MACOZINONE (PBTZ 169) PROJECT

NEARMEDIC GROUP

October 2020

MACOZINONE (PBTZ 169) – a new unique drag for the treatment of all forms of tuberculosis

EPFL | YOU ARE | BY SCHOOL | ABOUT EPFL

EPFL › News

NEWS GLOBAL HEALTH INSTITUTE

Create an account Help

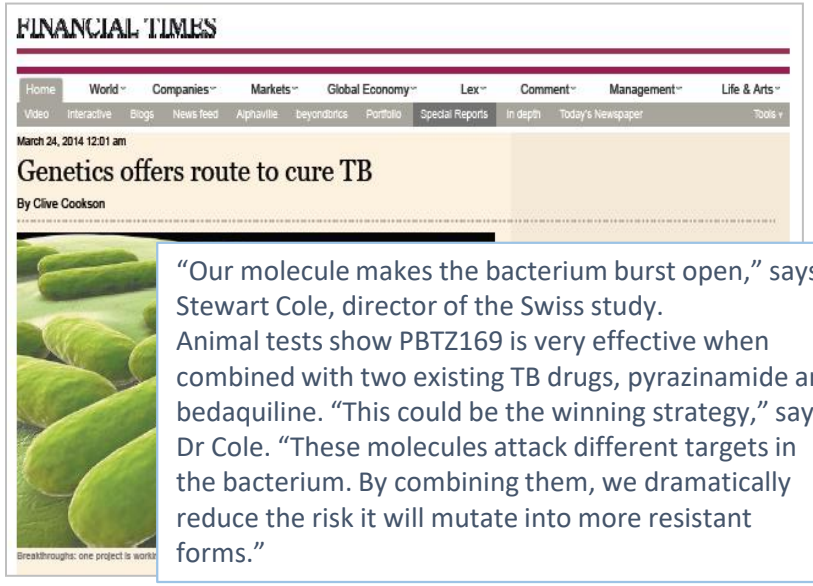
Share Print

EPFL Joins Forces with Pharmaceutical Company to Fight Tuberculosis

Source: Clifton E. Barry

In March, the school gav

25.07.14 - The pharmaceutical company Nearmedic is collaborating with EPFL to participate in the development of a treatment against tuberculosis.
The company bought a license covering the use of the molecule in most countries of the former Soviet Union, where multiresistant strains are prevalent.



FINANCIAL TIMES

Home World Companies Markets Global Economy Lex Comment Management Life & Arts

Video Interactive Blogs News feed Alphaville beyondbrics Portfolio Special Reports In depth Today's Newspaper Tools

March 24, 2014 12:01 am

Genetics offers route to cure TB

By Clive Cookson

Breakthroughs: one project is workl

"Our molecule makes the bacterium burst open," says Stewart Cole, director of the Swiss study.
Animal tests show PBTZ169 is very effective when combined with two existing TB drugs, pyrazinamide and bedaquiline. "This could be the winning strategy," says Dr Cole. "These molecules attack different targets in the bacterium. By combining them, we dramatically reduce the risk it will mutate into more resistant forms."

- **École Polytechnique Fédérale de Lausanne (EPFL) is the sole owner of international patent application PCT/IB2011/055209 published under number WO/2012/066518 and related to the drug candidate PBTZ169, which was invented by Professor Stewart Cole (Paris) and Dr. Vadim Makarov (Russia)**

- **The official signing of the License Agreement between the NEARMEDIC PLUS and the EPFL took place at the end of May 2014.**

- ***According to the License Agreement, EPFL grants to NEARMEDIC PLUS and its Affiliate(s) an exclusive license:***

i) to research, develop, make, have made, use, Licensed Products within the Field of Use and in the Territory and

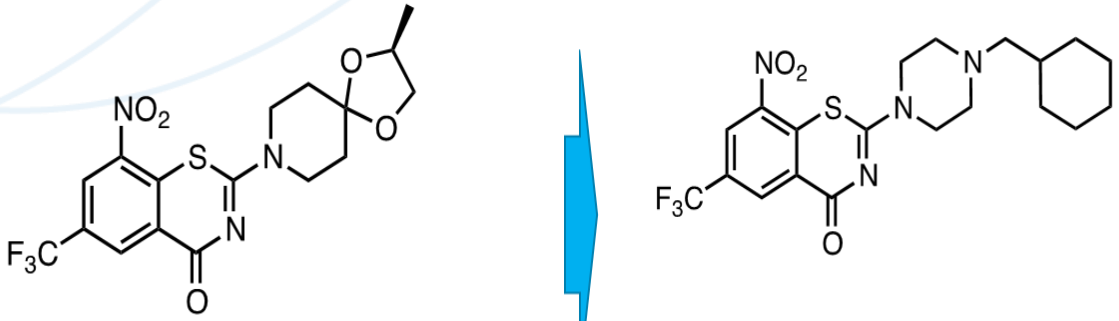
ii) to sell and have sold Commercial Products within the Field of Use and in the Territory

