BTZ-043 drug development programme

A development by the University of Munich and the Hans-Knoell Institute in Jena in cooperation with PanACEA & DZIF

Supported by:

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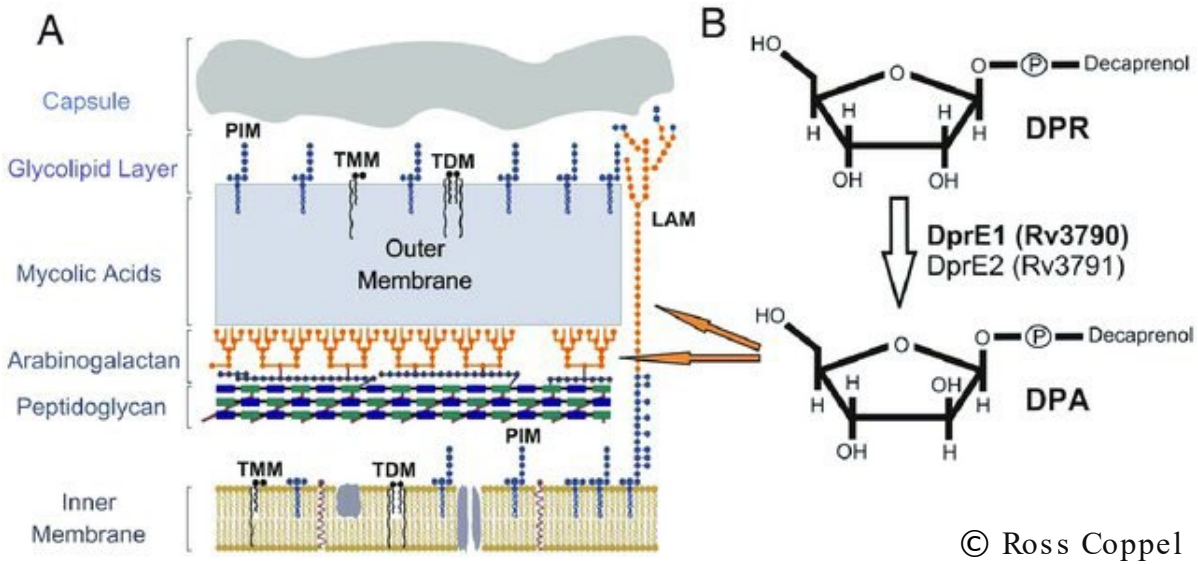
DPRE1 is an essential enzyme for formation of the mycobacterial cell wall



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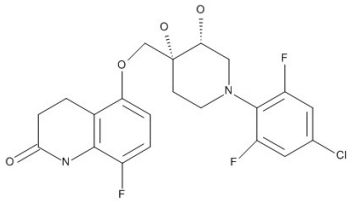
Non-covalent binding DPRE1 inhibitors

