TB Alliance
Stakeholders Association

Symposium on Emerging Resistance to Novel Tuberculosis Drugs

Mel Spigelman

President and CEO, TB Alliance

Columbia University

March 20-21, 2024

2024 Global New TB Drug Pipeline[1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP

Oxazolidinones

DnaE1 / Nargenicin analogs

Early Stage Development

FIM-253

TBD10 (MK-3854)

CLB-073*

SPR720*

MPL-447*

JSF-3285*

CPZEN-45*

NTB-3119*

MBX-4888A (1810)*

FNDR-20364*

GMP / GLP Tox.

GSK-839*

OTB-658

Phase 1

TBD09 (MK-7762)

GSK-286*

TBAJ-587

TBI-223

Macozinone* (PBTZ-169)

Phase 2

Telacebec* (Q203)

Alpibectir (BVL-GSK098)*

TBAJ-876

Sanfetrinem

Delpazolid, Sutezolid, Tedizolid

BTZ-043*

TBA-7371*

Quabodepistat (OPC-167832*)

Ganfeborole (GSK-656*/070)

Pyrifazimine (TBI-166)

SQ-109*

Phase 3

Sudapyridine (WX-081)

Bedaquiline*

Delamanid*

Pretomanid*

Regulatory Market Approvals

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2024

Clinical Trials Evaluating New TB Regimens

Updated for World TB Day, March 2024

WORKING GROUP ON NEW TB DRUGS

Trial Phase

2

DRAMATIC (2)
BDQ DLM LZD CFZ

Boston University

View Registry

Otsuka DBO (2b 2c)
BDQ DLM QOD

Otsuka

View Registry

PanACEA - STEP2C-01 (2b 2c)
Regimen 1: MZF PZA INH RIF

Regimen 2: MZF PZA INH RIF

Regimen 3: BDQ DLM SZD MZF

PanACEA

View Registry

SUDOCU (2b)
BDQ DLM SZD MZF

PanACEA

View Registry

NC-009 (2)
Regimen 1: 876 PMD LZD

Regimen 2: BDQ PMD LZD

TB Alliance

View Registry

CRUSH-TB (2c)
Regimen 1: BDQ MZF PZA Rb

Regimen 2: BDQ MZF PZA DLM

US Centers for Disease Control and Prevention (CDC)

View Registry

Opti-Q (2)
LFX OBR

US Centers for Disease Control and Prevention (CDC)

View Registry

DECODE (2b)
BDQ DLM DZD MZF

LegoChem Biosciences, Inc

View Registry

PAN-TB XBOS (2)
Regimen 1: BDQ PMD SZD QOD

Regimen 2: BDQ DLM SZD QOD

Bill & Melinda Gates Medical Research Institute

View Registry

PRESCIENT (2c)
BDQ DLM PZA CFZ

Brigham and Women's Hospital

View Registry

SimpliciTB (2c)
BDQ PMD MZF PZA

TB Alliance

View Registry

Study 31/A5349 (2c)
Regimen 1: PZA INH RPT EMB

Regimen 2: MZF PZA INH RPT

US Centers for Disease Control and Prevention (CDC)

View Registry

3

endTB-Q (3)
BDQ DLM LZD CFZ

Médecins Sans Frontières

View Registry

Nix-TB (3)
BDQ PMD LZD

TB Alliance

View Registry

Zenix (3)
BDQ PMD LZD

TB Alliance

View Registry

End TB (3)
Regimen 1: BDQ MZF PZA

Regimen 2: BDQ LZD LFX PZA CFZ

Regimen 3: BDQ DLM LZD LFX PZA

Regimen 4: DLM LZD LFX PZA CFZ

Regimen 5: DLM MZF PZA CFZ

Médecins Sans Frontières

View Registry

Sponsors

Bill & Melinda Gates Medical Research Institute
Boston University
Brigham and Women's Hospital
LegoChem Biosciences, Inc
Médecins Sans Frontières
Otsuka
PanACEA
TB Alliance
US Centers for Disease Control and Prevention (CDC)

