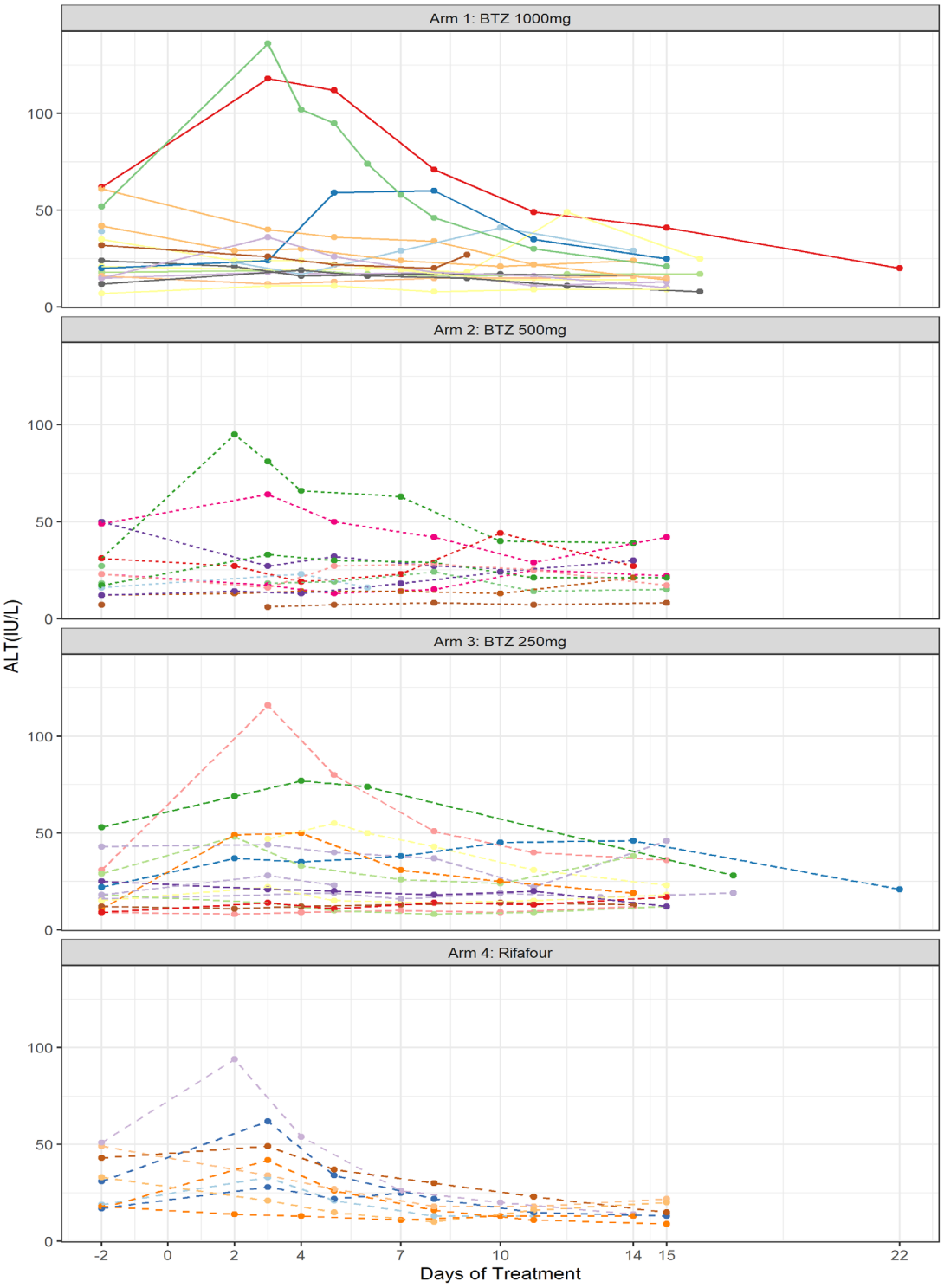

Figure S2: individual values of Alanine aminotransferase (ALT) over time by treatment arm, stage 2.

