Tuberculosis (TB) is described as the second ‘leading killer’ among infectious diseases worldwide. In 2012, World Health Organization (WHO) registered about 8.6 million incident cases of tuberculosis and 1.3 million deaths related to this disease. It is estimated that the mortality rate has fallen by 45% since 1990. Although there has been shown a declining tendency of the incidence and death rates since 2008, the global burden of tuberculosis remains a challenge for medicine and researchers (1). Alarming epidemiological indicators suggesting increased amount of incidents of tuberculosis tended to search for new compounds with potential antituberculosis activity.

The first line antituberculosis drugs for adults recommended by WHO are: isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. The combination of these molecules is classified as the group 1 of drugs and used for drug susceptible TB treatment (2). On the other hand, it is estimated that 3.6 percent of new diagnosed cases and 20.2 percent of previously diagnosed and treated patients suffer from MDR-TB (multidrug-resistant tuberculosis) (1). MDR-TB arises as a result of a prescription of inadequate medicines, the low quality of antituberculosis drugs, long breaks during therapy, an absence of standardized guidelines and a premature termination of therapy (3).

MDR-TB is described as resistance to at least two of the first line antituberculosis drugs: isoniazid and rifampicin. It is classified into two groups: primary and acquired MDR-TB infection. The first type of MDR-TB occurs in cases when patients have previously not suffered from tuberculosis resistant to treatment. In turn, the acquired MDR-TB occurs in patients after receiving the inefficient antituberculosis therapy (1, 4). The list of second line antituberculosis drugs which are considered as effective in MDR-TB treatment for adults, contains e.g., amino-glycosides, fluoroquinolones, thioamides, para-aminosalicylic acid, cycloserine and other drugs with unclear role in treating drug-resistant TB (2). Globally, the main difficulties in the therapy and safety are caused by XDR-TB (extensively drug-resistant tuberculosis), which occurred in 92 countries in 2012 and is becoming an important threat. This type of tuberculosis is characterized as MDR-
TB with additional resistance to fluoroquinolones and second line injectable agents (1).

The previously shown statistics suggest that there is an urgent need to discover the new potential drugs with the novel mechanisms of actions against MDR-TB. In this review we focus on bedaquiline, which was approved by FDA in December 2012 and received an conditional approval of the European Union in March 2014. Another new and promising drug, delamanid (dihydro-nitroimidazooxazole derivative, phase III), has recently received a first global approval in the European Union. Some new molecules which are tested in clinical trials include: AZD5847 (oxazolidinone derivative, phase II), pretomanid (nitroimidazole derivative, phase III), sutezolid (oxazolidinone derivative, phase II) and SQ109 (ethambutol analogue, phase II). Furthermore, some interesting molecules are also examined in preclinical studies: SQ609, SQ641 and CPZEN-45.

Bedaquiline

**Mechanism of action and indications**

\[(1R,2S)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-naphthal-1-yl-1-phenylbutan-2-ol\]

Bedaquiline is described as a drug with the novel mechanism of action in comparison with other medicines prescribed so far. This diarylquinoline derivative interfere with the new target, mycobacterial ATP synthase. ATP synthase is a key enzyme used by tubercle bacilli in generation of energy. The process of inhibition of ATP synthesis results in bactericidal action on replicating and non-replicating strains of *Mycobacterium tuberculosis*. Bedaquiline may also act bacteriostatically on some non-tuberculous species of mycobacteria. What is more, its intracellular activity after using mainly intraperitoneal macrophages or macrophage-like cell line seems to be superior than extracellular bactericidal activity of this drug (5, 6).

It is known that this drug has lower affinity to human ATP synthase (5). Bedaquiline is intended to treat multidrug-resistant pulmonary tuberculosis in adult patients in combination with other drugs in case of impossibility of using other regimens due to intolerability or resistance (6).

**Preclinical trials**

Preclinical data characterized the most effective combinations of antimycobacterial drugs included bedaquiline as an addition to standard regimens.

The experiments conducted by Shang et al. (7) in guinea pigs demonstrated the efficacy of combination therapy containing bedaquiline, rifampin and pyrazinamide. The bacteria level decreased to hardly detectible in the lungs, lymph nodes and spleens after 4 weeks of therapy. The reduction of the area of lungs with lesions was also observed in six weeks of cure. Unfortunately, the study proves that the relapse may occur in 10 to 11 months after the completion of treatment (7). In turn, Zhang et al. (8) showed that bedaquiline in combination therapy with rifapentin were more active than rifampin tested with isoniazid and rifapentine with isoniazid in mouse model. The study describes that bedaquiline in co-administration with rifapentin and pyrazinamide and also bedaquiline alone are more effective in preventing from relapse than other drugs combinations (8).

