



In Vitro Activity of Bedaquiline and Delamanid against Nontuberculous Mycobacteria, Including Macrolide-Resistant Clinical Isolates

Dae Hun Kim,^a Byung Woo Jhun,^a Seong Mi Moon,^a Su-Young Kim,^a Kyeongman Jeon,^a O Jung Kwon,^a Hee Jae Huh,^b Nam Yong Lee,^b Sung Jae Shin,^{c,d,e} Charles L. Daley,^{f,g} Won-Jung Koh^a

^aDivision of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

^bDepartment of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

^cDepartment of Microbiology, Yonsei University College of Medicine, Seoul, South Korea

^dInstitute for Immunology and Immunological Disease, Yonsei University College of Medicine, Seoul, South Korea

^eBrain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, South Korea

^fDivision of Mycobacterial and Respiratory Infections, National Jewish Health, Denver, Colorado, USA

^gDepartment of Medicine, University of Colorado, Aurora, Colorado, USA

ABSTRACT We evaluated the *in vitro* activities of the antimicrobial drugs bedaquiline and delamanid against the major pathogenic nontuberculous mycobacteria (NTM). Delamanid showed high MIC values for all NTM except *Mycobacterium kansasii*. However, bedaquiline showed low MIC values for the major pathogenic NTM, including *Mycobacterium avium* complex, *Mycobacterium abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. kansasii*. Bedaquiline also had low MIC values with macrolide-resistant NTM strains and warrants further investigation as a potential antibiotic for NTM treatment.

KEYWORDS *Mycobacterium abscessus*, *Mycobacterium avium* complex, *Mycobacterium kansasii*, bedaquiline, delamanid, nontuberculous mycobacteria

The incidence and prevalence of pulmonary disease (PD) associated with nontuberculous mycobacteria (NTM) are increasing worldwide (1, 2). *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus*, and *Mycobacterium kansasii* are the most common pathogens for NTM PD worldwide (3–5). Macrolide antibiotics, such as clarithromycin and azithromycin, are key drugs for treating NTM PD, especially MAC PD (1, 2). Treatment outcomes are still not satisfactory (6–9), however, and the development of acquired resistance to macrolides can further worsen treatment outcomes (10, 11). Moreover, *M. abscessus* isolates can have intrinsic inducible macrolide resistance or acquired macrolide resistance, and *M. abscessus* PD is the most difficult-to-treat type of NTM PD (12–14). Therefore, discovery of new and repurposed drugs is urgently needed (15).

Bedaquiline and delamanid are new drugs for the treatment of multidrug-resistant tuberculosis (16–20). Bedaquiline is a diarylquinoline that inhibits the proton pump of mycobacterial ATP synthase, and delamanid is a compound derived from nitroimidazooxazole that inhibits mycolic acid synthesis (21–23). Previous studies reported that the MICs of bedaquiline and delamanid for *Mycobacterium tuberculosis*, including multidrug-resistant isolates, were very low (24, 25).

Recently, the MICs of bedaquiline against MAC, including *M. avium* and *Mycobacterium intracellulare*, have been reported (26–28). In those studies, most macrolide-sensitive MAC isolates showed low MICs for bedaquiline (26–28). In addition, *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* have low MIC values for bedaquiline (28–30).

Citation Kim DH, Jhun BW, Moon SM, Kim S-Y, Jeon K, Kwon OJ, Huh HJ, Lee NY, Shin SJ, Daley CL, Koh W-J. 2019. *In vitro* activity of bedaquiline and delamanid against nontuberculous mycobacteria, including macrolide-resistant clinical isolates. *Antimicrob Agents Chemother* 63:e00665-19. <https://doi.org/10.1128/AAC.00665-19>.

Copyright © 2019 American Society for Microbiology. All Rights Reserved.

Address correspondence to Won-Jung Koh, wjkoh@skku.edu.

D.H.K. and B.W.J. contributed equally to this work.