- ***"Territory"** means i) EAPO countries (Eurasian Patent Organization), including the Russian Federation, and ii) Ukraine, Georgia, Mongolia and Uzbekistan.*

MACOZINONE (PBTZ169): new original drug to cure tuberculosis

MACOZINONE

Benzothiazinones (BTZ-PBTZ) as antimycobacterial agents



BTZ043 → PBTZ169

2-[4-R-piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-4*H*-1,3-benzothiazin-4-one

Lead compound
Highly active *in vitro & in vivo*
Expensive stereochemical synthesis
Potentially toxic due to ketal moiety

More active
Simple synthesis
Stable salt form
Drug-like profile
Longer patent life

PCT/EP2006/004942
PCT/IB2011/055209

2009 → **2012**

- Highly active against M. tuberculosis (MIC 1-10 ng/ml) and other actinobacteria
- Active against all clinical isolates including MDR- and XDR-TB
- One pot synthesis, 3 steps, 70% yield, from commercially available reagents
- Excellent CoG
- Fine safety profile

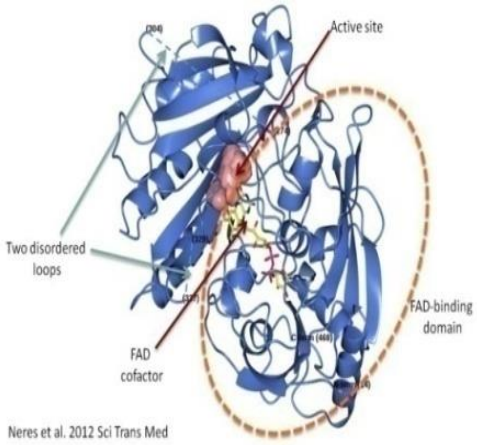
- **Science. 2009** Benzothiazinones kill Mycobacterium tuberculosis by blocking arabinan synthesis.
- **Antimicrob Agents Chemother. 2010** Clinical isolates of Mycobacterium tuberculosis in four European hospitals are uniformly susceptible to benzothiazinones.
- **Mol Microbiol. 2010** Biological and structural characterization of the Mycobacterium smegmatis nitroreductase NfnB, and its role in benzothiazinone resistance.
- **J Am Chem Soc. 2010**. Benzothiazinones: prodrugs that covalently modify the decaprenylphosphoryl-β-D-ribose 2'-epimerase DprE1 of Mycobacterium tuberculosis.
- **Science. Trans Med. 2012** Structural basis for benzothiazinone-mediated killing of Mycobacterium tuberculosis.
- **Antimicrob Agents Chemother. 2012** In vitro combination studies of Benzothiazinone lead compound BTZ043 against Mycobacterium tuberculosis.
- **EMBO Molecular Medicine.** 2014 Towards a new combination therapy for tuberculosis with next generation benzothiazinones

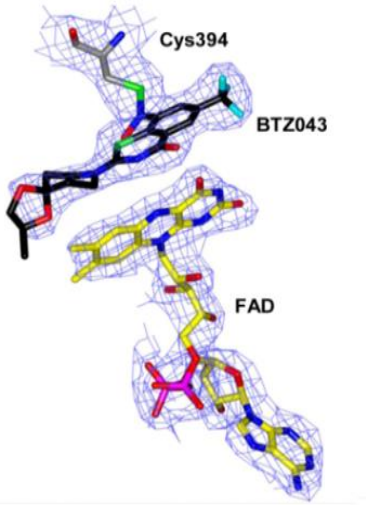
MACOZINONE (PBTZ169): new original drug to cure tuberculosis

MACOZINONE

- ***Unique target:*** vital enzyme of the cell wall of mycobacteria decaprenyl-phosphory l ribose epimerase DprE1
(Science. 2009. Benzothiazinones kill Mycobacterium tuberculosis by blocking arabinan synthesis)

- ***Proved mechanism of action:*** inhibits synthesis of arabinogalactan (one of the key component of the cell wall of M.Tuberculosis
(*Science. Trans Med. 2012. Structural basis for benzothiazinone-mediated killing of Mycobacterium tuberculosis)*





High efficacy and safety parameters of PBTZ169:

- **The best known active substance, active against M.Tuberculosis:** Minimum inhibitory concentration (MIC)< 0.2 ng/mL for M. Tuberculosis H37Rv strain.
- **Effective against MDR and XDR forms of tuberculosis** – demonstrated on clinically isolated strains from different parts of the world.
- **No antagonism** with other anti-TB drugs.
- **Safety and good tolerability of PBTZ169 were proved in pre-clinical and clinical trials in EU and Russia.** These characteristics are especially important taking into account the long period of treatment TB.
- **Broad spectrum of activity –** active also against M. Leprae (lepra), anaerobic actinomycetes etc.

