BTZ043: a development update

Michael Hoelscher, Julia Dreisbach, Sarah Konsten, Norbert Heinrich
Division of Infectious Diseases and Tropical Medicine
Medical Center of the LMU
Contents of this talk

• Update on BTZ043 preclinical
• Phase 1 & 2a Plans
• BTZ043 inhibits the MTB cell wall synthesis by blocking DprE1, which is necessary for the synthesis of arabinofuranose, a component of arabinogalactan and arabinomannan.
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
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

Time pi [weeks]:
- 3
- 7
- 9
- 11

CFU in lungs
Mouse Models for BTZ043 and PBTZ169

- **Makarov & Cole**
  - Chronic mouse model
  - EFPL

- **DZIF**
  - Chronic mouse model
  - Borstel & Munich

**Graph 1:**
- Log$_{10}$ CFU
- Time after infection [weeks]
- D0, NT, INH, RIF, BTZ, PBTZ
- Vehicle: INH 25 mg/kg before treatment
- Doses: 50 mg/kg BTZ 043, 100 mg/kg BTZ 043, 250 mg/kg BTZ 043, 500 mg/kg BTZ 043, 1000 mg/kg BTZ 043
- Spleen and Lung comparison

**Graph 2:**
- CFU [log$_{10}$] / lung
- Time after infection [weeks]
- 3, 7, 9, 11
- Infection Research
Mouse Models for BTZ043 and PBTZ169

![Graph showing CFU (log_{10} / lung) over time after infection (days) for different treatments.]

- Vehicle
- 50 mg/kg BTZ043
- 100 mg/kg BTZ043
- 250 mg/kg BTZ043
- 500 mg/kg BTZ043
- 1000 mg/kg BTZ043
- INH 25 mg/kg
Safety + Phase 1 plans

- All preclinical toxicology models uncritical
- NOAEL in rats 170 mg/KG
- NOAEL in mini-pigs 360 mg/KG
Safety + Phase 1 plans

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

Phase 1a (2017):
- 200 mg
- 400 mg
- 800 mg
- 1600 mg
- 3200 mg

Phase 1b:
- Two well tolerated doses from phase 1a
From Phase 2 onward: join PanACEA

WP1: Phase Ia
High RIF
max. tolerated dose RIF$_{high}$

Optimal PZA dose defined through modelling of existing data

WP2: Q203 Phase Ila
HR$_{high}$

14+ 14 SMART

Alternative Backbone + Q203
(pending external funding)

WP3: STEP Phase II b/c
Control: HRZE
HR$_{high}$Z$_{high}$E

HRZQ203

HR$_{high}$Z$_{high}$Q203

One potential multi-arm PHASE III

Future studies

High RIF
Standard Regimen Optimization

High PZA

Q203
Phased funded by Qurient

BTZ043

Animal Tox
Safety Pharmacology

DZIF

Development of alternative regimen

Ongoing studies by GTBA, TBTC, ACTG, MRC may lead to a novel regimen that can be used as an alternative backbone
Classical Phase 2a study design

- Pre-Treatment
- Randomization

Day 1
- HRZE control
- IMP dose 1
- IMP dose 2
- IMP dose 3

Day 14
PanACEA SMART 14+14 study concept

Day 1
- HRZE control

Day 14
- IMP dose 1
- IMP dose 2
- IMP dose 3

Pre-Treatment
Randomization
2nd Randomization
PanACEA SMART 14+14 study concept

Day 1
- Pre-Treatment
- Randomization
  - IMP dose 1
  - IMP dose 2
  - IMP dose 3

Day 14
- 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

Day 28
- 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

Pre-Treatment
Randomization
2nd Randomization
PanACEA SMART 14+14 study concept

**PK – 1st dose**

- IMP dose 1
- IMP dose 2
- IMP dose 3

**PK – steady state**

- 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

**PK – with companion drugs (DDI)**

- HRZE control

**Day 1**

- HRZE control
- IMP dose 1
- IMP dose 2
- IMP dose 3

**Day 14**

- 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

**Day 28**

Pre-Treatment

Randomization

2nd Randomization

accumulation enzyme induction

interaction
PanACEA SMART 14+14 study concept

PK – 1st dose

- IMP dose 1
- IMP dose 2
- IMP dose 3

PK – steady state

- 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

PK – with companion drugs (DDI)

Day 1

- Pre-Treatment
- Randomization

Day 14

- HRZE control

Day 28

- 2nd Randomization

Probe drug cocktail pre-dose

steady state with companion drugs

PK – 1st dose

PK – steady state

PK – with companion drugs (DDI)
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