NHS England

Evidence review: Bedaquiline and/or delamanid for multi-drug resistant tuberculosis in adults

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Prepared by:	Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1 Introduction

Existing guidance from the National Institute for Health and Care Excellence (NICE)

- We found no guidance from NICE about the use of bedaquiline and/or delamanid for multi-drug resistant tuberculosis in adults.

The indication and epidemiology

- Tuberculosis (TB) is an infection. In humans, the most common causal bacterium is *Mycobacterium tuberculosis* and the most usual site is the lung. There is great variation in distribution of TB in England; certain subgroups, such as new migrants, ethnic minority groups and those with social risk factors are disproportionally affected. The most deprived 10% of the population have an incidence of TB more than seven times higher than the least deprived 10%, and people born outside the UK have a rate 13 times higher than people born in the UK (Public Health England 2018).
- TB incidence in England peaked at 8,280 in 2011. Since then the number of people notified with TB has fallen by nearly 40% to 5,102 people in 2017. At 9.2 per 100,000, this was the lowest incidence of TB ever recorded in England and, for the first time, England is considered to be a low incidence country under current World Health Organisation (WHO) definitions (Public Health England 2018).
- TB can be treated successfully with antibiotics. However, *M tuberculosis* has evolved resistance to many of the antibiotics to which it was previously susceptible, making treatment more difficult. Patients usually acquire drug-resistant disease either as a result of spread of a drug-resistant strain from another person or as a result of inappropriate or incomplete treatment.
- Multi-drug-resistant tuberculosis (MDR-TB) is diagnosed when the infecting bacteria fail to respond to rifampicin and isoniazid, two first-line antibiotics used to treat the illness. Treatment of MDR-TB requires second-line drugs such as fluoroquinolones and aminoglycosides, which in general are less effective, more toxic, require longer courses of treatment and are more expensive than first-line drugs. Also, aminoglycosides are given by injection, a further disadvantage of their use (NHS England).
- Extensively drug-resistant tuberculosis (XDR-TB) is resistant to rifampicin, isoniazid, at least one fluoroquinolone and at least one injectable agent.
- Treatment of MDR- and XDR-TB is less likely to be successful. These conditions are more often fatal than infection with TB sensitive to rifampicin and isoniazid.
- MDR-TB is rare in England. The number of people with confirmed MDR-TB or rifampicin-resistant TB fell from 60 (1.7% of cases) in 2016 to 55 (1.8%) in 2017. The percentage rose slightly because the denominator (the total number of TB cases) fell faster than the number of MDR-TB cases. Only three of these 55 people had confirmed XDR-TB at diagnosis, fewer than each of the previous two years (Public Health England 2018).

Standard treatment and pathway of care

- Standard treatment of pulmonary TB in England is with six months of isoniazid and rifampicin, along with pyrazinamide and ethambutol for the first two months of the six-month treatment period (NHS UK).
- MDR-TB and XDR-TB require treatment with at least six antibiotics to which the mycobacterium is likely to be sensitive. These may include aminosalicylic acid, amikacin, capreomycin, cycloserine, azithromycin, clarithromycin and moxifloxacin

(British National Formulary).

The intervention

- Bedaquiline is a novel antibiotic, effective against strains of *M tuberculosis* resistant to other agents. It belongs to a new class of anti-mycobacterial drugs known as diarylquinolines, and exerts a bactericidal and sterilizing activity against *M tuberculosis* by inhibiting adenosine triphosphate synthase (Chahine et al 2014).
- Delamanid is also a new antibiotic with similar indications. It is a member of the nitroimidazole class. It acts by inhibiting the synthesis of methoxy-mycolic acid and keto-mycolic acid, both mycobacterial cell wall components (Xavier et al 2014).
- Both drugs are licensed in the UK for use in combination treatment of MDR-TB (British National Formulary). Both licenses are for 24 weeks treatment.
- WHO also recommends the use of bedaquiline or delamanid for a maximum of 24 weeks, along with other anti-TB drugs. WHO does not recommend the concurrent use of bedaquiline and delamanid. WHO describes the evidence on the safety and effectiveness of bedaquiline and delamanid beyond six months, and the evidence about concurrent use of these drugs, as "insufficient for review" (World Health Organization 2018).

Rationale for use

- The addition of drugs to which MDR-TB is sensitive may increase the chances of cure. Treating patients with several antibiotics concurrently reduces the risk of the emergence of drug resistance. However, it is uncertain whether using bedaquiline and delamanid for longer than six months, concurrently or sequentially would be effective, safe or cost effective.

2 Summary of results

- There is little research within scope of the questions identified for this review. We found a total of six studies suitable for inclusion.

PICO I: Bedaquiline use for over 6 months

One unrandomised controlled trial (Guglielmetti et al 2017, n=45) and one systematic review and meta-analysis (WHO 2016)

Cure

- Guglielmetti et al 2017 reported a cure rate after less than 190 days bedaquiline (dose not reported) of 7/12 (58%) and after more than 190 days bedaquiline (dose not reported) of 27/33 (82%), p=0.13. The authors do not define cure, but usually cure of TB means that that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Treatment completion

- Guglielmetti et al 2017 reported a treatment completion rate after less than 190 days bedaquiline (dose not reported) of 2/12 (17%) and after more than 190 days bedaquiline

(dose not reported) of 0/33 (0%), p=0.067. The authors do not define treatment completion, but usually it occurs when treatment is completed but there are fewer than five cultures performed during the last 12 months.

Mortality

- Guglielmetti et al 2017 reported a mortality rate after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 1/33 (3%), p=1.0.

Treatment failure

- Guglielmetti et al 2017 reported a treatment failure rate after less than 190 days bedaquiline (dose not reported) of 1/12 (8%) and after more than 190 days bedaquiline (dose not reported) of 2/33 (6%), p=1.0. The authors do not define treatment failure, but usually it means that a patient had two or more positive cultures among five collected during the final 12 months of treatment or had a positive culture among the final three sputum cultures collected.

