

Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus,
Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and
Médecins Sans Frontières

1-2 March , 2017, MINSK , BELARUS

Clinical update- landscape of new TB drugs

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Overview

- What are we talking about
- What new drugs are on the horizon
- What new combinations are being tested
- What can we expect in the next 5-10 years

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What are we talking about

- Pre-clinical phases (trials on animals)
 - many steps *
 - difficult to be fund...often called **THE DEATH VALLEY**
- Clinical phases (human trials):
 - Phase I: healthy volunteers, safety, tolerability, pharmacokinetics.
 - Phase II :small numbers of sick patients, efficacy , more safety
 - Phase III large numbers of patients , safety and efficacy

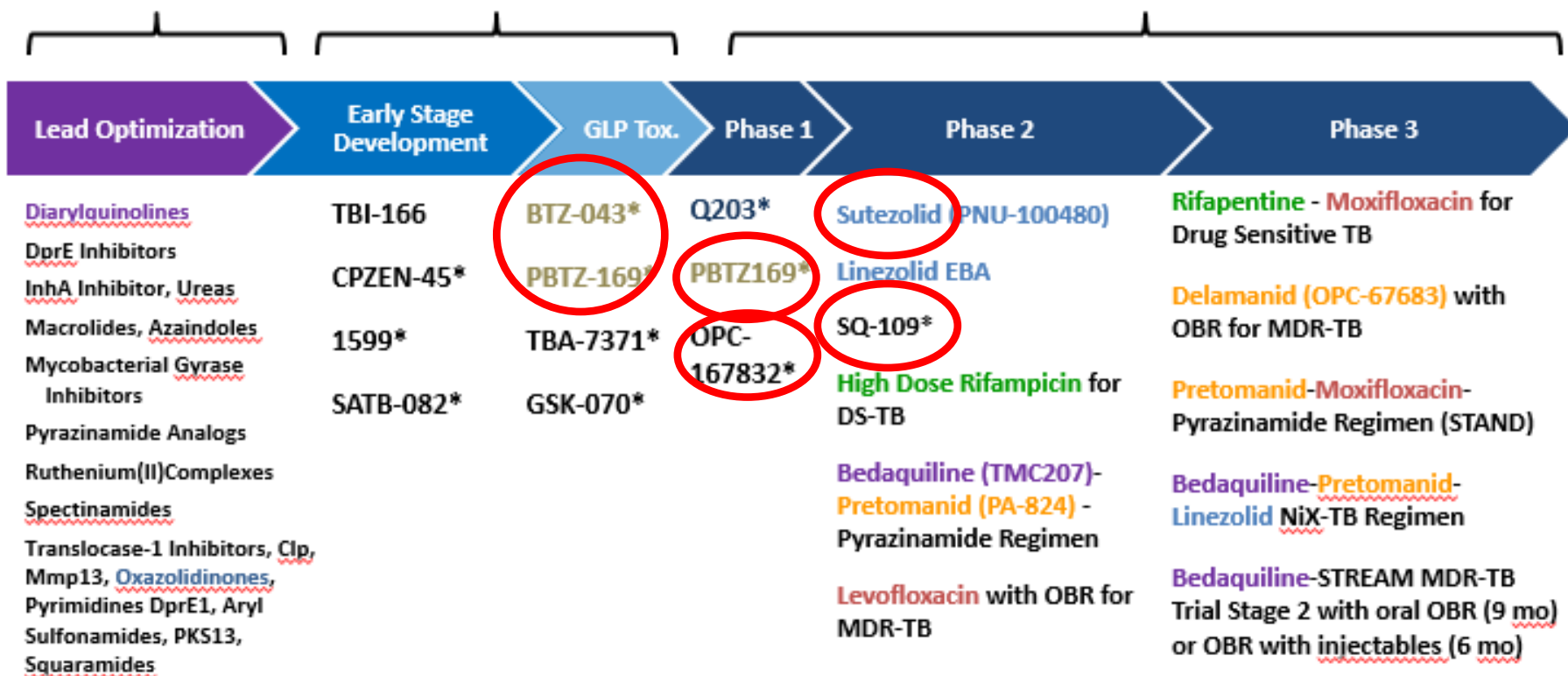
*ADME profile, GMP manufacture, API, toxicology, make the tablets, preparation of regulatory documents

Global TB Drug Pipeline ¹

Discovery

Preclinical Development

Clinical Development



Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide. New chemical class*

¹ Details for projects listed can be found at <http://www.newtbdugs.org/pipeline.php> and ongoing projects without a lead compound series identified can be viewed at <http://www.newtbdugs.org/pipeline-discovery.php>

²OBR = Optimized Background Regimen



www.newtbdugs.org

Updated: October 2016

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OPC-167832

3,4-carbostyryl derivative

- Otsuka, announced union TB conference 2016
- DS and DRTB effective in mouse models
- Different mechanism of action than all currently approved TB drugs
- Otsuka working on a PAN-TB (DS and DRTB) combination with Dlm + other TB drugs

Where are we?