Received 28 March 2019

Returned for modification 23 April 2019

Accepted 4 June 2019

Accepted manuscript posted online 10 June 2019

Published 25 July 2019

In contrast to those bedaquiline studies, there has been only one study on the MICs of delamanid for MAC (31), and delamanid MICs for other NTM species have not been reported. In addition, there has been no comparative analysis of MIC values for bedaquiline and delamanid with various NTM, including macrolide-resistant NTM. The purpose of the present study was to evaluate the MICs of bedaquiline and delamanid against major pathogenic NTM clinical isolates, including macrolide-resistant NTM.

For this study, which was initially approved by the institutional review board (IRB) of Samsung Medical Center in 2008 and has received IRB approval once a year (IRB approval no. 2008-09-016; last updated 2 February 2019), we included 251 clinical isolates of five major pathogenic NTM (*M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. kansasii*) isolated from patients newly diagnosed with NTM PD. We also included 56 clinical isolates of acquired-macrolide-resistant NTM (*M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense*), which were confirmed to have a 23S rRNA gene mutation associated with the acquisition of macrolide resistance (32–34). *In vitro* susceptibility testing with bedaquiline and delamanid was performed by measuring the MIC using the broth microdilution method, according to Clinical and Laboratory Standards Institute guidelines (35). *Mycobacterium peregrinum* ATCC 700686, *M. abscessus* ATCC 19977, *M. avium* ATCC 700898, and *M. kansasii* ATCC 12478 were used as controls.

Table 1 shows the MIC, MIC₅₀, and MIC₉₀ values of bedaquiline and delamanid for 251 isolates from newly diagnosed NTM PD patients. All MAC, *M. abscessus* subsp. *massiliense*, and *M. kansasii* isolates were susceptible to macrolides; most *M. abscessus* subsp. *abscessus* isolates, except for 11 macrolide-susceptible isolates, had inducible resistance to macrolides, which was confirmed using sequence analysis of the *erm*(41) gene. MAC and *M. kansasii* isolates had very low bedaquiline MIC₅₀ (≤ 0.016 $\mu\text{g/ml}$) and MIC₉₀ (≤ 0.016 $\mu\text{g/ml}$) values. Although the *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* isolates also had very low bedaquiline MIC₅₀ (0.062 $\mu\text{g/ml}$) and MIC₉₀ (0.125 $\mu\text{g/ml}$) values, the MICs were higher than those for MAC and *M. kansasii* isolates.

In contrast, MAC, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense* isolates had very high delamanid MIC₅₀ (8 to >16 $\mu\text{g/ml}$) and MIC₉₀ (>16 $\mu\text{g/ml}$) values. Compared to those NTM, *M. kansasii* had relatively low delamanid MIC₅₀ (0.25 $\mu\text{g/ml}$) and MIC₉₀ (1 $\mu\text{g/ml}$) values.

The MIC, MIC₅₀, and MIC₉₀ values for bedaquiline and delamanid with 56 isolates of macrolide-resistant NTM are shown in Table 2. All macrolide-resistant NTM isolates showed very low bedaquiline MIC₅₀ (≤ 0.016 to 0.062 $\mu\text{g/ml}$) and MIC₉₀ (≤ 0.016 to 0.25 $\mu\text{g/ml}$) values. For all macrolide-resistant NTM isolates, however, the delamanid MIC₅₀ (4 to >16 $\mu\text{g/ml}$) and MIC₉₀ (>16 $\mu\text{g/ml}$) values were very high (Table 2).

In this study, we evaluated the bedaquiline and delamanid MICs for major pathogenic NTM clinical isolates, including acquired-macrolide-resistant NTM isolates. Consistent with previous studies, our results showed that MAC, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense* isolates, as well as *M. kansasii* isolates, had low bedaquiline MIC₅₀ and MIC₉₀ values.

In particular, the low bedaquiline MICs for macrolide-resistant NTM isolates, including MAC, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense* isolates, are notable in this study. Although the clarithromycin MIC₅₀ and MIC₉₀ values for all macrolide-resistant NTM isolates were >64 $\mu\text{g/ml}$, the macrolide-resistant NTM isolates showed significantly lower bedaquiline MIC₅₀ (≤ 0.016 to 0.062 $\mu\text{g/ml}$) and MIC₉₀ (≤ 0.016 to 0.25 $\mu\text{g/ml}$) values. These results suggest that bedaquiline may be an effective antimicrobial for treatment of macrolide-resistant NTM strains.