PBTZ (BTZ) resistance in M. tuberculosis clinical isolates

MACOZINONE

TABLE 1. MICs of BTZ043 for *M. tuberculosis* clinical isolates

Isolate source and group	No. of isolates (%)	No. of HIV-positive isolates (%)	BTZ043 MIC (ng/ml) or resistance status[a]
Sondalo Hospital			
Sensitive	78 (66.1)	1 (1.2)	0.75–3
MDR	16 (13.6)	0	0.75–3
Resistant	24 (20.3)	0	0.75–3
Total	118	1 (8.4)	0.75–3
Spallanzani Hospital			
Sensitive	36 (46.2)	1 (2.8)	3–6
XDR	1 (1.2)	0	3–6
MDR	13 (16.8)	2 (7.7)	3–6
Resistant	28 (35.8)	2 (7.4)	3–6
Total	78	5 (5.1)	3–6
Ambroise Paré Hospital			
Sensitive	28 (87.5)	1 (3.5)	<15*
MDR	2 (6.25)	0	<15
Resistant	2 (6.25)	0	<15
Total	32	1 (3.1)	<15*
Central Institute of Tuberculosis			
MDR	7 (58.6)	0	3–6
Resistant	5 (41.4)	0	3–6
Total	12	0	3–6
Total			
Sensitive	142 (59.2)	3 (2.1)	S
XDR	1 (0.4)	0	S
MDR	38 (15.8)	2 (5.2)	S
Resistant	59 (24.6)	2 (3.4)	S
Total	240	7 (2.9)	S

[a] * indicates three strains with MICs of 30 ng/ml. S, sensitive.

"PBTZ169 is very effective when combined with two existing TB drugs, pyrazinamide and bedaquiline. "This could be the winning strategy," says Dr Cole. "These molecules attack different targets in the bacterium. By combining them, **we dramatically reduce the risk it will mutate into more resistant forms.**"

Stewart Cole.
Financial Times. March 2014

Pasca et al. (2010) Antimicr. Agents Chemother.

** PBTZ 169 – is improved chemical modification of BTZ 043*

MACOZINONE: Key Competitive Benefits

«First in class» anti-tuberculosis drug

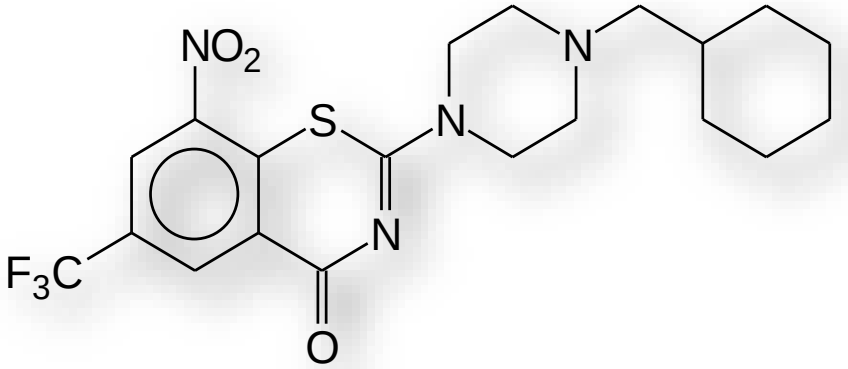
Unique target - mycobacterial cell walls enzyme DprE1
Unique mechanism of action

Low probability of appearance of M.tuberculosis resistance

Bactericide action – active against MDR & XDR TB types

A favorable safety profile is confirmed by the results of preclinical and clinical studies

Synergism and additive effect with combination tuberculosis therapy drugs



Class:

Benzothiazinone

Chemical name:

2-[4-(cyclohexylmethyl)piperazin-1-yl]-8-nitro-6-(trifluoromethyl)-1,3-benzothiazin-4-one

INN (WHO approved in 2018):

Macozinone

ATC:

Antituberculsis drug

MACOZINONE: CLINICAL TRIALS IN RUSSIA

* FIRST IN MAN SAFETY, TOLERABILITY & PHARMACOKINETICS STUDY OF PBTZ169 (Macozinone), capsules 40 mg

40 healthy volunteers received PBTZ169:

- Single ascending doses – 40, 80, 160, 320, 640 mg
- Multiple ascending doses – 320 and 640 mg daily for 14 days

Main results:

✓ **PBTZ169 had an acceptable safety profile and was well-tolerated**

- No serious adverse events (SAE), no negative effects on vital signs, no increase in adverse events (AE) frequency with increasing doses

✓ **PK data obtained:**

- Linear dose dependences of absorption, distribution and excretion parameters was shown
- The drug was rapidly absorbed (T max = 1,5-2,5 h) and excreted
- High dose-dependent volume of distribution

The data allowed to design a clinical study in patients with tuberculosis

*https://clinicaltrials.gov/ct2/results?term=PBTZ169&draw=2&rank=4#rowId3.

MACOZINONE: CLINICAL TRIALS IN RUSSIA

*EFFICACY, SAFETY & PHARMACOKINETICS STUDY OF PBTZ169, capsules 80 mg, IN PATIENTS WITH TUBERCULOSIS

In accordance with **FDA and EMA recommendations**, the **efficacy** of PBTZ169 in patients with newly diagnosed tuberculosis was evaluated in terms of **early bactericidal activity (EBA)** after 14 days of monotherapy.

