Telacebec: an investigational antibacterial for the treatment of tuberculosis (TB)

Bei Shi Lee[1], Kevin Pethe[1,2]

[1]School of Biological Sciences, Nanyang Technological University, Singapore. 60 Nanyang Drive, Singapore 637551.

[2]Lee Kong Chian School of Medicine, Nanyang Technological University, Experimental Medicine Building, Singapore. 59 Nanyang Drive, Singapore 636921.

Correspondence should be addressed to Kevin Pethe (kevin.pethe@ntu.edu.sg)

Abstract

Introduction
Tuberculosis is an infectious disease that affected more than 50 million people and killed 6.7 million patients in the past 5 years alone. Additionally, rising incidence of treatment resistance threatens the global effort to eradicate this disease. With limited options available, additional novel antibiotics are needed for the treatment of multidrug-resistant tuberculosis (MDR-TB). Telacebec is a first-in-class antibiotic that targets the pathogen's energy metabolism.

Areas covered
This paper provides an overview of the recent progress in the development and testing of telacebec. We discuss published clinical data and examine the design and setup of its clinical trials. We also offer insights on the therapeutic potential of telacebec and aspects of which should be evaluated in the future.

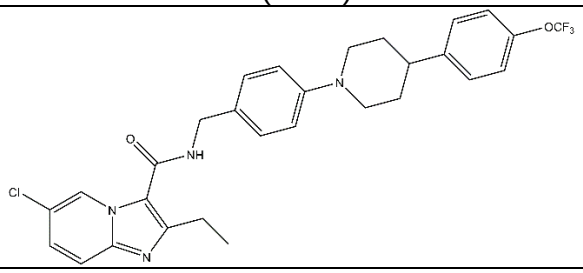
Expert opinion
The first phase 2a trial showed a correlation between dosage and bacterial load in patient sputum, which should be confirmed using a direct measurement method such as colony-forming unit counting. Its clinical efficacy, favorable pharmacokinetic properties, low arrhythmogenic risk, and activity against MDR-TB strains make telacebec a suitable candidate for further development. Future clinical testing in combination with approved second-line drugs will reveal its full potential against MDR-TB. Considering recent preclinical studies, we also recommend initiating clinical trials for Buruli ulcer and leprosy.

Article highlights

- Telacebec is a first-in-class antibiotic that inhibits growth of *M. tuberculosis* by targeting its energy metabolism. The compound has undergone three clinical studies, the latest being a phase 2a efficacy trial
- Telacebec was established as a safe oral drug in single as well as multiple dosing, with no reported arrhythmogenic alerts
- Preliminary result of the phase 2a study revealed a positive relationship between sputum bacterial load and drug dosage
- Telacebec is suitable for further development where the effect of longer treatments as well as its combination with other antitubercular drugs should be explored, especially against drug-resistant tuberculosis

Keywords: Cytochrome *bcc:aa*$_3$, *Mycobacterium tuberculosis*, oxidative phosphorylation, Q203, respiration

Drug Summary Box

Drug name	Telacebec (Q203)
Phase	2a
Indication	Tuberculosis
Mechanism of action	Inhibits *M. tuberculosis* energy metabolism by targeting the QcrB subunit of cytochrome *bcc:aa*$_3$ complex in the pathogen's oxidative phosphorylation pathway
Route of administration	Oral administration (tablet)
Chemical structure	

1. Introduction

Mycobacterium tuberculosis is the bacterium responsible for tuberculosis in humans. While the pathogen can infect many parts of our body, pulmonary tuberculosis is the most problematic form due to its transmissibility via air droplets expelled through coughing or speaking. Tuberculosis is one of the deadliest communicable diseases. There was an estimated 10 million new cases and 1.4 million deaths in 2019 [1]. A majority of cases were found in the Southeast Asian, African, and Western Pacific regions [1]. Eight countries with the highest disease burden accounted for two-thirds of the global cases: India, Indonesia, China, The Philippines, Pakistan, Nigeria, Bangladesh, and South Africa [1].

