BTZ043: a development update

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German Center for
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Contents of this talk

- Update on BTZ043 preclinical
- Phase 1 & 2a Plans

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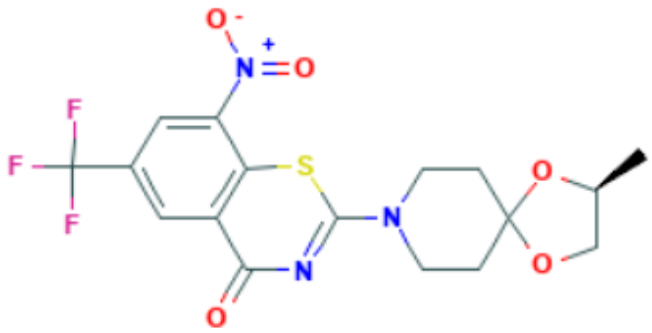
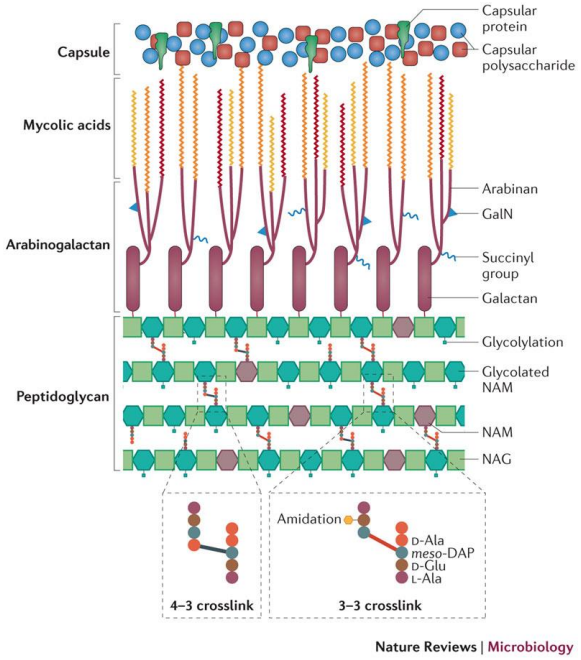
BTZ043

- BTZ043 inhibits the MTB cell wall synthesis by blocking DprE1, which is necessary for the synthesis of arabinofuranose, a component of arabinogalactan and arabinomannan.





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Clinical development plan BTZ043

2006	Filing of BTZ043 patent by Hans-Knöll-Institute (HKI) / Institut Pasteur / V. Makarov
2009	Publication in Science and sublicence to Clondiag / Alere for preclinical development
2010	Filing of PBTZ169 patent by EFPL, S. Cole and V. Makarov
2013	Alere stopps BTZ/PBTZ development
2014	HKI is sole patent holder for BTZ043
2015	Cooperation agreement between HKI + LMU German Center for Infection Research (DZIF) funds finalisation of preclinical development
2017	BfArM (German EMA) scientific advice – Preclinical toxicity complete
	9 Mio € funding for further clinical development until phase IIa by BMBF, DZIF, EDCTP
2017	GMP-Synthesis and GMP drug manufacturing, in Q4 SAD Phase Ia
2018	MAD phase Ib
2019	Phase IIa EBA within PanACEA

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Efficacy of BTZ043 in chronic infection model BALB/c mice dose escalation