Major results:

- ✓ An **acceptable safety profile of PBTZ169 for patients** with tuberculosis has been **confirmed**
- ✓ Patients' PK data obtained
- ✓ The drug efficacy evaluated
- ✓ The **effective dose determined**

Statistically significant EBA_{0-14} of Macozinone, 640 mg was demonstrated

Mycobacterial count (agar inoculation) for group 3 (**PBTZ169 640 mg**)

The maximum studied dose 640 mg = the effective dose

A study of possibility of **dose escalation** was required

*https://clinicaltrials.gov/ct2/results?term=PBTZ169&draw=2&rank=4#rowId3.

MACOZINONE: CLINICAL TRIALS IN RUSSIA

*SAFETY, TOLERABILITY & PHARMACOKINETICS STUDY OF PBTZ169, capsules 80 mg, IN HEALTHY VOLUNTEERS: **DOSE ESCALATION** & **REGIMENS**

60 healthy volunteers received PBTZ169 (640 to 1280 mg):

- **Dose escalation** up to 1280 mg single / daily dose and dose proportionality assessment
- **Food effect** (PK parameters of PBTZ169 640 mg before / after meals intake compared)
- **Once daily** (OD) and **twice-daily** (BiD) **regimens** compared (1280 mg vs 640 mg twice a day)
- Multiple dosing (OD dosing of 1280 mg after meals for 14 days) with **cumulation** assessment

Major results:

- ✓ The possibility of **dose escalation** while maintaining a **favorable safety profile** is confirmed
- ✓ A statistically significant increase in the main PK parameters of **PBTZ169, 640 mg**, administered **after meals** was demonstrated
- ✓ **BiD** dosing provides **higher exposure** compared to OD
- ✓ **No cumulation** for the multiple dosing was observed

*https://clinicaltrials.gov/ct2/results?term=PBTZ169&draw=2&rank=4#rowId3.

MACOZINONE: CLINICAL TRIALS

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Study to Evaluate the Safety, Tolerability and Pharmacokinetics of **PBTZ169** in Multiple Dosing	• Tuberculosis, Pulmonary	• Drug: **PBTZ169** • Drug: Placebo	• Division of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne, Vaud, Switzerland
2	☐	Terminated Has Results	Phase 2a Study of **PBTZ169**	• Tuberculosis	• Drug: **PBTZ169** • Drug: Isoniazid	
3	☐	Completed	Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Ex-vivo Antitubercular Activity of **PBTZ169** Formulation	• Tuberculosis • Tuberculosis, Pulmonary	• Drug: **PBTZ169** Formulation • Drug: Placebo • Drug: **PBTZ169** NCP	• Division of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne, Vaud, Switzerland
4	☐	Completed Has Results	Safety, Tolerability, Pharmacokinetics and Food Effects Study of **PBTZ169**	• Healthy Subjects	• Drug: **PBTZ169** 640 mg OD • Drug: **PBTZ169** 640 mg BiD • Drug: **PBTZ169** 960 mg SD • (and 2 more...)	• Clinical hospital at the Yaroslavl station of the Open Joint Stock Company Russian Railways Yaroslavl, Russian Federation
5	☐	Completed Has Results	Phase 1 Study of **PBTZ169**	• Tuberculosis	• Drug: **PBTZ169** - 40 mg • Drug: **PBTZ169** - 80 mg • Drug: **PBTZ169** - 160 mg • (and 4 more...)	

https://clinicaltrials.gov/ct2/results?term=PBTZ169&draw=2&rank=4#rowId3.

MACOZINONE: CLINICAL TRIALS *in press*

applied sciences

MDPI

Review

Development of Macozinone for TB treatment: An Update

Vadim Makarov [1,*] and Katarína Mikušová [2]

[1] Federal Research Center "Fundamentals of Biotechnology RAS", Leninsky prospect 33, bld. 2, 119071 Moscow, Russia
[2] Department of Biochemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, 84215 Bratislava, Slovakia; katarina.mikusova@uniba.sk
* Correspondence: makarov@inbi.ras.ru

Received: 5 March 2020; Accepted: 25 March 2020; Published: 26 March 2020

check for updates

Abstract: Macozinone, a piperazine-benzothiazinone PBTZ169, is currently undergoing Phase 1/2 clinical studies for the treatment of tuberculosis (TB). In this review we summarize the key findings that led to the development of this compound and to identification of its target, decaprenylphospohoryl ribose oxidase DprE1, which is involved in the synthesis of the essential arabinan polymers of the cell wall in a TB pathogen, *Mycobacterium tuberculosis*. We present the results of the pilot clinical studies, which raise optimism regarding its further development towards more efficient TB drug regimens.