Median time to sputum smear conversion

- Guglielmetti et al 2017 reported a median time to sputum smear conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 110 days, p=0.002. Time to sputum smear conversion is the elapsed time between treatment starting and the first sputum sample free of TB on microscopy.

Median time to sputum culture conversion

- Guglielmetti et al 2017 reported a median time to sputum culture conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 91 days, p=0.021. Time to sputum culture conversion is the elapsed time between treatment starting and the first sputum sample free of TB on culture.

Odds of culture conversion

- Guglielmetti et al 2017 do not report an odds ratio comparing less than 190 days bedaquiline (dose not reported) and more than 190 days bedaquiline (dose not reported), but state that p=0.702. The odds of culture conversion after multivariate adjustment indicate whether treatment duration is associated with the probability of TB being cultured from a sputum sample, adjusting for potential confounders. The authors do not report which potential confounders they selected for adjustment.

Severe adverse effects

- Guglielmetti et al 2017 reported a rate of severe adverse effects after less than 190 days bedaquiline (dose not reported) of 5/12 (42%) and after more than 190 days bedaquiline (dose not reported) of 23/33 (70%), p=0.163. Severe adverse effects are defined in this study as those causing severe, life-threatening or fatal effects.

Prolongation of the corrected QT interval

- Guglielmetti et al 2017 reported a rate of prolongation of the corrected QT interval after

less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 5/33 (15%), p=0.303. Prolongation of the corrected QT interval is an electrocardiographic abnormality associated with bedaquiline and delamanid.

- The WHO (2016) systematic review included data on patients treated with bedaquiline for more than six months. Because this evidence was "limited", WHO recommended that use of bedaquiline be for six months only.

- We found no evidence about the cost-effectiveness or subgroup effects of bedaquiline used for more than six months.

Conclusion

- The available evidence does not indicate better results from use of bedaquiline beyond six months, the maximum specified in the drug's licence.

PICO II: Delamanid use for over 6 months

Two unrandomised controlled trials (Kuksa et al 2017, n=19 and Skripconoka et al 2013, n=421) and one case series (Chang et al 2018, n=11).

Cure

- Chang et al 2018 reported a cure rate after delamanid 200mg/day for a median of 12 months (range 6 to 22 months) of 9/11 (82%). The authors did not define cure.
- Kuksa et al 2017 reported a cure rate after delamanid (dose not reported) for more than 26 weeks of 9/9 (100%) and after delamanid (dose not reported) for 26 weeks or less of 7/7 (100%), p=1.0. The authors define cure as meaning that treatment was completed as recommended without failure and three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.
- Skripconoka et al 2013 reported a cure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 110/192 (57.3%, 95% confidence interval (CI) 50.0% to 64.4%), and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 111/229 (48.5%, 95% CI 41.8% to 55.1%), p≥0.05. Prescription of delamanid for two months is outside the product licence, which is for treatment courses of 24 weeks' duration. The authors define cure as meaning that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Treatment completion

- Skripconoka et al 2013 reported a treatment completion rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 33/192 (17.2%, 95% CI 12.1% to 23.3%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 15/229 (6.6%, 95% CI 3.7% to 10.6%), p<0.001. The authors define treatment completion as meaning that the participant finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months.

Mortality

- Skripconoka et al 2013 reported a mortality rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 2/192 (1.0%, 95% CI 0.1% to 3.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of

19/229 (8.3%, 95% CI 5.1% to 12.7%), p<0.001.

Treatment failure

- Skripconoka et al 2013 reported a treatment failure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 32/192 (16.7%, 95% CI 11.7% to 22.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 26/229 (11.4%, 95% CI 7.6% to 16.2%), p≥0.05. The authors define treatment failure as meaning that the participant had two or more positive cultures among five collected during the final 12 months, or a positive culture among the final three sputum cultures collected from the patient.

Default from treatment

- Skripconoka et al 2013 reported a treatment default rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 15/192 (7.8%, 95% CI 4.4% to 12.6%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 58/229 (25.3%, 95% CI 19.8% to 31.5%), p<0.001. The authors define treatment default as meaning that treatment was interrupted for more than two consecutive months for any reason without medical approval.

- We found no evidence about the safety, cost-effectiveness or subgroup effects of delamanid used for more than six months.

Conclusion

- For two outcomes (cure and treatment failure), there were no significant differences between those who had had delamanid for no more than two months or had had a placebo, versus those who had received the drug for six or eight months, nor between those who had delamanid for more than 26 weeks, versus those with 26 weeks' treatment or less.

- Longer-term treatment was more often associated with treatment completion, lack of default from treatment and survival. However, this result is unreliable. The participants who received short-term treatment only did so because they did not enter the second or third studies included within Skripconoka at al 2013's analysis, leaving the research programme after only two months. The authors report no data comparing these participants with those who entered the later studies. If these participants had more severe TB or had a worse prognosis for some other reason, such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse rates of treatment completion, default and survival. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.

- For this reason, Skripconoka et al 2013 cannot be interpreted as indicating advantages from use of delamanid beyond six months. Kuksa et al 2017 is similarly inconclusive. Chang et al 2018 is uncontrolled and hence can shed no light on the relative effectiveness of regimens of different duration.

PICO III: Bedaquiline and delamanid combined use for over 6 months

One case series (Guglielmetti et al 2018, n=3).

Cure

- Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Sputum culture conversion

- Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Sputum culture conversion is the disappearance of TB from cultures of sputum.

Prolongation of the corrected QT interval

- Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/3 (67%).

- We found no evidence about the cost-effectiveness or subgroup effects of bedaquiline and delamanid combined use.

Conclusion

- These data are far too limited to provide any useful information on the effectiveness and safety of combined use of bedaquiline and delamanid.

PICO IV: Bedaquiline and delamanid sequential use

One case series (Guglielmetti et al 2018, n=2).

Cure

- Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 2/2 (100%). The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Sputum culture conversion

- Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 1/1 (100%).

Prolongation of the corrected QT interval

- Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 0/2 (0%).

- We found no evidence about the cost-effectiveness or subgroup effects of bedaquiline and delamanid sequential use for more than six months.