Therapy: Start 3 weeks after infection

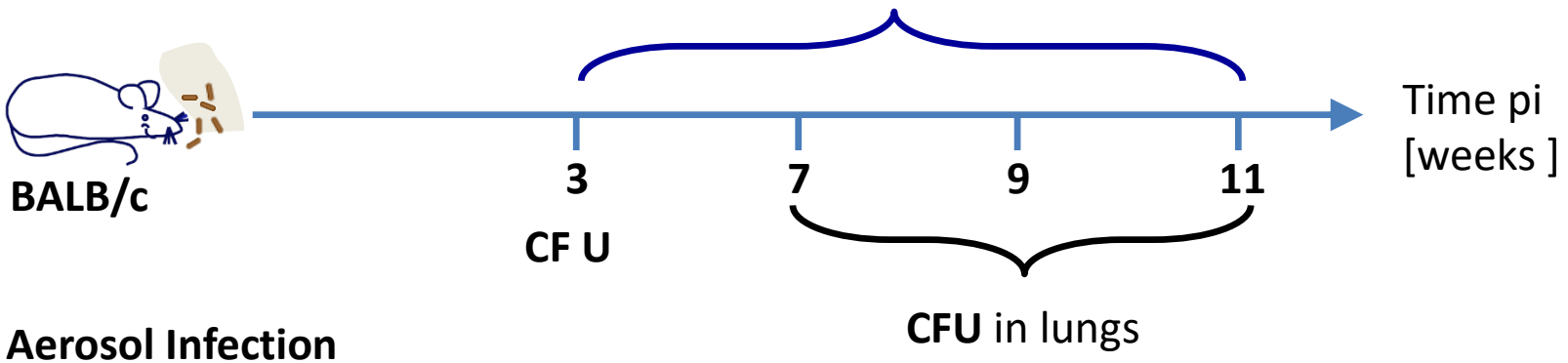
Drug dosages [mg/kg body weight]:

BTZ043 50, 100, 250, 500, 1000

vehicle (1% CMC)

INH 25

Oral administration 5x / week



Aerosol Infection
175 CFU H37Rv

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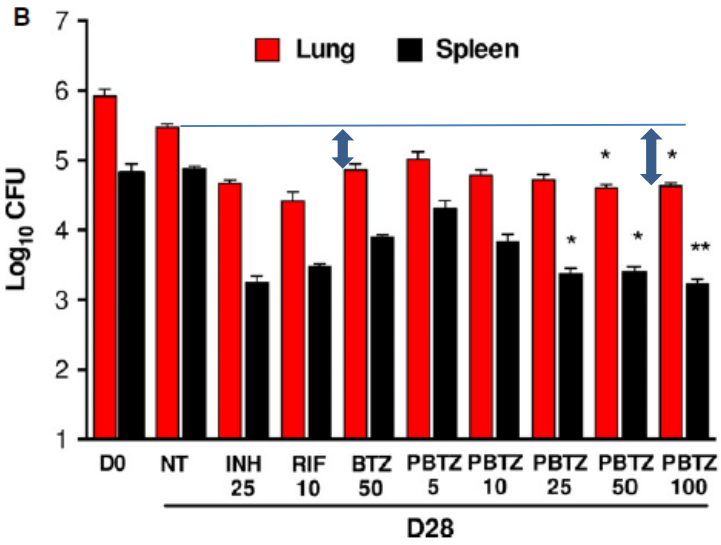
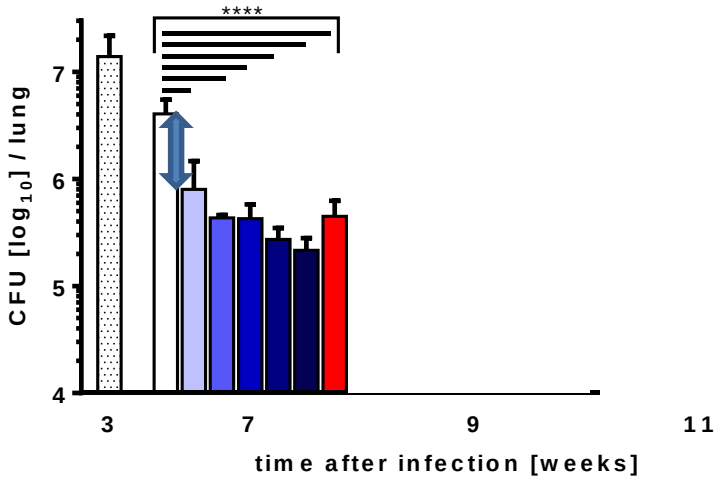
Mouse Models for BTZ043 and PBTZ169