Status

- Enrolling
- Enrolment Complete
- Pending Publication
- Published

Disease

Drug Sensitive

Drug Resistant

Drugs and Drug Candidates

Diarylquinolones
- BDQ Bedaquiline
- 876 TBAJ-876

Nitromidazoles
- DLM Delamanid
- PMD Pretomanid

Oxazolidinones
- DZD Delpazolid
- LZD Linezolid
- SZD Sutezolid

Carbostyril
- QOD Quabodepistat

PZA Pyrazinamide

OBR Optimized Background Regimen

Riminophenazine
- CFZ Clofazamine

Rifamycins
- Rb Rifabutin
- RIF Rifampicin
- RPT Rifapentine

Carbohydrazide
- INH Isoniazid

Ethnolamides
- EMB Ethambutol

Fluoroquinolones
- LFX Levofloxacin
- MZF Moxifloxacin

One-Dose Efficacy of Long-Acting Injectable Diarylquinoline in Mouse Model of TB Preventive Therapy

881

James Hobson[1,2], Si-Yang Li[3], Nicole Ammerman[3], Jonathan Massam[1,2], Jo Sharp[1,4], Nader Fotouhi[5], Steve Rannard[1,2], Andrew Owen[1,4], Eric Nuermberger[3]
[1]Centre of Excellence in Long-acting Therapeutics (CELT), University of Liverpool, Liverpool, UK. [2]Department of Chemistry, University of Liverpool, Liverpool, UK.
[3]Center for TB Research, Johns Hopkins University, Baltimore, Maryland, USA. [4]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK, [5]TB Alliance, New York, New York, USA

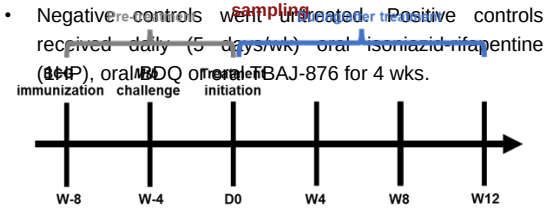
BACKGROUND

- Use of long-acting injectables (LAIs) has the potential to simplify tuberculosis preventive therapy (TPT), addressing issues such as pill burden and adherence.
- Bedaquiline (BDQ) is a key sterilizing drug in new, shorter regimens for treatment of rifampin-resistant TB and is being studied in novel regimens for drug-susceptible TB. Thus, it could fill the unmet need for a short-course "pan"-TPT option.
- BDQ and other diarylquinolines (DARQs) have physico-chemical and pharmacokinetic (PK) properties amenable to LAI formulations.
- TBAJ-876 is a next-generation DARQ with greater potency and lower potential to prolong the QTc interval than BDQ.
- The aim of this work was to evaluate the PK and efficacy of novel TBAJ-876 formulations prepared by single phase spray drying as LAIs in a validated mouse model of TPT.

METHODS

- Three reproducible TBAJ-876 LAI formulations (A-C) with 80% (w/w) API and differing excipients were identified.
- Single intramuscular (IM) dose PK profiles were determined in mice at doses of 250, 500 and 1000 mg/kg.
- Based on PK results at the 250 mg/kg dose showing plasma concentrations ≥36 ng/mL (the EC_{50} previously established in a mouse model of active TB) at 8 wks post-dose, formulation B was tested for efficacy in a validated BALB/c mouse model of TPT (Fig. 1) at single IM doses of 62.5, 125 and 250 mg/kg, aiming to maintain plasma concentrations ≥36 ng/mL for 4-8 wks. Formulations A and C were tested only at a single IM dose of 125 mg/kg.
- Negative controls were untreated. Positive controls received daily (5 days/wk) oral isoniazid-rifapentine (1HP), oral BDQ or oral TBAJ-876 for 4 wks.

Fig. 1: TPT Model, Drug administration and CFU sampling



Long-acting injectable formulations for TBAJ-876 demonstrate encouraging exposure profiles and efficacy in a mouse model of tuberculosis preventive therapy

- Bacterial colony-forming units (CFU) were enumerated monthly by quantitative cultures of lung homogenates on 7H11 agar supplemented with 0.4% activated charcoal. Group mean CFU counts were analyzed using 1-way ANOVA.
- Plasma DARQ concentrations were measured using a validated LC-MS/MS method. Median plasma AUC was calculated using the trapezoidal rule.