The treatment for tuberculosis involves an aggressive four-drug cocktail – isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) – for two months, followed by a combination of isoniazid-rifampicin for another four months. This treatment regimen is highly effective with a cure rate of 85% [1]. However, the potency of the therapy is marred by the inevitable emergence of drug resistance. Incidence of multi-drug resistance (defined as resistance to both isoniazid and rifampicin) is on the rise. In such instances, treatment becomes more uncertain as the two most effective antibiotics are swapped out with less potent, more toxic drugs. Treatment for MDR-TB is suboptimal, this is evident from the long treatment time (up to 24 months) yet moderate success rate of 52-64% [1]. The rising number of drug-resistant cases of tuberculosis is a strong indication that novel therapeutics are in demand. After decades of stagnation, some progress has recently been made in the pipeline for new TB therapeutics. This included three drugs which received approval for the treatment of MDR-TB, as well as an additional 17 new drug candidates in ongoing clinical trials. In this review, we will discuss the discovery and study findings of a drug candidate: telacebec, which has successfully completed its first phase 2 human clinical trial.

2. Market overview

The year 2012 saw a breakthrough in therapeutics for TB: the US Food and Drug Administration (FDA) approved bedaquiline (Sirturo®) for the treatment of MDR-TB. Bedaquiline was the first antibiotic to be approved for the treatment of tuberculosis in more than four decades. The first-in-class drug kills *M. tuberculosis* by inhibiting the F_1F_o ATP synthase, thereby hindering energy production [2]. Due to the novelty of its mechanism of action, the antibiotic showed no cross-resistance with isoniazid and rifampicin, and was therefore effective against MDR-TB [3]. Closely following bedaquiline's approval, delamanid, yet another compound of a novel drug class was also approved by the European Medicines Agency based on its efficacy against MDR-TB [4]. While efficacious against the pathogen, both antibiotics have been associated with QT prolongation in patients, potentially putting some patients at higher risk of cardiotoxicity. Bedaquiline's clinical efficacy study reported an increase in all-cause mortality and incidences of QT-prolongation in the test cohort compared to the placebo group [5]. This has led to the issue of a black box warning that accompanied its FDA approval. This shortcoming also complicates the combination of these novel drugs with existing anti-tuberculosis drugs due to the concern that they may incur additive liability on cardiovascular health. For instance, moxifloxacin and levofloxacin, two second-line anti-TB fluoroquinolones also induce QT-prolongation [6]. However, bedaquiline still has an excellent safety profile compatible with the development of a paediatric formulation [7, 8]. In 2019, pretomanid, which belongs to the same drug class as delamanid, received approval by the US FDA under its Limited Population Pathway for Antibacterial and Antifungal Drugs. This conditionally approves its use in the fixed pretomanid-bedaquiline-linezolid regimen in patients with treatment intolerance, XDR-TB, or non-responsive MDR-TB [9]. While the combination is highly effective, the added-value of pretomanid to the bedaquiline-linezolid combination remains to be studied in subsequent clinical trials.

Besides bedaquiline, delamanid and pretomanid, there are 23 anti-TB drugs currently in clinical testing [1]. Six (clofazimine, levofloxacin, linezolid, moxifloxacin, high-dose rifampicin, and rifapentine) are approved compounds undergoing additional testing as part of novel

drug combinations or formulations for MDR-TB or paediatric cases. The rest of the compounds are new chemical entities with diverse binding targets and mechanisms of action.

3. Telacebec

3.1 Introduction

Telacebec (also known as Q203) is an orally active drug candidate that acts by inhibiting the cytochrome *bcc:aa$_3$* terminal oxidase in the pathogen's oxidative phosphorylation pathway. The small molecule belongs to the imidazopyridine amide (IPA) chemical series. The early hit compounds were identified in a high-content screening assay involving infected macrophages [10]. Telacebec was the product of lead optimisation efforts and is a first-in-class IPA antibacterial to be in clinical development. To date, telacebec has undergone three clinical studies for tuberculosis. The most recent early bactericidal activity (EBA) efficacy trial was completed in September 2019 and its outcome was released in March 2020 [11].