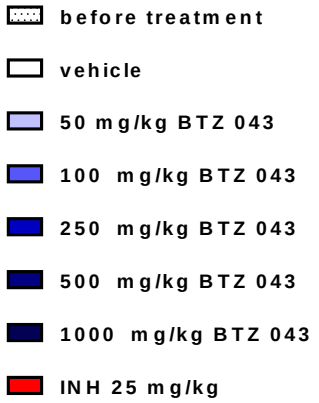
Makarov & Cole
Chronic mouse model
EFPL



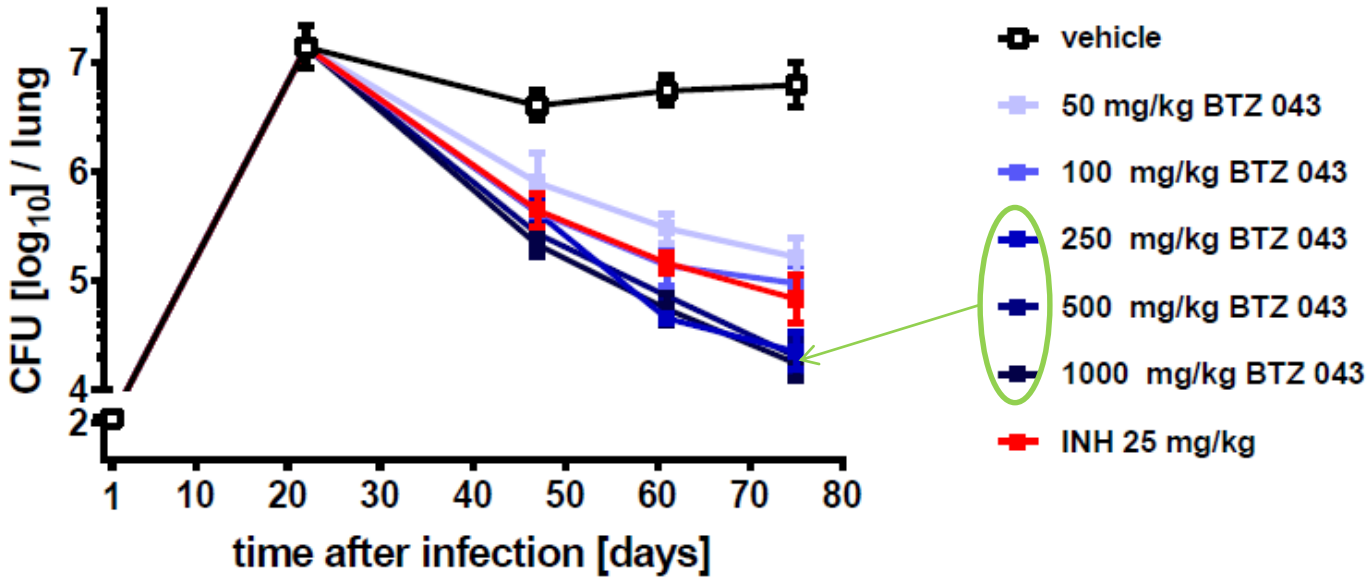
spleen
lung

DZIF
Chronic mouse model
Borstel & Munich





Mouse Models for BTZ043 and PBTZ169



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Safety + Phase 1 plans

- All preclinical toxicology models uncritical
- NOAEL in rats 170 mg/KG
- NOAEL in mini-pigs 360 mg/KG