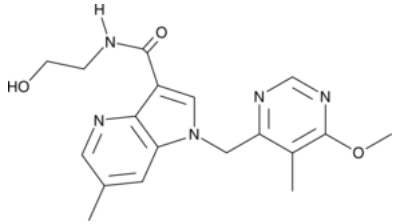
Otsuka

OPC-167832



TB ALLIANCE

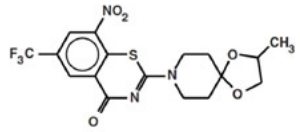
TBA-7371



Covalent binding DPRE1 inhibitors

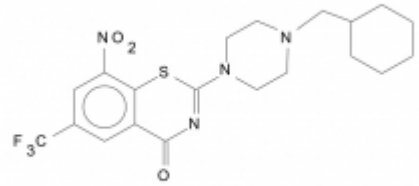
LEIBNIZ HKI LMU

BTZ-043



iM4TB
innovative medicines for tuberculosis

PBTZ-169



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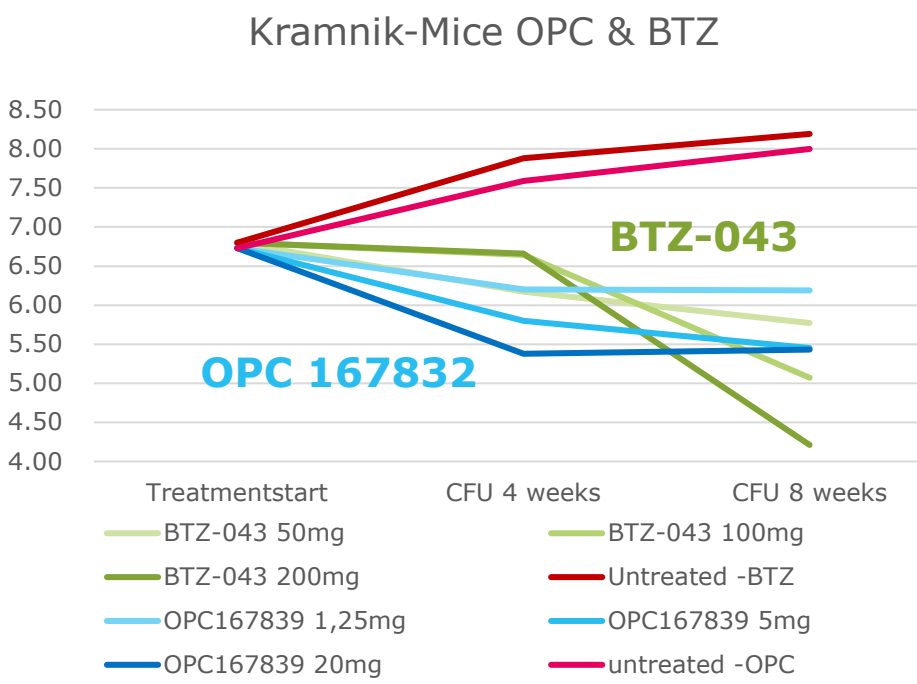
Kramnik Mouse data

Anne Lenaerts / Gregory Robertson

Chronic C3HeB/FeJ (Kramnik) Mouse Model, low dose aerosol infection, 4 resp. 8 weeks- treatment started 8 weeks post infection
Killing kinetic and leasion PK analysis

	Covalent binding DprE-1 Inhibitors						Non-covalent binding DprE-1 Inhibitors					
Killing rates in mouse lungs	BTZ-043			PBTZ169			OPC167832			TBA-7371		
Dose (mg/Kg)	**50**	**100**	**200**	**25**	**50**	**100**	**1,25**	**5**	**20**	**50**	**100**	**200**
0-8 weeks log10 CFU/ml*d	0,019	0,031	**0,046**	-0.010	0.004	0.005	0,008	0,028	0,031	-0.008	0.011	0.004
0-4 weeks log10 CFU/ml*d	0,023	0,006	0,007	-0.025	-0.037	-0.030	0,016	0,032	**0,052**	-0.014	0.000	0.008
4-8 weeks log10 CFU/ml*d	0,015	0,056	**0,086**	0.005	0.047	0.041	-0,001	0,024	0,01	-0.001	0.021	-0.001



BTZ-043 has the strongest bactericidal activity over 8 weeks

Comparative Analysis of Pharmacodynamics in the C3HeB/FeJ Mouse Tuberculosis Model for DprE1 Inhibitors TBA-7371, PBTZ169, and OPC-167832.Robertson GT, et. al.
Antimicrob Agents Chemother. 2021 Oct 18;65(11):e0058321. doi: 10.1128/AAC.00583-21. Epub 2021 Aug 9.