In contrast, in this study, the delamanid MICs were high for most major pathogenic NTM isolates. The exception was *M. kansasii*, for which the delamanid MIC₅₀ and MIC₉₀ values were relatively low, compared to the values for other NTM isolates. These results, especially the delamanid MICs for MAC isolates, differed from those of one previous study (31). Although studies on delamanid resistance have reported that five genes (*ddn*, *fgd1*, *fbiA*, *fbiB*, and *fbiC*) are associated with delamanid resistance in *M. tuberculosis*

TABLE 1 MIC ranges and MIC₅₀ and MIC₉₀ values of bedaquiline and delamanid for 251 clinical NTM isolates

NTM species and antibiotic	No. (%) of isolates with MIC of:											MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)			
	≤0.016 μg/ml	0.031 μg/ml	0.062 μg/ml	0.125 μg/ml	0.25 μg/ml	0.5 μg/ml	1 μg/ml	2 μg/ml	4 μg/ml	8 μg/ml	16 μg/ml			>16 μg/ml		
<i>M. avium</i> (54 isolates)																
Bedaquiline	50 (93)	1 (2)	1 (2)	2 (4)	2 (4)	1 (2)	3 (6)	5 (9)	10 (19)	13 (24)	3 (6)	17 (32)	≤0.016	≤0.016		
Delamanid						2 (4)							8	>16		
<i>M. intracellulare</i> (48 isolates)																
Bedaquiline	45 (94)		1 (2)	2 (4)	2 (4)		5 (10)	5 (10)	4 (8)	1 (2)	13 (27)	19 (40)	≤0.016	≤0.016		
Delamanid	1 (2)												16	>16		
<i>M. abscessus</i> subsp. <i>abscessus</i> (49 isolates)																
Bedaquiline	2 (4)	7 (14)	31 (63)	5 (10)	4 (8)						12 (24)	37 (76)	0.062	0.125		
Delamanid													>16	>16		
<i>M. abscessus</i> subsp. <i>massiliense</i> (53 isolates)																
Bedaquiline	3 (6)	21 (40)	18 (34)	6 (11)	5 (9)						16 (30)	37 (70)	0.062	0.125		
Delamanid													>16	>16		
<i>M. kansasii</i> (47 isolates)																
Bedaquiline	46 (98)	1 (2)	4 (9)	11 (23)	11 (23)	14 (30)	3 (6)	1 (2)				2 (4)	≤0.016	≤0.016		
Delamanid													0.25	1		

TABLE 2 MIC ranges and MIC₅₀ and MIC₉₀ values of bedaquiline and delamanid for 56 macrolide-resistant clinical NTM isolates

NTM species and antibiotic	No. (%) of isolates with MIC of:											MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)				
	≤0.016 μg/ml	0.031 μg/ml	0.062 μg/ml	0.125 μg/ml	0.25 μg/ml	0.5 μg/ml	1 μg/ml	2 μg/ml	4 μg/ml	8 μg/ml	16 μg/ml			>16 μg/ml			
<i>M. avium</i> (10 isolates)																	
Bedaquiline	10 (100)				1 (10)												≤0.016
Delamanid						2 (20)		1 (10)								5 (50)	>16
<i>M. intracellulare</i> (16 isolates)																	
Bedaquiline	15 (94)			1 (6)													≤0.016
Delamanid						2 (13)		1 (6)								13 (81)	>16
<i>M. abscessus</i> subsp. <i>abscessus</i> (12 isolates)																	
Bedaquiline	3 (25)	1 (8)	4 (33)	3 (25)	1 (8)												0.062
Delamanid																12 (100)	>16
<i>M. abscessus</i> subsp. <i>massiliense</i> (18 isolates)																	
Bedaquiline	1 (6)	1 (6)	7 (39)	7 (39)	1 (6)	1 (6)											0.062
Delamanid																18 (100)	>16

losis (36), a similar association has not yet been reported for NTM. Given the high delamanid MICs that we observed with MAC and *M. abscessus* clinical isolates, additional studies to identify genes that contribute to delamanid resistance in NTM are needed.