According to Andreis et al. (9) experiments, bedaquiline administered with pyrazinamide, rifapentin or with pyrazinamide, rifapentin, moxifloxacin and also bedaquiline 1/2 in combination with pyrazinamide and rifapentin are the most bactericidal regimens and have low rate of relapse (9).

Furthermore, the treatment of MDR-TB in mice by Veziris et al. provides information that addition of bedaquiline to amikacin, ethionamide, pyrazinamide and moxifloxacin reduces the therapy to 6 months and the relapse rate remains at the same level. It has been shown that regimen excluding amikacin and ethionamide maintains the similar relapse rate and the treatment duration (10). In turn, Ibrahim et al. demonstrated that regimens containing bedaquiline shortens the therapy to 4 months in comparison with 6-month-lasting standard regimen in mice. The new diarylquinoline combinations treatments are more effective than those containing moxifloxacin (11).

The previously conducted study by Veziris et al. (12) described the efficacy of triple combination of drugs: bedaquiline, rifapentin, pyrazinamide in mice treated once per week. Ibrahim et al. (13) showed that bedaquiline is more effective than the other antituberculosis drugs in mice against tuberculosis. This ATP synthase inhibitor coupled to rifampin, isoniazide, pyrazinamide or moxifloxacin brought to culture-negative lung homogenates in 70 to 100 percent of mice. What is more, the addition of pyrazinamide revealed synergistic action of these two drugs.
**Clinical trials**

The phase I open-label clinical trial in 37 healthy volunteers who received 400 mg dose of bedaquiline alone and then 400 mg of this drug with concomitant steady-state efavirenz was conducted to assess the pharmacokinetic interactions between these medications. Bedaquiline is a CYP3A substrate and efavirenz can induce CYP3A isoforms. It has been shown that changes connected to co-administration of these drugs are not clinically relevant. Some adverse events which were reported during the study included serum transaminase elevations and hypoglycemia. No statistically relevant adverse events associated with prolonged QT intervals were registered (14).

Plasma concentrations of bedaquiline and M2 (N-monodesmethyl metabolite) was also determined during polytherapy with nevirapine or ritonavir-lopinavir during two trials of phase I. It has been demonstrated that nevirapine does not influence on pharmacokinetics of bedaquiline substantially. On the other hand, the decrease of clearance of bedaquiline and its N-monodesmethyl metabolite was noted in case of ritonavir-lopinavir co-administration (15, 16).

Another phase I study was conducted to evaluate the effects of bedaquiline (which is converted to M2 by CYP3A4) co-administration with rifamycin antibiotics (CYP3A4 inducers). Thirty-two volunteers took part in this experiment. The results included a significant increase in bedaquiline and M2 clearance both in case of rifampicin and rifapentin addition. There was also observed the decrease in steady-state concentrations of the drug and metabolite. It is not recommended to take bedaquiline and rifamycin antibiotics together (17).

According to Rustomjee et al. (18) presented data of phase Ia trial, 75 patients with sputum smear-positive pulmonary tuberculosis were randomized to 5 treatment groups: once-daily oral bedaquiline (25 mg, 100 mg or 400 mg), 600 mg rifampin and 300 mg isoniazid for 7 days. The decrease in colony forming unit accounts in bedaquiline group and M2 clearance both in case of rifampicin and rifapentin addition. There was also observed the decrease in steady-state concentrations of the drug and metabolite. It is not recommended to take bedaquiline and rifapentin addition. There was also observed the decrease in steady-state concentrations of the drug and metabolite. It is not recommended to take bedaquiline and rifapentin together (17).

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Randomized, double-blind phase II trial of 68 sputum smear-positive pulmonary tuberculosis patients surveyed the 14-day efficacy against tuberculosis of daily doses of 100, 200, 300 and 400 mg bedaquiline preceded by single daily loading dosages of this drug. However, the fall in log_{10} CFU occurred in each of the group, the highest bactericidal activity was observed in 400 mg group. The decrease continued until the 14th day of the study. Skin abnormalities, headache, nausea or vomiting were reported as mild to moderate events during the study. Asymptomatic transient elevation of aspartate aminotransferase from 78 U/L to 125 U/L, which was observed in one patient in 100 mg group, was considered as severe. There were no adverse events connected to QT intervals prolongation (19).