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Phase Ib-IIa study design

Rod Dawson, Kim Narunsky, Andreas Diacon & Veronique de Jager

250 mg Tablet

Stage 1 = Phase Ib *Continual reassessment method*

24 patients total

3 patients each dose, no control
High caloric meal on day 14

2000 mg
1750 mg
1500 mg
1250 mg
1000 mg
750 mg
500 mg
250 mg

Safety review ahead of every dose escalation by PI, Stats and Sponsor (clinic, lab, ECG)

Review of full data set, including efficacy and PK

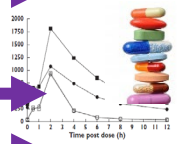
Three doses selected for stage 2: 250/500/1000 mg

Decision for a standard breakfast

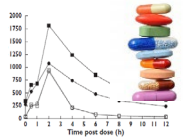
Stage 2: 250/500/1000 mg BTZ (with a Standard breakfast) were taken further

54 patients total

14 patients each dose,
11 controls



DDI: probe cocktail or dolutegravir



14th November 2019 — November 2020

Feb 2021 – Feb 2022

Food effect observed

No effect on Dolutegravir, Caffeine, Digoxin, Dextromethorphan, Midazolam. Weak inhibition of Tolbutamide

DDI-results: comparison of AUC_{0-24h} on day 0 (without BTZ) and day14 (with BTZ), by Lindsey teBrake, Chaima Mouhdad