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Safety + Phase 1 plans

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- NOAEL in rats 170 mg/KG
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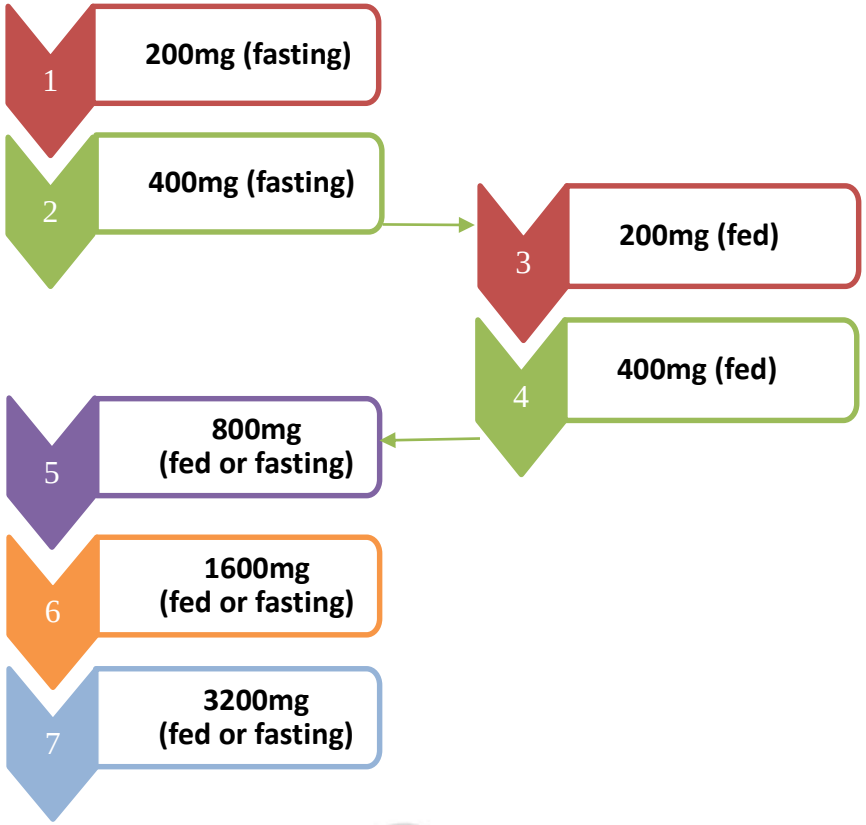
Phase 1a (2017):

- 200 mg
- 400 mg
- 800 mg
- 1600 mg
- 3200 mg



Phase 1b:

- Two well tolerated doses from phase 1a

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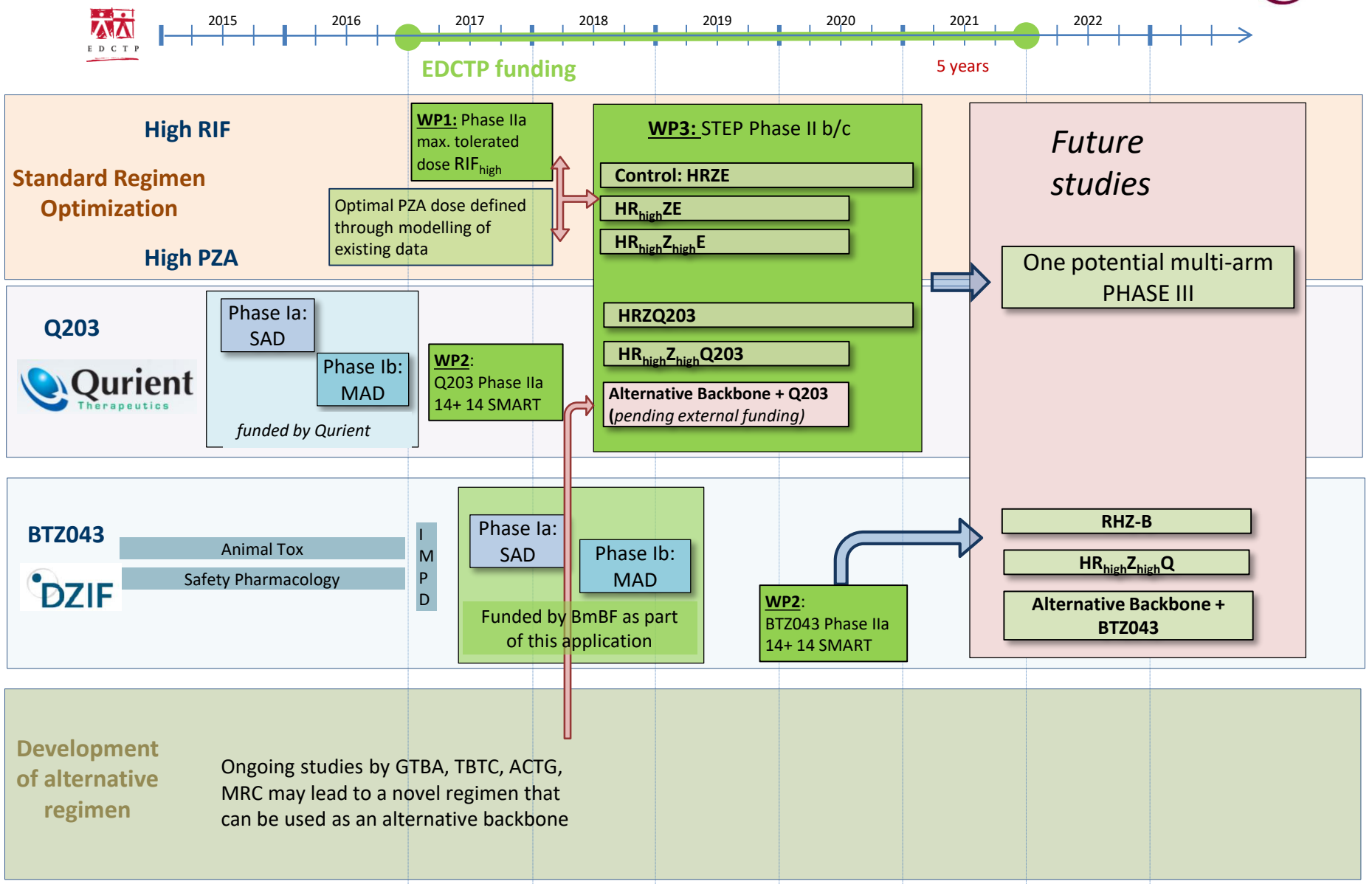
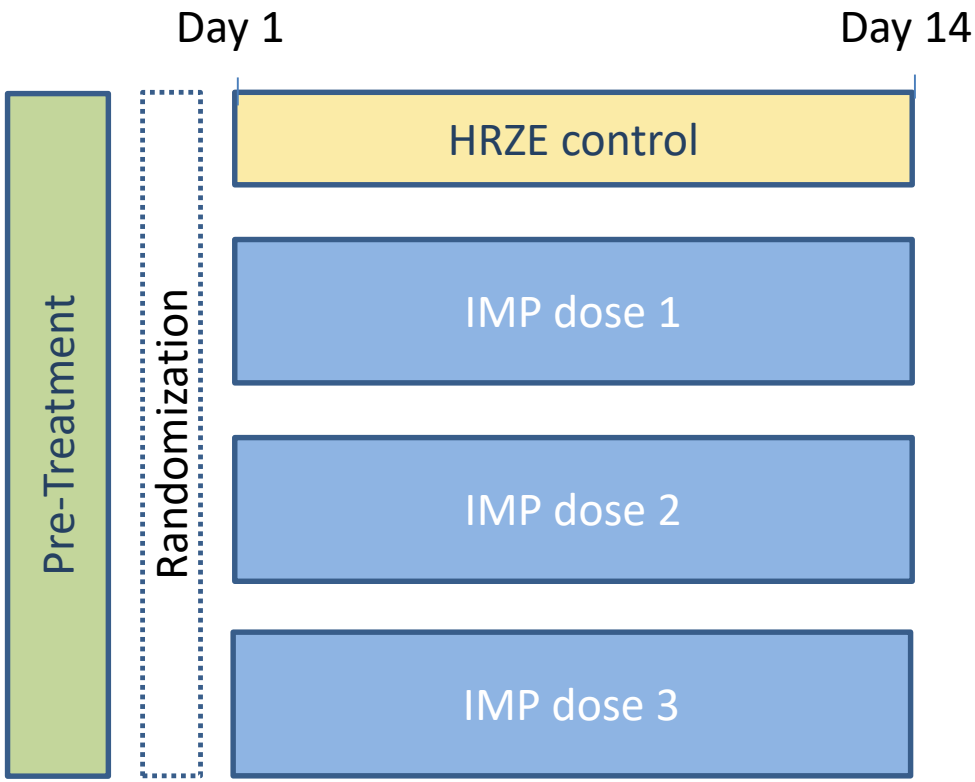
From Phase 2 onward: join PanACEA



