MACOZINONE (PBTZ 169) PROJECT
NEARMEDIC GROUP

October 2020
MACOZINONE (PBTZ 169) – a new unique drug for the treatment of all forms of tuberculosis

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.

"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.”
MACOZINONE (PBTZ169): new original drug to cure tuberculosis

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

Benzothiazinones (BTZ-PBTZ) as antimycobacterial agents

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

- 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.
- EMBO Molecular Medicine. 2014 Towards a new combination therapy for tuberculosis with next generation benzothiazinones
MACOZINONE (PBTZ169): new original drug to cure tuberculosis

- **Unique target:** vital enzyme of the cell wall of mycobacteria decaprenyl-phosphoryl 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

All 240 *M. tuberculosis* clinical isolates (including MDR and XDR strains) do not have mutations in *dprE1* gene and are sensitive to BTZ*.

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

“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

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:
Antituberculosis 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

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

The maximum studied dose 640 mg = the effective dose
A study of possibility of dose escalation was required

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

# MACOZINONE: CLINICAL TRIALS

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Development of Macozinone for TB treatment: An Update

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

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Tuberculosis is a chronic infection disease, usually localized in the respiratory system and representing one of the most important global social and biomedical problems associated with the spread of therapy-resistant and extensively drug-resistant tuberculosis. One of the most promising targets for the development of antitubercular drugs is the enzyme PhtE, which is involved in the synthesis of the cell wall of mycobacteria. In the series of PhtE inhibitor drugs, the most advanced drug is PBTZ169 (PPTZ169). Clinical trials (CTTs) of the efficacy and safety of makozinone are conducted by the pharmaceutical company NAKEMEDIC PLUS in the Russian Federation, and in other countries: Spornova Innovative Medicines for Tuberculosis Foundation, Côte d’Ivoire, The Tuberculosis Foundation of Ukraine, and WHO. The presentation describes results of completed I, II, and phase III trials conducted in the Russian Federation.

The main goal of phase I-III was to assess the safety, tolerability and pharmacokinetics (PK) of PBTZ169: 40 mg/kg, after single and multiple administration under fasting conditions in increasing doses in healthy volunteers. The goal of phase IV was to study the efficacy in terms of early bacteriological activity - EBA, safety and PK of the drug PBTZ169, 80 mg/kg, in various doses, when used as monotherapy in patients with newly diagnosed pulmonary tuberculosis with bacillary concentration and related sensitivity to isoniazid and rifampicin. The purpose of phase IV consists of evaluating the safety, tolerability, PK of PBTZ169, 80 mg/kg, after single and multiple administration under fasting conditions in increasing doses, as well as the effect of food on 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, 40 mg/kg, and 80 mg/kg, in the dose range 40 mg/kg - 1200 mg/kg of PBTZ169, obtained during phase I, II and III CTTs were analyzed. During I, phase II, safety, tolerability, PK, and of the drug after single and multiple administration under fasting condition and after meals at dosing were evaluated. The safety assessment included evaluation of A/SAEs, vital signs, ECG results, and laboratory tests results in the safety population. In the course of phase II CTT, in addition to safety, tolerability, PK evaluation, the efficacy of the drug (in terms of EBA) using open comparison with a traditional DST (from CTT 2), according to the new method and quantification (method 2) was evaluated.

Results. During the G1 phase, 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 dosages range up to 640 mg/kg for single and multiple administration, a statistically significant increase of EBA of the drug after monotherapy at the dose of 64 mg/kg was demonstrated, and it was concluded that the preferred regimen of the drug PBTZ169 is the initial administration after failure. Good tolerability and a favorable safety profile of the drug in the studied dosage range were demonstrated during all the CTTs.

Conclusion. One of the most promising and currently studied drug-inhibitors of PhtE, a new target for the cell wall of mycobacteria, is PBTZ169 or makozinone, which is being developed by the Russian pharmaceutical company NAKEMEDIC PLUS.

Keywords: tuberculosis, drug-resistant tuberculosis, extensively drug-resistant tuberculosis, macozinone, PBTZ169, antituberculosis, PhtE inhibitor, makozinone, new anti-tuberculosis drugs.
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

- Development of a new modified bioavailability/release finished dosage form

**Inclusion complex, GRDF**

- compliance improvement
- exposure/bioavailability improvement

**MACOZININONE**

*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

- Gasrtoretentive tablet with prolonged release

OR

- compliance improvement
MACOZINONE: Developing of new dosage form

2017
Capsules, 80 mg
DONE

2018
Tablet for preparing oral suspension, 640 mg
DONE

2019
Gasrtoretentive tablet with prolonged release, 500 mg
DONE

Daily Dose: 1280 mg
8 capsules
**Efficacy**

- Compliance is not enough

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

Daily Dose: 1280 mg
2 tablets
**Efficacy**

Increasing of compliance

Daily Dose: 500 mg
1 tablet
**Efficacy**
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.

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

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

Controlled manufacturing process development is completed.
Stability studies – DONE (Gastroretentive tablet is stable).
An industrial technology for the synthesis of API and the DF have been developed.

25.12.2019. 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 complaints problem)

A new dosage form (Gasroretentive 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.

Ila 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

2019 Global New TB Drug Pipeline¹

Preclinical Development

- Early Stage
  - GMP / GLP Tox.
- Phase 1
  - GSK-286*
  - SPR720*
  - GSK-656*

Clinical Development

- Phase 2
  - TBI-223
  - OPC-167832*
  - Telacebec
  - Daplovazol
  - Sutezolid
  - Pretomanid*

- Phase 3
  - TBAJ-587
  - Macozinone*
  - PBTZ-169

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, 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. Underline = new to Phase since March 2019

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

Updated: October 2019
Patent Application filed with № 2018123363/201037027 from 27.06.2019