Keywords: macozinone; DprE1 inhibitor; clinical studies

1. Introduction

Tuberculosis (TB) as both an acute and chronic infectious disease is still unbeaten and represents an important social, medical, and biological challenge for the healthcare worldwide [1]. The infection caused by *Mycobacterium tuberculosis* strains is most often located in the respiratory tract from which it is transmitted in the population by aerosols. At the same time, mycobacteria can be disseminated also to other organs. However, it is now well acknowledged that even in its primary location, the TB pathogen is present in different microenvironments and thus in various metabolic states, which substantially complicates the treatment [2]. According to the last Global Tuberculosis Report issued by the World Health Organization (WHO) [3], in 2018 the death rate was estimated to be about 1.45 million people. Among the estimated 10 million new cases of TB, 3.4% had multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB). This number increased to 18% in previously treated cases, with the highest proportions (>50% in previously treated cases) in countries of the former Soviet Union. Although efficient TB treatment is available, only 7 million new cases were treated for the disease in 2018, while an estimated 3 million patients did not have access to quality care or were not reported, and only one in three people with drug-resistant TB accessed care [3].

In addition to interventions in the social area and point-of-care management of TB, one of the key challenges in making the fight against TB more effective is to improve treatment options. The current chemotherapy for the drug-sensitive TB takes about six months and requires administration of four different medicines (isoniazid, rifampicin, ethambutol, pyrazinamide) to avoid development of drug resistance. The length of the treatment and its adverse effects result in bad compliance and thus it is imperative to find novel drugs and regimens that would be less demanding on patients [4].

During recent years, three novel drugs against TB were approved. These are bedaquiline [5], delamanid [6] and pretomanid [7], which are currently undergoing several clinical trials aimed at treatment of the drug-resistant TB, as well as at shortening standard TB treatment [8]. The efforts and hope for better TB drugs are exemplified also by the pipeline of several new molecules, that

Makarov, Vadim, and Katarína Mikušová. "Development of Macozinone for TB treatment: An Update." *Applied Sciences* 10.7 (2020): 2269. https://www.mdpi.com/2076-3417/10/7/2269

The main results of clinical trials of the efficacy, safety and pharmacokinetics of the perspective anti-tuberculosis drug makozinone

A.O. Mariandyshev[1], A.L. Khokhlov[2], S.V. Smerdin[3], V.S. Shcherbakova[4], O.V. Igumnova[4], I.V. Ozerova[5], A.A. Bolgarina[4], N.A. Nikitina[4]

[1]Northern State Medical University, Arkhangelsk, Russia;
[2]Yaroslavl State Medical University, Yaroslavl, Russia;
[3]Moscow Regional Clinical Tuberculosis Dispensary, Moscow, Russia;
[4]NEARMEDIC PHARMA ltd., Obninsk, Russia;
[5]Zakusov Research Institute of Pharmacology, Moscow, Russia

Tuberculosis is a chronic infectious disease, usually localized in the respiratory system and representing one of the most important global social and biomedical health problems associated with the spread of therapy-resistant forms (multidrug-resistant and extensively drug-resistant tuberculosis). One of the most promising targets for the development of antimycobacterial drugs is the enzyme DprE1, which is involved in the synthesis of the cell wall of mycobacteria. In the series of DprE1 inhibitor drugs, the most advanced drug is PBTZ169 (INN macozinone). Clinical trials (CT) of the efficacy and safety of macozinone are conducted by the pharmaceutical company LLC NEARMEDIC PLUS in the Russian Federation, and in other countries (Sponsors: Innovative Medicines for Tuberculosis Foundation, École polytechnique fédérale de Lausanne and Bill and Melinda Gates Foundation). The publication describes results of completed I, IIa and Ib phases CT, conducted in the Russian Federation.

Aim. The goal of phase I CT was to assess the safety, tolerability and pharmacokinetics (PK) of PBTZ169, 40 mg capsule, after single and multiple administration under fasting conditions in increasing doses in healthy volunteers. The goal of phase IIa CT was to study the efficacy (in terms of early bactericidal activity – EBA), safety and PK of the drug PBTZ169, 80 mg capsules, in various doses, when used as monotherapy in patients with newly diagnosed respiratory tuberculosis with bacterial excretion and retained sensitivity to isoniazid and rifampicin. The purpose of phase Ib CT was to evaluate the safety, tolerability, PK of PBTZ169, 80 mg capsule, after single, double and multiple administration under fasting conditions in increasing doses, as well as the effect of food on its bioavailability in healthy volunteers.

Materials and methods. The data of 100 healthy volunteers and 15 patients with newly diagnosed pulmonary tuberculosis, who received the study medication PBTZ169, capsules 40 mg and 80 mg, in the dose range 40 mg – 1280 mg of PBTZ169, obtained during phase I, IIa and Ib CTs were analyzed. During I phases CTs, safety, tolerability, and PK of the drug after a single and multiple administration under fasting condition and after meals at rising doses were evaluated. The safety assessment included evaluation of AE/SAE, vital signs, ECG results, and laboratory tests results in the safety population. In the course of phase IIa CT, in addition to safety, tolerance, and PK evaluation, the efficacy of the drug (in terms of EBA) using sputum culture on agar with CFU/ml counting (main method) and quantitative PCR method (auxiliary method) was evaluated.