Patients with sputum smear-positive pulmonary multidrug-resistant tuberculosis took part in phase II trial. The aim of the study was to assess effectiveness, safety and tolerability of bedaquiline. Participants (233) received 400 mg of the new drug twice daily with standard drugs for two weeks and then, from week 3 to week 24, bedaquiline was administered in 200 mg dosage three times daily with background regimens (which was taken alone from week 25 till the end of the study). The number of registered serious adverse events was 47 and included e.g., pneumothorax, hemoptysis, pneumonia. Twelve deaths were noted during the trial (20).

In another phase IIb study bedaquiline with background regimens was administered to 160 patients in comparison to group who received placebo in combination with standard drugs. Participants suffered from smear-positive, multidrug-resistant tuberculosis. As the results, the number of deaths was higher in bedaquiline group. However, the level of adverse events was comparable in both cases (21).

In turn, randomized, double-blind and placebo-controlled phase II study in 47 patients (23 in bedaquiline group and 24 in placebo group) with newly diagnosed pulmonary tuberculosis and resistance to isoniazid and rifampin conducted by Diacco et al. describes the safety, tolerability, pharmacokinetics and efficacy of bedaquiline after addition to a background regimen including kanamycin, ofloxacin, ethionamide, pyrazinamide and cycloserine or terizodone. The experiment contains two stages which last 8 and 24 weeks. After the addition of bedaquiline to the background regimens the decrease of the median log_{10} CFU count occurs quicker in the tested drug group than in the placebo.
group. The results showed that patients who received bedaquiline avoided acquiring resistance in higher level in comparison to control. The most frequent adverse events, which occur during 8-week treatment, were similar in 2 groups and included nausea (significantly more often in bedaquiline group), unilateral and bilateral deafness, arthralgia, viral infection, acne, hemoptysis, hyperuricemia, pain of extremities, rash and chest pain. The intensity of adverse events was described as mild or moderate. Two patients experienced a serious adverse event (one in bedaquiline group: grade 4 diabetic ketoacidosis and one in placebo group: grade 4 pneumothorax). None of them was connected to the tested drug. No clinically relevant changes in QT intervals were observed (22, 23).

AZD5847

(5R)-3-[(4-[(1R)(2S)-2,3-dihydroxypropanoyl]-3,6-dihydro-2H-pyridin-4-yl]-3,5-difluorophenyl]-5-(1,2-oxazol-3-yloxymethyl)-1,3-oxazolidin-2-one

The new molecule which belongs to the group of oxazolidinone derivatives, AZD5847, is the orally administered drug in phase II clinical trials. This compound is a prodrug. AZD5847 disodium phosphate (AZD5847 DSP) is converted to active form of this molecule. This compound inhibits the protein synthesis by binding to the 50S ribosomal subunit and resulting in inhibition of the process of translation as was confirmed by macromolecular incorporation assay. This group of drugs interferes with PTC - the peptidyl transferase center. The inhibition occurs by competing at the site A of PTC (24-27).

Pretomanid (PA-824)

(6S)-2-nitro-6-[(4-(trifluoromethoxy)phenyl)methoxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

Pretomanid (PA-824) is a bicyclic nitroimidazole derivative, examined in phase III, clinically active against both replicating and non-replicating strains of Mycobacterium tuberculosis. It has been shown that its mechanism of action depends on the presence or lack of oxygen. The inhibition of mycolic acids biosynthesis is characteristic for aerobic conditions. In this case, the interruption of creation of ketomycolates and the increase of the level of accumulated hydroxymycolates have been observed. Pretomanid is a prodrug which requires conversion by Ddn (the deazaflavin dependent nitroreductase). In the opposite situation, PA-824 acts by nitric oxide release and may have poisoning influence on the respiratory complex. Pretomanid was compared to potassium cyanide which acts as the respiratory inhibitor. It is suggested that this molecule, as a NO donor, may have influence on the electron flow and the level of ATP (28).

Preclinical trials of this compound described the co-administration of some new antituberculosis agents. The addition of PA-824 to some first-line antituberculosis drugs in mice has been studied. The experiment demonstrated the improvement of therapy when PA-824 was added in 50 and 100 mg/kg/day dosages to rifampin and pyrazinamide. After two months of administration the mice were culture-negative and no relapse was observed after four months of therapy (29).