3.2 Binding Target and Mechanism of Action

Telacebec binds to the QcrB subunit of the *M. tuberculosis* cytochrome *bcc:aa$_3$* supercomplex. The cytochrome *bcc:aa$_3$* is a dimeric complex comprising two *bcc* menaquinol reductases and *aa$_3$* oxidases [12, 13]. The supercomplex is part of the pathogen's electron transport chain (ETC) in the oxidative phosphorylation pathway. It is homologous to complexes III and IV found in the mammalian mitochondria ETC. The cytochrome *bcc:aa$_3$* supercomplex acts as a terminal oxidase in the ETC and functions to catalyse the transfer of electrons to molecular oxygen, reducing it to water. The complex also contributes to the proton motive force (*pmf*), which is essential for ATP synthesis as well as other enzymatic functions such as active transport of xenobiotics through efflux pumps [14]. The cytochrome *bcc:aa$_3$* is important for optimum growth in mycobacteria and deletion of the genes encoding the respiratory complex in *M. tuberculosis* resulted in a significant growth defect [15, 16].

Like bedaquiline, telacebec targets *M. tuberculosis* by inhibiting its energy metabolism. Telacebec is potent *in vitro* with an MIC_{50} of 1-3 nM in culture broth and appears more potent against intracellular mycobacteria [10]. Whole genome analyses of telacebec-resistant mutants revealed single nucleotide polymorphisms in *qcrB*, confirming the drug's binding target [10]. Additionally, the position of these key residues in the structural model of the cytochrome *bcc:aa*$_3$ complex also implicated that telacebec binds to, or near, the menaquinol oxidation (Q_p) site [10], which was recently confirmed in a study that resolved the structure of the telacebec-bound complex using cryo-EM [17].

Preclinical studies demonstrated that telacebec had an interesting safety profile. The drug candidate was not cytotoxic, was deemed to have low risk for cardiotoxicity and genotoxicity, and was well-tolerated in acute toxicity studies in mice up to a single dose of 1000 mg/kg [10]. Pharmacokinetic studies in mice revealed an excellent oral bioavailability of 90%, a terminal half-life of 23.4 h [10] and activity in a model of tuberculosis infection [10]. From the preclinical studies, the long-terminal half-life was of concern since the clinical significance of drug accumulation overtime is that it may lead to potential toxic events.

3.3 Clinical Efficacy

Following the promising results from preclinical studies, three clinical trials have successively been launched and completed: a first-in-human trial (NCT02530710); a phase 1 ascending multiple dose study (NCT02858973); and a phase 2a multiple-dose trial for the evaluation of early bactericidal activity (NCT03563599) (Table 1).

Table 1 Summary of clinical studies of telacebec for the treatment of tuberculosis

	Trial details	Finding(s)
Phase 1a [11, 18]	• First-in-human trial • Telacebec was administered as single ascending doses (up to 800 mg) • Food effect was evaluated	• No serious adverse events reported • Adverse events did not correlate to drug dosage • Plasma concentration of telacebec was significantly higher when administered in a fed state
Phase 1b [11]	• Ascending multiple dose trial • Telacebec was administered with food daily for 14 days	• No serious adverse events reported • No reports of ECG-related adverse events
Phase 2a [11]	• First efficacy trial to evaluate early bactericidal activity of telacebec • 100, 200, or 300 mg of telacebec was given to treatment-naïve, drug-susceptible TB patients daily for 14 days	• Mycobacterial load in patient sputum decreased over time during the treatment period • Higher telacebec dosage correlated to faster mycobacteria reduction