Previous studies reported that mutations within the *atpE*, Rv0678, and *pepQ* genes are involved in bedaquiline resistance in *M. tuberculosis* (37). In addition, recent studies on bedaquiline-resistance-related genes in NTM have been reported. Alexander and colleagues found that mutations in the *mmpT5* and *atpE* genes were associated with bedaquiline resistance in MAC strains (38). In addition, in *M. abscessus* subsp. *abscessus*, mutations in the *atpE* and MAB_2299c genes have been reported to be associated with bedaquiline resistance (39, 40). Therefore, if bedaquiline is used for NTM treatment, then the possibility of bedaquiline resistance due to mutation in a bedaquiline-resistance-related gene should be considered, although most NTM isolates had very low bedaquiline MIC values in this study.

In summary, we evaluated the *in vitro* activities of bedaquiline and delamanid against major pathogenic NTM clinical isolates. Our results showed that bedaquiline had good *in vitro* activity against major pathogenic NTM but delamanid did not. Bedaquiline has the potential to be a potent agent for the treatment of NTM PD, including macrolide-resistant NTM PD.

ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF), funded by the South Korean Ministry of Science, Information, and Communications Technologies (grant NRF-2018R1A2A1A05018309 to W.-J.K.), and by the Basic Science Research Program through the NRF, funded by the Ministry of Education (grant NRF-2016R1A6A3A11930738 to D.H.K.).

C.L.D. has received grants from Insmad, Inc., and served on advisory boards for Otsuka, Insmad, Johnson and Johnson, Spero, and Horizon, not associated with the submitted work. W.-J.K. has received a consultation fee from Insmad, Inc., for the Insmad advisory board meeting, not associated with the submitted work. Otherwise, we have no conflicts of interest to declare.

REFERENCES

- Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ, Jr, Winthrop K. 2007. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 175:367–416. <https://doi.org/10.1164/rccm.200604-571ST>.
- Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurensen IF, Leitch A, Loebinger MR, Milburn HJ, Nightingale M, Ormerod P, Shingadia D, Smith D, Whitehead N, Wilson R, Floto RA. 2017. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax* 72(Suppl 2):ii1–ii64. <https://doi.org/10.1136/thoraxjnl-2017-210927>.
- Stout JE, Koh WJ, Yew WW. 2016. Update on pulmonary disease due to non-tuberculous mycobacteria. *Int J Infect Dis* 45:123–134. <https://doi.org/10.1016/j.ijid.2016.03.006>.
- Adjemian J, Daniel-Wayman S, Ricotta E, Prevots DR. 2018. Epidemiology of nontuberculous mycobacteriosis. *Semin Respir Crit Care Med* 39:325–335. <https://doi.org/10.1055/s-0038-1651491>.
- Kwon YS, Koh WJ. 2016. Diagnosis and treatment of nontuberculous mycobacterial lung disease. *J Korean Med Sci* 31:649–659. <https://doi.org/10.3346/jkms.2016.31.5.649>.
- Pasipanodya JG, Ogbonna D, Deshpande D, Srivastava S, Gumbo T. 2017. Meta-analyses and the evidence base for microbial outcomes in the treatment of pulmonary *Mycobacterium avium-intracellulare* complex disease. *J Antimicrob Chemother* 72(Suppl 2):i3–i19. <https://doi.org/10.1093/jac/dkx311>.
- Kwak N, Park J, Kim E, Lee CH, Han SK, Yim JJ. 2017. Treatment outcomes of *Mycobacterium avium* complex lung disease: a systematic review and meta-analysis. *Clin Infect Dis* 65:1077–1084. <https://doi.org/10.1093/cid/cix517>.
- Diel R, Nienhaus A, Ringshausen FC, Richter E, Welte T, Rabe KF, Loddenkemper R. 2018. Microbiologic outcome of interventions against *Mycobacterium avium* complex pulmonary disease: a systematic review. *Chest* 153:888–921. <https://doi.org/10.1016/j.chest.2018.01.024>.
- Koh WJ, Moon SM, Kim SY, Woo MA, Kim S, Jhun BW, Park HY, Jeon K, Huh HJ, Ki CS, Lee NY, Chung MJ, Lee KS, Shin SJ, Daley CL, Kim H, Kwon OJ. 2017. Outcomes of *Mycobacterium avium* complex lung disease based on clinical phenotype. *Eur Respir J* 50:1602503. <https://doi.org/10.1183/13993003.02503-2016>.
- Griffith DE. 2018. Treatment of *Mycobacterium avium* complex (MAC). *Semin Respir Crit Care Med* 39:351–361. <https://doi.org/10.1055/s-0038-1660472>.
- Kwon YS, Koh WJ, Daley CL. 2019. Treatment of *Mycobacterium avium* complex pulmonary disease. *Tuberc Respir Dis* 82:15–26. <https://doi.org/10.4046/trd.2018.0060>.
- Koh WJ, Jeong BH, Kim SY, Jeon K, Park KU, Jhun BW, Lee H, Park HY, Kim DH, Huh HJ, Ki CS, Lee NY, Kim HK, Choi YS, Kim J, Lee SH, Kim CK, Shin SJ, Daley CL, Kim H, Kwon OJ. 2017. Mycobacterial characteristics and treatment outcomes in *Mycobacterium abscessus* lung disease. *Clin Infect Dis* 64:309–316. <https://doi.org/10.1093/cid/ciw724>.
- Koh WJ, Stout JE, Yew WW. 2014. Advances in the management of pulmonary disease due to *Mycobacterium abscessus* complex. *Int J Tuberc Lung Dis* 18:1141–1148. <https://doi.org/10.5588/ijtld.14.0134>.
- Strnad L, Winthrop KL. 2018. Treatment of *Mycobacterium abscessus* complex. *Semin Respir Crit Care Med* 39:362–376. <https://doi.org/10.1055/s-0038-1651494>.
- Wu ML, Aziz DB, Dartois V, Dick T. 2018. NTM drug discovery: status, gaps