Another new regimens were tested. Standard first line antituberculosis agents: rifampin, isoniazid and pyrazinamide were compared with co-administration of PA-824, moxifloxacin and pyrazinamide in guinea pigs model. After 2 months of complete therapy, no relapse was observed in both groups (30). Further trial demonstrated that new examined molecules such as: bedaquiline, PA-824, sutezolid and clofazimine acted stronger than first-line antituberculosis agents in murine model of tuberculosis. Bedaquiline and sutezolid were the most efficient drug combination (31). It was also suggested that PA-824, when added to another new compounds, had antagonistic influence on them in mice (32).

Two clinical trials of phase I were conducted to assess safety and the influence of food on pharmacokinetics parameters after single dosage orally administration of PA-824. Healthy volunteers received the drug in different doses: 50, 200 or 1000 mg after meal or after 10 hours break. It has been proved that food may have influence on pharmacokinetics of this compound. What is more, all dosages were well-tolerated and no adverse events were observed (33).

Another phase I study focused on interactions between PA-824 and antiretroviral drugs (lopinavir-ritonavir, efavirenz) or rifampin in healthy participants. PA-824 is metabolized by CYP3A in about 20%. The results described different influence of another drugs on pharmacokinetic parameters of the new antituberculosis agent. Due to the study, the
most preferred was coupling of PA-824 with lopinavir-ritonavir. Each of the tested polytherapy was well tolerated (34).

Two studies of phase I conducted with 58 healthy volunteers were also conducted to evaluate the pharmacokinetics, safety and tolerability of PA-824. No significant adverse reactions were noted. Pharmacokinetics parameters were promising and consistent with dosing regimen (35).

The next step to test this molecule was to conduct more studies. The aim of the phase IIa trial was to evaluate the early bactericidal activity of PA-824. This drug was administered for 14 days in four different doses: 200, 600, 1000 and 1200 mg once daily. A control group of patients received standard anti-tuberculosis drugs. It has been shown that PA-825 is effective against tuberculosis in 14 days therapy in all tested dosages. What is more, the maximum effect was observed at the group of patients who received the lowest dosage of PA-824. This molecule was found to be also well tolerated and safe (36).

Another phase II study examined lower dosages of PA-824 in patients with pulmonary tuberculosis. Patients received orally 50, 100, 150 or 200 mg/kg of PA-824 for 14 days. A positive control consisted of isoniazid, rifampin, pyrazinamide and ethambutol. The study proved the safety and tolerability of the drug. Importantly, no relevant QT prolongation was observed. It was decided to choose a dose of 100–200 mg to examine its co-administration with standard drugs regimen (37).

What is more, PA-824 was tested in phase IIa clinical trials with another antituberculosis drugs and was compared with bedaquiline-including regimens. Patients with drug-susceptible disease received: bedaquiline alone, bedaquiline with PA-824 or pyrazinamide, PA-824 in co-administration with pyrazinamide or moxifloxacin and pyrazinamide. The last group included isoniazid, rifampicin, pyrazinamide and ethambutol to assess early bactericidal activity of 14-days therapy. The most promising results were observed in PA-824, moxifloxacin and pyrazinamide group. No clinically relevant adverse events were noted excepting one patient’s withdrawal in case of QT interval prolongation (38).

Sutezolid

Sutezolid is the second promising oxazolidinone derivative in phase II clinical trials tested against *Mycobacterium tuberculosis*. This drug is a thiomorpholinyl analogue of linezolid and acts by binding to the 23S ribosome, resulting in inhibition of protein biosynthesis. As previously mentioned, oxazolidinone derivatives inhibit the initial phase of translation as a consequence of impossibility of the creation of 70S complex. Sutezolid, when orally administered, is converted to an active sulfoxide metabolite. It is supposed that this active metabolite exhibits more potent activity against extracellular tuberculosis than sutezolid. However, it was found that the parent molecule was 17-fold more efficacious in killing intracellular tuberculosis in patients with pulmonary disease (39, 40).

The new tested drug combinations, consisting the new antituberculosis agents, were examined in preclinical trials in murine model of tuberculosis. The most active regimens included bedaquiline, sutezolid and PA-824. It has been proved that there is no two-drug-containing regimens superior other than bedaquiline alone. Future clinical trials of MDR-LTBI (multidrug-resistant – latent tuberculosis infection) with these drugs in combination therapy are needed (41, 42).