Conclusion

- These data are far too limited to provide any useful information on the effectiveness and

safety of sequential use of bedaquiline and delamanid.

PICO V: Delamanid and Bedaquiline sequential use

- We found no evidence relevant to the scope of this PICO and questions.

Overall conclusions

- We found no reliable evidence to support any extension in the use of bedaquiline or delamanid beyond their product licences.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- An initial description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic. Unusually, this rapid evidence review covers five PICOs (see section 9) and was conducted using an accelerated timeline for completion.
- The PICO was used to search for relevant publications in Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1 January 2008 and 19 December 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

PICO I: Bedaquiline use for over 6 months

Two papers were included comparing bedaquiline used in combination with other TB drugs for over six months duration with use for six months or less duration. One paper (Guglielmetti et al 2017) was an unrandomised controlled trial of bedaquiline (dose not reported) for no more than 190 days (standard treatment, n=12) versus bedaquiline (dose not reported) for more than 190

days (prolonged treatment, n=33). The second paper (World Health Organization 2016) was a systematic review with meta-analysis, found by our literature search.

1. **In adults with MDR-TB or XDR-TB, what is the clinical effectiveness of bedaquiline used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

Clinical effectiveness outcomes reported included cure, treatment completion, mortality, treatment failure, median time to sputum smear conversion, median time to sputum culture conversion and odds of culture conversion after multivariate adjustment.

Cure
Guglielmetti et al 2017 reported a cure rate after less than 190 days bedaquiline (dose not reported) of 7/12 (58%) and after more than 190 days bedaquiline (dose not reported) of 27/33 (82%), p=0.13. The authors do not define cure, but usually cure of TB means that that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Treatment completion
Guglielmetti et al 2017 reported a treatment completion rate after less than 190 days bedaquiline (dose not reported) of 2/12 (17%) and after more than 190 days bedaquiline (dose not reported) of 0/33 (0%), p=0.067. The authors do not define treatment completion, but usually it occurs when treatment is completed but there are fewer than five cultures performed during the last 12 months.

Mortality
Guglielmetti et al 2017 reported a mortality rate after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 1/33 (3%), p=1.0.

Treatment failure
Guglielmetti et al 2017 reported a treatment failure rate after less than 190 days bedaquiline (dose not reported) of 1/12 (8%) and after more than 190 days bedaquiline (dose not reported) of 2/33 (6%), p=1.0. The authors do not define treatment failure, but usually it means that a patient had two or more positive cultures among five collected during the final 12 months of treatment or has a positive culture among the final three sputum cultures collected.

Median time to sputum smear conversion
Guglielmetti et al 2017 reported a median time to sputum smear conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 110 days, p=0.002. Time to sputum smear conversion is the elapsed time between treatment starting and the first sputum sample free of TB on microscopy.

Median time to sputum culture conversion
Guglielmetti et al 2017 reported a median time to sputum culture conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 91 days, p=0.021. Time to sputum culture conversion is the elapsed time between treatment starting and the first sputum sample free of TB on culture.

Odds of culture conversion
Guglielmetti et al 2017 do not report an odds ratio comparing less than 190 days bedaquiline (dose not reported) and more than 190 days bedaquiline (dose not reported), but state that p=0.702. The odds of culture conversion after multivariate adjustment indicate whether treatment duration is associated with the probability of TB being cultured from a sputum sample, adjusting for potential confounders. The authors do not report which potential confounders they selected for

adjustment.

The WHO's high-quality systematic review included some then-unpublished data on patients treated with bedaquiline for more than six months which was later reported by Guglielmetti et al 2017. These data were not reported separately or meta-analysed and so are not reported in this review. The WHO authors described the quality of the evidence for the use of bedaquiline in MDR-TB treatment as "very low" due to imprecision, indirectness, inconsistency, and risk of bias. The panel emphasised that due to limitations in the design of studies included in the review, "potential serious biases could have been introduced". Noting that this evidence was "limited", WHO recommended that use of bedaquiline be for six months only.

2. **In adults with MDR-TB or XDR-TB, what is the safety of bedaquiline used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

Severe adverse effects
Guglielmetti et al 2017 reported a rate of severe adverse effects after less than 190 days bedaquiline (dose not reported) of 5/12 (42%) and after more than 190 days bedaquiline (dose not reported) of 23/33 (70%), p=0.163. Severe adverse effects are defined in this study as those causing severe, life-threatening or fatal effects.

Prolongation of the corrected QT interval
Guglielmetti et al 2017 reported a rate of prolongation of the corrected QT interval of more than 500ms after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 5/33 (15%), p=0.303. Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid.

3. **In adults with MDR-TB or XDR-TB, what is the cost effectiveness of bedaquiline used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

We found no evidence relevant to this question.

4. **From the evidence selected, are there any subgroups of patients that may benefit from bedaquiline used in combination with other TB drugs for over 6 months duration more than the wider population of interest? (eg over and under 65 years of age)**

We found no evidence relevant to this question.

PICO II: Delamanid use for over 6 months

Two papers were included comparing delamanid used in combination with other TB drugs for over six months duration compared to use for six months or less duration. Skripconoka et al 2013 was an unrandomised controlled trial of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months (long-term treatment, n=192) versus delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months (short-term treatment, n=229). Prescription of delamanid for two months is outside the product licence, which is for treatment courses of 24 weeks' duration. Kuksa et al 2017 was an unrandomised controlled trial of delamanid (dose not reported) for more than 26 weeks (long-term treatment, n=10) versus delamanid (dose not reported) for 26 weeks or less (short-term treatment, n=9).

Chang et al 2018 reported results, without a control treatment, of delamanid 100mg twice daily for "one to two months", then 200mg daily for a median of 12 months (range 6 to 22 months).

1. **In adults with MDR-TB or XDR-TB, what is the clinical effectiveness of delamanid used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

Clinical effectiveness outcomes reported in the study included cure, treatment completion, mortality, treatment failure and default from treatment.

Cure

Chang et al 2018 reported a cure rate of 9/11 (82%) after delamanid 100mg twice daily for "one to two months", then 200mg daily for a median of 12 months (range 6 to 22 months). The authors did not define cure.