Table S2: Adverse Events of Grade 3 or higher, Stages 1 and 2 combined

Preferred term	Severity/Intensity	SAE	BTZ-043 dose	Study stage	Causality to Drug	Outcome
Haemoptysis	Grade 3 - Severe	Yes	1750 mg	1	Unrelated	Resolved
Hyponatraemia	Grade 3 - Severe	No	1750 mg	1	Unlikely Related	Resolved
Anaemia	Grade 3 - Severe	No	250 mg	2	Possibly Related	Resolved
Hyperkalaemia	Grade 3 - Severe	No	250 mg	2	Unlikely Related	Resolved
Pharyngeal abscess	Grade 3 - Severe	No	1000 mg	2	Unrelated	Unchanged
Pulmonary embolism	Grade 3 - Severe	Yes	1000 mg	2	Unrelated	Unchanged
QTcF prolongation*	Grade 3 - Severe	No	500 mg	2	Possibly Related	Resolved
Pulmonary tuberculosis aggravated	Grade 3 - Severe	Yes	250 mg	2	Unrelated	Resolved
Pulmonary embolism**	Grade 5 - Death	Yes	500 mg	2	Unrelated	Fatal

Table S2: adverse events of grade 3 or higher, with dose and investigator assessment of causality. SAE: serious adverse event.

**The event of QTcF prolongation was associated with a markedly slower heart rate (heart rate pre-dose 105/min; 1h post dose 71/min, 2h post-dose 70/min; 8h post-dose 121/min; QTcF pre-dose 376 ms, 1h post-dose 427ms; 2h post dose 444ms, 8h post dose; 8h post dose: 356); therefore the sponsor deviated from investigator assessment and held this to be due to Friderica undercorrection rather than an effect of BTZ-043 (2).*

***The death due to pulmonary embolism occurred before the first dose of BTZ-043 was administered, the patient is therefore not part of the safety population.*

Table S3: Bactericidal Activity stage 1: summary of EBA by MGIT TTP and solid media CFU

Cohort	Dose (mg)	MGIT EBA with 95% CI, log10(TTP) increase per day on treatment	CFU EBA with 95% CI, log10(CFU) increase per day on treatment.
Cohort 1	250	0.0146 (0.0012, 0.0280)	-0.0668 (-0.1658, 0.0323)
Cohort 2	500	0.0138 (0.0015, 0.0262)	-0.0606 (-0.1522, 0.0310)
Cohort 3	750	0.0195 (0.0072, 0.0318)	-0.1140 (-0.2086, -0.0194)
Cohort 4	1000	0.0206 (0.0028, 0.0384)	-0.1145 (-0.2425, 0.0136)
Cohort 5	1250	0.0116 (-0.0007, 0.0239)	-0.0681 (-0.1628, 0.0265)
Cohort 6	1500	0.0193 (0.0069, 0.0316)	-0.1592 (-0.2511, -0.0673)
Cohort 7	1750	0.0167 (0.0065, 0.0269)	-0.0795 (-0.1646, 0.0055)

Table S3: bactericidal activity of BTZ-043 in stage 1 (multiple ascending dose) stage of the trial over days 1-14. MGIT – mycobacterium growth indicator tube, CFU – colony forming unit, EBA – early bactericidal activity.

Table S4. Food effect

	Ratio M0		**Ratio M1**		**Ratio M2**		**Ratio BTZ-043$_{total}$**	
	C_{max}	**$AUC_{0\text{-}last}$**	**C_{max}**	**$AUC_{0\text{-}last}$**	**C_{max}**	**$AUC_{0\text{-}last}$**	**C_{max}**	**$AUC_{0\text{-}last}$**
Mean	3.47	4.71	1.39	1.34	2.63	3.27	2.62	3.26
Standard deviation	2.83	2.3	0.46	0.53	1.03	1.3	1.07	1.26
Geometric mean	2.63	4.13	1.32	1.25	2.48	2.98	2.46	2.99
90%CI of geometric mean	0.760 – 9.12	1.65 – 10.3	0.765 – 2.28	0.656 – 2.39	1.42 – 4.32	1.35 – 6.54	1.40 – 6.55	1.39 – 6.41
Min	0.89	1.25	0.61	0.5	1.28	0.83	1.29	0.85
Median	2.26	4.33	1.36	1.23	2.49	3.22	2.53	3.37
Max	11.8	8.97	2.42	2.92	6.19	5.15	6.33	5.11

Table S4: Summary of exposure ratios of BTZ-043 taken after high caloric breakfast to fasting for each analyte, calculated based on 19 stage 1 participant with data on day 12 and 14.