Classical Phase 2a study design



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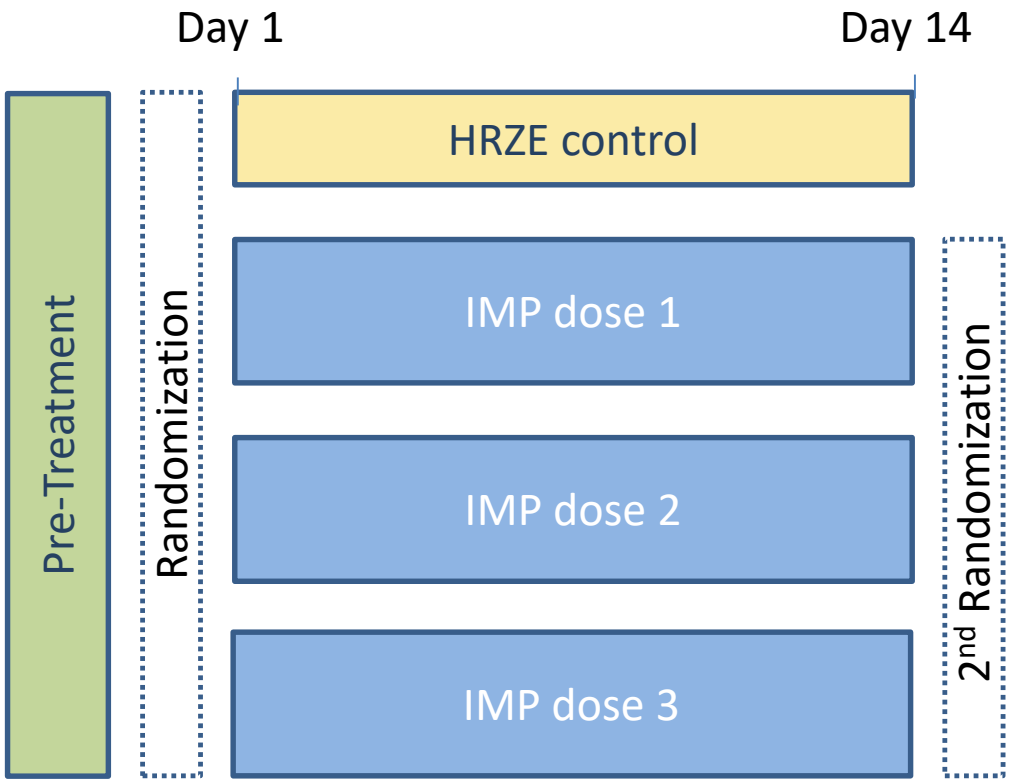
PanACEA SMART 14+14 study concept