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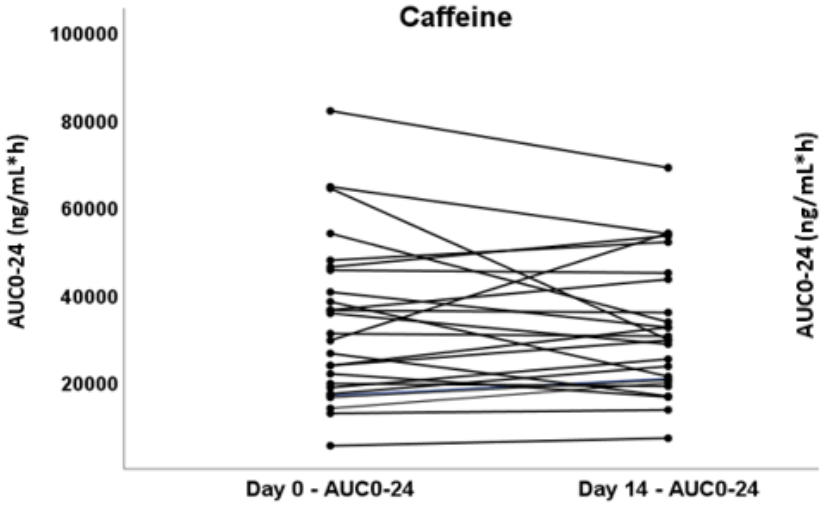
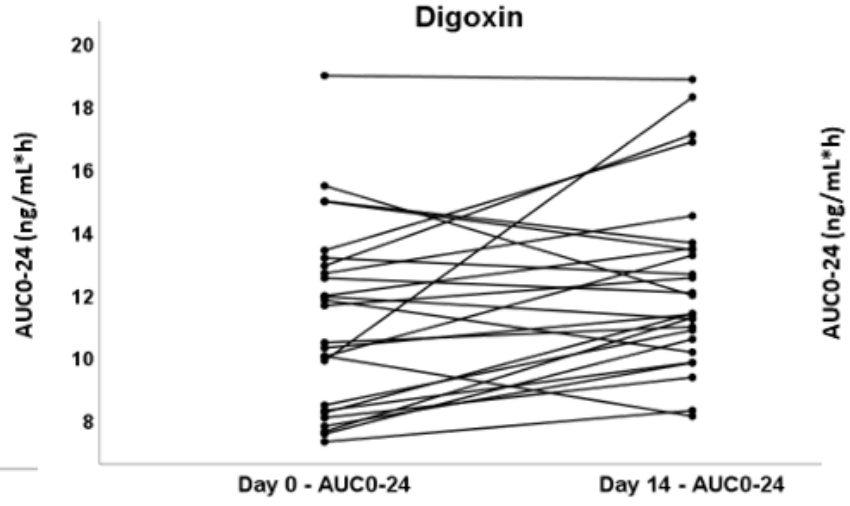
