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PanACEA

EDCTP

This project is part of the EDCTP2 programme supported by the European Union

PanACEA SUDOCU trial: sutezolid as part of a 4-drug combination

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On behalf of the PanACEA consortium

NIMR - MMRC
Mbeya Medical Research Center

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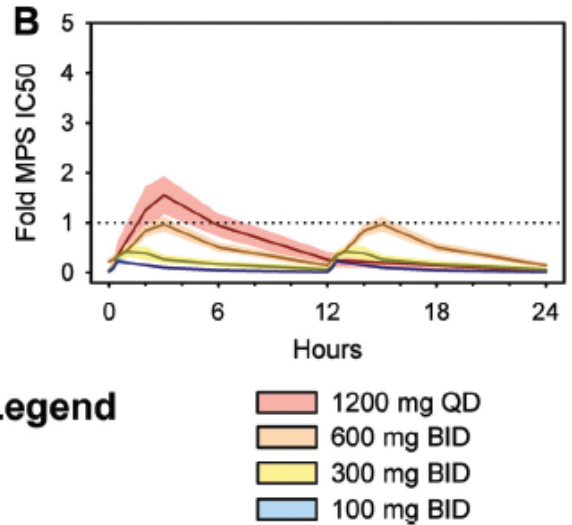
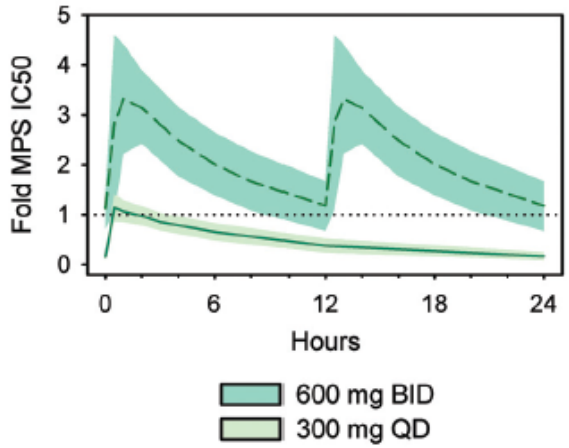
Sutezolid – better and safer than Linezolid?

- Sutezolid – an oxazolidinone drug candidate developed by Sequella and Global TB Alliance
- Previously evaluated up to phase 2A (14d montherapy)
- Less mitochondiral toxicity predicted
- 7 sutezolid-treated subjects (14%) experienced mild or moderate increases in alanine transaminase (grade 1-2; Wallis, 2014)

Sutezolid (STZ)



Linezolid (LZD)



MPS IC50:

- sutezolid 15.5 µg/ml
- major metabolite 4.4 µg/ml
- minor metabolite 6.7 µg/ml

- Linezolid 5.5 µg/ml

Metabolism: CYP3A4, flavine monooxagenases

Wallis RS, Antimicrob Agents Chemother. 2011 Feb;55(2):567-74.

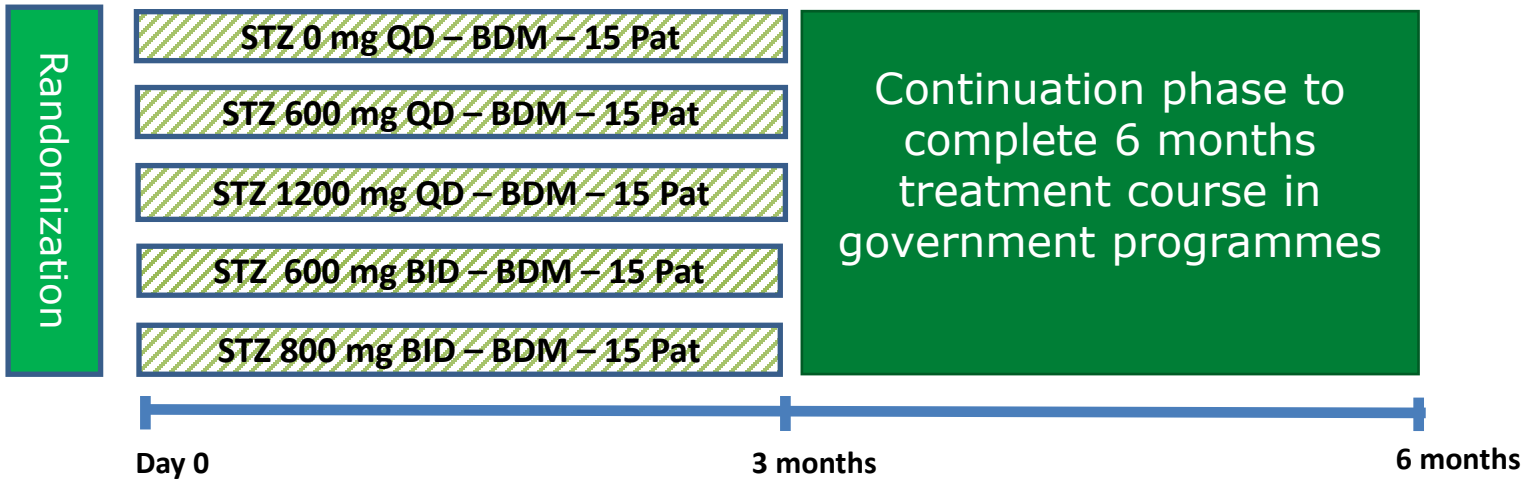
SUDOCU – sutezolid dose-finding and combination development

Objectives:

- Exposure – response modelling
- Exposure - toxicity modelling
- Select sutezolid dose with good safety and efficacy
- Assess CYP 3A4 enzyme induction potential

Primary Endpoint:

- Change in bacterial load as measured by MGIT TTP, over 12 weeks



STZ – sutezolid. BDM – bedaquiline, delamanid, moxifloxacin at standard doses.