- and the way forward. *Drug Discov Today* 23:1502–1519. <https://doi.org/10.1016/j.drudis.2018.04.001>.
16. Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghai P, Bang D, Barry PM, Bastos ML, Behera D, Benedetti A, Bisson GP, Boeree MJ, Bonnet M, Brode SK, Brust JCM, Cai Y, Caumes E, Cegielski JP, Centis R, Chan PC, Chan ED, Chang KC, Charles M, Cirule A, Dalcolmo MP, D'Ambrosio L, de Vries G, Dheda K, Esmail A, Flood J, Fox GJ, Frechet-Jachym M, Fregona G, Gayoso R, Gegia M, Gler MT, Gu S, Guglielmetti L, Holtz TH, Hughes J, Isaakidis P, Jarlsberg L, Kempker RR, Keshavjee S, Khan FA, Kipiani M, Koenig SP, Koh WJ, Kritski A, Kuksa L, Kvasnovsky CL, Kwak N, Lan Z, Lange C, Laniado-Laborin R, Lee M, Leimane V, Leung CC, Leung EC, Li PZ, Lowenthal P, Maciel EL, Marks SM, Mase S, Mbuagbaw L, Migliori GB, Milanov V, Miller AC, Mitnick CD, Modongo C, Mohr E, Monedero I, Nahid P, Ndjeka N, O'Donnell MR, Padayatchi N, Palmero D, Pape JW, Podewils LJ, Reynolds I, Riekstina V, Robert J, Rodriguez M, Seaworth B, Seung KJ, Schnippel K, Shim TS, Singla R, Smith SE, Sotgiu G, Sukhbaatar G, Tabarsi P, Tiberi S, Trajman A, Trieu L, Udwadia ZF, van der Werf TS, Veziris N, Viiklepp P, Vilbrun SC, Walsh K, Westenhoe J, Yew WW, Yim JJ, Zetola NM, Zignol M, Zmies D. 2018. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 392: 821–834. [https://doi.org/10.1016/S0140-6736\(18\)31644-1](https://doi.org/10.1016/S0140-6736(18)31644-1).
 17. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, Hughes J, Ferreira H, Padanilam X, Romero R, Te Riele J, Conradie F. 2018. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 6:699–706. [https://doi.org/10.1016/S2213-2600\(18\)30235-2](https://doi.org/10.1016/S2213-2600(18)30235-2).
 18. Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, Padanilam X, Enwerem M, Chotoo S, Singh N, Hughes J, Variava E, Ferreira H, Te Riele J, Ismail N, Mohr E, Bantubani N, Conradie F. 2018. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. *Eur Respir J* 52: 1801528. <https://doi.org/10.1183/13993003.01528-2018>.
 19. Kim CT, Kim TO, Shin HJ, Ko YC, Hun Choe Y, Kim HR, Kwon YS. 2018. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. *Eur Respir J* 51: 1702467. <https://doi.org/10.1183/13993003.02467-2017>.
 20. Mok J, Kang H, Hwang SH, Park JS, Kang B, Lee T, Koh WJ, Yim JJ, Jeon D. 2018. Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea. *J Antimicrob Chemother* 73:503–508. <https://doi.org/10.1093/jac/dkx373>.
 21. Andries K, Verhasselt P, Guillemont J, Gohlmann HW, Neefs JM, Winkler H, Van Gestel J, Timmerman P, Zhu M, Lee E, Williams P, de Chaffoy D, Huitric E, Hoffner S, Cambau E, Truffot-Pernot C, Lounis N, Jarlier V. 2005. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 307:223–227. <https://doi.org/10.1126/science.1106753>.