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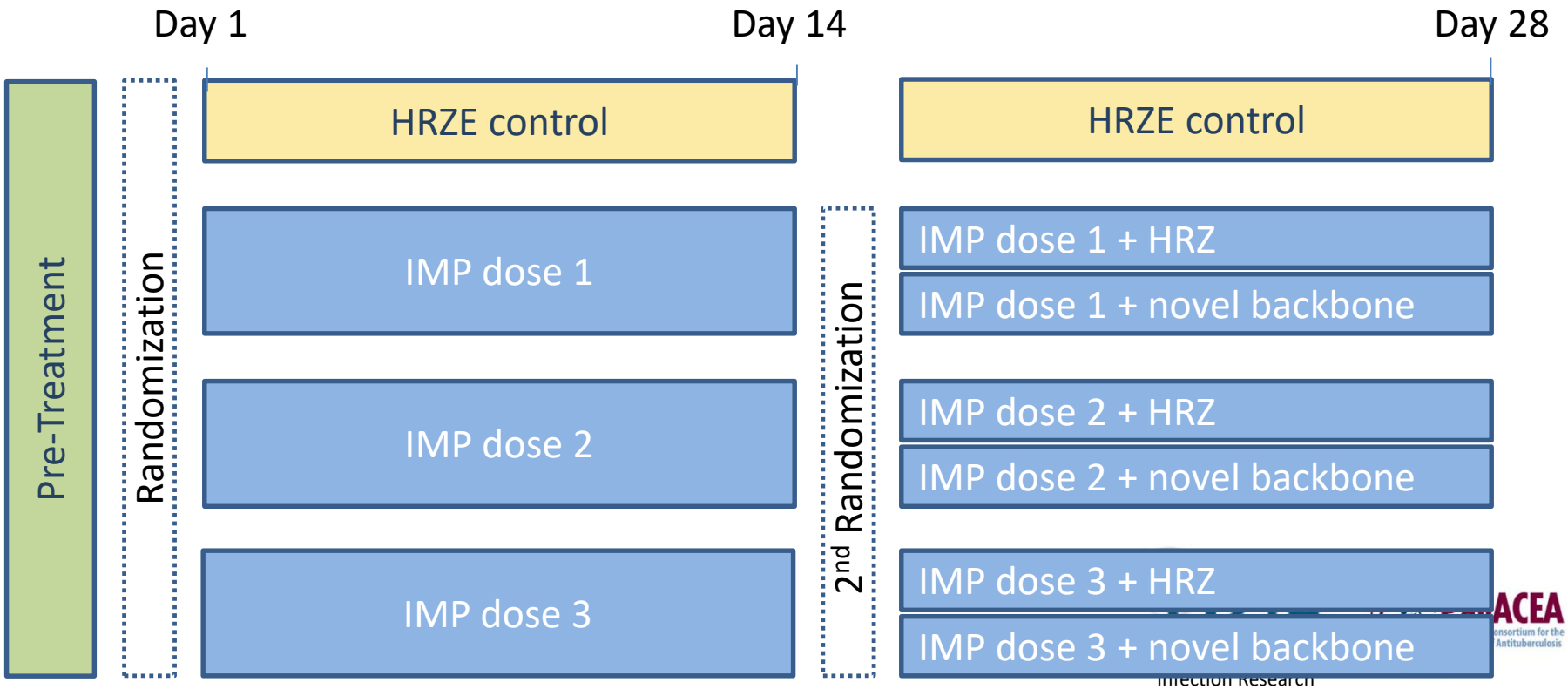
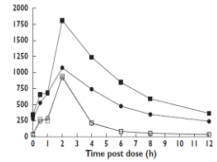


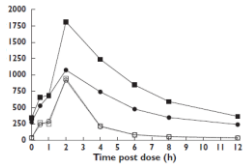
PanACEA SMART 14+14 study concept

PK – 1st dose



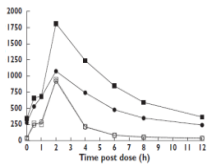
accumulation
enzyme induction

PK – steady state



interaction

PK – with
companion drugs (DDI)



Day 1 | Day 14 | Day 28

Pre-Treatment

Randomization

HRZE control

IMP dose 1

IMP dose 2

IMP dose 3

2nd Randomization

HRZE control

IMP dose 1 + HRZ

IMP dose 1 + novel backbone

IMP dose 2 + HRZ

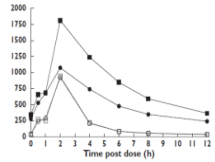
IMP dose 2 + novel backbone

IMP dose 3 + HRZ

IMP dose 3 + novel backbone

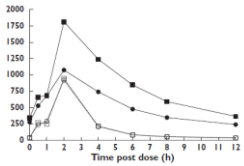
PanACEA SMART 14+14 study concept

PK – 1st dose



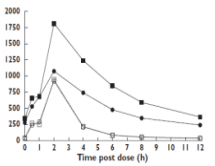
probe drug cocktail
pre-dose

PK – steady state



steady state

PK – with
companion drugs (DDI)



with companion drugs

Day 1

Day 14

Day 28

Pre-Treatment

Randomization

HRZE control

IMP dose 1

IMP dose 2

IMP dose 3

2nd Randomization

HRZE control

IMP dose 1 + HRZ

IMP dose 1 + novel backbone

IMP dose 2 + HRZ

IMP dose 2 + novel backbone

IMP dose 3 + HRZ

IMP dose 3 + novel backbone

Acknowledgements

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