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The PanACEA consortium – SUDOCU Partners

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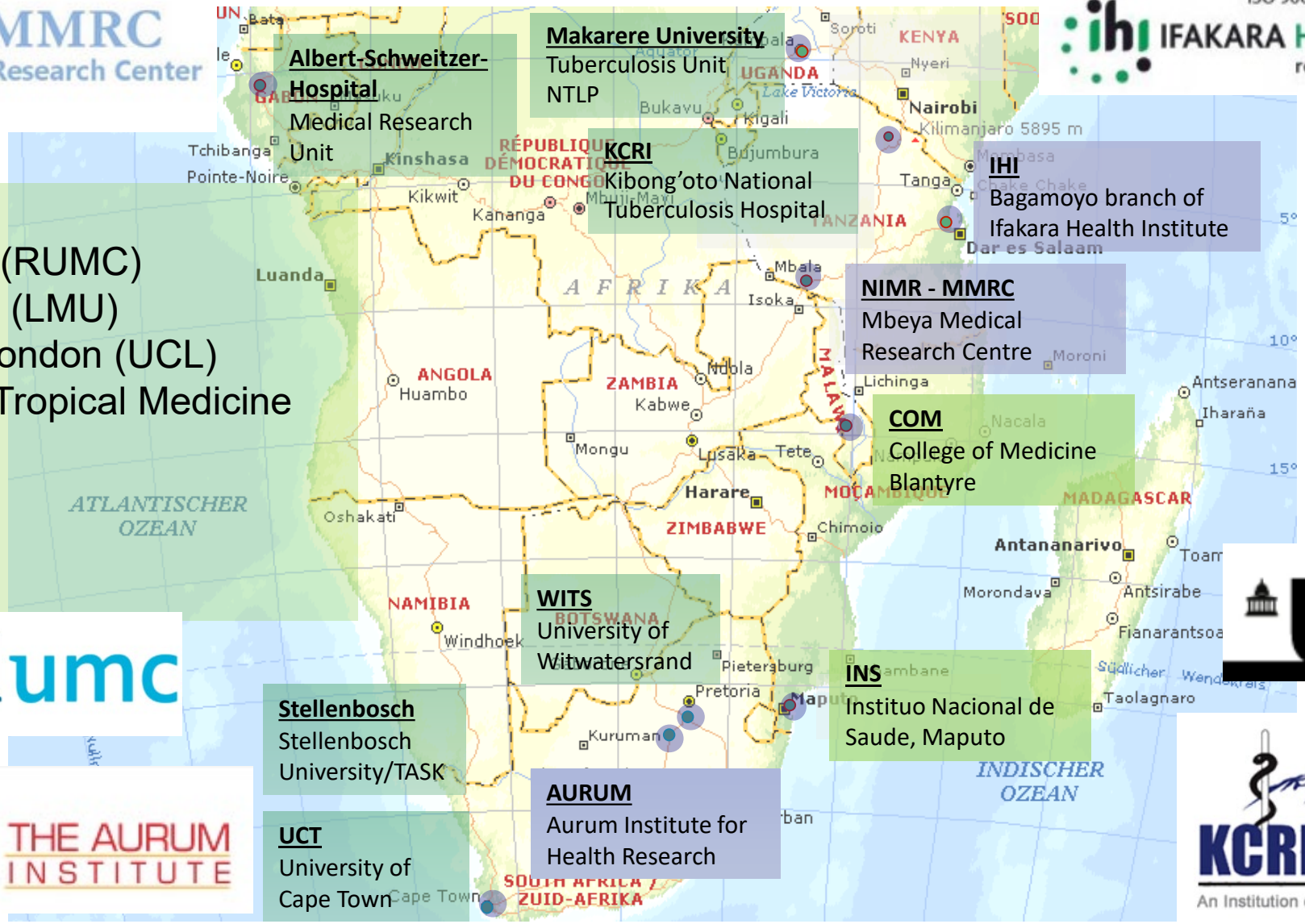
Northern Partners:

- Radboud University (RUMC)
- University of Munich (LMU)
- University College London (UCL)
- Liverpool School of Tropical Medicine
- Swiss TPH
- UCSF
- Sequella, Inc
- Otsuka



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Participant characteristics

N (%) unless otherwise stated	Arm 1: U0	Arm 2: U600	Arm 3: U1200	Arm 4: U600BD	Arm 5: U800BD	Total
Total randomized	16	15	14	15	15	75
Sex						
Female	3 (18.8%)	4 (26.7%)	3 (21.4%)	5 (33.3%)	4 (26.7%)	19 (25.3%)
Male	13 (81.2%)	11 (73.3%)	11 (78.6%)	10 (66.7%)	11 (73.3%)	56 (74.7%)
Age						
Median [Min, Max]	30.0 [20.0, 54.0]	33.0 [21.0, 48.0]	35.0 [22.0, 53.0]	36.0 [22.0, 58.0]	34.0 [22.0, 54.0]	33.0 [20.0, 58.0]
Race						
Black	16 (100%)	15 (100%)	14 (100%)	15 (100%)	15 (100%)	75 (100%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity						
Hispanic or Latino	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Hispanic or Latino	16 (100%)	15 (100%)	14 (100%)	15 (100%)	15 (100%)	75 (100%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Weight						
Median [Min, Max]	54.9 [45.0, 75.5]	50.0 [43.6, 65.0]	55.2 [47.0, 76.5]	54.8 [42.2, 75.0]	49.1 [42.5, 65.0]	53.0 [42.2, 76.5]
HIV Status*						
Positive	1 (6.7%)	0	0	1 (11.1%)	0	2 (2.7%)
Negative	14 (93.3%)	15 (100.0%)	14 (100.0%)	14 (93.3%)	15 (100.0%)	72 (97.3%)

