Supplemental Table 1 – Pathology Score adapted from (24, 25)

Parameters	Score used
Inoculation site granuloma (right axillary subcutis)	
Granuloma(s) ≥3.5 cm in diameter with caseous necrosis	4
Granuloma(s) ≥2.5 cm in diameter with caseous necrosis	3
Granuloma(s) ≥1.5 cm in diameter ± caseous necrosis	2
Granuloma(s) ≥0.5 cm in diameter	1
No lesion	0
Right axillary lymph node	
Granuloma(s) ≥2.0 cm in diameter with caseous necrosis	4
Granuloma(s) ≥1.5 cm in diameter with caseous necrosis	3
Granuloma(s) ≥1.0 cm in diameter ± caseous necrosis	2
Granuloma(s) ≥0.5 cm in diameter	1
No lesion respectively of normal size (≤0.5 cm)	0
Spleen*	
Numerous granulomas (miliary type)	4
Many granulomas	3
Few granulomas	2
Single granulomas	1
No lesion	0
Liver*	
Numerous granulomas (miliary type)	4
Many granulomas	3
Few granulomas	2
Single granulomas	1
No lesion	0

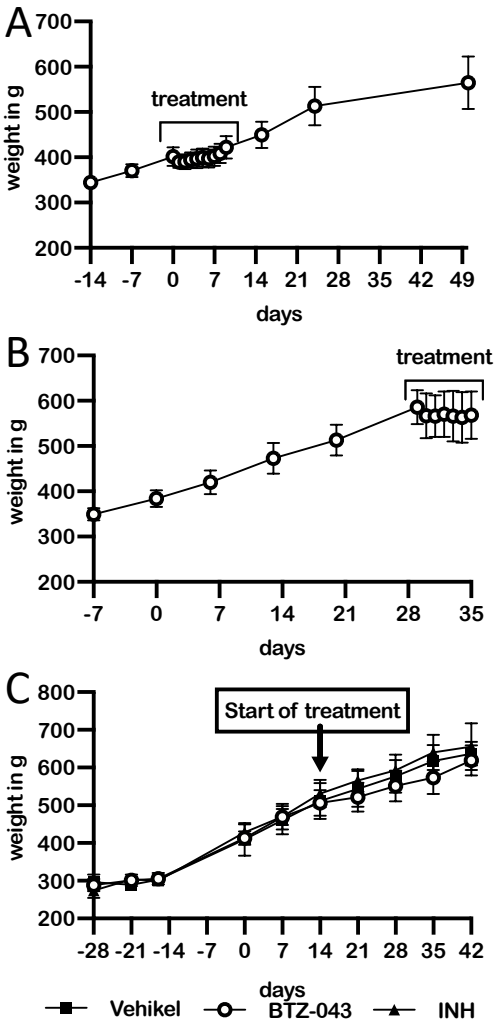
*granulomas in spleen and liver were randomly distributed and 0.3 - 0.4 cm in diameter large

Supplemental Table 2 – PK parameters for M0 and M1 calculated by WinNonLin

Administration	Variable	C_{max} [ng/mL]	T_{max} [h]	AUC_{0-t} [h*ng/mL]	AUC_{0-inf} [h*ng/mL]	AUC_{extra} [%]
50 mg/kg micronized	M0	1239	1	5042	7626	34
	M1	119	2	352	-	-
200 mg/kg (micronized)	M0	984	1	3566	4053	12
	M1	1786	2	10003	10036	0
200 mg/kg (wet-milled)	M0	885	2	3305	3312	0
	M1	1377	2	8489	8560	1
400 mg/kg (micronized)	M0	2213	2	15220	39819	62
	M1	1678	4	19034	-	-