Clinical trials are essential to deliver information about some parameters of the drug in human organisms. In two phase I clinical trials researchers studied whole-blood bactericidal activity and pharmacokinetic parameters of sutezolid and its two metabolites. Participants received two dosages of this drug in the first group or placebo in the second group. Eight healthy volunteers took linezolid four times per day in 300 mg dosages. It has been demonstrated that sutezolid was well-tolerated in all dosages and showed a stronger effect in comparison to linezolid. Good absorption was also observed. No serious adverse events were noted during the study (43).

The phase II study conducted by Wallis et al. in patients with drug sensitive pulmonary tuberculosis delivered some information about the tolerability and safety of sutezolid. These compound was administered twice daily in 600 mg dosage and once daily in 1200 mg dosage for 14 days. Changes in log10 CFU was observed in both dosing schedules. No patients discontinued the trial because of the drug-related intolerability. Seven patients in sutezolid group (14%) have mild or moderate increase in alanine transaminase level. There was no cases of QTc interval prolongation, anemia and thrombocytopenia (44).

Moreover, the activity of the three oxazolidinones: linezolid, sutezolid and AZD5847 against
latent tuberculosis was compared in separate in vitro and in vivo studies. In vitro study demonstrated that all drugs have bacteriostatic activity against replicating but bactericidal against nonreplicating cells. In mice model of tuberculosis, two molecules – sutezolid and linezolid – exhibited promising efficacy after two months of therapy. Both AZD5847 and its prodrug delivered no promising outcomes in murine model. It is suggested that sutezolid can be essential in creating the new combination against this disease because of its more potent efficacy in comparison with linezolid (45).

Delamanid

Another molecule tested in phase III clinical trials in drug-resistant tuberculosis treatment is delamanid, also known as OPC-67683. It is classified as a dihydro-nitroimidazooxazole derivative. The mechanism of action is described as inhibiting the synthesis of the bacteria cell walls elements - mycolic acids: ketomycolic and methoxymycolic acids. Delamanid is converted in human organisms by mycobacteria. This interaction leads to production of reactive species via bioreduction of delamanid’s nitro groups. This process requires e.g., an essential reduced form of deazaflavin cofactor F420. Delamanid is approved in the UE countries to treat multidrug-resistant tuberculosis in adult patients in case of appearance of ineffectiveness and unsafety of standard regimens (46, 47).

The lowest plasma concentration of delamanid was noted in mice in comparison with standard drugs. However, delamanid exhibited a long-lasting half-life. What is more, this drug reduced the amount of mycobacteria in dose-dependent manner. The evaluation of combination antituberculosis therapy was also examined in this study. Delamanid administered with standard drugs may shorten therapy of tuberculosis (48).

The phase II study of delamanid included 481 patients with pulmonary multidrug-resistant tuberculosis. The patients were divided into three groups and received 100 mg of delamanid twice daily, 200 mg of delamanid twice daily or placebo in combination with drugs recommended by World Health Organization. The treatment lasted two months. The study demonstrated that delamanid exhibited an improvement in sputum-culture conversion in both groups, 100 mg and 200 mg of the drug twice daily with the results of 45.4 and 41.9%, respectively, in comparison with the placebo group (29.6%). The appearance of QT-interval prolongation was significantly more often in both groups of patients who received delamanid. On the other hand, the frequency of hepatotoxicity was higher in the placebo group. Most adverse events were classified as mild to moderate (49).

Early bactericidal activity of delamanid was studied in phase IIa clinical trial. Forty eight patients, who suffered from smear-positive tuberculosis, took part in that research. Delamanid was administered for 14 days in four dosages: 100, 200, 300 and 400 mg once per day. It has been shown that there is no significant difference between doses of delamanid in relation to the early bactericidal activity. However, the most promising results were observed in the groups of patients who received 200 and 300 mg of the drug. According to the aim of the study, it has been shown that this dihydro-nitroimidazooxazole derivative seems to be safe and well tolerated in the human organisms (50).

It is worth mentioning that the in vitro study conducted to evaluate the influence of delamanid and its metabolites on the CYP enzyme system demonstrated that this drug is probably not responsible for drug-drug interactions relevant in clinical practice. It seems to be important in the case of HIV co-infection occurrence and antiretroviral therapy. Human hepatocytes or liver microsomes were used to indicate the minimal effect of this drug on CYP isoforms (51).