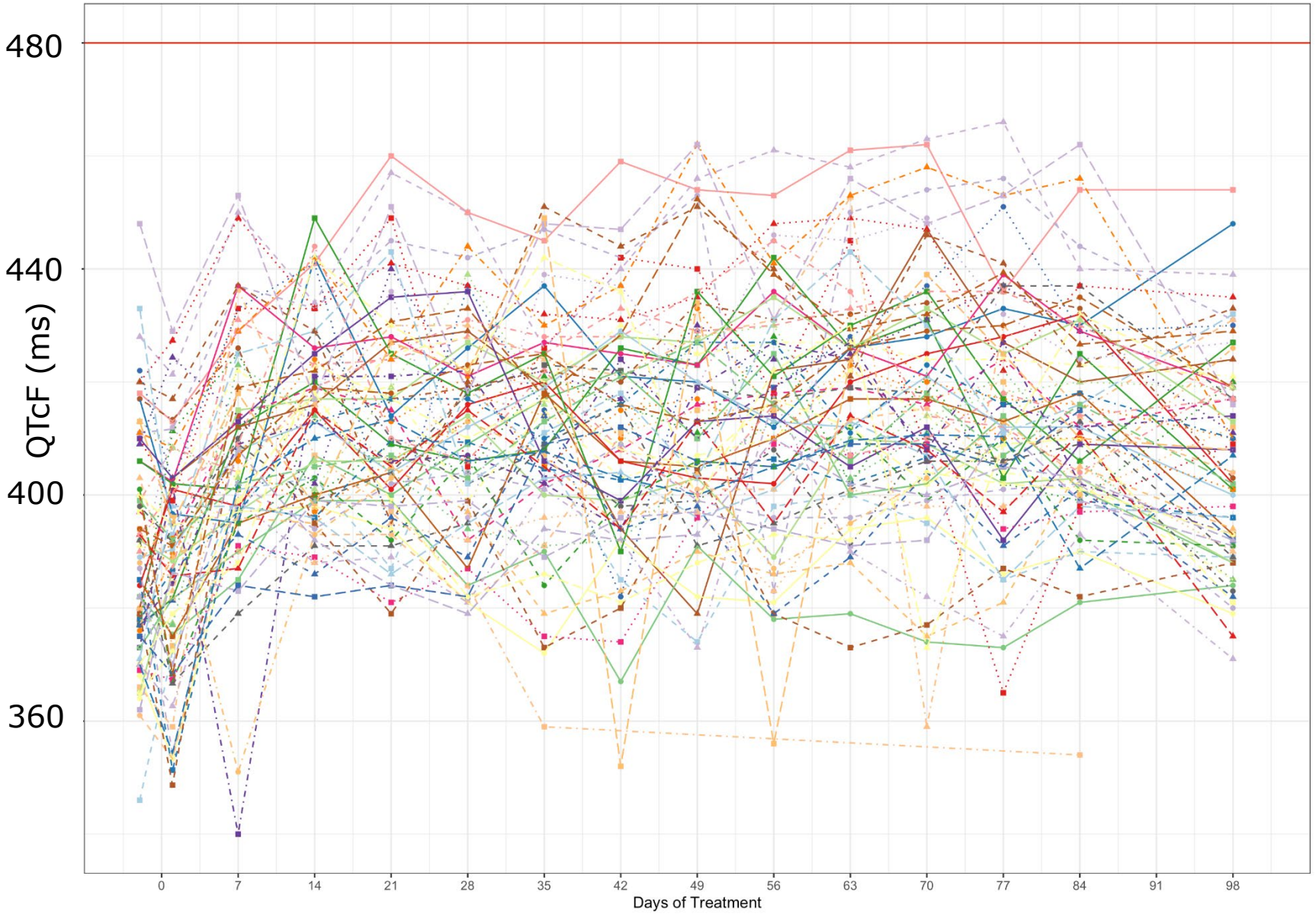
*No HIV info for patient 103026

Safety

	Arm 1: U0	Arm 2: U600	Arm 3: U1200	Arm 4: U600 BD	Arm 5: U800 BD	Total
Total randomized	16	15	14	15	15	75
Number of AEs reported	10	12	12	22	8	64
Number of Participants with AEs	6 (37.5%)	5 (33.3%)	7 (50%)	7 (46.7%)	4 (26.7%)	29 (38.67%)
Number of SAEs reported	0	1	2	5	1	9
Number of Participants with SAEs	0	1 (6.67%)	1 (7.1%)	4 (26.7%)	1 (6.67%)	7 (9.3%)
Number of AEs by Severity	**Arm 1: U0**	**Arm 2: U600**	**Arm 3: U1200**	**Arm 4: U600 BD**	**Arm 5: U800 BD**	**Total**
Grade 1: Mild	5	2	2	4	1	14
Grade 2: Moderate	3	7	5	9	3	27
Grade 3: Severe	1	2	5	5	4	17
Grade 4: Life Threatening	1	1	0	3	0	5
Grade 5: Death	0	0	0	1	0	1

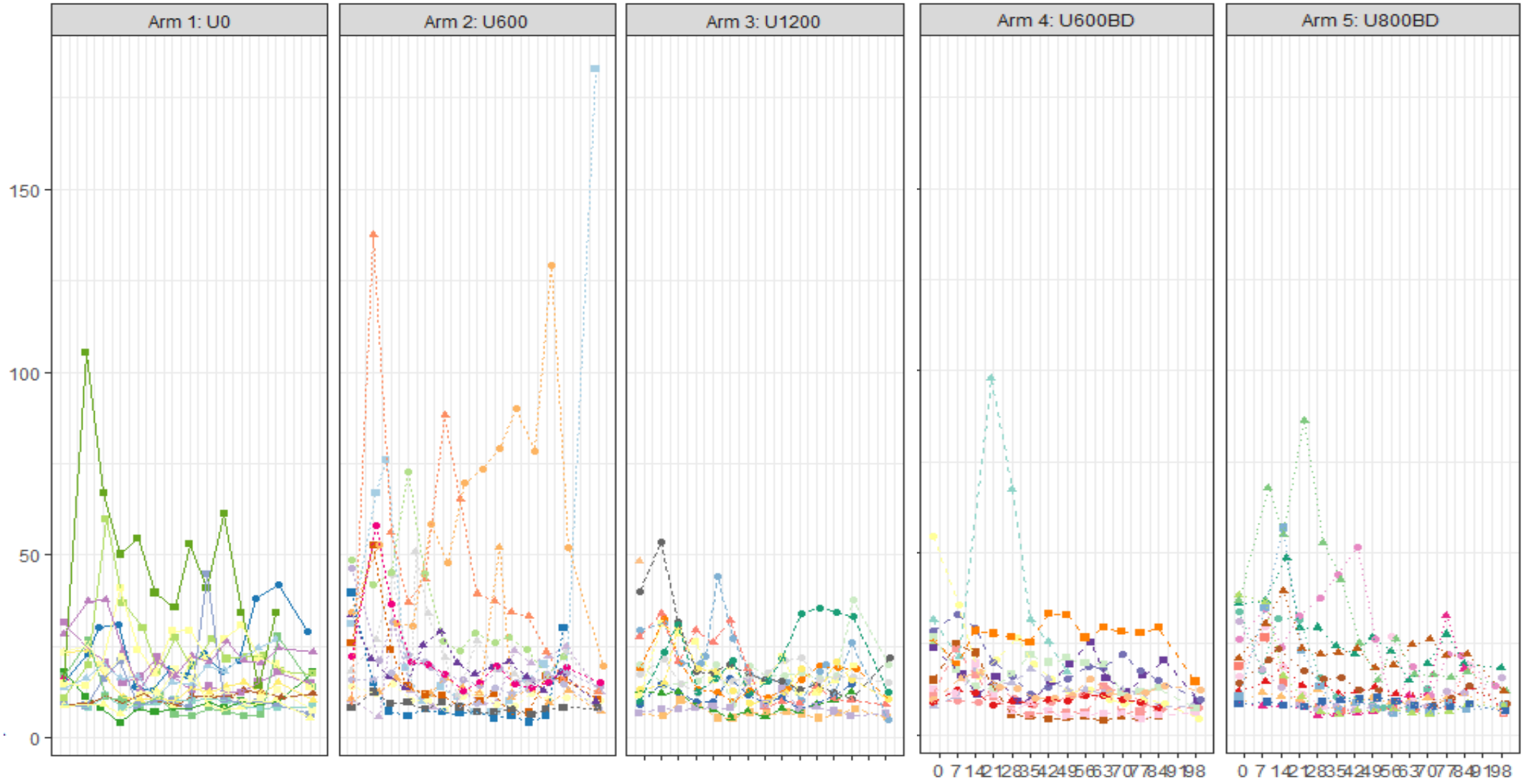
- NO neuropathy
- 1 grade 4 neutropenia - 600BD (possible „benign ethnic neutropenia“)
- 1 grade 4 DILI - 600 BD
- 1 COVID-19 related death - 600 BD
- 4 events of QT prolongation >60ms (no prolongation >500ms absolute)

