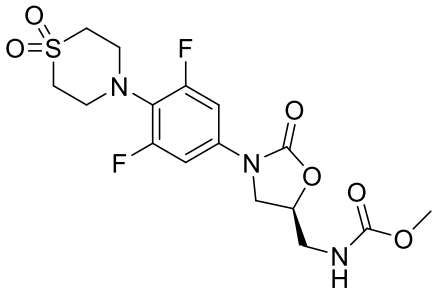
1078 (2013), Yang et al., *J. Med. Chem.* 58:6389-6409 (2015), Shaw *et al.*, Ann. N.Y. Acad. Sci. 1241:48-70 (2011). Additionally, PCT Publication No. WO2017/070024 discloses oxazolidinone antibiotics for the treatemtent of tuberculosis.

Several oxazolidinone antibiotics have been approved or are in clinical trials for the treatment of gram-positive bacterial infections such as methicillin resistant *Staphylococcus aureus*. Examples of oxazolidinone antibiotics include linezolid (Zyvox™, Pfizer Inc., New York, NY) and tedizolid (Sivextro™, Merck Sharp & Dohme Corp., Kenilworth, NJ). Tedizolid is used to treat acute bacterial skin and skin structure infections caused by specific susceptible gram-positive bacteria. Linezolid is indicated for the treatment of several infections caused by susceptible strains of gram-positive microorganisms including nosocomial pneumonia, complicated skin and skin structure infections, and community-acquired pneumonia. In addition, it has been tested for the treatment of multi-drug resistant (MDR) and extensively drug-resistant (XDR) *Mycobacterium tuberculosis* (Mtb) in clinical trials. Lee *et al*., *N. Engl. J. Med* 367: 1508-18 (2012). Despite clinical efficacy in treating these diseases, long-term use of linezolid has been associated with adverse events including myelosuppression (including anemia and leukopenia) (Hickey *et al.*, Therapy 3(4):521-526 (2006), neuropathy, and serotonin syndrome. These adverse events are hypothesized to be associated with the inhibition of mitochondrial protein synthesis. Flanagan *et al*., *Antimicrobial Agents and Chemotherapy* 59(1):178-185 (2015).

Development of oxazolidinone antibiotics that are safer than approved oxazolidinones yet at least as effective would greatly benefit Mtb patients.

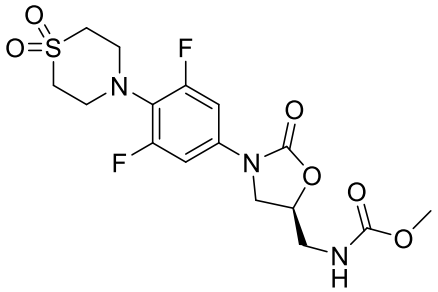
SUMMARY

The present disclosure is directed to an oxazolidinone compound which has antibacterial activity. The compound, and its pharmaceutically acceptable salts can be useful, for example, for the treatment of bacterial infections, for example, mycobacterial infections. In one aspect, the present disclosure includes the compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

In another aspect, the present disclosure relates to a compound of Formula I



(I).

In another aspect, the present disclosure relates to a pharmaceutical composition which comprises a therapeutically effective amount of the compound as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In another aspect, the present disclosure relates to a pharmaceutical composition which comprises a therapeutically effective amount of the compound as defined above and a pharmaceutically acceptable carrier. The present disclosure also relates to a pharmaceutical composition for treating a bacterial infection in a subject, particularly an *M. tuberculosis* infection, comprising the oxazolidinone compound of Formula I and/or a pharmaceutically acceptable carrier, diluent or excipient.

The compound of Formula I and/or pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting the growth of *Mycobacterium tuberculosis*, and/or for treating or preventing tuberculosis in a patient. Without being bound by any specific theory, it is believed that uses of the oxazolidinone compound of the invention for the treatment of tuberculosis is likely to cause less myelosuppression than known oxazolidinone compounds such as linezolid because they are not associated with a high degree of inhibition of mitochondrial protein synthesis and/or have higher separation between potency against *M. tuberculosis* and inhibition of mitochondrial protein

synthesis. Also, the compound described herein demonstrates a pharmacokinetic profile that, in combination with its potency against *M. tuberculosis*, is more likely to offer once-a-day (QD) dosing at reasonable dosages in humans than known oxazolidinones. Additionally, based on its pharmacokinetic profile, the compound described herein is more likely to have a smaller difference between its maximal and minimal concentrations in the body 24 hours after dosing than known oxazolidinones, which could allow for better separation between efficacy and potential adverse effects in the treatment of Mtb.

The present disclosure is also directed to 1) methods of treating tuberculosis in a subject in need of treatment thereof, comprising administering to the subject an effective amount of the oxazolidinone compound of Formula I; and 2) uses of the oxazolidinone compound of Formula I for the treatment of tuberculosis.

In another aspect, the present disclosure relates to use of the compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a bacterial infection.

In another aspect, the present disclosure relates to use of the compound as defined above in the manufacture of a medicament for the treatment of a bacterial infection.