The first-in-human trial was conducted between August 2015 and July 2016. The trial was a randomised, double-blind, placebo-controlled, dose-ascending study designed primarily to evaluate the safety and tolerability of telacebec [18]. The study involved 56 healthy male and female subjects, with 42 subjects receiving a single dose of telacebec at 10 mg, 30 mg, 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg. The drug or placebo was administered orally in the form of tablets in a fasted state. The cohort that received a 100 mg dose of telacebec was also enrolled for the investigation of food effect on the pharmacokinetics of telacebec. The drug candidate was well-tolerated with no incidences of serious adverse events. In terms of pharmacokinetics, the maximum plasma concentration (C_{max}) as well as the area under the curve (AUC) increased with the dosage that was administered [18]. The mean AUC from time zero to last measurement (AUC_{last}) has a statistically significant dose proportionality relationship. The half-life of telacebec increased with its dosage and ranged from 21.13 h to 150.79 h. A food effect was observed: serum levels of telacebec were significantly higher in a fed state compared to a fasted state [18].

The second trial that took place between August 2016 and May 2018 aimed at evaluating the safety, tolerability, and pharmacokinetic effects of multiple doses of telacebec. A total of 47 healthy volunteers were enrolled and were randomly allocated to one of the six cohorts receiving daily doses of either placebo or telacebec at 20 mg, 50 mg, 100 mg, 160 mg, 250 mg, or 320 mg for 14 days. The subjects received the drug orally in the form of tablets alongside a standard meal. Detailed report of the findings remains to be released, but a summary statement included in the phase 2 trial protocol declared that all reported adverse events in the study were mild and none were serious or life-threatening [11]. There was no correlation between telacebec dosage and the number of subjects experiencing side effects. In general, it was found that telacebec was well-tolerated in all tested doses and no specific safety signals were identified.

A phase 2a clinical study was conducted between July 2018 and September 2019 in Cape Town, South Africa. The proof-of-concept study was designed to evaluate the early bactericidal activity (EBA) of telacebec in tuberculosis patients within a 14-day treatment period. The study recruited male and female adult patients (18 to 65 years) newly diagnosed with drug-susceptible pulmonary tuberculosis who were treatment-naïve at the point of recruitment. Sixty-one recruited subjects were randomly assigned to receive one of the following treatments daily: 100 mg telacebec, 200 mg telacebec, 300 mg telacebec, or the standard pulmonary TB treatment, Rifafour e-275® (Rifampicin (150 mg), Isoniazid (75 mg), Pyrazinamide (400 mg), Ethambutol (275 mg)), for 14 days. To evaluate the efficacy of telacebec, patient sputum samples were collected daily and were cultured using the BACTEC MGIT 960 system. The primary outcome measurement was determined using the rate of change of $\log_{10}$ time to positivity (TTP) in the sputum samples [11]. Usually, TTP measurement using MGIT have been shown to closely correlate to colony forming units (CFU) counting on agar plates and the measurement further possesses the advantage of quicker and more sensitive detection of live bacilli [19]. Telacebec showed a dose-dependent reduction in the load of viable mycobacteria in the sputum: patients administered

with higher doses of telacebec showed prolonged TTP, which indicated a faster reduction in number of live bacilli [11]. Overall, telacebec was well-tolerated, and showed a positive trend between dosage and EBA. While the sputum bacterial load was concurrently evaluated by CFU counting in this study, the results have yet to be released.

3.4 Safety and tolerability

In all three clinical studies, no serious drug-associated adverse events were reported. In the first-in-human study, the most common drug-related adverse event was headache, which was reported in six subjects receiving telacebec and one subject receiving placebo [11, 18]. Abdominal discomfort was also noted more frequently in the cohorts receiving telacebec compared to placebo [18]. The incidences of adverse events did not appear to be associated with the dosage of telacebec. In both phase I studies, assessment of vital signs, including body temperature, blood pressure, and heart rate, yielded no clinically significant findings associated with the drug [11]. Additionally, there were no clinically significant changes in subjects' haematology, serum chemistry, and urinalysis tests following the administration of telacebec [11].