Figure S3: Individual probe drug concentration – time curves

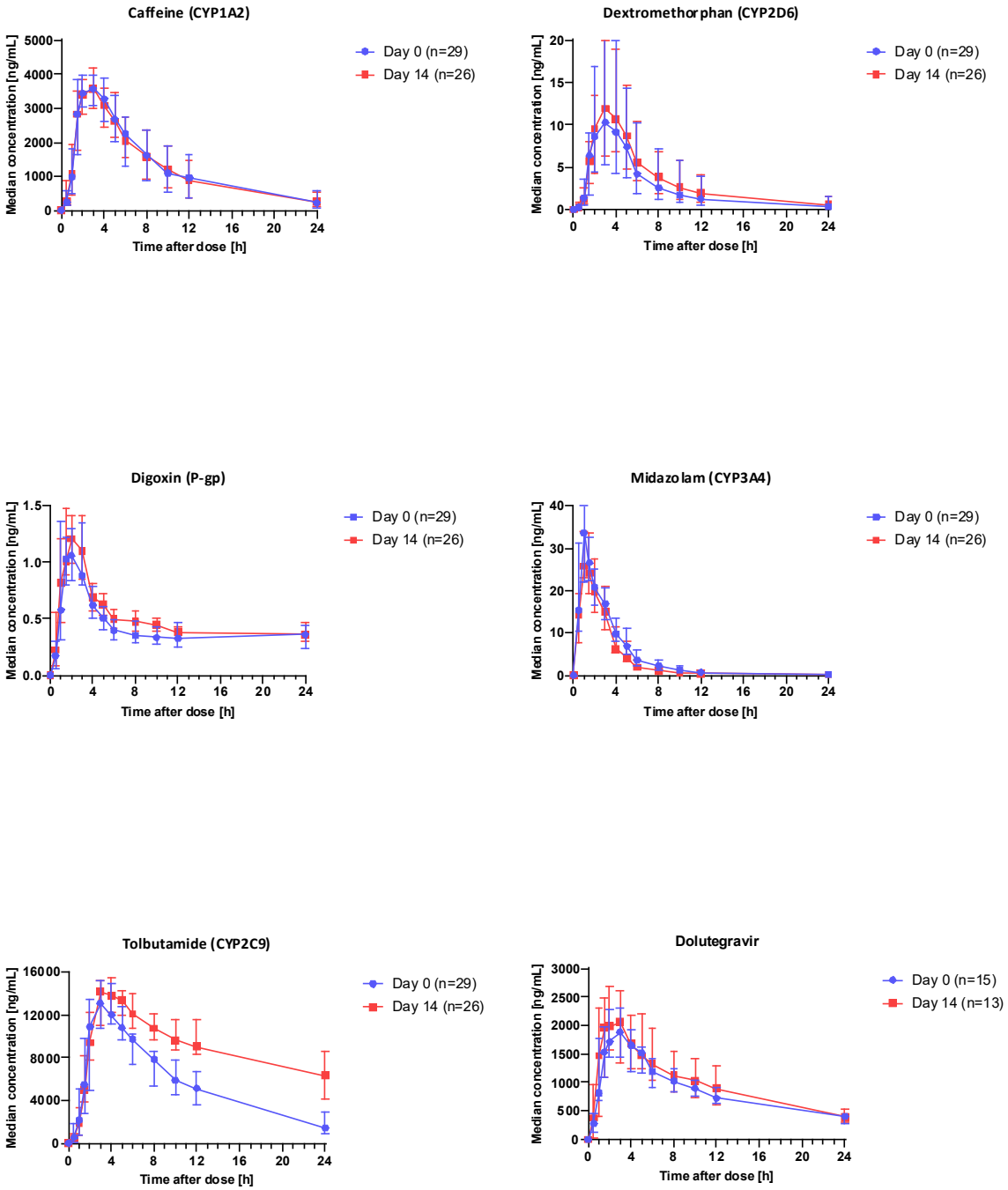

Figure S3: Median concentration (with error bars) of probes drugs on day 0 and day 14. Subjects received BTZ on day 14. The error bars represent the interquartile range

Table S5: Bioequivalence analysis of AUCinf for probe drugs.

	N Day 0	N Day 14	AUC, Day 0 (without BTZ) Geometric mean [h*ng/mL]	AUC, Day 14 (with BTZ) Geometric mean [h*ng/mL]	Geom. Mean Ratio % (90% CI)	CI within 80 – 125%	CI within 70 – 143%	Paired t-test Significant difference in mean
Caffeine AUC0-∞ (CYP1A2, NAT2))	29	26	30112.73	31085.83	100.01 (86.31 – 115.88)	Yes	Yes	No (p=0.92)
Dextromethorphan AUC0-∞ (CYP2D6)	29	26	91.83	100.58	116.20 (104.62 – 129.06)	No	Yes	Yes (p=0.021)
Digoxin **AUC_{0-24h}**[a] **(P-gp, OATP4C1)**	29	26	10.29	12.06	113.41 (105.88 – 121.48)	Yes	Yes	Yes (p=0.001)
Midazolam AUC0-∞ (CYP3A)	29	26	92.11	75.24	76.96 (69.19 – 85.61)	No	No	Yes (p<0.001)
Tolbutamide AUC0-∞[b] (CYP2C9, OAT2)	29	26	163462.60	405719.74	252.73 (230.71 – 276.85)	No	No	Yes (p<0.001)
Dolutegravir AUC0-∞ (UGT 1A1)	15	13	26201.36	29345.88	106.06 (91.50 – 122.94)	Yes	Yes	No (p=0.63)

Table S5: result of drug-drug-interaction pharmacokinetics, ratios of AUC_{0-24h} of day 14 when given with BTZ-043, over day 0 pre-dose. $AUC_{0-\infty}$: area under the curve from 0h to infinity.

[a.] For digoxin AUC0-24h was selected as PK parameter, as extrapolation until infinity was unreliable based on limited observations in the terminal elimination phase

[b.] Tolbutamide tablets (500 mg) were quartered before administration, average tablets weighed 0.15 (range: 0.14 – 0.17) in the first session and 0.15 (0.14 – 0.17) in the second session