SQ109

N’-(2-adamantyl)-N-[(2E)-3,7-dimethylocta-2,6-diynyl]ethane-1,2-diamine

SQ109 is an ethambutol analogue currently tested in phase II clinical trials against tuberculosis. However, the mechanism of action remains unclear. It is suggested that the target of this molecule is MmpL3, a transporter of trehalose monomycolate (the precursor of trehalose dimycolate and mycolates in the cell wall) in Mycobacterium. As a consequence, the trehalose monomycolate has been accumulated. SQ109, a diamine, prevents from gathering of mycolic acids into mycobacterial cell wall core (52).

SQ109 was compared to isoniazid and ethambutol in vitro and in vivo. SQ109 was proved to act better against intracellular Mycobacterium tuberculosis.
than ethambutol and at a similar level as isoniazid in vitro. In mice SQ109 acted less potently than isoniazid and at the same level as ethambutol. Lungs contain the highest concentration (>MIC) of SQ109 (53).

The phase IIa study of SQ109 was conducted in patients with smear-positive pulmonary disease. Patients received SQ109 orally once per day for 14 days and were divided into 6 groups: 3 of them took SQ109 alone in different doses (75, 150 and 300 mg), the next received rifampicin alone (10 mg/kg) and the last 2 groups took both rifampicin and SQ109 (150 or 300 mg). The most often adverse events were connected to gastrointestinal tract and were classified as mild to moderate. No episodes of relevant QT-prolongation were observed. The study has shown that SQ109 seems not to be active when administered alone and not potentiate the action of rifampicin in 14 days treatment (54).

There are studies showing the evaluation of bedaquiline and SQ109 when administered together. In vitro study was conducted to examine the interactions between two new antituberculosis agents: bedaquiline and SQ109. It has been shown that bedaquiline MIC was higher by 4- to 8-fold in the presence of SQ109. The postantibiotic effect was prolonged by 4 h and the improvement of the rate of killing mycobacteria was observed. Addition of rifampin had no influence on bedaquiline and SQ109 interactions (55). Another in vitro probe described the evaluation of connection of SQ109 and sutezolid and its metabolite. The results were promising and exhibited the increase of the rate of mycobacteria killing (56). What is more, it has been also suggested that SQ109 is synergistic to two of the first-line antituberculosis drugs: isoniazid and rifampicin (57).

Drugs in preclinical trials – the novel mechanisms of actions

Preclinical studies are focused on many compounds with varied and interesting modes of action to counteract tuberculosis, in particular MDR- and XDR-tuberculosis. The literature mentions e.g., about CPZEN-45, SQ609, SQ641 (58).

CPZEN-45

SQ609

SQ641

The preclinical search of new molecules resulted in SQ609 evaluation. This structure was chosen from a library of dipiperidine derivatives. In vitro intracellular activity against tuberculosis was assessed in mice macrophages. More than 90% of mycobacteria increase was inhibited. No weight loss in mice treated with SQ609 was noted (59). Another substance tested in preclinical trials is SQ641. This capuramycin analogue is naturally produced by Streptomyces griseus. Capuramycin inhibits the action of an enzyme, translocase I, which is connected to biosynthesis of peptidoglycan. Specificity of translocase I to bacteria may result in depletion of toxicity. In vitro studies demonstrated the long lasting postantibiotic effect of SQ641 of 55 h. This molecule is lowly solubilized in water and in consequence is less active against intracellular bacteria. Another dissolvents of this compound were tested in murine model of tuberculosis (60-62). CPZEN-45 is also a naturally-occurring nucleoside antibiotic produced by Streptomyces sp. This antibiotic inhibits an enzyme, the decaprenylphosphate-GlcNAc-1-phosphate transferase, responsible for synthesis of the cell wall core (biosynthesis of mycolylarabinogalactan) in Mycobacterium tuberculosis. This molecule also demonstrated narrower spectrum in comparison with caprazamycins. What is more, there has not been noted cytotoxic and mutagenic action of CPZEN-45 so far (60, 63).

Summary

Despite the increasing numbers of new-diagnosed cases of tuberculosis in developed countries and the disease still remaining one of the most frequent reasons of deaths worldwide, clinical and preclinical data indicate the improvement of effectiveness of the cure. The high activity and safety of...
bedaquiline led to an approval of this drug by FDA and EMA. Disturbing statistics of frequency of newly recognized tuberculosis or multi-drug resistant tuberculosis was a step to counteract this disease and give some perspectives in clinical trials. The first global approval of delamanid in the European Union may influence the improvement of efficacy and safety or even let shorten therapy of tuberculosis. The hope in new antituberculosis agents, still tested in clinical studies and the creation of new regimens, which include these described above, is essential.

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