Kuksa et al 2017 reported a cure rate after delamanid (dose not reported) for more than 26 weeks of 9/9 (100%) and after delamanid (dose not reported) for 26 weeks or less of 7/7 (100%), p=1.0. The authors define cure as meaning that treatment was completed as recommended without failure and three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.

Skripconoka et al 2013 reported a cure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 110/192 (57.3%, 95% CI 50.0% to 64.4%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 111/229 (48.5%, 95% CI 41.8% to 55.1%), p≥0.05. The authors define cure as meaning that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Treatment completion

Skripconoka et al 2013 reported a treatment completion rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 33/192 (17.2%, 95% CI 12.1% to 23.3%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 15/229 (6.6%, 95% CI 3.7% to 10.6%), p<0.001. The authors define treatment completion as meaning that the participant finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months.

Mortality

Skripconoka et al 2013 reported a mortality rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 2/192 (1.0%, 95% CI 0.1% to 3.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 19/229 (8.3%, 95% CI 5.1% to 12.7%), p<0.001.

Treatment failure

Skripconoka et al 2013 reported a treatment failure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 32/192 (16.7%, 95% CI 11.7% to 22.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 26/229 (11.4%, 95% CI 7.6% to 16.2%), p≥0.05. The authors define treatment failure as meaning that the participant had two or more positive cultures among five collected during the final 12 months, or a positive culture among the final three sputum cultures collected from the patient.

Default from treatment

Skripconoka et al 2013 reported a treatment default rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 15/192 (7.8%, 95% CI 4.4% to 12.6%) and after delamanid

100mg twice daily or 200mg twice daily or placebo for 2 months of 58/229 (25.3%, 95% CI 19.8% to 31.5%), p<0.001. The authors define treatment default as meaning that treatment was interrupted for more than two consecutive months for any reason without medical approval.

2. **In adults with MDR-TB or XDR-TB, what is the safety of delamanid used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

We found no evidence relevant to this question.

3. **In adults with MDR-TB or XDR-TB, what is the cost effectiveness of delamanid used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

We found no evidence relevant to this question.

4. **From the evidence selected, are there any subgroups of patients that may benefit from delamanid used in combination with other TB drugs for over 6 months duration more than the wider population of interest? (eg over and under 65 years of age**)

We found no evidence relevant to this question.

PICO III: Bedaquiline and delamanid combined use for over 6 months

One paper reported the combined use of bedaquiline and delamanid for more than six months. Guglielmetti et al 2018 was a case series which reported three participants who received a combination of bedaquiline and delamanid for more than six months.

1. **In adults with MDR-TB or XDR-TB, what is the clinical effectiveness of bedaquiline and delamanid used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

Cure
Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Sputum culture conversion
Guglielmetti et al 2018 reported a sputum culture conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Sputum culture conversion is the disappearance of TB from cultures of sputum.

2. **In adults with MDR-TB or XDR-TB, what is the safety of bedaquiline and delamanid used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

Prolongation of the corrected QT interval
Guglielmetti et al 2018 reported prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/3 (67%).

3. **In adults with MDR-TB or XDR-TB, what is the cost effectiveness of bedaquiline and delamanid used in combination with other TB drugs for over 6 months duration compared to use for 6 months or less duration?**

We found no evidence relevant to this question.

4. **From the evidence selected, are there any subgroups of patients that may benefit from bedaquiline and delamanid used in combination with other TB drugs for over 6 months duration more than the wider population of interest? (eg over and under 65 years of age)**

We found no evidence relevant to this question.

PICO IV: Bedaquiline and delamanid sequential use

Guglielmetti et al 2018 was a case series which reported two participants who received bedaquiline then delamanid, each for more than six months.

1. **In adults with MDR-TB or XDR-TB, what is the clinical effectiveness of bedaquiline then delamanid used sequentially in combination with other TB drugs compared to bedaquiline alone in combination with other TB drugs?**

Cure
Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 2/2 (100%). The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Sputum culture conversion
Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 1/1 (100%). One participant had negative sputum culture at the start of treatment, so the denominator is 1, not 2.

2. **In adults with MDR-TB or XDR-TB, what is the safety of bedaquiline then delamanid used sequentially in combination with other TB drugs compared to bedaquiline alone in combination with other TB drugs?**

Prolongation of the corrected QT interval
Guglielmetti et al 2018 reported prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 0/2 (0%).

3. **In adults with MDR-TB or XDR-TB, what is the cost effectiveness of bedaquiline then delamanid used sequentially in combination with other TB drugs compared to bedaquiline alone in combination with other TB drugs?**

We found no evidence relevant to this question.

4. **From the evidence selected, are there any subgroups of patients that may benefit**

from bedaquiline followed by delamanid in combination with other TB drugs more than the wider population of interest? (eg over and under 65 years of age)

We found no evidence relevant to this question.

PICO V: Delamanid and bedaquiline sequential use

We found no evidence relevant to this PICO.

5 Discussion

PICO I: Bedaquiline use for over 6 months

Guglielmetti et al 2017, a small and low-powered study, compared patients receiving bedaquiline for over 190 days with those receiving it for less than 190 days and reported no significant difference between the groups in results for seven of the nine included outcomes: cure, treatment completion, mortality, treatment failure, adjusted odds of culture conversion, severe adverse effects and prolongation of the corrected QT interval. The study reported better results after prolonged treatment for two outcomes: median time to sputum smear conversion and median time to sputum culture conversion. However, these results were the result of imbalance between the two treatment groups; after multivariate adjustment for these imbalances, the odds of culture conversion were not significantly different from what would be expected if the two treatments did not differ in effectiveness.

The systematic review published by the WHO in 2016 did not include any evidence of the effects of the use of bedaquiline beyond six months.

The available evidence therefore does not indicate better results from use of bedaquiline beyond six months, the maximum specified in the drug's licence.

