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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Médecins Sans Frontières

MEDECINS SANS FRONTIERES

МІНІСТЭРСТВА АХОВЫ ЗДАРОЎЯ РЭСПУБЛІКА БЕЛАРУСЬ

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**

Lead Optimization

- Diarylquinolines
- DprE Inhibitors
- InhA Inhibitor, Ureas
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II)Complexes
- Spectinamides
- Translocase-1 Inhibitors, Clp, Mmp13, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

Early Stage Development

- TBI-166
- CPZEN-45*
- 1599*
- SATB-082*

GLP Tox.

- BTZ-043*
- PBTZ-169*
- TBA-7371*
- GSK-070*

Phase 1

- Q203*
- PBTZ169*
- OPC-167832*

Phase 2

- Sutezolid (PNU-100480)
- Linezolid EBA
- SQ-109*
- High Dose Rifampicin for DS-TB
- Bedaquiline (TMC207)-Pretomanid (PA-824) - Pyrazinamide Regimen
- Levofloxacin with OBR for MDR-TB

Phase 3

- Rifapentine - Moxifloxacin for Drug Sensitive TB
- Delamanid (OPC-67683) with OBR for MDR-TB
- Pretomanid-Moxifloxacin-Pyrazinamide Regimen (STAND)
- Bedaquiline-Pretomanid-Linezolid NiX-TB Regimen
- Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
- Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

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

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

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: October 2016

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OPC-167832

3,4-carbostyril derivative

- Ostuka, 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

http://www.professionalabstracts.com/union2016/iplanner/#/grid

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

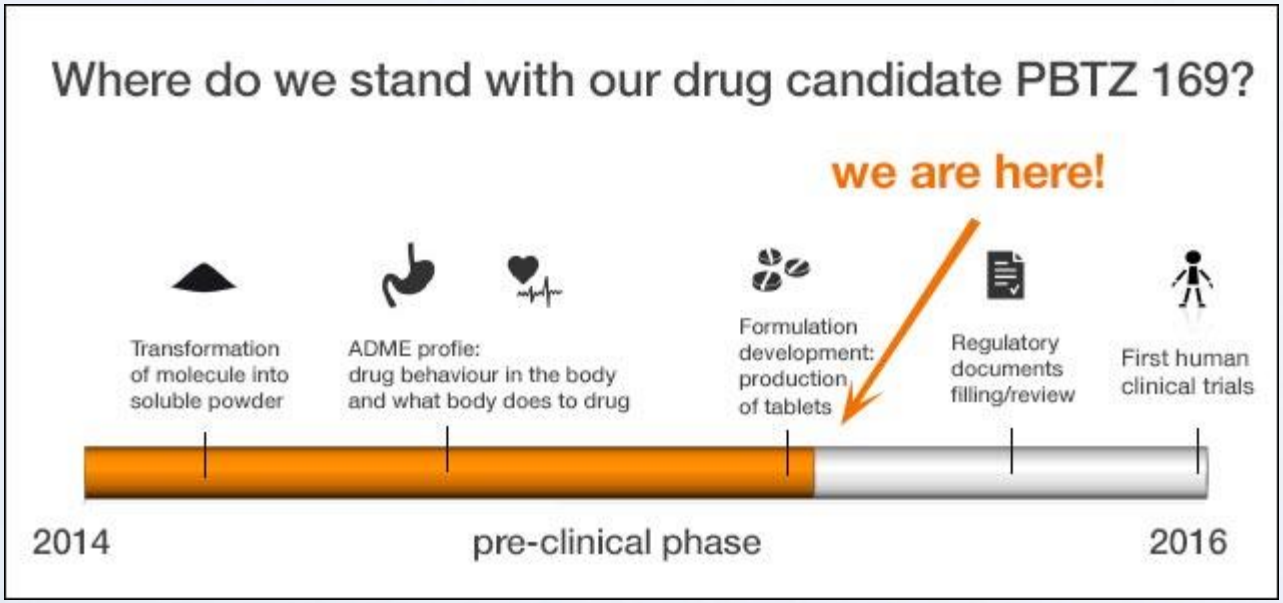
Benzothiazinone

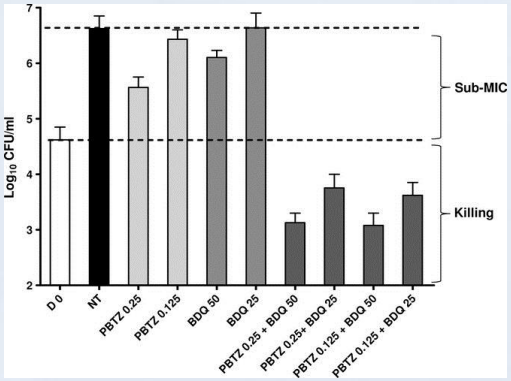
- Active against DS and DRTB
- Synergy with Cfz and Bdq
- Compatible with other drugs