- Public-private partnership
- Fast track status from FDA
- Dosing study started October 2016



FIGHTBACK
Union World Conference on Lung Health - 2016
Liverpool, England

Progress in scaling up delamanid use and introducing Otsuka's second anti-TB compound

Otsuka
TB innovation for tomorrow.

Sutezolid (PNU-100480)

Oxazolidinone

- Inhibit protein synthesis
- Like **linezolid** but early testing:
 - more potent in vitro and in the mouse
 - less toxic

Where are we?

- Early study results published in 2014, BUT NO FURTHER DEVELOPMENT
- **Geneva, 25 January 2017 — Medicines Patent Pool signed a licence with Johns Hopkins University to facilitate the clinical development **sutezolid****

SQ-109

Ethambutol analogue

- Blocks cell wall synthesis AND prevents efflux of companion drugs from macrophages
- 10 times more active than Ethambutol in preclinical studies
- Synergistic with H, R and Bdq and active against E resistant strains

Where are we?

- phase 1 complete
- Phase II (high dose R with H- or H-Z-Mfx): complete

PBTZ169

Benzothiazinone

- Active against DS and DRTB
- Synergy with Cfz and Bdq
- Compatible with other drugs

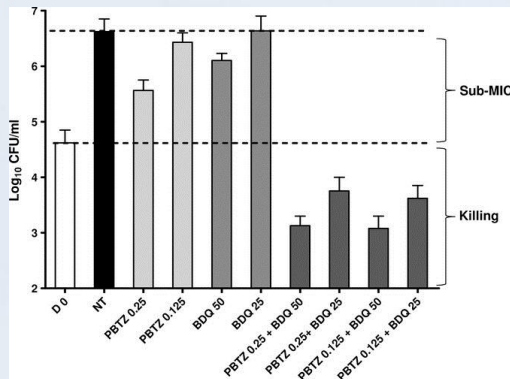
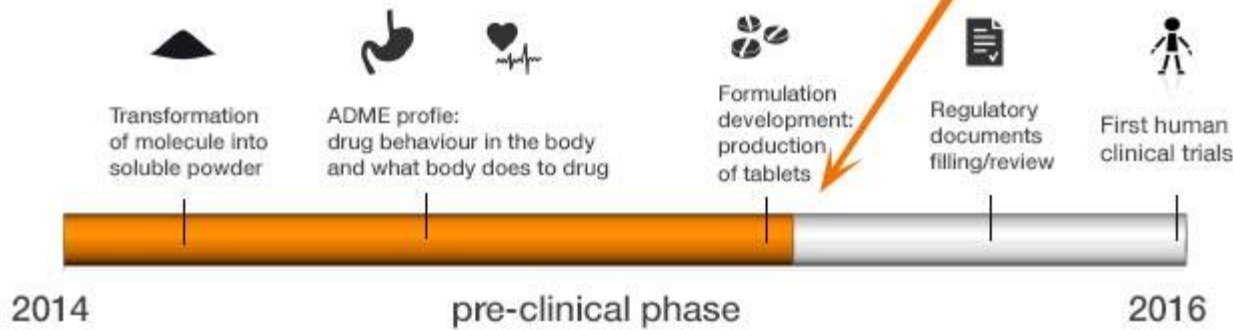
Where are we?

- Phase I (Nearmedic, Russia)
 - completed July 2016
 - safety, tolerability and pharmacokinetics up to 640 mg.
- Phase I (Innovative Medicines For Tuberculosis (iM4TB) , Switzerland
 - planned 2017
- Phase IIa planned toward end of 2016

PBTZ169

Where do we stand with our drug candidate PBTZ 169?

we are here!



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Trial record 1 of 1 for: PBTZ169

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Phase 1 Study of PBTZ169

This study has been completed.