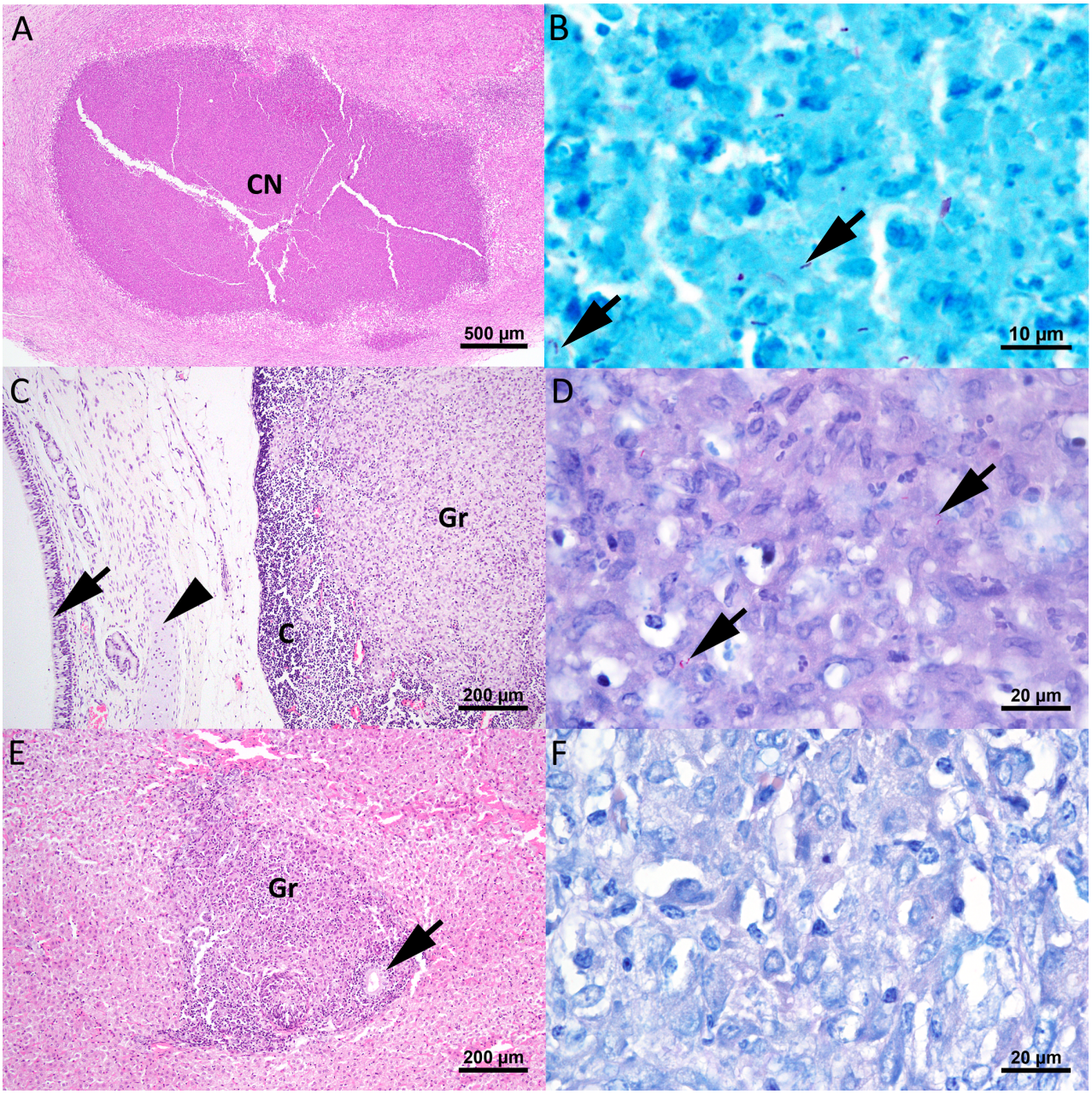
Note: "-" means that data were not available by the calculation of WinNonLin.