In another aspect, the present disclosure relates to use of the pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of a bacterial infection.

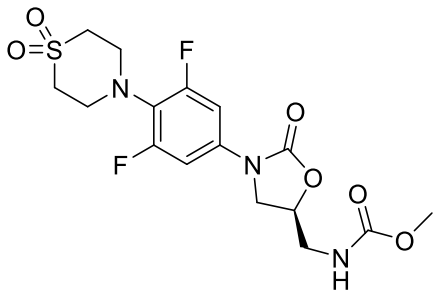
In another aspect, the present disclosure relates to the pharmaceutical composition as defined above for use as a medicament.

In another aspect, the present disclosure relates to the compound as defined above, or a pharmaceutically acceptable salt thereof, for use as a medicament.

Embodiments, sub-embodiments and features of the present disclosure are either

WHAT IS CLAIMED

1. A compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition which comprises a therapeutically effective amount of the compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

3. Use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a bacterial infection.

4. Use of the pharmaceutical composition according to claim 2 in the manufacture of a medicament for the treatment of a bacterial infection.

5. The use of claim 3, wherein the bacterial infection is due to *Mycobacterium tuberculosis*.

6. The use of claim 4, wherein the bacterial infection is due to *Mycobacterium tuberculosis*.

7. The use of claim 3, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered orally, parenterally, or topically.

8. The use of claim 4, wherein the pharmaceutical composition is to be

administered orally, parenterally, or topically.

9. The use of claim 5, wherein the *M. tuberculosis* is a drug resistant mycobacterial strain.

10. The use of claim 6, wherein the *M. tuberculosis* is a drug resistant mycobacterial strain.

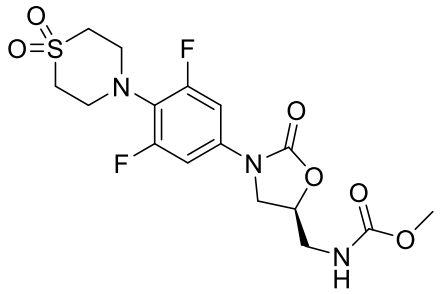
11. The use of clam 3, further comprising a second therapeutic agent for treating *M. tuberculosis* to be administered.

12. The use of claim 11, wherein the second therapeutic agent is selected from the group consisting of: ethambutol, pyrazinamide, isoniazid, levofloxacin, moxifloxacin, gatifloxacin, ofloxacin, kanamycin, amikacin, capreomycin, streptomycin, ethionamide, prothionamide, cycloserine, teridídone, para-aminosalicylic acid, clofazimine, clarithromycin, amoxicillin-clavulanate, pretomanid, bedaquiline, GSK 3036656, gepotidacin, thiacetazone, meropenem-clavulanate, TBA-7371 a decaprenylphosphoryl-β-D-ribose 2'-oxidase (DprE1) Inhibitor, OPC-167832 from Otsuka Pharmaceutical, Telacebec (Q203) from Qurient Co., Ltd and thioridazine.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.

14. The pharmaceutical composition of claim 2 for use as a medicament.

15. A compound of Formula I


(I).

16. A pharmaceutical composition which comprises a therapeutically effective amount of the compound of claim 15 and a pharmaceutically acceptable carrier.

17. Use of the compound of claim 15 in the manufacture of a medicament for the treatment of a bacterial infection.

18. Use of the pharmaceutical composition according to claim 16 in the manufacture of a medicament for the treatment of a bacterial infection.

19. The use of claim 17, wherein the bacterial infection is due to *Mycobacterium tuberculosis*.

20. The use of claim 18, wherein the bacterial infection is due to *Mycobacterium tuberculosis*.

21. The use of claim 17, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered orally, parenterally, or topically.

22. The use of claim 18, wherein the compound or the pharmaceutically acceptable salt thereof is to be administered orally, parenterally, or topically.

23. The use of claim 19, wherein the *M. tuberculosis* is a drug resistant mycobacterial strain.

24. The use of claim 20, wherein the *M. tuberculosis* is a drug resistant

mycobacterial strain.

25. The use of clam 17, further comprising a second therapeutic agent for treating *M. tuberculosis* to be administered.

26. The use of claim 25, wherein the second therapeutic agent is selected from the group consisting of: ethambutol, pyrazinamide, isoniazid, levofloxacin, moxifloxacin, gatifloxacin, ofloxacin, kanamycin, amikacin, capreomycin, streptomycin, ethionamide, prothionamide, cycloserine, teridídone, para-aminosalicylic acid, clofazimine, clarithromycin, amoxicillin-clavulanate, pretomanid, bedaquiline, GSK 3036656, gepotidacin, thiacetazone, meropenem-clavulanate, TBA-7371 a decaprenylphosphoryl-β-D-ribose 2'-oxidase (DprE1) Inhibitor, OPC-167832 from Otsuka Pharmaceutical, Telacebec (Q203) from Qurient Co., Ltd and thioridazine.

27. The compound of claim 15, or a pharmaceutically acceptable salt thereof, for use as a medicament.

28. The pharmaceutical composition of claim 16 for use as a medicament.