All subjects were also monitored using computerised 12-lead electrocardiograms (ECG) where standard parameters such as heart rate, PR interval, QRS duration, QT interval, and QTc interval were measured. There were no reports of ECG-related adverse events. In the first clinical study, there were no QRS complex prolongations of >120 ms. No prolongation of QTcF beyond 480 ms was reported, and the biggest shift in the mean QTcF of any cohort from baseline was +1.5 ms. Similarly, multiple dosing of telacebec in the second phase I study also revealed no prolongation of QTcF >450 ms, indicating that telacebec is not arrhythmogenic.

Safety and tolerability of telacebec has not been evaluated in pregnant or breastfeeding individuals or in the paediatric population. Its use in vulnerable populations should be evaluated in the future.

4. Conclusion

In general, the various clinical studies of telacebec have shown that the drug could be safely administered to humans with no reports of serious adverse events. Pharmacokinetic analysis also confirmed that telacebec had good bioavailability and was able to achieve plasma concentrations significantly higher than its inhibitory concentration. Importantly, preliminary findings in the phase 2a study showed that increasing telacebec dosage corresponded to prolongation of TTP, which suggested greater reduction in live bacilli in the sputum. Its efficacy in the study, coupled with its low arrhythmogenic risk, are encouraging signs that support further development with other anti-tuberculosis agents. However, additional clinical trials are needed to evaluate the potency of telacebec using a direct method such as CFU count, and in combination with approved second-line drugs against MDR tuberculosis.

5. Expert opinion

Thus far, telacebec has displayed a favourable safety profile and adequate pharmacokinetics parameters, and the outcome of the preliminary efficacy study was positive. However, more detailed reports of telacebec's clinical data are needed for a more accurate evaluation of the drug's potential.

Consistent with findings from preclinical studies, pharmacokinetic analysis of telacebec in the first-in-human trial revealed that telacebec has an extended half-life (321.12 ± 227.29 h) [18]. One concern about drugs with long half-lives is that it may take days or weeks to reach their steady state concentrations, thus possibly raising safety concerns due to drug accumulation over time. When telacebec is given daily, subtherapeutic plasma concentration is not a concern since the drug concentration is still well-above the established *in vitro* minimum inhibitory concentration 24 hours after dosing [18]. Preliminary results from the first phase 2a efficacy trial revealed early bactericidal activity especially in the cohort given the 300 mg daily dose [11]. However, further analysis of the drug's pharmacokinetic properties after multiple dosing must be conducted to guide the development of optimum dosing

formulations. Importantly, due to good drug tolerability and safety profile, there is flexibility in adjusting to higher loading doses if necessary. Subsequent intermittent dosing can be adjusted based on the desired steady state concentration.

Another potential issue stemming from telacebec's long half-life is that prolonged subtherapeutic exposure after its treatment cessation may facilitate the selection of drug resistance. This highlights one of the most important strategies to ensure treatment success: a combination of individually efficacious antibiotics. If telacebec treatment was stopped before complete eradication, special care should be taken to ensure an effective drug cocktail continues after or immediately follows the cessation of telacebec treatment so as to minimise the risk of drug resistance emergence.

From a technical standpoint, the published results of the phase 2a study relied on the rate of change of $\log_{10}$ TTP using the BACTEC MGIT 960 system as a primary outcome measurement. The MGIT assay detects mycobacterial oxygen respiration using a fluorometric sensor. There are a few points of concern that may raise the question if MGIT is an appropriate method to establish the efficacy of telacebec. Given telacebec's excellent bioavailability profile (in particular its long terminal half-life and high serum concentration) and its low nanomolar potency, possible issues related to drug carryover should not be overlooked. Indeed, failure to eliminate telacebec totally from the sputum samples may interfere with the MGIT system. As with bedaquiline [20], studies should be conducted to explore experimental approaches to limit drug carryover effect of telacebec during clinical development.