 22. Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, Shimokawa Y, Komatsu M. 2006. OPC-67683, a nitro-dihydroimidazo[4,5-b]pyridine derivative with promising action against tuberculosis *in vitro* and in mice. *PLoS Med* 3:e466. <https://doi.org/10.1371/journal.pmed.0030466>.
 23. Kwon YS, Koh WJ. 2016. Synthetic investigational new drugs for the treatment of tuberculosis. *Expert Opin Investig Drugs* 25:183–193. <https://doi.org/10.1517/13543784.2016.1121993>.
 24. Pang Y, Zong Z, Huo F, Jing W, Ma Y, Dong L, Li Y, Zhao L, Fu Y, Huang H. 2017. *In vitro* drug susceptibility of bedaquiline, delamanid, linezolid, clofazimine, moxifloxacin, and gatifloxacin against extensively drug-resistant tuberculosis in Beijing, China. *Antimicrob Agents Chemother* 61:e00900-17. <https://doi.org/10.1128/aac.00900-17>.
 25. Lopez B, Siqueira de Oliveira R, Pinhata JMW, Chimara E, Pacheco Ascencio E, Puyen Guerra ZM, Wainmayer I, Simboli N, Del Granado M, Palomino JC, Ritacco V, Martin A. 2019. Bedaquiline and linezolid MIC distributions and epidemiological cut-off values for *Mycobacterium tuberculosis* in the Latin American region. *J Antimicrob Chemother* 74:373–379. <https://doi.org/10.1093/jac/dky414>.
 26. Brown-Elliott BA, Phillely JV, Griffith DE, Thakkar F, Wallace RJ, Jr. 2017. *In vitro* susceptibility testing of bedaquiline against *Mycobacterium avium* complex. *Antimicrob Agents Chemother* 61:e01798-16. <https://doi.org/10.1128/AAC.01798-16>.
 27. Vesenbeckh S, Schonfeld N, Krieger D, Bettermann G, Bauer TT, Russmann H, Mauch H. 2017. Bedaquiline as a potential agent in the treatment of *M. intracellulare* and *M. avium* infections. *Eur Respir J* 49: 1601969. <https://doi.org/10.1183/13993003.01969-2016>.
 28. Pang Y, Zheng H, Tan Y, Song Y, Zhao Y. 2017. *In vitro* activity of bedaquiline against nontuberculous mycobacteria in China. *Antimicrob Agents Chemother* 61:e02627-16. <https://doi.org/10.1128/AAC.02627-16>.
 29. Li B, Ye M, Guo Q, Zhang Z, Yang S, Ma W, Yu F, Chu H. 2018. Determination of MIC distribution and mechanisms of decreased susceptibility to bedaquiline among clinical isolates of *Mycobacterium abscessus*. *Antimicrob Agents Chemother* 62:e00175-18. <https://doi.org/10.1128/AAC.00175-18>.
 30. Brown-Elliott BA, Wallace RJ, Jr. 2019. *In vitro* susceptibility testing of bedaquiline against *Mycobacterium abscessus* complex. *Antimicrob Agents Chemother* 63:e01919-18. <https://doi.org/10.1128/aac.01919-18>.
 31. Krieger D, Schonfeld N, Vesenbeckh S, Bettermann G, Bauer TT, Russmann H, Mauch H. 2016. Is delamanid a potential agent in the treatment of diseases caused by *Mycobacterium avium-intracellulare*? *Eur Respir J* 48:1803–1804. <https://doi.org/10.1183/13993003.01420-2016>.