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) , Switzeland
  - planned 2017
- Phase IIa planned toward end of 2016

PBTZ169


Where do we stand with our drug candidate PBTZ 169?
we are here!
Transformation of molecule into soluble powder
ADME profie: drug behaviour in the body and what body does to drug
Formulation development: production of tablets
Regulatory documents filling/review
First human clinical trials
2014
pre-clinical phase
2016


Log10 CFU/ml
Sub-MIC
Killing
D 0
NT
PBTZ 0.25
PBTZ 0.125
BDQ 50
BDQ 25
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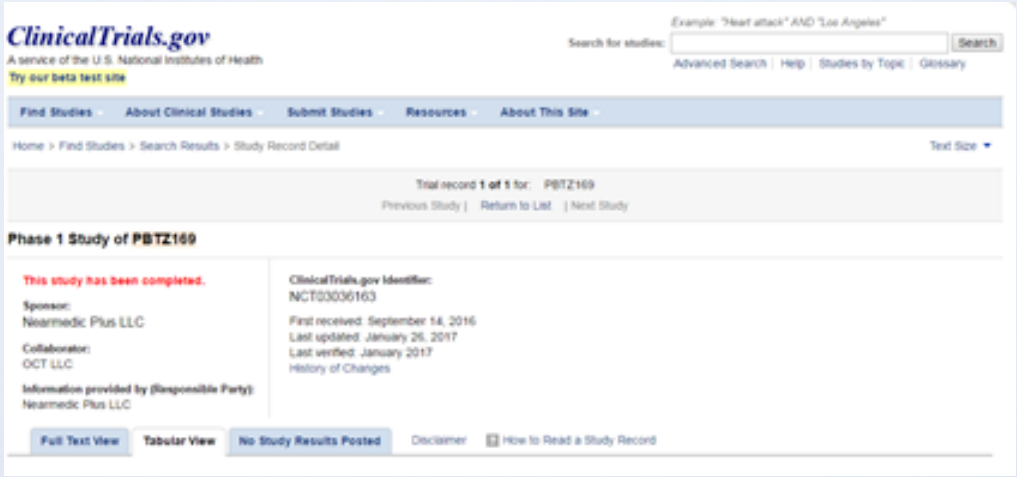
PBTZ 0.25+ BDQ 25
PBTZ 0.125 + BDQ 50
PBTZ 0.125 + BDQ 25


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Try our beta test site
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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site
Home > Find Studies > Search Results > Study Record Detail
Text Size
Trial record 1 of 1 for: PBTZ169
Previous Study | Return to List | Next Study
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 14, 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,

nature medicine

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NATURE MEDICINE | LETTER

日本語要約

Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis

Kevin Pethe, Pablo Bifani, Jichan Jang, Sunhee Kang, Seijin Park, Sujin Ahn, Jan Jiricek, Juyoung Jung, Hee Kyoung Jeon, Jonathan Cechetto, Thierry Christophe, Honggun Lee, Marie Kempf, Mary Jackson, Anne J Lenaerts, Ha Pham, Victoria Jones, Min Jung Seo, Young Mi Kim, Mooyoung Seo, Jeong Jea Seo, Dongsik Park, Yoonae Ko, Inhee Choi, Ryangyeo Kim + et al.

Affiliations | Contributions | Corresponding authors

Nature Medicine 19, 1157–1160 (2013) | doi:10.1038/nm.3262

Received 28 March 2013 | Accepted 04 June 2013 | Published online 04 August 2013

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 (pretonamid)**
  - 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 20 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)

Pretonamid + Linezolid

(XDRTB, 6-9 m)

- Nix ongoing
- PRACTECAL (enrolling)

With Pretonamid + 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 of 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 nevel approaches to treatment shortening in DS and DRTB