Drug carryover issue aside, the MGIT system detects mycobacterial oxygen consumption within the culture, which is incidentally driven in part by the cytochrome *bcc:aa*$_3$, the target of telacebec. While a lot remains to be understood about *M. tuberculosis* energy metabolism after telacebec exposure, metabolic remodelling is one of the pathogen's adaptation strategies to chemical inhibition of its oxidative phosphorylation (OXPHOS) pathway [21, 22]. It is thus a possibility that there are viable bacilli in the sputum that are not respiring or

respiring much slower due to their adaptation to telacebec exposure. Hence, using MGIT as a measurement of number of viable bacilli in this instance may inaccurately amplify telacebec's potency. These concerns by no means invalidate the measurement of viable bacterial load in patient sputum but emphasise the need to evaluate the CFU counting conducted as part of the study according to the clinical trial protocol [11]. Disclosure of the clinical data showing CFU and TTP data side by side will dispel the concerns about the suitability of the MGIT assay to evaluate the potency of telacebec and related energy metabolism inhibitors.

Metabolic remodelling induced by OXPHOS inhibitors is also associated with delayed bactericidal action [21, 23]. Telacebec, like bedaquiline, is slow acting in both *in vitro* and *in vivo* studies compared to other anti-tuberculosis antibiotics such as isoniazid. In the mouse model of established tuberculosis, telacebec caused less than one-log reduction in bacterial load in the lungs after two weeks of treatment, but bacterial load rapidly dropped by three orders of magnitude after four weeks. Correspondingly, this suggests that longer clinical studies are needed in order to evaluate the full therapeutic potential of telacebec.

All three clinical studies revealed that telacebec did not carry significant arrhythmogenic properties. This confers an advantage over other new anti-TB drugs such as bedaquiline and delamanid as it is compatible with anti-tuberculosis agents with known QT-prolongation effects such as bedaquiline, delamanid, moxifloxacin, or clofazimine without additional cardiovascular liabilities. Without such complications, telacebec is more versatile in forming different treatment combinations compared to other drugs approved for MDR treatment. Assessment of a TB drug candidate's drug-drug interaction is especially critical because anti-TB drugs are administered alongside each other. Additionally, TB-HIV co-infection is commonplace in high-disease burden countries. This highlights the importance of compatibility with existing antiretroviral drugs. Unlike rifampicin, telacebec is not a CYP450 inducer [10]. As such, it is not expected to influence the metabolism of co-administered drugs that depend on cytochrome P450 for efficacy. Telacebec was also shown to act

synergistically with several anti-TB drug candidates *in vitro* [24-26], which highlights its potential to be part of efficacious drug cocktails for TB treatment. Clinical assessment of telacebec's compatibility with anti-TB drugs, especially second-line antibiotics, as well as various novel drug candidates in similar stages of clinical development, would be a critical step in determining its application in the clinic and its contribution to MDR/XDR TB treatment.

Recent preclinical studies aimed at understanding the bacteriostatic nature of telacebec against *M. tuberculosis* [27] led to the discovery of the exceptional promise of telacebec for the treatment of Buruli ulcer and leprosy [28-30]. Those exciting results, further supported by the drug candidate's excellent pharmacokinetics and safety profile, advocate for randomized control trials of telacebec for Buruli ulcer and leprosy.

Unlike *M. tuberculosis*, *M. leprae* and *M. ulcerans* (classical lineage) have both functionally lost the alternative terminal oxidase – the cytochrome *bd* oxidase (Cyt-*bd*) – which accounted for their exquisite sensitivity towards telacebec [28-30]. The functional redundancy of having two terminal oxidases in *M. tuberculosis* has allowed the pathogen to circumvent cell death by telacebec treatment *in vitro* [10, 27]. However, most likely due to differences in the pathogen's microenvironment, the gene expression, and subsequently the functional role of cyt-*bd* in animal infection models as well as human infections differs from *in vitro* conditions [31, 32]. As such, it is difficult to predict how the existence of a second terminal oxidase may affect the efficacy of telacebec in humans. However, the preliminary analysis from the phase 2a efficacy study seems promising as it reflected a reduction in sputum mycobacterial load when telacebec was administered [11]. Additionally, cyt-*bd* inhibitors recently reported [24, 33] conceptually proved that the complex is druggable and their further development could mean that telacebec can be boosted by a second companion drug to make an even more efficacious treatment in the future.