QTcF intervals

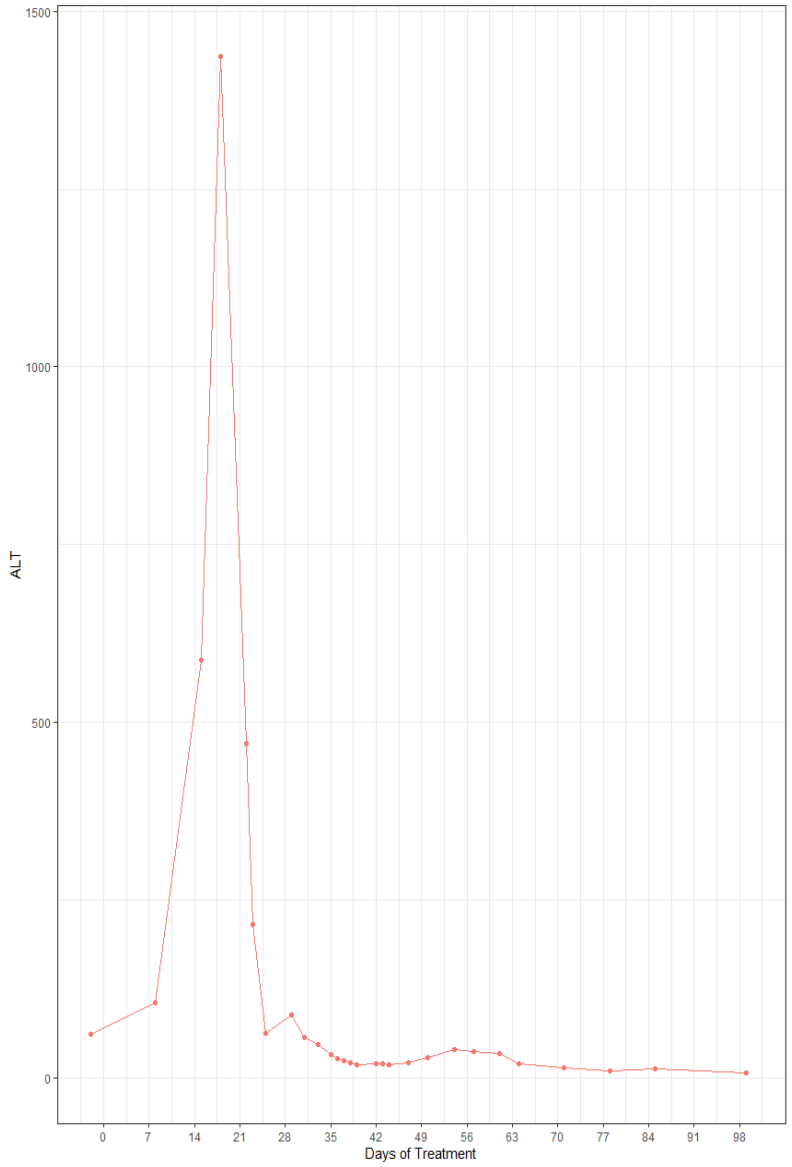


AESIS: Hepatic safety - ALT (U/l)

preliminary – please don‘ t distribute



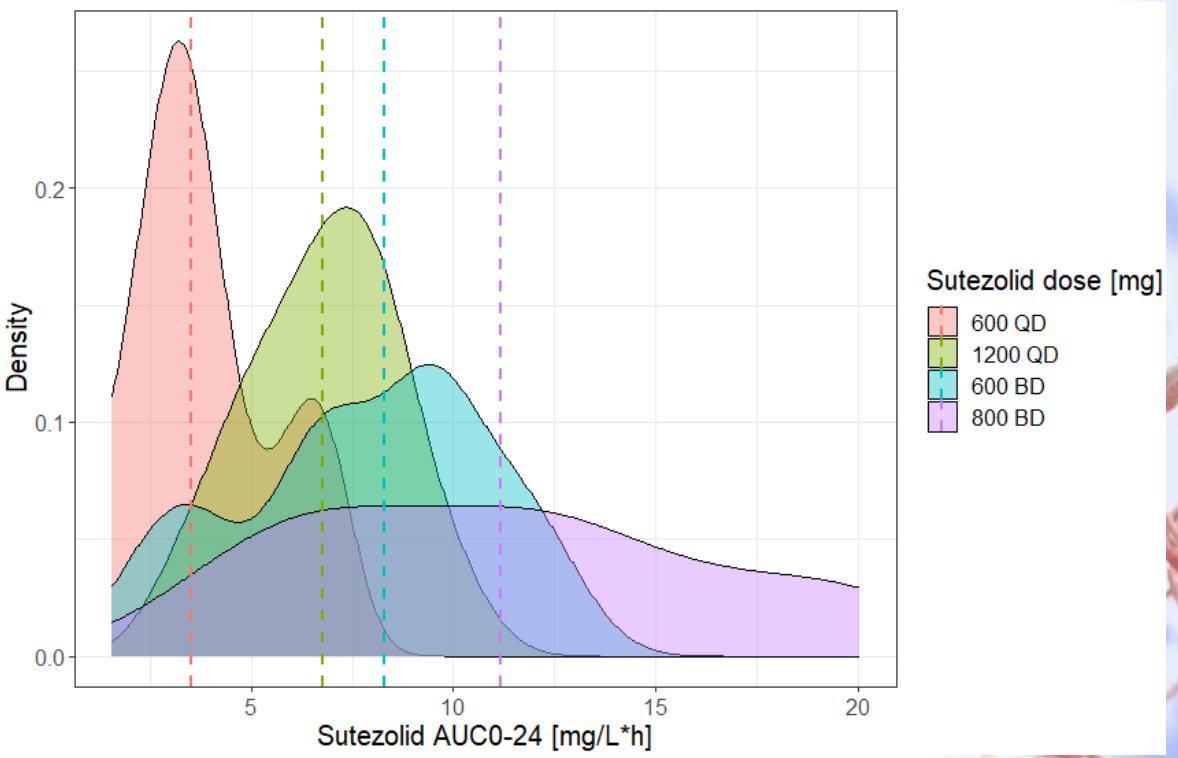
Hepatic safety: ALT (U/l) – Grade 4 Hepatotoxicity