Fig S1



Supplement Figure 1 During BTZ-043 treatment guinea pigs show decelerated weight gain: For calculation of the right medication dosage and medical assessment guinea pigs were weighed regularly during the trials. (A) The weight curve of the multidose application study is shown, were guinea pigs were given daily 400 mg/kg BTZ-043 orally. Guinea pigs were weighed daily during and weekly before and after treatment. Error bars indicate the standard error of the mean (SEM). (B) Guinea pigs were s.c. infected with BCG on day zero and treated with 400 mg/kg BTZ-043 orally for seven days from day 29 on. The weight was measured weekly before and daily during the trial. Error bars indicate the SEM. (C) All guinea pigs were infected s.c. with virulent mycobacteria on day 0. From day 14 on they were either treated orally with 300 mg/kg BTZ-043 or 60 mg/kg isoniazid (INH) daily. As negative control guinea pigs were given vehicle solution. Guinea pigs were weighed weakly. Error bars indicate the SEM.

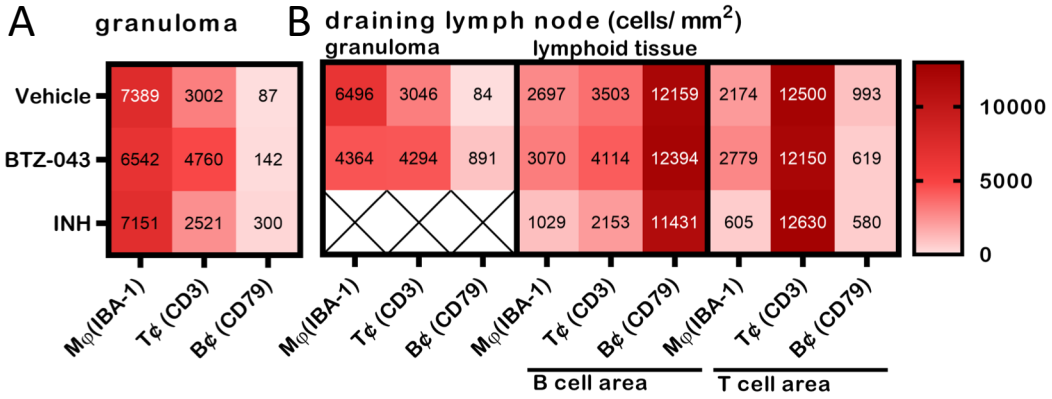
Fig S2



Supplemental Figure 2 Lesion characteristics and detection of acid-fast mycobacteria (AFB) in the vehicle control group 42 days after subcutaneous infection

(A) Granuloma in the axillary subcutaneous infection site of animal no. 4 with a central core of caseous necrosis (CN) and a peripheral rim of activated macrophages and fibrosis. (B) Within the caseous necrosis shown in Figure A few extracellular acid fast mycobacteria (arrows) are detectable. (C) Next to the trachea with intact respiratory epithelium (arrow) and cartilage (arrowhead), an extensive non-caseating granuloma (Gr) is evident in the *Ln. tracheobronchialis* of animal no. 4. (D) Few AFB reside in the cytoplasm of activated macrophages (arrows). (E) In the liver of animal no. 5 a non-caseating granuloma is shown in the periportal zone as outlined by a bile duct (arrow). (F) The hepatic granuloma is devoid of AFB. A, C, E; Hematoxylin eosin stain; Ziehl-Neelsen stain; F, H; Fite-Faraco-stain.

Fig S3



Supplement Figure 3 Guinea pigs treated with BTZ-043 have higher T cell numbers in granuloma and lymph node: Formaldehyde fixed, paraffin embedded tissue sections of the infection site granulomas and draining lymph nodes from all groups were investigated with selected immune cell markers by immunohistochemistry (IHC). (A) Consecutive sections of granulomas were stained for macrophage marker Iba-1, T cell marker CD3 and B cell marker CD79. Positive cells were counted using QuPath. The heatmap shows a comprehensive overview of the numbers of positive cells per mm^2 counted within the granulomas. Rows correspond to the three treated groups, columns to the tested surface marker or transcript. Figures represent mean values. (B) As above consecutive slides of axillary lymph nodes were stained for macrophages, T cells and B cells and positive cells were counted. It was differentiated between normal lymph node parenchyma (lymphoid tissue) with the corresponding T and B cell areas and granulomas (granulomatous area).