In conclusion, the three clinical trials have established telacebec to be safe for use in humans. Its potency displayed in the most recent study supports further development of telacebec. Telacebec possesses a novel mechanism of action and has conserved potency

across MDR and XDR isolates *in vitro,* indicating that it is a suitable candidate for further study as part of drug combinations for the treatment of MDR-TB. Finding the right companion drugs to be administered with telacebec will be critical. In the near future, clinical studies designed to evaluate the value of telacebec as part of drug regimens for the treatment of MDR-TB should be conducted.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Funding

This work was supported by the National Research Foundation (NRF) Singapore under its Investigatorship Program (grant NRF-NRFI06-2020-0004) and NRF Competitive Research Programme (Project Award Number NRF-CRP18-2017-01).

References

1. WHO. Global Tuberculosis Report 2020; 2020.
2. Koul A, Dendouga N, Vergauwen K, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nature chemical biology 2007 Jun;3(6):323-4.
3. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 2005 Jan 14;307(5707):223-7.
4. Pharmaceutical O. Otsuka Wins European Marketing Authorization for Deltyba(TM) (delamanid). [Media Release] 2014 April 30 [cited 2021 November 1]; Available from: http://www.otsuka.co.jp/en/company/release/2014/0430_01.html
5. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014 Aug 21;371(8):723-32.
6. Briasoulis A, Agarwal V, Pierce WJ. QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. Cardiology 2011;120(2):103-10.
7. Johnson J. U.S. FDA Approves New Pediatric Formulation of SIRTURO® (bedaquiline) as Part of Combination Therapy to Treat Children with Pulmonary Multidrug-Resistant Tuberculosis. [Media Release] 2020 May 27 [cited 2021 November 11]; Available from: https://www.jnj.com/u-s-fda-approves-new-pediatric-formulation-of-sirturoo-bedaquiline-as-part-of-combination-therapy-to-treat-children-with-pulmonary-multidrug-resistant-tuberculosis
8. Moodliar R, Aksenova V, Frias MVGI, et al. Bedaquiline for multidrug-resistant TB in paediatric patients. The International Journal of Tuberculosis and Lung Disease 2021;25(9):716-24.
9. Keam SJ. Pretomanid: First Approval. Drugs 2019 Nov;79(16):1797-803.
10. Pethe K, Bifani P, Jang J, et al. Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis. Nat Med 2013 Sep;19(9):1157-60.
    *This article reports on the development of telacebec and on its preclinical evaluation.
11. de Jager VR, Dawson R, van Niekerk C, et al. Telacebec (Q203), a New Antituberculosis Agent. N Engl J Med 2020 Mar 26;382(13):1280-81.
    * Preliminary results from Telacebec's first phase 2a efficacy trial was presented.
12. Gong H, Li J, Xu A, et al. An electron transfer path connects subunits of a mycobacterial respiratory supercomplex. Science 2018 Nov 30;362(6418):eaat8923.
13. Wiseman B, Nitharwal RG, Fedotovskaya O, et al. Structure of a functional obligate complex III2IV2 respiratory supercomplex from Mycobacterium smegmatis. Nat Struct Mol Biol 2018 Dec;25(12):1128-36.
14. Black PA, Warren RM, Louw GE, et al. Energy metabolism and drug efflux in Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy 2014;58(5):2491-503.
15. Beites T, O'Brien K, Tiwari D, et al. Plasticity of the Mycobacterium tuberculosis respiratory chain and its impact on tuberculosis drug development. Nat Commun 2019 Oct 31;10(1):4970.
16. Matsoso LG, Kana BD, Crellin PK, et al. Function of the cytochrome bc1-aa3 branch of the respiratory network in mycobacteria and network adaptation occurring in response to its disruption. J Bacteriol 2005 Sep;187(18):6300-8.
17. Yanofsky DJ, Di Trani JM, Król S, et al. Structure of mycobacterial CIII(2)CIV(2) respiratory supercomplex bound to the tuberculosis drug candidate telacebec (Q203). Elife 2021;10:e71959.
18. Kim J, Choi J, Kang H, et al. Safety, Tolerability, and Pharmacokinetics of Telacebec (Q203), a New Antituberculosis Agent, in Healthy Subjects. Antimicrob Agents Chemother 2021 Oct 25:Aac0143621.
    *This paper details telacebec's safety profile as well as its pharmacokinetic properties based on a first-in-human clinical study.
19. Diacon AH, Maritz JS, Venter A, et al. Time to liquid culture positivity can substitute for colony counting on agar plates in early bactericidal activity studies of antituberculosis