Pharmacokinetics

- Exposure metrics derived from population pharmacokinetic model

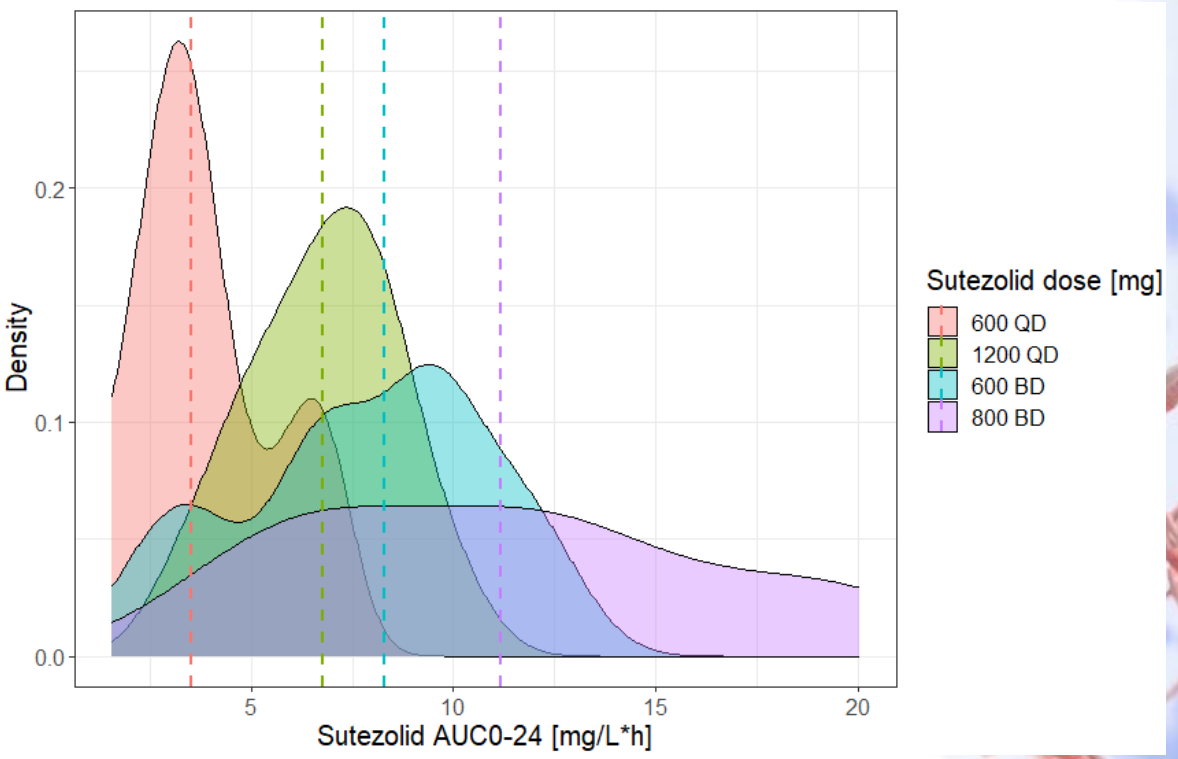
Sutezolid dose	Median Sutezolid AUC0-24 (min-max) [mg/L*h]	Median Sutezolid Cmax (min-max) [mg/L]	Median Sutezolid-Sulfoxide AUC0-24 (min-max) [mg/L*h]	Median Sutezolid-Sulfoxide Cmax (min-max) [mg/L]
600 mg QD	3.52 (1.56-6.85)	0.59 (0.19-1.27)	18.25 (12.98-24.21)	2.35 (1.36-3.01)
1200 mg QD	6.79 (3.35-9.91)	1.04 (0.59-1.42)	33.13 (23.21-47.61)	3.67 (2.76-5.87)
600 mg BD	8.29 (2.36-12.36)	0.84 (0.29-1.14)	35.00 (20.92-50.95)	3.04 (1.48-3.67)
800 mg BD	11.18 (4.42-20.04)	1.05 (0.39-1.71)	48.50 (27.11-82.01)	3.68 (1.62-5.60)