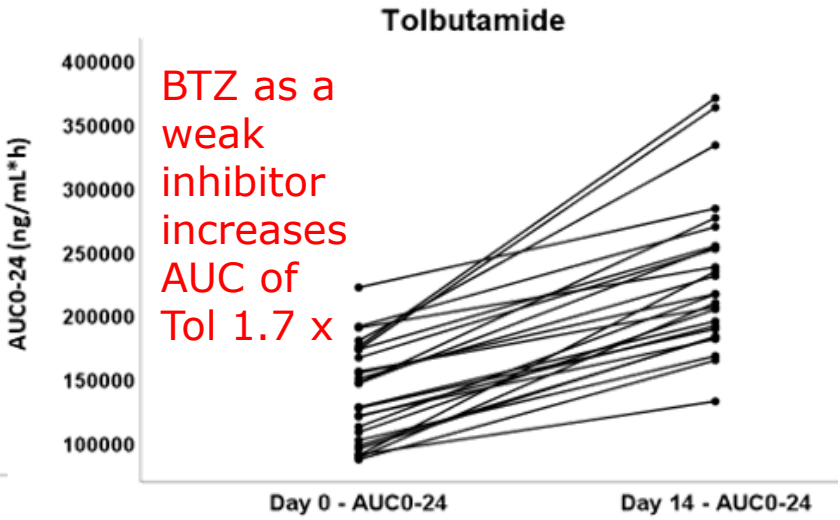
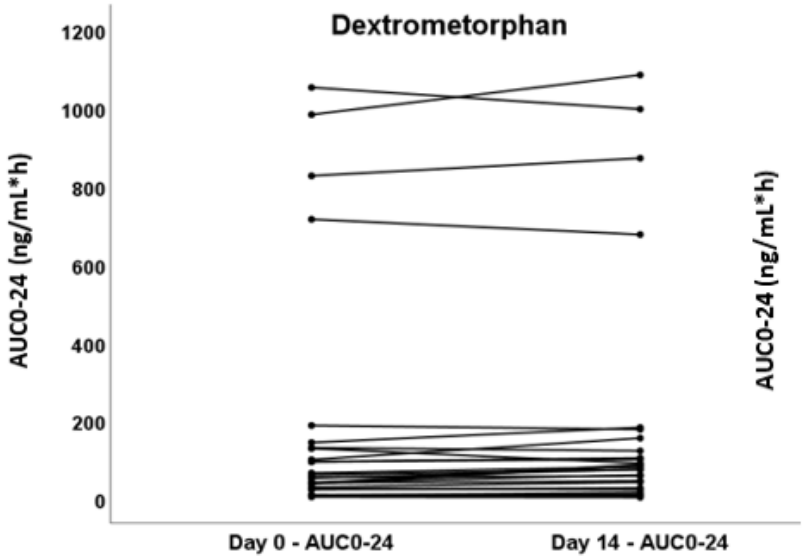
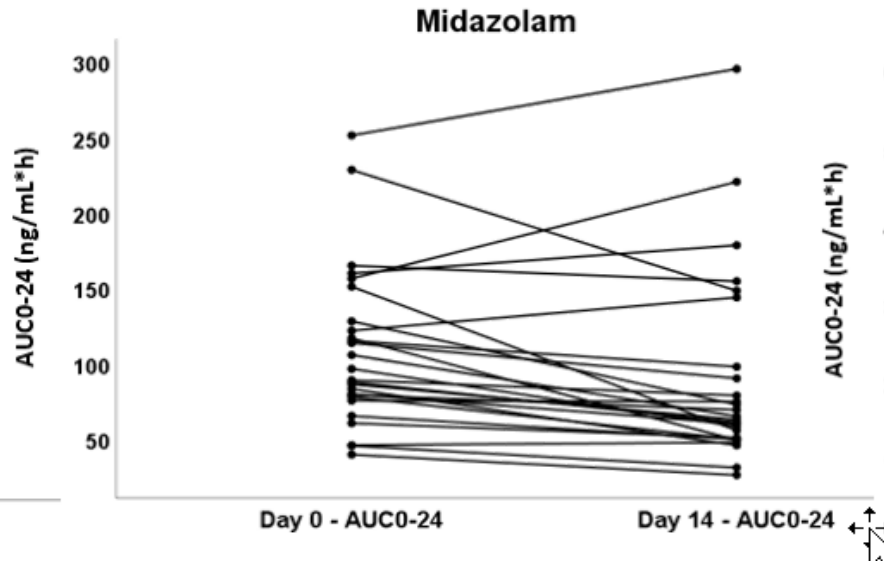