Table S6: doses of Standard TB treatment in the Comparator Arm

Pre-Treatment Body Weight	Number of fixed-dose tablets (per tablet: R 150mg, H 75mg, Z 400mg, E 275 mg
30-37 kg	2 tabs
38.54 kg	3 tabs
55-70 kg	4 tabs
>70 kg	5 tabs

Table S6: doses of standard anti-TB drugs in the comparator arm. R: rifampicin, H: isoniazid, Z: pyrazinamide, E: ethambutol. From: South African National Tuberculosis Management Guidelines 2014.

Table S7: Adverse Events by MedDRA Lower Level Term, Stage 1

Dose of BTZ-043	**250**, N = 3	**500**, N = 17	**750**, N = 3	**1000**, N = 4	**1250**, N = 15	**1500**, N = 10	**1750**, N = 14	**Overall**, N = 66[2]
Lower Level Term								
Abdominal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
ALT increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Blurred vision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (1.5%)
Conjunctival irritation	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.0%)
COVID-19 virus test positive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	3 (30.0%)	0 (0.0%)	4 (6.1%)
Dry eye syndrome	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Dyspnoea	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Elevated liver enzymes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Epistaxis	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	2 (3.0%)
Fatigue	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Fever	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Generalised pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Gingivitis	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	2 (3.0%)
Haemoptysis	0 (0.0%)	1 (5.9%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)	5 (7.6%)