Results. During all CTs, a high safety and tolerability profile was shown, the main PK parameters of the drug and the efficacy were described. PBTZ169 demonstrated linear PK in the dosage range up to 640 mg after single and multiple administration, a statistically significant of EBA of the drug after monotherapy at the dose of 640 mg/day was demonstrate, and it was concluded that the preferred regimen of the drug PBTZ169 intake is administration after meals. Good tolerability and a favorable safety profile of the drug in the studied doses range were demonstrate during all the CTs.

Conclusion. One of the most promising and currently studied drugs-inhibitors of DprE1, a new target for the cell wall of mycobacteria, is PBTZ169 or macozinone, which is being develop by the Russian pharmaceutical company NEARMEDIC PLUS ltd.

Keywords: tuberculosis, multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis, macozinone, PBTZ169, benzothiazinones, DprE1 inhibitors, DprE1, isoniazid, new antituberculosis drugs.

For citation: Mariandyshev A.O., Khokhlov A.L., Smerdin S.V., et al. The main results of clinical trials of the efficacy, safety and pharmacokinetics of the perspective anti-tuberculosis drug makozinone. Therapeutic Archive. 2020; 92 (3): 61–72. DOI: 10.26442/00403660.2020.03.000621

Mariandyshev, A. O., et al. "The main results of clinical trials of the efficacy, safety and pharmacokinetics of the perspective anti-tuberculosis drug makozinone (PBTZ169)." *Terapevticheskii arkhiv* 92.3 (2020): 61-72. https://ter-arkhiv.ru/0040-3660/article/view/33905

MACOZINONE: CLINICAL TRIALS IN RUSSIA

MAJOR CONCLUSIONS: PBTZ169, capsules

Clinical study results showed:

- **Efficacy of PBTZ169 in the dose 640 mg in terms of early bactericidal activity**
- **Possibility of dose escalation due to favorable safety profile**
- **Regimen of drug intake "after meals" was determined based on significant effect of food on the PK parameters**
- **PK parameters suggest necessity of drug intake at least 2 times a day, which may reduce patients' compliance and increase the treatment course cost compared to OD intake regimen**

PK profile of the drug needs to be improved

Ways of development

Increase of API bioavailability and exposure

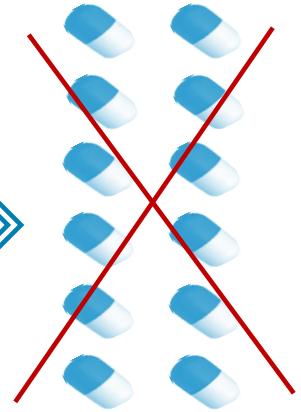
Development of new FDF

Macozinone / bioavailability: solution.

Features

- Physical and chemical properties
- PD and PK properties
- Technological properties

Changing of a low-dosage instant finished form (capsules 80 mg) with a high-dosage form



DT* 320 / 640 mg

- *compliance improvement*
  +
- *exposure improvement*

Development of a new modified bioavailability/release finished dosage form

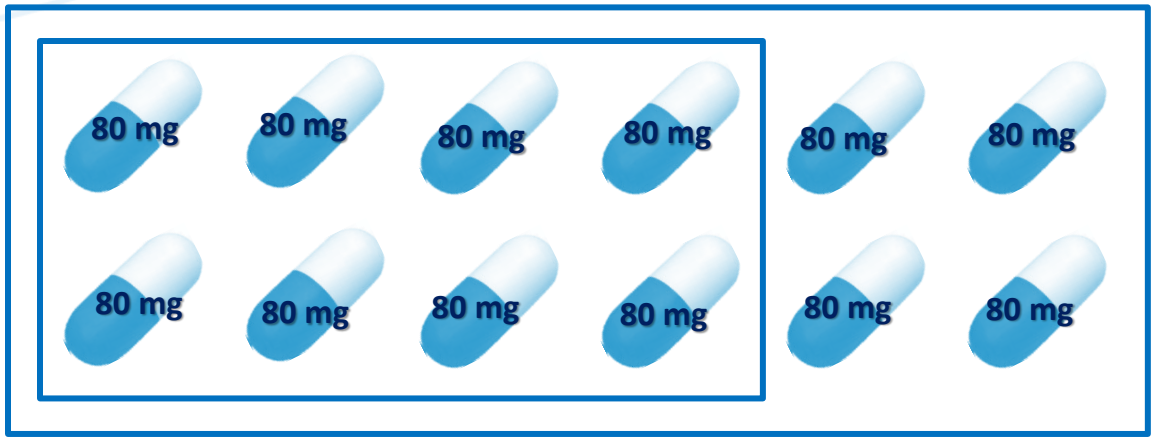
Inclusion complex, GRDF

- *compliance improvement*
  +
- *exposure/bioavailability improvement*

DT - Dispersible Tablet, ** GRDF – Gastroretentive Dosage Form with prolonged release