Pharmacokinetics

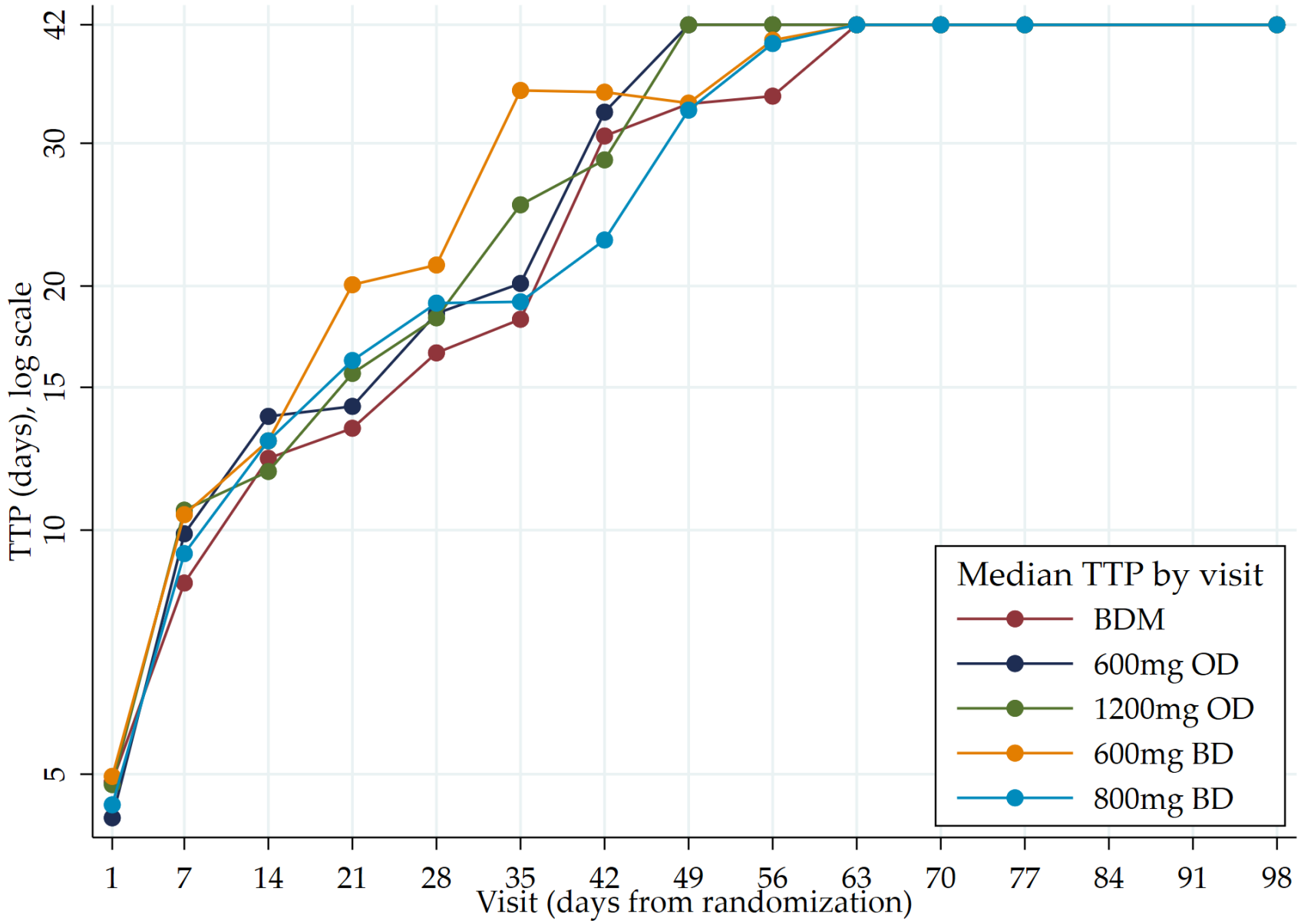
- Exposure metrics derived from population pharmacokinetic model

Sutezolid dose	Median Sutezolid AUC0-24 (min-max) [mg/L*h]	Median Sutezolid Cmax (min-max) [mg/L]	Median Sutezolid-Sulfoxide AUC0-24 (min-max) [mg/L*h]	Median Sutezolid-Sulfoxide Cmax (min-max) [mg/L]
600 mg QD				
1200 mg QD	6.79 *(7.13)**	1.04 *(1.97)**	33.13 *(36.82)**	3.67 *(7.05)**
600 mg BD	8.29 *(6.49)**	0.84 *(0.97)**	35.00 *(39.1)**	3.04 *(4.36)**
800 mg BD				



* Wallis RS, Antimicrob Agents Chemother. 2011 Feb;55(2):567-74

Primary efficacy Endpoint: Median TTP (ITT population)