RESULTS – TBAJ-876 Plasma Pharmacokinetics

- Each TBAJ-876 LAI formulation demonstrated sustained release profiles in uninfected BALB/c mice in the pilot PK study (Fig. 2) and in infected mice in the efficacy study (Fig 3). Wk 12 results are pending.
- In a pilot PK study, median TBAJ-876 C_{max} was <1 µg/mL for each formulation and dose; and plasma concentrations were ≥36 ng/mL for ≥8 wks after 250, 500 and 1000 mg/kg doses of each formulation. Mice receiving formulation A at 1000 mg/kg developed thigh swelling suggesting an excipient-mediated reaction, and required euthanasia. Other doses and formulations were well tolerated.
- In the efficacy study, median plasma $AUC_{0\text{-}tau}$ values were 143, 206 and 391 µg-h/mL and plasma concentrations were ≥36 ng/mL for 4, 6 and >6 wks after the 62.5, 125 and 250 mg/kg doses of formulation B, respectively.

Fig. 2: TBAJ-876 LAI Plasma PK after IM injection in uninfected BALB/c mice

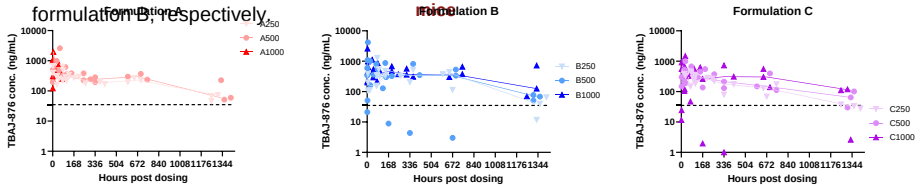
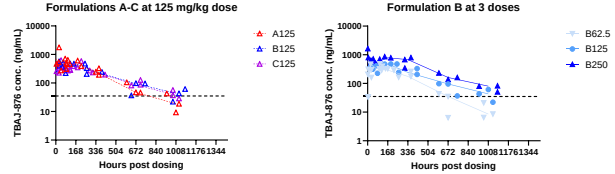


Fig. 3: TBAJ-876 LAI Plasma PK after IM injection in infected mice

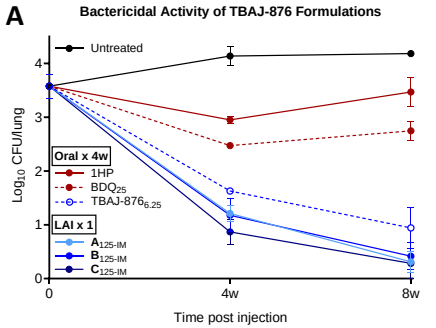


Plasma TBAJ-876 Exposure for Formulation B	
Dose (mg/kg)	$AUC_{0\text{-}tau}$ (µg.h/L)
62.5	143
125	206
250	391

RESULTS – TPT Efficacy Study

- All LAI regimens had similar bactericidal activity that was superior to 1HP ($p<0.0001$) and oral BDQ ($p<0.0001$) and at least similar in magnitude to the same total TBAJ-876 dose given orally over 4 wks (e.g., 125 mg/kg LAI vs. 6.25 mg/kg orally) (Fig. 4A). Activity was dose-dependent for formulation B (Fig. 4B) and consistent with bactericidal activity for as long as plasma TBAJ-876 concentrations were ≥36 ng/mL, if not longer.

Fig. 4: CFU Data



CONCLUSIONS

- These data provide proof-of-concept for a highly efficacious pan-TPT regimen comprised of a single IM dose of a TBAJ-876 LAI formulation.
- Further preclinical development including cross-species PK studies to enable human dose projections, evaluation of injection site safety/tolerability, and assessment of chemistry and manufacturing controls (CMC) procedures is warranted.

AUTHOR CONTACT INFORMATION: James Hobson: j.hobson@liverpool.ac.uk; Eric Nuermberger: enuermb@jhmi.edu

Acknowledgements: This work was funded by NIH-NIAID (R61-AI-

The Future of TB Treatment

Discover, develop, and deliver better and faster TB treatments

Our Vision

To treat latent TB infections in one day

To treat active TB infections in one month

Achieving our vision will require:

- A sustainable pipeline of highly effective and safe novel therapeutics
- Leveraging advances in formulation science and much greater understanding of host responses to *M.tb*
- All TB treatments available for special populations such as children