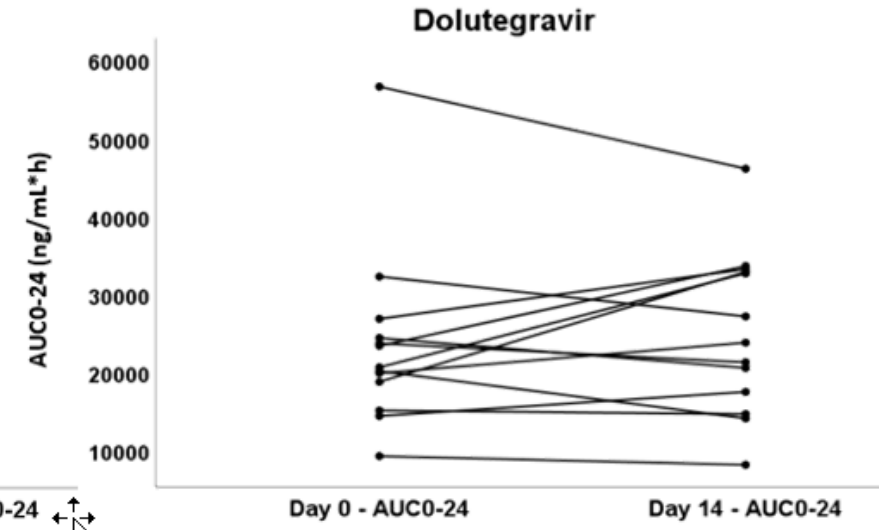




BTZ as a weak inhibitor increases AUC of Tol 1.7 x







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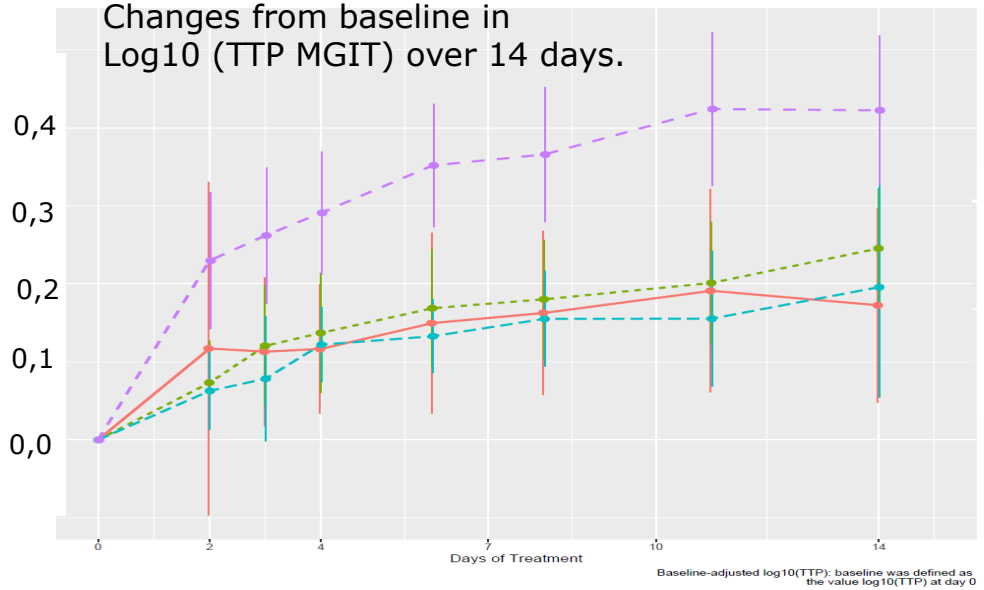
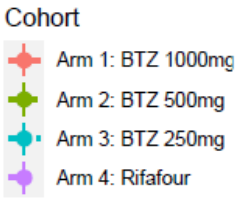
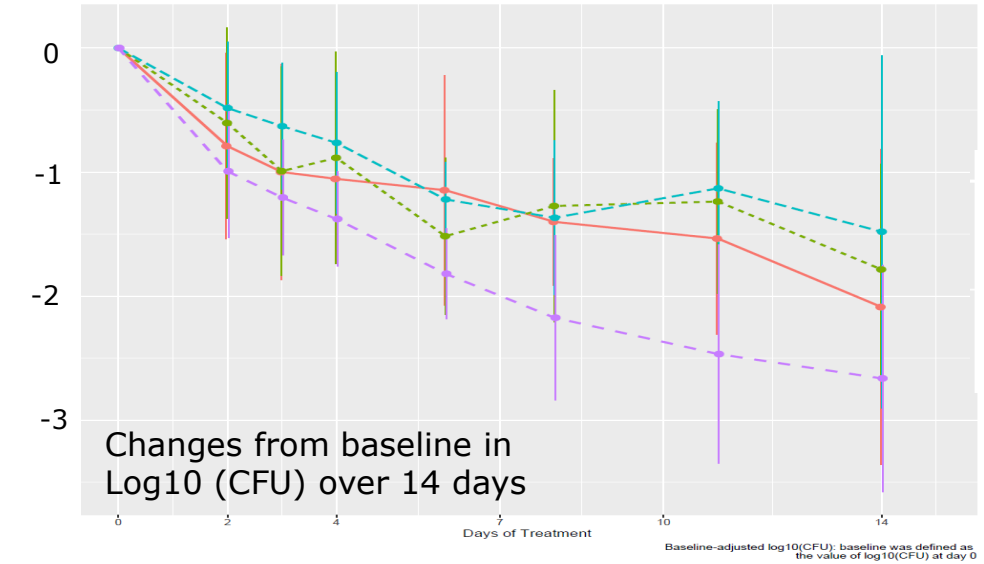
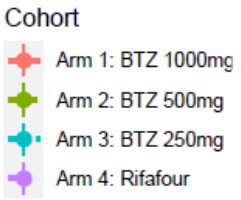
EBA studies (final results)

Andreas Diacon & Rod Dawson, Molly Gong & Patrick Phillips, Elin Svensson









Cohort	MGIT Estimates (95% CI)	CFU Estimates (95% CI)
HRZE control	0.028 (0.022, 0.034) N = 9	-0.179 (-0.241, -0.117) N = 8
BTZ 250	0.013 (0.008, 0.018) N = 15	-0.101 (-0.151, -0.050) N = 13
BTZ 500	0.015 (0.010, 0.019) N = 13	-0.100 (-0.152, -0.047) N = 11
BTZ 1000	0.013 (0.008, 0.018) N = 16	-0.115 (-0.162, -0.069) N = 14
Rifampicin (10mg/kg):	0.020 (0.016, 0.025) N=15	-0.093 (-0.126, -0.059) N=15