Sponsor:
Nearmedic Plus LLC

Collaborator:
OCT LLC

Information provided by (Responsible Party):
Nearmedic Plus LLC

ClinicalTrials.gov Identifier:
NCT03036163

First received: September 18, 2016
Last updated: January 26, 2017
Last verified: January 2017
[History of Changes](#)

[Full Text View](#)

[Tabular View](#)

[No Study Results Posted](#)

[Disclaimer](#)

[How to Read a Study Record](#)

Q203

Imidazopyridine

- Developed by Qurient (Korea)
- Blocks growth of TB bacilli
- Targets respiratory cytochrome bc1 complex,



Where are we?

- Phase 1 : Dose-Escalation Study to Evaluate Safety, Tolerability and Pharmacokinetics of **Single** Doses of Q203 in Normal, Healthy, Male and Female Volunteers
- Phase IB: Dose-Escalation Study to Evaluate Safety, Tolerability and Pharmacokinetics of **Multiple** Doses of Q203 in Normal Healthy Male and Female Volunteers

Drugs you already know...

Nitroimidazoles

- **PA-824 (pretomanid)**
 - Developed by Global TB alliance
 - Under testing for DS and DRTB
- **Delamanid (OPC-67683)**
 - Inhibits mycolic acid synthesis
 - Phase III completed, results 2018
 - Recommended by WHO from 6 years old

Diarylquinoline

- Bedaquiline (TMC207)

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What new combinations are being tested

- http://www.resisttb.org/?page_id=1602

RESIST-TB
Research Excellence to Stop TB Resistance

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DR-TB Clinical Trials Progress Report

[View the Clinical Trials Progress Report as a PDF here](#)

[View the Clinical Trials Progress Report as a Power Point here](#)

Show entries Search:

Trial Name	Description	Status	Phase	Trial Registry Identifier (link)	Expected Study Completion Date
Janssen C211	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Bedaquiline in combination with MDR-TB therapy for HIV uninfected children and adolescents	Open for participant enrollment	Phase 2	NCT02354014	2022

Combinations of new drugs for MDRTB: BEDAQUILINE

In the shortened regimen

9m: Km, Mfx, Cfz, E, Z, HdH, Pto

9m: Lfx, Cfz, E, Z, HdH, Pto

6 m: Km, Lfx, Cfz, Z, HdH

- STREAM 2(ongoing)

No injectable (6-9 months)

Lzd, Lfx, Eto, HdH, Z

- NeXT (enrolling)

Pretomanid + Linezolid

(XDRTB, 6-9 m)

- NiX ongoing
- PRACTECAL (enrolling)

With Pretomanid + Mfx + Z

- NC-005 (fully enrolled)

Combinations of new drugs for MDRTB: DELAMANID

Bedaquiline and Delamanid
Drug-drug interactions, QT

- DELIBERATE (open)

In children

- Otsuka: 233 < 6 yrs (open)

In children with HIV

- Otsuka: 232
 - 6-11 yr, 12-17 yr complete
 - 3-5 yr open
 - 0-2 yr to be decided

Lzd + Lfx + Z
(9-12 m)

- MDR-end: enrolling Korea

Combinations with repurposed or TB drugs: DR and DSTB

MDRTB: Increased dose of Lfx

- Opti Q

H resistant TB: High dose H

- ACTG5312

MDRTB: molecular testing Z

- China PZA trial

DSTB: rifapentine +/- MFX to shorten DSTB treatment 4m

- TBTC study/A5349: enrolling

DSTB: higher dose rifampicin to shorten DSTB treatment

- PanACEA, HIRIF, ReDEFINe

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In the next 4-5 years...maybe...

- New MDRTB regimens: shorter, all oral, less adverse events (but requiring monitoring) and better than conventional treatments
- Some new drugs ready to be used under CU

=> get ready

- Compassionate use a good tool for early use
- Strengthen patient monitoring and aDSM now
- Innovate on how to get the drugs to patients
« patient orientated ».... Drugs are not the only problem!!

Data sources and references

- <https://clinicaltrials.gov>
- <http://www.resisttb.org/>
- Website union conference liverpool 2017
<http://www.professionalabstracts.com/union2016/iplanner/#/grid>
- <http://www.medicinespatentpool.org/the-medicines-patent-pool-announces-first-licence-for-tuberculosis-treatment/>
- <http://www.newtbdrugs.org/pipeline>
- WHO global report 2016
- AIDS clinical rounds, UCSan Diego, Constance A. benson: New drugs and novel approaches to treatment shortening in DS and DRTB