PICO II: Delamanid use for over 6 months

Skripconoka et al 2013 used a complicated design, observing over the longer term participants from an earlier randomised trial and a shorter observational study which followed it. For two outcomes (cure and treatment failure), there were no significant differences between those who had had delamanid for no more than two months or had had a placebo, and those who had received the drug for six or eight months.

Longer-term treatment was more often associated with treatment completion, lack of default from treatment and survival. However, this result is unreliable. The participants who received short-term treatment only did so because they did not enter the second or third studies, leaving the research programme after only two months. The authors report no data comparing these participants with those who entered the later studies. If these participants had more severe TB or had a worse prognosis for some other reason, such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse rates of treatment completion, default and survival. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.

The fact that some participants only received placebo reduces the suitability of this study as a comparison of two durations of delamanid treatment.

For this reason, Skripconoka et al 2013 cannot be interpreted as indicating advantages from use of delamanid beyond six months, as specified in its license.

Chang et al 2018 is a small uncontrolled study which only reported use of delamanid for more than six months. It indicates a high cure rate.

Kuksa et al 2017 is a small controlled study which showed no advantages from longer term use of delamanid.

PICO III: Bedaquiline and delamanid combined use for over 6 months

The case series by Guglielmetti et al 2018 only reported three participants who received concomitant bedaquiline and delamanid for more than six months. It was uncontrolled, so we cannot know what these participants' outcomes would have been with other treatment. All experienced sputum culture clearance and were cured of TB, but two of the three showed prolongation of the corrected QT interval, a potentially serious adverse effect but one that may not have been the result of these drugs.

These data are far too limited to provide any useful information on the effectiveness and safety of combined use of bedaquiline and delamanid.

PICO IV: Bedaquiline and delamanid sequential use

Guglielmetti et al 2018 also reported results for two participants who received bedaquiline then delamanid, each for more than six months. The one who had positive sputum culture when treatment started later showed culture conversion, and both participants were cured.

These data are far too limited to provide any useful information on the effectiveness and safety of sequential use of bedaquiline and delamanid.

PICO V: Delamanid and bedaquiline sequential use

We found no evidence relevant to this PICO.

More randomized controlled trials are needed to test hypotheses about the safety and effectiveness of bedaquiline and delamanid used outside their product licences and 2018 WHO recommendations.

6 Conclusion

The quality of the evidence for the use of bedaquiline in MDR-TB treatment reviewed for the SRMA published in 2016 was described by the authors as "very low, due to imprecision, indirectness, inconsistency and risk of bias", emphasising that "due to limitations in the design of these observational studies, potential serious biases could have been introduced" (WHO 2016). The evidence about the use of bedaquiline beyond six months or concomitantly or sequentially with delamanid is much scantier and too limited to draw any clear conclusions.

Evidence in favour of delamanid's use beyond six months or concomitantly or sequentially with bedaquiline is also extremely limited and inadequate as a basis for conclusions.

7 Evidence Summary Table

For abbreviations see list after tables

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Guglielmetti et al 2017 Three hospitals in France	P1: Unrandomised controlled trial. Patients were recruited between 1 January, 2011 and 31 December 2013, and followed up after the end of treatment for 24 months or to 31 March 2016, whichever was the earlier.	45 adults with culture-proven MDR-TB. Median age 38 years, median 7 drugs in regime, HIV infection 2/45 (4%), hepatitis C infection 21/45 (47%). 24/45 (53%) had XDR-TB. 12/45 (27%) participants received bedaquiline for no more than 190 days ("the standard duration of 24 weeks plus a buffer period of 3 weeks needed by the [treatment authority] to assess bedaquiline treatment duration"). 33/45 (73%) participants received bedaquiline for more than 190 days because they had a delayed	Bedaquiline (dose not reported) for no more than 190 days (standard treatment, median treatment 183 days, IQR 168 to 185 days, n=12) versus Bedaquiline for more than 190 days (prolonged treatment, median treatment 418 days, IQR 292 to 665 days. n=33). All participants received other anti-TB drugs. Median duration of bedaquiline administration 360 days. IQR	Primary outcome Clinical effectiveness	Cure[1]	Standard treatment 7/12 (58%), prolonged treatment 27/33 (82%), p=0.13.	6	Direct	11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. Six months is about 182 days, slightly less than the 190 day cut-off used in this study.
				Primary outcome Clinical effectiveness	Treatment completion[2]	Standard treatment 2/12 (17%), prolonged treatment 0/33 (0%), p=0.067.			
				Primary outcome Clinical effectiveness	Mortality	Standard treatment 0/12 (0%), prolonged treatment 1/33 (3%), p=1.0.			
				Primary outcome Clinical effectiveness	Treatment failure[3]	Standard treatment 1/12 (8%), prolonged treatment 2/33 (6%), p=1.0.			
				Primary outcome Clinical effectiveness	Median time to sputum smear conversion	Standard treatment 71 days, prolonged treatment 110 days, p=0.002.			
				Primary outcome Clinical effectiveness	Median time to sputum culture conversion	Standard treatment 71 days, prolonged treatment 91 days, p=0.021.			

[1] Not defined, but usually cure of TB means that the patient completed treatment with at least five consecutive negative cultures during the last 12 months

[2] Not defined, but usually treatment completion means that the patient finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months.

[3] Not defined, but usually treatment failure means that a patient had two or more positive cultures among five collected during the final 12 months of treatment or has a positive culture among the final three sputum cultures collected.