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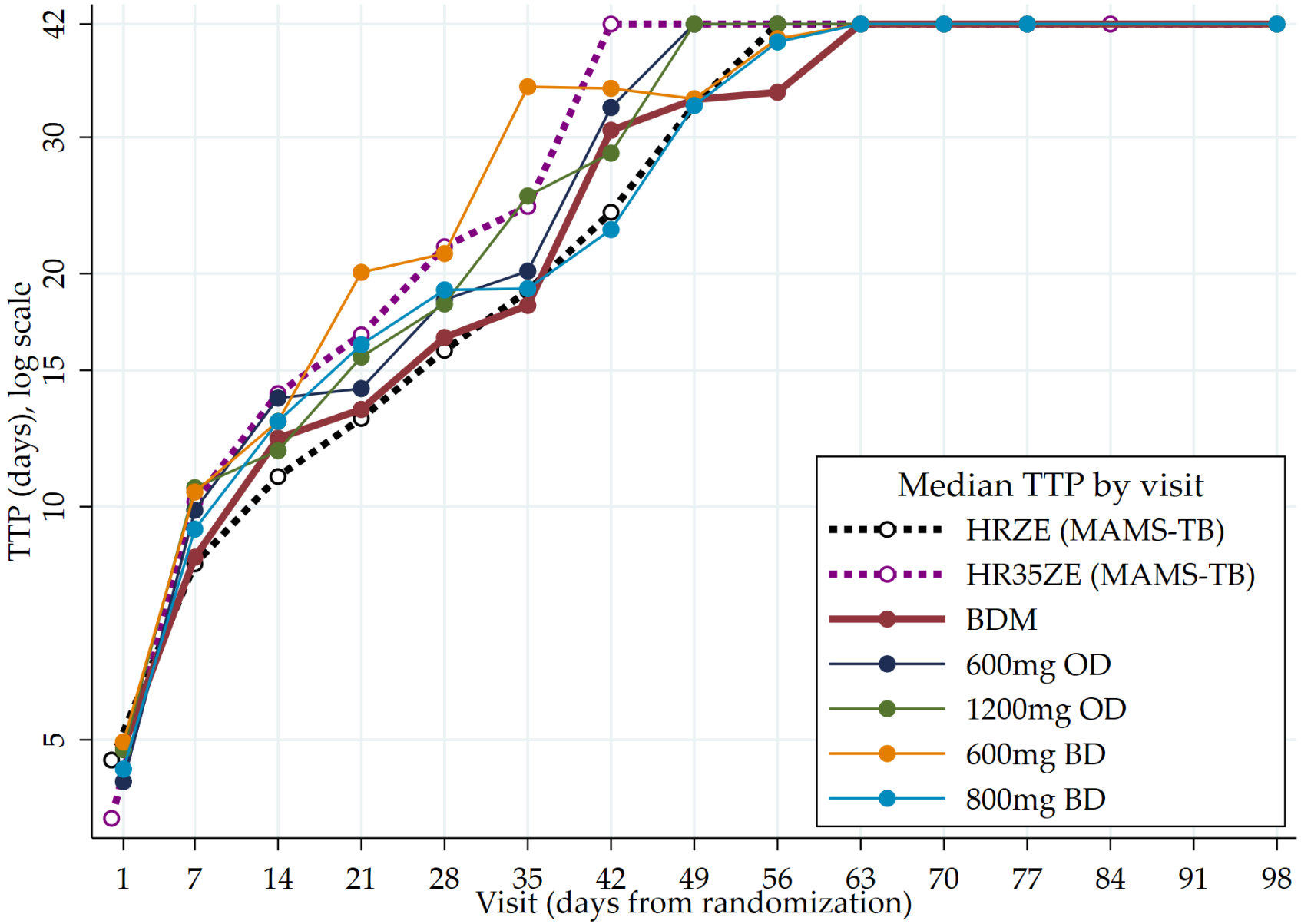
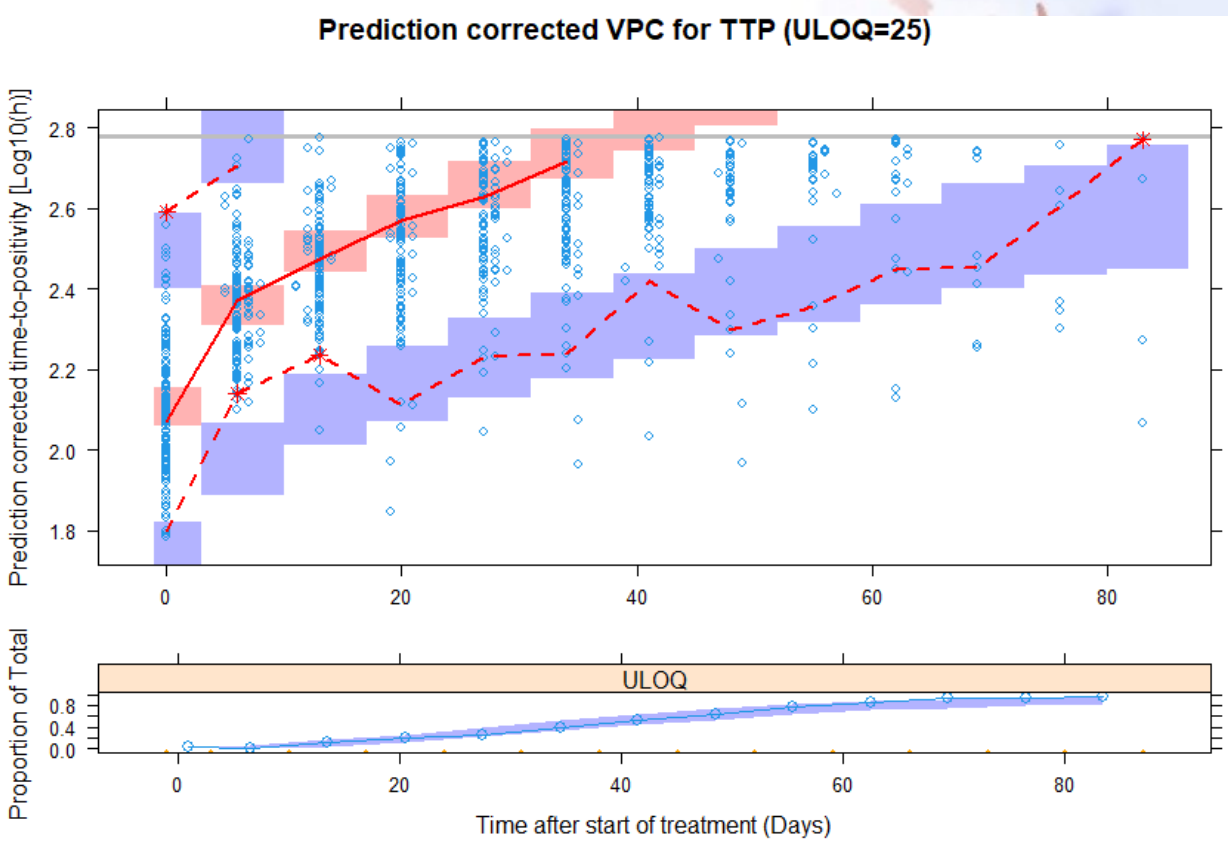


!!MAMS trial: historical comparison from similar sites, similar patient population!!