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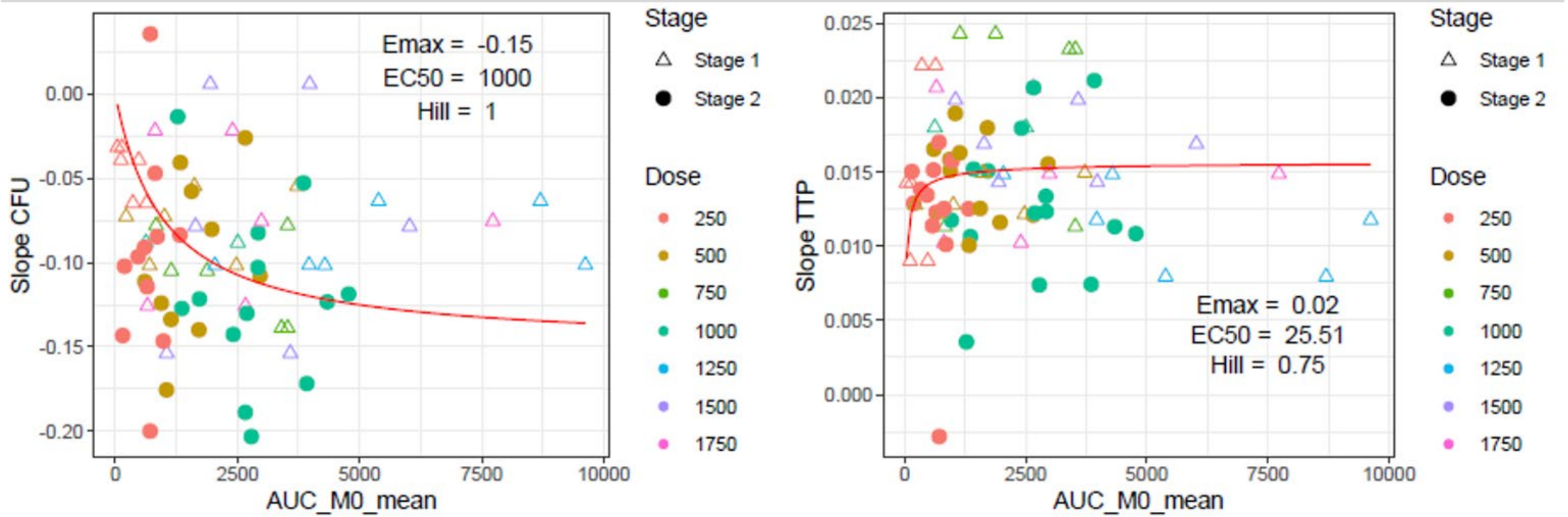
Dose &exposure response in EBA

Molly Gong &Patrick Phillips, Elin Svensson



Special thanks to …

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Patrick Philipps

Michael Hoelscher
Julia Dreisbach
Susanne Schulz
Christina Froehlich
Petra Groß-Demel
Norbert Heinrich
Wandini Lutchmun
Leoni Matt

Andreas Diacon
Veronique de Jager
Atica Mosa
Will Oosthuysen

Anne Lenaerts
Gregory Robertson

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Phase Ib / IIa: DDI results

Andreas Diacon &Rod Dawson, Molly Gong &Patrick Phillips, Elin Svensson, Lindsey teBrake, Chaima Mouhdad

Table: DDI (weak inhibition by BTZ) shown only for Tolbutamide

N=15 for Dolutegravir N=29 for the other drugs	Geometric mean AUC0-24 (ng*h/ml)		Ratio (%) Weak inhibitor: ≥125 - 200
	Day 0	Day 14	
Caffeine (CYP1A2 and NAT2)	27525.79	28204.89	102.47
Dextromethorphan (CYP2D6)	74.86	81.70	109.15
Digoxin (p-glycoprotein/ OATP4C1)	10.28	12.06	117.29
Midazolam (CYP3A)	91.26	74.79	81.96
Tolbutamide (CYP2C9/OAT2)	135063.73	223382.69	165.39
Dolutegravir (UGT 1A1)	20310.00	22860.80	112.56