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		microbiological response, weak treatment regimens due to intolerance or drug resistance and/or individual risk factors for poor outcomes. No reported demographic or other data on these 33 participants.	31 to 768 days	Primary outcome Clinical effectiveness	Odds of culture conversion after multivariate adjustment (factors not reported)	Standard treatment versus prolonged duration: odds ratio not reported, p=0.702.			
				Primary outcome Safety	Severe adverse effects (those causing severe, life-threatening or fatal effects)	Standard treatment 5/12 (42%), prolonged treatment 23/33 (70%), p=0.163.			
				Primary outcome Safety	Prolongation of the corrected QT interval[4] of more than 500ms	Standard treatment 0/12 (0%), prolonged treatment 5/33 (15%), p=0.303.			
World Health Organization 2016	S1: Systematic review with meta-analysis of 5 studies, of which 2 were unpublished, in which bedaquiline was used with other drugs for at least 6 months in	537 participants, 64% male, mean age 36.4 years. Most patients received bedaquiline for six months. In a French cohort (later reported in Guglielmetti et al 2017), however, the average duration of treatment with bedaquiline was 12.3 months and 32/45 (71%) of patients, received bedaquiline	Bedaquiline 400mg once daily for 2 weeks, then 200mg three times a week	Primary outcome Clinical effectiveness	All	No reported analysis by duration of treatment	9	Direct	This high-quality systematic review included some then-unpublished data on patients treated with bedaquiline for more than 6 months which was later reported by Guglielmetti et al 2017. These data were not reported separately or meta-analysed and so are not included in this evidence table. Guglielmetti et al 2017 reported 33 patients receiving bedaquiline for more than 6 months, whereas only 32 were reported in this systematic review. WHO describe the quality of the evidence for the use of bedaquiline in MDR-TB treatment as “very low, due to imprecision, indirectness, inconsistency, and risk of bias”. The panel “emphasised that due to
				Primary outcome Safety	All	No reported analysis by duration of treatment			

[4] An electrocardiographic abnormality associated with bedaquiline and delamanid.

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	adults with MDR-TB. Search date not reported, but no later than June 2016	for more than 6 months.							limitations in the design of these observational studies, potential serious biases could have been introduced". Noting that this evidence was "limited", WHO recommended that use of bedaquiline be for six months only.

II. Delamanid for more than six months versus delamanid for less than six months in multi-drug resistant tuberculosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Kuksa et al 2017 Latvia	P1: Unrandomised controlled trial.	19 people with culture-proven MDR-TB. Mean age 42 years, 2 participants were less than 18 years old. 13 drugs in regime, HIV infection 1/19 (5%), XDR-TB 9/19 (47%). No reported analysis by duration of treatment.	Delamanid (dose not reported) for more than 26 weeks (long-term treatment, n=10) versus delamanid (dose not reported) for no more than 26 weeks (short-term treatment, n=9)	Primary outcome Clinical effectiveness	Cure[5]	Long-term treatment 9/9 (100%), short-term treatment 7/7 (100%), p =1.0.	5	Direct	Three patients were lost to follow up. The small size of this study and lack of information about patient characteristics in the different treatment groups makes it difficult to draw conclusions from this study relevant to this review's research questions.
Skripconoka et al 2013 Nine countries in the Americas, Asia, Europe and the Mediterranean region	P1: Unrandomised controlled trial.	421 adults with MDR-TB treated in a randomised trial and two observational studies. Median age 34 years, 66% male. 56 (13%) had XDR-TB and 284 (68%) had cavitary TB. 4 (1%) had HIV infection. All participants received other anti-TB drugs. No reported data on demographic or other differences between the two groups studied.	Delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months (long-term treatment, n=192) versus delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months (short-term treatment, n=229).	Primary outcome Clinical effectiveness	Cure[6]	Long-term treatment 110/192 (57.3%, 95% CI 50.0% to 64.4%), short-term treatment 111/229 (48.5%, 95% CI 41.8% to 55.1%), p ≥0.05.	6	Direct	Results were from longer term observation of participants in two sequential studies. The first study randomised participants between delamanid 100mg twice daily or delamanid 200mg twice daily or placebo, each for two months. The second study was observational, involving initial treatment (after a delay of more than four months in a third of cases) with delamanid 100mg twice daily, increased to 200mg twice daily after two weeks at the prescribers' discretion. Participants who received placebo in the first study received active treatment in the second. 268 of 481 (56%) participants from the first trial did not participate in the second one. A flowchart is in the Appendix of this review. Rates of cure and treatment completion were very similar in participants who
				Primary outcome Clinical effectiveness	Treatment completion[7]	Long-term treatment 33/192 (17.2%, 95% CI 12.1% to 23.3%), short-term treatment 15/229 (6.6%, 95% CI 3.7% to 10.6%), p<0.001.			
				Primary outcome Clinical effectiveness	Mortality	Long-term treatment 2/192 (1.0%, 95% CI 0.1% to 3.7%), short-term treatment 19/229 (8.3%, 95% CI 5.1% to 12.7%), p<0.001.			
				Primary outcome Clinical	Treatment failure[8]	Long-term treatment 32/192 (16.7%, 95% CI 11.7% to 22.7%), short-term treatment 26/229 (11.4%, 95% CI			

[5] defined as a patient who completed treatment as recommended without failure with at least three consecutive negative cultures taken at least 30 days apart after the intensive phase.

[6] defined as a patient who completed treatment with at least five consecutive negative cultures during the last 12 months

[7] defined as a patient who completed finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months.

[8] defined as a patient who had two or more positive cultures among five collected during the final 12 months, or who had a positive culture among the final three sputum cultures collected from the patient

II. Delamanid for more than six months versus delamanid for less than six months in multi-drug resistant tuberculosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				effectiveness		7.6% to 16.2%), p≥0.05.			received delamanid at either dose for eight months and those who received delamanid at either dose for six months. These patients were therefore combined in the long-term treatment group. Furthermore, outcomes in those who received two months of delamanid at either dose were similar to outcomes in those treated with placebo; these patients were therefore combined in the short-term treatment group. 59/481 (12.3%) of participants in the first study were not reported in Skripconoka et al 2013, presumably lost to follow-up, though this is not reported. Short-term treatment was only received by those who completed the first study but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter. The fact that some participants only received placebo reduces the suitability of this study as a comparison of two durations of delamanid treatment.
				Primary outcome Clinical effectiveness	Default from treatment[9]	Long-term treatment 15/192 (7.8%, 95% CI 4.4% to 12.6%), short-term treatment 58/229 (25.3%, 95% CI 19.8% to 31.5%), p<0.001.			

[9] defined as a patient whose treatment was interrupted for more than 2 consecutive months for any reason without medical approval.

II. Delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Chang et al 2018 Hong Kong	P1: Unrandomised uncontrolled trial.	11 people with culture-proven MDR-TB. 7 females, median age 48 years (range 29 to 59 years). 4 males, median age 53 years (range 44 to 59 years). Diabetes mellitus 4/11 (36%), dermatomyositis 1/11 (9%), HIV 0/11 (0%).	Delamanid 100mg twice daily for "one to two months", then 200mg daily Median duration of delamanid treatment 12 months, range 6 to 22 months	Primary outcome Clinical effectiveness	Cure (not defined)	9/11 (82%)	5	Direct	One patient was lost to follow-up, and one died of TB. The small size of this study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.

III. Bedaquiline and delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Guglielmetti et al 2018 Three hospitals in France and one in Latvia	P1: Uncontrolled case series Recruited between 1 January 2013 and 31 August 2015.	3 adults starting treatment for MDR-TB All patients were male. No other details for the concomitantly treated group were reported.	Combination of bedaquiline (dose not reported) and delamanid (dose not reported) for more than 6 months. All participants received other anti-TB drugs.	Primary outcome Clinical effectiveness	Cured[10]	3/3 (100%)	5	Direct	The small size of this study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
				Primary outcome Clinical effectiveness	Sputum culture conversion[11]	3/3 (100%)			
				Primary outcome	Prolongation of the	2/3 (67%)			

[10] Not defined, but usually cure of TB means that treatment was completed as recommended by local policy without evidence of failure and with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase of treatment

[11] The disappearance of TB from cultures of sputum.

III. Bedaquiline and delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Safety	corrected QT interval[12] of more than 500 ms				

IV. Bedaquiline and delamanid sequential use in multi-drug resistant tuberculosis (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Guglielmetti et al 2018 Three hospitals in France and one in Latvia	P1: Uncontrolled case series Recruited between 1 January 2013 and 31 August 2015.	Four adults starting treatment for MDR-TB of which two received bedaquiline "exposure" for more than six months, prior to commencing treatment with delamanid. Delamanid replaced bedaquiline because of resistance to the latter drug. All were "exposed"[13] to a combination of bedaquiline and delamanid for at least 30 days; bedaquiline	Bedaquiline (dose not reported) for more than six months followed by delamanid (dose not reported) for more than six months. All participants received other anti-TB drugs.	Primary outcome Clinical effectiveness	Cured[14]	2/2 (100%)	5	Direct	Two aspects of the paper make interpretation difficult. First, it is not clear the extent to which the washout period should be regarded as part of treatment as specified in the PICO. The prescribing physician had withdrawn bedaquiline, so the patient was no longer being actively treated with it. Notwithstanding the long half-life of bedaquiline, tissue concentrations were falling and its effect diminishing. It is unclear whether inclusion of washout periods is a reliable way of assessing the effect of sequential prescription of the two drugs of interest. Second, for one participant included here, the reported duration of exposure to both drugs was 109 days, less than bedaquiline's washout period, which
				Primary outcome Clinical effectiveness	Sputum culture conversion[15]	1/1[16] (100%)			
				Primary outcome Safety	Prolongation of the corrected QT interval[17] of more than 500 ms	0/2 (0%)			

[12] An electrocardiographic abnormality associated with bedaquiline and delamanid.
[13] Exposure was defined as the sum of the duration of concomitant treatment and the duration of a washout period for one drug after stopping it, while taking the other drug.
[14] Not defined, but usually cure of TB means that treatment was completed as recommended by local policy without evidence of failure and with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase of treatment
[15] The disappearance of TB from cultures of sputum.
[16] One participant had negative sputum culture at the start of treatment.
[17] An electrocardiographic abnormality associated with bedaquiline and delamanid.

IV. Bedaquiline and delamanid sequential use in multi-drug resistant tuberculosis (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		washout was 180 days and delamanid 5 days. All patients were male. No other details for the sequentially treated group were reported.							appears incompatible with the authors' definition of total exposure. So it is unclear if the authors applied their definitions consistently. For these reasons, it is unclear if the participants fall within the scope of the PICO. These issues, the small size of the study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.

CI = confidence interval; HR=hazard ratio; IQR = inter-quartile range.

8 Grade of Evidence Table

For abbreviations see list after each table

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Cure	Guglielmetti et al 2017	6	Direct	C	The authors do not define cure, but usually cure of TB means that that treatment was completed with at least five consecutive negative cultures during the last 12 months. Guglielmetti et al 2017 reported a cure rate after less than 190 days bedaquiline (dose not reported) of 7/12 (58%) and after more than 190 days bedaquiline (dose not reported) of 27/33 (82%), p=0.13. Cure is of very high value to patients. This study does not indicate that more patients are cured by courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Treatment completion	Guglielmetti et al 2017	6	Direct	C	The authors do not define treatment completion, but usually it occurs when treatment is completed but there are fewer than five cultures performed during the last 12 months. Guglielmetti et al 2017 reported a treatment completion rate after less than 190 days bedaquiline (dose not reported) of 2/12 (17%) and after more than 190 days bedaquiline (dose not reported) of 0/33 (0%), p=0.067. Treatment completion without confirmed cure is an indication of compliance and may be associated with cure. Its value to patients is dependent on whether cure occurred. This study does not indicate that more patients complete courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Mortality	Guglielmetti et al 2017	6	Direct	C	Mortality is the proportion of participants dying during the study. Guglielmetti et al 2017 reported a mortality rate after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 1/33 (3%), p=1.0. The avoidance of mortality is of very high value to patients. This study does not indicate that more patients survive after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Treatment failure	Guglielmetti et al 2017	6	Direct	C	The authors do not define treatment failure, but usually it means that a patient had two or more positive cultures among five collected during the final 12 months of treatment or has a positive culture among the final three sputum cultures collected. Guglielmetti et al 2017 reported a treatment failure rate after less than 190 days bedaquiline (dose not reported) of 1/12 (8%) and after more than 190 days bedaquiline (dose not reported) of 2/33 (6%), p=1.0. Treatment failure is likely to lead to recurrent symptoms and possibly fatal progression, so avoiding it is likely to be of high value to patients. This study does not indicate that fewer patients have treatment failure after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study,