Macozinone: Developing of new dosage form

CONCERN



- low compliance

PROPOSED SOLUTIONs

Dispersible tablet for oral suspension

OR

Gasrtoretentive tablet with prolonged release

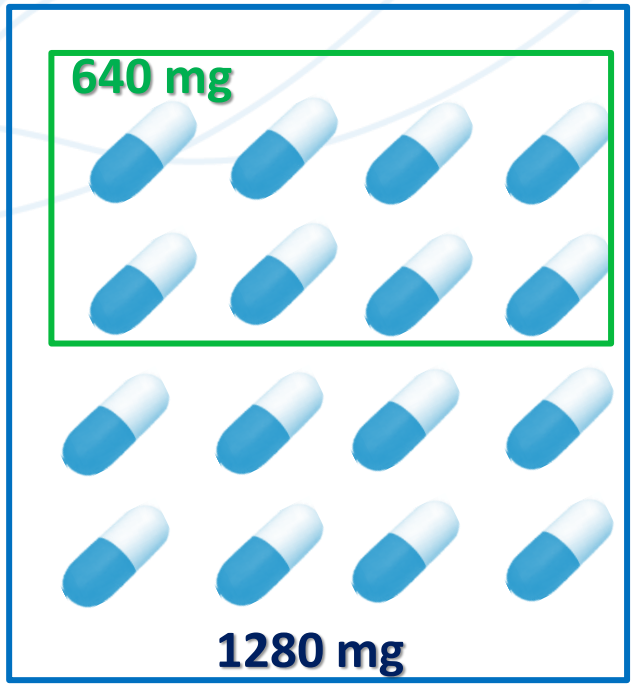
- compliance improvement

MACOZINONE: Developing of new dosage form

2017

Capsules, 80 mg

DONE



Daily Dose: 1280mg

8 capsules

Efficacy

- **Complaince is not enough**

2018

Tablet for preparing oral suspension, 640 mg

DONE

Daily Dose : 1280 mg

2 tablets

Efficacy

Increasing of compliance

2019

Gasrtoretentive tablet with prolonged release, 500 mg

DONE

Daily Dose 500 mg

1 tablet

Efficacy

Increasing of effective concentration in Blood
Increasing of Bioavailability
Reduction of Daily Dose without loss of efficiency
Reduction of substance consumption loss of efficiency

Project technology development status in Russia

MACOZINONE

API (DONE)

- Controlled manufacturing process was developed and validated on the GMP-certified plant
- Documentary manufacturing process is fully completed
- Specifications, industrial regulations and techniques: fully completed
- Regular production API batches
- The industrial module for the production of API in the territory of Nearmedic new pharmaceutical GMP-certified plant (Russia): completed

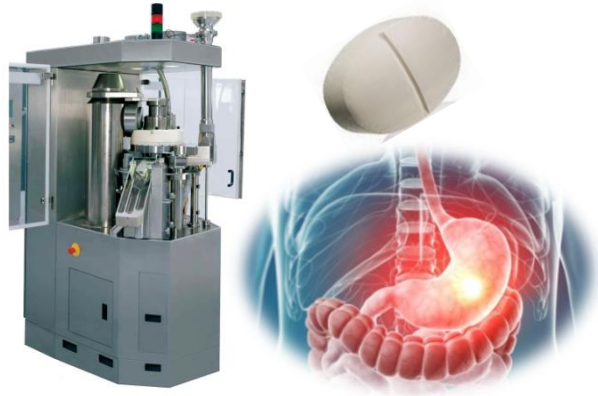
CAPSULES (DONE)

- Controlled manufacturing process was developed and validated on the GMP-certified plant (Russia)
- Specifications, industrial regulations and techniques are issued
- Regular production

DISPERSIBLE TABLET (DONE)

- Controlled manufacturing process development is completed
- Specifications, industrial regulations and techniques are issued

GASTRORETENTIVE TABLET (DONE)



- Controlled manufacturing process development is completed
- Stability studies – DONE (Gasrtortentive tablet is stable)

MACOZINONE Project: aggregated current status: 2020

Technology

- **An industrial technology** for the synthesis of API and the DF **have been developed.**
- **25.12.2019г. A dossier** on a pharmaceutical substance which produced at an industrial site in the city of Obninsk **was filed** for registration in the Ministry of Health of the Russian Federation.
- **A transfer** of industrial technology for the synthesis of API to the production site of LLC NIARMEDIC PLUS **was carried out.**
- A new dosage form has been developed - a dispersible tablet **(solution to the complains problem)**
- **A new dosage form (Gasrtoretentive tablet with modified release) with improved bioavailability parameters has been developed and patented now.**

Preclinical Studies

- **A full range** of preclinical in vitro and in vivo studies of pharmaceutical substances has been **carried out** in the EU and Russia, where have been **shown a synergism and additive effect** in combination with anti-TB drugs.
- **Efficacy** against M. tuberculosis, including species characterized by multidrug and extensive drug resistance (MDR, XDR) **was shown.**
- **Safety was Proven**

Clinical Trials

Ia Phase (RUS): A favorable safety profile and good tolerance were shown (single dosing and **multiple dosing with a maximum dose of 640 mg)**

Ib Phase (RUS): The possibility of increasing the dosage of the drug (to increase effectiveness) and improving efficacy (pharmacokinetics) with a favorable safety profile and good tolerance was shown.