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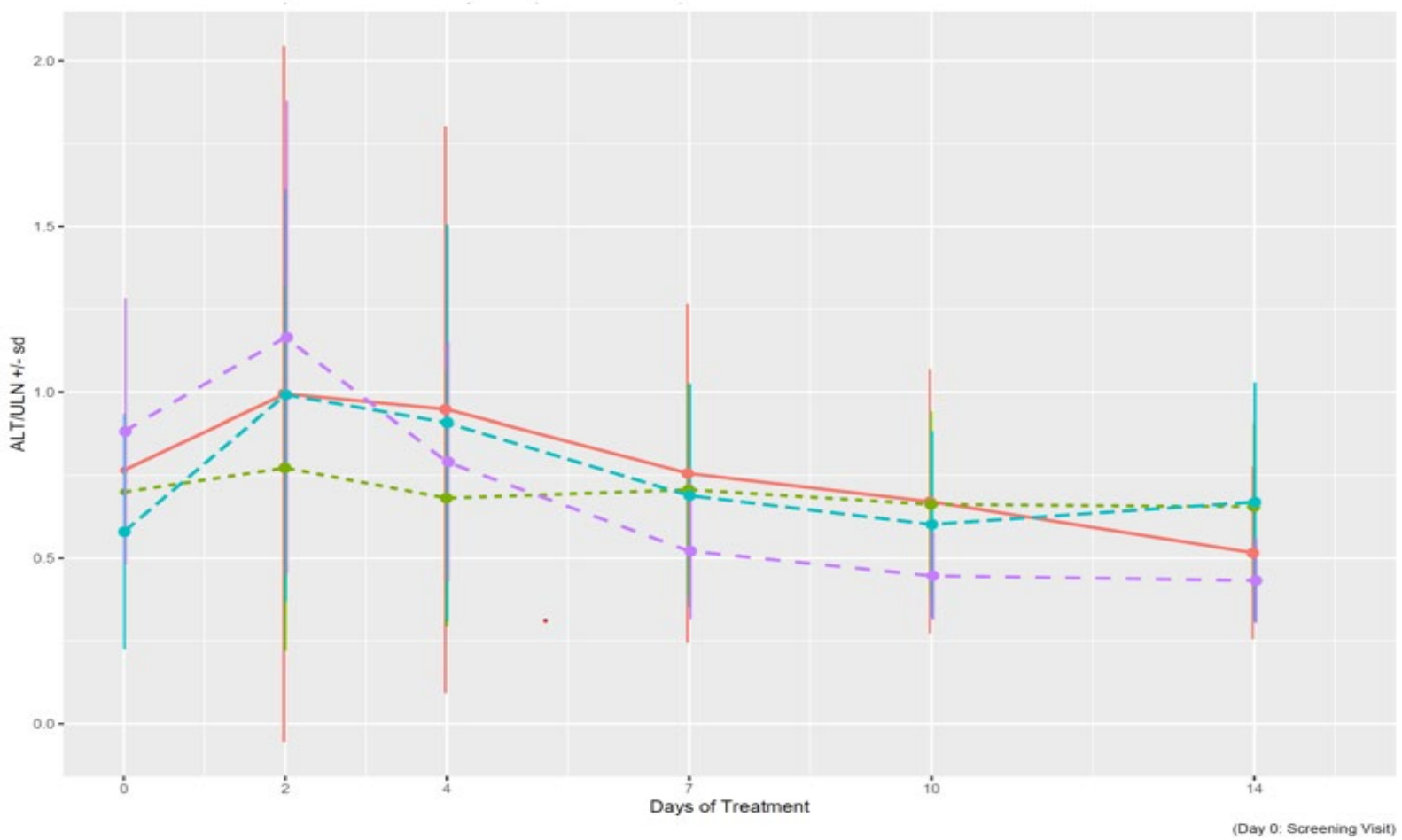
Phase Ib / IIa safety data ALT

Alalinaminotransferase ALT Mean Value(Units of × ULN), N=54 patients in stage 2

Figure: Stage 2 Mean Value of ALT times ULN by Cohort



1000 mg BTZ
500 mg BTZ
250 mg BTZ
HRZE