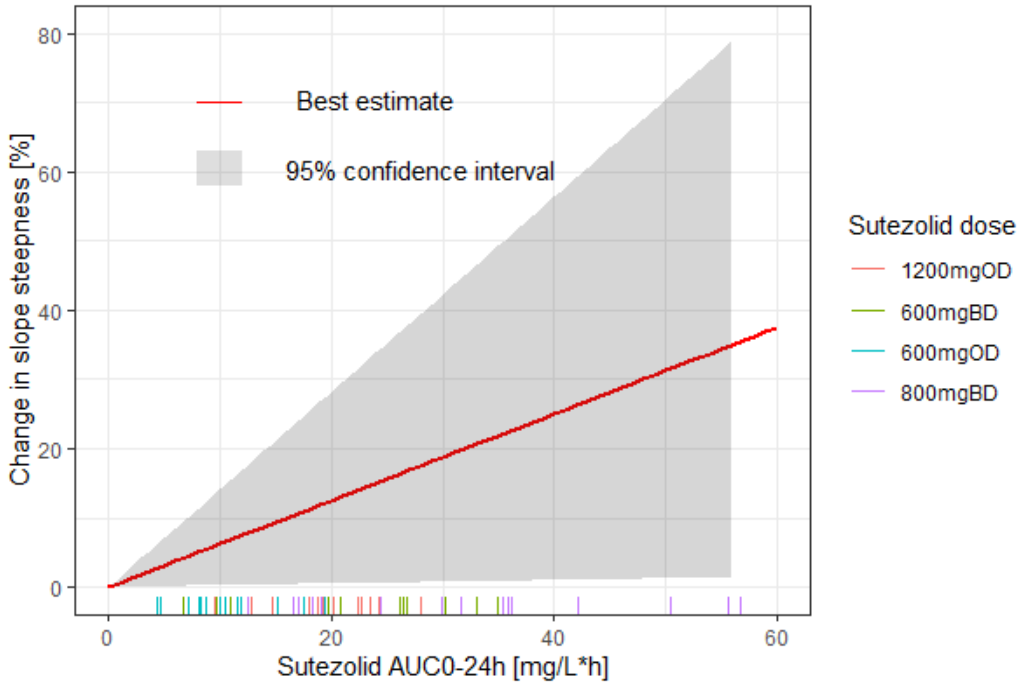
Exposure-response modelling - methods

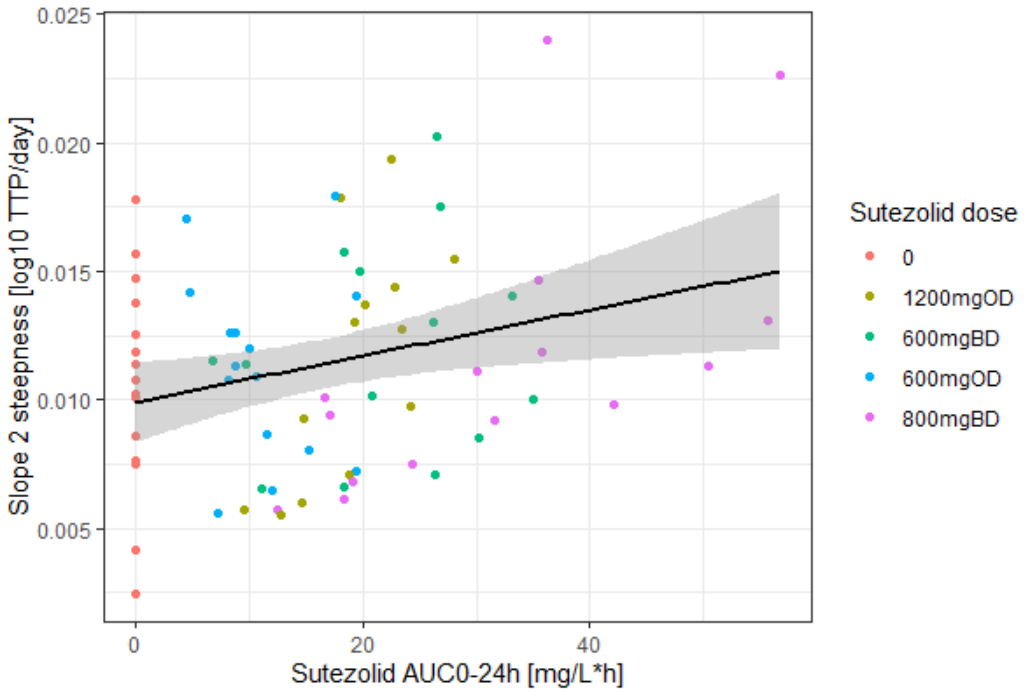
- Mixed-effects methodology
- TTP continuous variable censored at **25** or 42 days
- Bi-linear model with estimated node point at ~8 weeks
- Negative values included with model for probability of being above censoring limit



Exposure-response modelling

- Baseline bacterial load correlated with first slope (p = 0.008)
- Ralph-score quantifying lung damage correlated with second slope (p<0.001)
- Sutezolid AUC0-24h correlated with both slopes (p=0.04)
- Approx 40% steeper slope for highest observed AUCs





Summary

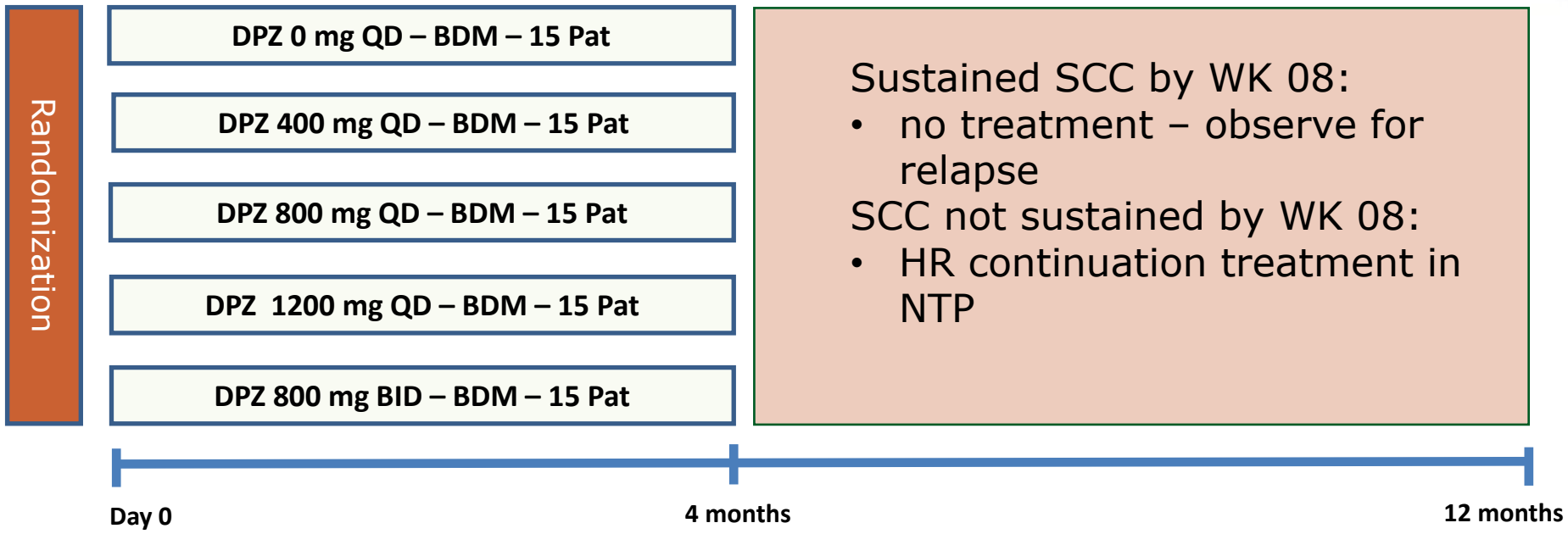
Safety:

- Good safety of the combination +/- sutezolid
- 4 SAEs QTcF prolongation: due to 60ms cutoff; no measurements beyond 470 ms
- 1 case of grade 4 liver toxicity, 1 case of neutropenia

Efficacy:

- BDM backbone similar to HRZE in historical comparison;
- PK-PD: 40% steeper slope for highest observed sutezolid exposures
- Sutezolid added efficacy to BDM
- No plateau in exposure or efficacy seen in SUDOCU

Outlook: DECODE



DPZ - delpazolid. BDM – bedaquiline, delamanid, moxifloxacin at standard doses. SCC: sputum culture conversion.

Objectives:

- Exposure – response modelling
- Exposure - toxicity modelling
- Select delpazolid dose with good safety and efficacy

- LPI Sep 2022
- Soft Database Lock imminent

Thank you for your attention!

Special thanks to:

- Study participants
- The PanACEA consortium, led by Martin Boeree/RUMC
- The PIs and their teams:
- Christina Manyama, MMRC
- Stellah Mpagama, KIIDH/KCRI
- Francis Mhimbira, IHI
- Modulakgotla Sebe, Aurum
- Tim McHugh, Leticia Wildner, UCL
- The LMU team – esp. Larissa Hoffmann
- Sequella, Inc., Otsuka

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