Ia Phase (EPFL, EU): A favorable safety profile and good tolerance were shown (single dosing with a maximum dose of 640 mg)

All studies are conducted in accordance with GCP standards.

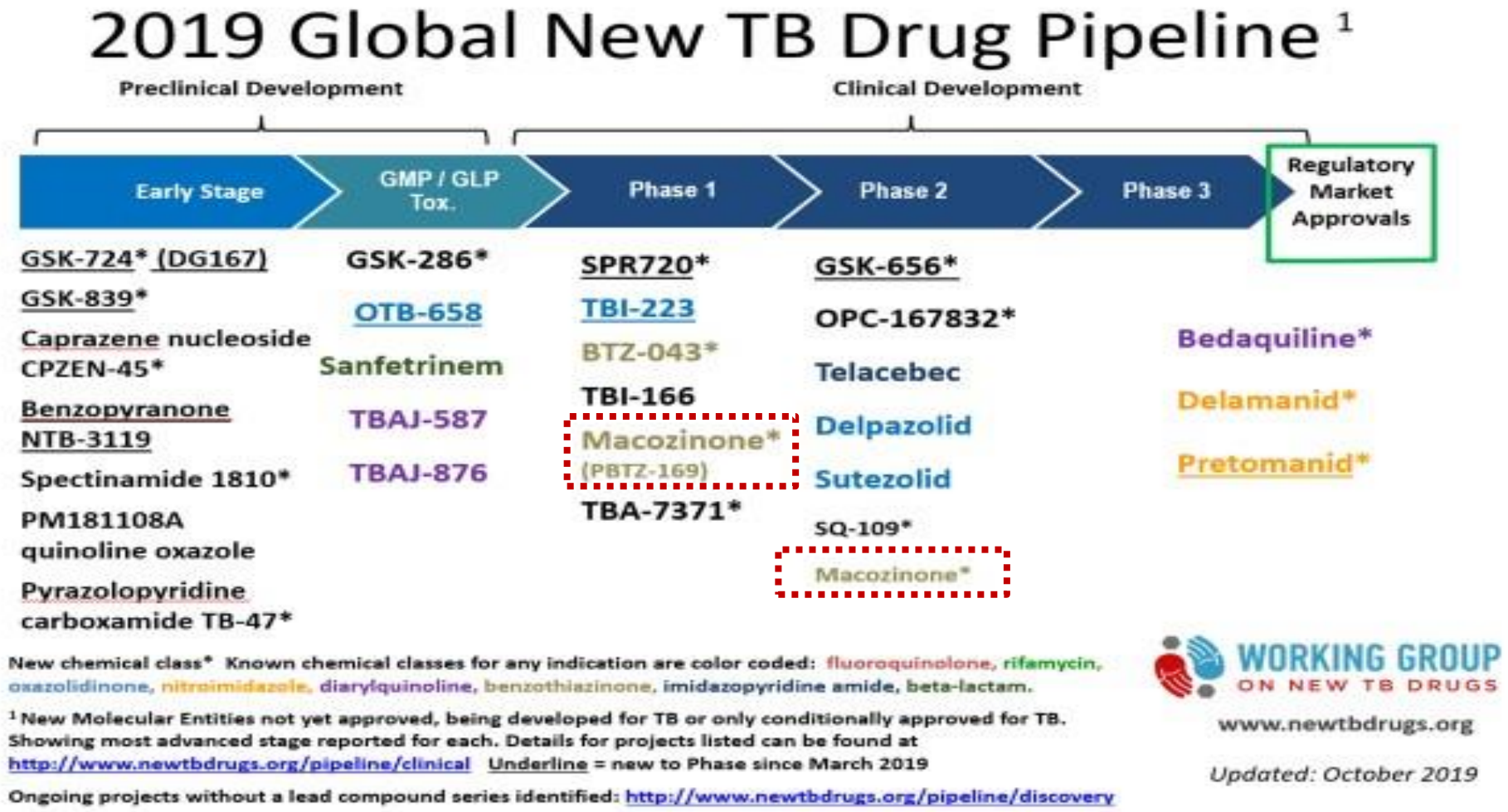
IIa Phase: early bactericidal activity in patients with newly diagnosed tuberculosis (RUS) :

A **high safety and tolerability level** for patients with tuberculosis has been shown.

A statistically significant **early bactericidal activity** of the drug was shown in patients with tuberculosis: **Macosinone – is effective**

The study was conducted in accordance with the standards of GCP and FDA (for patients with tuberculosis)

MACOZINONE Project: the tracking of the project development status by specialized international agencies



PATENT OF MACOZINONE NEW DOSAGE FORMS

Patent Application filed with № 2018123363/201037027 from 27.06.2019