 32. Moon SM, Park HY, Kim SY, Jhun BW, Lee H, Jeon K, Kim DH, Huh HJ, Ki CS, Lee NY, Kim HK, Choi YS, Kim J, Lee SH, Kim CK, Shin SJ, Daley CL, Koh WJ. 2016. Clinical characteristics, treatment outcomes, and resistance mutations associated with macrolide-resistant *Mycobacterium avium* complex lung disease. *Antimicrob Agents Chemother* 60:6758–6765. <https://doi.org/10.1128/AAC.01240-16>.
 33. Choi H, Kim SY, Kim DH, Huh HJ, Ki CS, Lee NY, Lee SH, Shin S, Shin SJ, Daley CL, Koh WJ. 2017. Clinical characteristics and treatment outcomes of patients with acquired macrolide-resistant *Mycobacterium abscessus* lung disease. *Antimicrob Agents Chemother* 61:e01146-17. <https://doi.org/10.1128/AAC.01146-17>.
 34. Choi H, Kim SY, Lee H, Jhun BW, Park HY, Jeon K, Kim DH, Huh HJ, Ki CS, Lee NY, Lee SH, Shin SJ, Daley CL, Koh WJ. 2017. Clinical characteristics and treatment outcomes of patients with macrolide-resistant *Mycobacterium massiliense* lung disease. *Antimicrob Agents Chemother* 61: e02189-16. <https://doi.org/10.1128/AAC.02189-16>.
 35. Clinical Laboratory Standards Institute. 2011. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes; approved standard—2nd ed. CLSI document M24-A2. Clinical Laboratory Standards Institute, Wayne, PA.
 36. Fujiwara M, Kawasaki M, Hariguchi N, Liu Y, Matsumoto M. 2018. Mechanisms of resistance to delamanid, a drug for *Mycobacterium tuberculosis*. *Tuberculosis (Edinb)* 108:186–194. <https://doi.org/10.1016/j.tube.2017.12.006>.
 37. Nguyen TVA, Anthony RM, Banuls AL, Nguyen TVA, Vu DH, Alffenaar JC. 2018. Bedaquiline resistance: its emergence, mechanism, and prevention. *Clin Infect Dis* 66:1625–1630. <https://doi.org/10.1093/cid/cix992>.
 38. Alexander DC, Vasireddy R, Vasireddy S, Phillely JV, Brown-Elliott BA, Pery BJ, Griffith DE, Benwill JL, Cameron AD, Wallace RJ, Jr. 2017. Emergence of *mmpT5* variants during bedaquiline treatment of *Mycobacterium intracellulare* lung disease. *J Clin Microbiol* 55:574–584. <https://doi.org/10.1128/JCM.02087-16>.
 39. Dupont C, Viljoen A, Thomas S, Roquet-Baneres F, Herrmann JL, Pethe K, Kremer L. 2017. Bedaquiline inhibits the ATP synthase in *Mycobacterium abscessus* and is effective in infected zebrafish. *Antimicrob Agents Chemother* 61:e01225-17. <https://doi.org/10.1128/AAC.01225-17>.
 40. Richard M, Gutierrez AV, Viljoen A, Rodriguez-Rincon D, Roquet-Baneres F, Blaise M, Everall I, Parkhill J, Floto RA, Kremer L. 2019. Mutations in the MAB_2299c TetR regulator confer cross-resistance to clofazimine and bedaquiline in *Mycobacterium abscessus*. *Antimicrob Agents Chemother* 63:e01316-18. <https://doi.org/10.1128/AAC.01316-18>.