Heartburn	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Hyponatremia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Increased blood pressure	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Light headedness	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Lymphadenopathy axillary	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Muscle spasm	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Muscular back pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Nausea	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	4 (40.0%)	1 (7.1%)	8 (12.1%)
Oral mucosal discolouration	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Petechiae	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Pleuritic pain	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	3 (4.5%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	2 (3.0%)
Pyrexia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (1.5%)
Raised liver function tests	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Refractive errors NOS	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Shingles	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Sore throat	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Toothache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Upper back pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Urticaria localised	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.0%)
Venipuncture site pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Venous ulceration	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Vision decreased	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.0%)

Visual acuity decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.5%)
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	2 (13.3%)	1 (10.0%)	1 (7.1%)	5 (7.6%)
[1]Summary is by event, not by participant								

Table S8: Adverse Events by MedDRA Lower Level Term, Stage 2

Dose of BTZ-043	**250**, N = 21	**500**, N = 17	**1000**, N = 35	**Rifafour**, N = 9	**Overall**, N = 82[12]
Lower Level Term					
Abdominal pain	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Abscess jaw	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Alkaline phosphatase increased	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	2 (2.4%)
Anaemia	1 (4.8%)	3 (17.6%)	0 (0.0%)	0 (0.0%)	4 (4.9%)
Anemia aggravated	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Asymptomatic COVID-19	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (1.2%)
AV block first degree	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Blurred vision	0 (0.0%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	2 (2.4%)
Conjunctival irritation	1 (4.8%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (2.4%)
Constipation	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
COVID-19 respiratory infection	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Diarrhoea	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Dizziness	1 (4.8%)	0 (0.0%)	5 (14.3%)	0 (0.0%)	6 (7.3%)
Dry eyes	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Dry skin face	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Electrocardiogram QTc interval prolonged	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Fatigue	2 (9.5%)	1 (5.9%)	1 (2.9%)	0 (0.0%)	4 (4.9%)
Fever	0 (0.0%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	2 (2.4%)

Fixed dilated pupils	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Flatulence	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Gamma GT increased	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Gamma-glutamyltransferase increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (1.2%)
General body pain	1 (4.8%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
Generalized rash	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
GGT increased	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Haemophilus influenza pneumonia	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Haemoptysis	1 (4.8%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (2.4%)
Haemorrhoids	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Headache	1 (4.8%)	5 (29.4%)	3 (8.6%)	0 (0.0%)	9 (11.0%)
Hyperkalemia	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Hyponatraemia	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Infected sebaceous cyst	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Loose stools	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Muscular back pain	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Nausea	0 (0.0%)	1 (5.9%)	2 (5.7%)	1 (11.1%)	4 (4.9%)
Orbital pain	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Painful R arm	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Papular rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (1.2%)
Perianal abscess	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Peripheral neuropathy	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Pharyngeal abscess	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Photophobia	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Pneumonia bacterial	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	2 (2.4%)
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Pulmonary tuberculosis aggravated	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Rash	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Rectal pain	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)
Venipuncture site pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (1.2%)
Viral upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (1.2%)
Vomiting	0 (0.0%)	2 (11.8%)	1 (2.9%)	0 (0.0%)	3 (3.7%)
[1]SAEs and AEs are categorized by their respective Lower Level Term					
[2]Summary is by event, not by participant					

Bibliography

1. Doroshyenko O, Rokitta D, Zadoyan G, Klement S, Schlafke S, Dienel A, et al. Drug cocktail interaction study on the effect of the orally administered lavender oil preparation silexan on cytochrome P450 enzymes in healthy volunteers. Drug Metab Dispos. 2013;41(5):987-93.
2. Olliaro PL, Merle C, Mthiyane T, Bah B, Kassa F, Amukoye E, et al. Effects on the QT Interval of a Gatifloxacin-Containing Regimen versus Standard Treatment of Pulmonary Tuberculosis. Antimicrob Agents Chemother. 2017;61(7).