agents. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2012 Jul;18(7):711-7.
20. Lounis N, Gevers T, Berg JVD, et al. Prevention of Drug Carryover Effects in Studies Assessing Antimycobacterial Efficacy of TMC207. Journal of clinical microbiology 2008;46(7):2212-15.
21. Koul A, Vranckx L, Dhar N, et al. Delayed bactericidal response of Mycobacterium tuberculosis to bedaquiline involves remodelling of bacterial metabolism. Nat Commun 2014 Feb 26;5:3369.
22. Berube BJ, Parish T. Combinations of Respiratory Chain Inhibitors Have Enhanced Bactericidal Activity against Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy 2017;62(1):e01677-17.
23. Bald D, Villellas C, Lu P, et al. Targeting Energy Metabolism in Mycobacterium tuberculosis, a New Paradigm in Antimycobacterial Drug Discovery. mBio 2017 Apr 11;8(2).
24. Lee BS, Hards K, Engelhart CA, et al. Dual inhibition of the terminal oxidases eradicates antibiotic-tolerant Mycobacterium tuberculosis. EMBO Mol Med 2021 Jan 11;13(1):e13207.
25. Flentie K, Harrison GA, Tükenmez H, et al. Chemical disarming of isoniazid resistance in Mycobacterium tuberculosis. Proc Natl Acad Sci U S A 2019 May 21;116(21):10510-17.
26. Lamprecht DA, Finin PM, Rahman MA, et al. Turning the respiratory flexibility of Mycobacterium tuberculosis against itself. Nat Commun 2016 Aug 10;7(1):12393.
27. Kalia NP, Hasenoehrl EJ, Ab Rahman NB, et al. Exploiting the synthetic lethality between terminal respiratory oxidases to kill Mycobacterium tuberculosis and clear host infection. Proc Natl Acad Sci U S A 2017 Jul 11;114(28):7426-31.
28. Chauffour A, Robert J, Veziris N, et al. Telacebec (Q203)-containing intermittent oral regimens sterilized mice infected with Mycobacterium ulcerans after only 16 doses. PLoS neglected tropical diseases 2020 Aug;14(8):e0007857.
29. Scherr N, Bieri R, Thomas SS, et al. Targeting the Mycobacterium ulcerans cytochrome bc1:aa3 for the treatment of Buruli ulcer. Nat Commun 2018 Dec 18;9(1):5370.
    *This study demonstrated that *M. ulcerans* is especially sensitive to telacebec due to loss of the alternative terminal oxidase, cyt-*bd*.
30. Thomas SS, Kalia NP, Ruf MT, et al. Toward a Single-Dose Cure for Buruli Ulcer. Antimicrob Agents Chemother 2020 Aug 20;64(9).
31. Arora K, Ochoa-Montano B, Tsang PS, et al. Respiratory flexibility in response to inhibition of cytochrome C oxidase in Mycobacterium tuberculosis. Antimicrob Agents Chemother 2014 Nov;58(11):6962-5.
32. Kalia NP, Lee BS, Ab Rahman NB, et al. Carbon metabolism modulates the efficacy of drugs targeting the cytochrome bc1:aa3 in Mycobacterium tuberculosis. Sci Rep 2019 Jun 13;9(1):8608.
33. Hopfner SM, Lee BS, Kalia NP, et al. Structure guided generation of thieno[3,2-d]pyrimidin-4-amine Mycobacterium tuberculosis bd oxidase inhibitors. RSC Med Chem 2021 Jan 1;12(1):73-77.