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Time to sputum smear conversion	Guglielmetti et al 2017	6	Direct	C	Time to sputum smear conversion is the elapsed time between treatment starting and the first sputum sample free of TB on microscopy. Guglielmetti et al 2017 reported a median time to sputum smear conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 110 days, p=0.002. Earlier sputum smear conversion indicates the earlier elimination of TB from sputum, and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This study might appear to indicate that sputum smear conversion occurs earlier after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. However, this result is not reliable: multivariate analysis showed that there were differences in confounding variables between the two groups (see below), and it is likely these biased this result. Both groups of patients had received the same treatment at the median time of conversion, further undermining any claim that longer treatment accelerates sputum conversion. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Time to sputum culture conversion	Guglielmetti et al 2017	6	Direct	C	Time to sputum culture conversion is the elapsed time between treatment starting and the first sputum sample free of TB on culture. Guglielmetti et al 2017 reported a median time to sputum culture conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					190 days bedaquiline (dose not reported) of 91 days, p=0.021. Earlier sputum culture conversion indicates the earlier elimination of viable TB from sputum, and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This study might appear to indicate that sputum culture conversion occurs earlier after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. However, this result is not reliable: multivariate analysis showed that differences in sputum culture conversion arose from differences in confounding variables between the two groups (see below). Both groups of patients had received the same treatment at the median time of conversion, further undermining any claim that longer treatment accelerates sputum conversion.11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Odds of culture conversion after multivariate adjustment (factors not reported)	Guglielmetti et al 2017	6	Direct	C	The odds of culture conversion after multivariate adjustment indicate whether treatment duration is associated with the probability of TB being cultured from a sputum sample, adjusting for potential confounders. The authors do not report which potential confounders they selected for adjustment. Guglielmetti et al 2017 do not report an odds ratio comparing less than 190 days bedaquiline (dose not reported) and more than 190 days bedaquiline (dose not reported), but state that p=0.702. Sputum culture conversion indicates the elimination of viable TB from sputum, and may be associated with remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This study indicates that sputum culture conversion is no more likely after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days, once confounding variables are taken into account. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Severe adverse effects	Guglielmetti et al 2017	6	Direct	C	Severe adverse effects are defined in this study as those causing severe, life-threatening or fatal effects. Guglielmetti et al 2017 reported rate of severe adverse effects after less than 190 days bedaquiline (dose not reported) of 5/12 (42%) and after more than 190 days bedaquiline (dose not reported) of 23/33 (70%), p=0.163. Avoiding severe adverse effects is likely to be of high value to patients. This study does not indicate a difference in rates of severe adverse effects after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.
Prolongation of the corrected QT interval of more than 500ms	Guglielmetti et al 2017	6	Direct	C	Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid. Guglielmetti et al 2017 reported rate of prolongation of the corrected QT interval after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 5/33 (15%), p=0.303. Prolongation of the corrected QT interval may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients. This study does not indicate a difference in rates of prolongation of the corrected QT interval after courses of bedaquiline of more than 190 days, compared with courses shorter than 190 days. 11% of patients were lost to follow-up during treatment and this rate increased during post-therapeutic follow-up, though data are not reported. This may bias the study, with poor outcomes in those on prolonged treatment being less likely to be reported, a particular problem as the study was retrospective. The

I. Bedaquiline for more than six months versus bedaquiline for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					study was small and lacked a reported power calculation. It was too small to detect all but large differences between the two groups. Those receiving prolonged treatment were more often previously treated for TB (data not reported, p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although none of these differences reached statistical significance. Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048). These factors likely biased the study against the group receiving prolonged treatment. The six months treatment period specified in the PICO is about 182 days, slightly less than the 190 day cut-off used in this study.

II. Delamanid for more than six months versus delamanid for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Cure	Skripconoka et al 2013	6	Direct	B	The authors define cure as meaning that treatment was completed with at least five consecutive negative cultures during the last 12 months. Skripconoka et al 2013 reported a cure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 110/192 (57.3%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 111/229 (48.5%), p≥0.05. Cure is of very high value to patients. This study does not indicate that more patients are cured by courses of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. Short-term treatment was only received by those who completed the first of two studies reported by Skripconoka et al 2013, but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.
	Kuksa et al 2017	5	Direct		
Treatment completion	Skripconoka et al 2013	6	Direct	C	The authors define treatment completion as meaning that the participant finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months. Skripconoka et al 2013 reported a treatment completion rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 33/192 (17.2%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 15/229 (6.6%), p<0.001. Treatment completion without confirmed cure is an indication of compliance and may

II. Delamanid for more than six months versus delamanid for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					be associated with cure. Its value to patients is dependent on whether cure occurred. This study may indicate that more patients completed treatment with delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. However, short-term treatment was only received by those who completed the first of two studies reported by Skripconoka et al 2013, but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.
Mortality	Skripconoka et al 2013	6	Direct	C	Mortality is the proportion of participants dying during the study. Skripconoka et al 2013 reported a mortality rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 2/192 (1.0%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 19/229 (8.3%), $p<0.001$. The avoidance of mortality is of very high value to patients. This study may indicate that fewer participants died when treated with delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. However, short-term treatment was only received by those who completed the first of two studies reported by Skripconoka et al 2013, but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.
Treatment failure	Skripconoka et al 2013	6	Direct	C	The authors define treatment failure as meaning that the participant had two or more positive cultures among five collected during the final 12 months, or a positive culture among the final three sputum cultures collected from the patient. Skripconoka et al 2013 reported a treatment failure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 32/192 (16.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 26/229 (11.4%), $p\geq0.05$. Treatment failure is likely to lead to recurrent symptoms and possibly fatal progression, so avoiding it is likely to be of high value to patients.

II. Delamanid for more than six months versus delamanid for less than six months in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					This study does not indicate that more patients have treatment failure with courses of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. Short-term treatment was only received by those who completed the first of two studies reported by Skripconoka et al 2013, but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.
Default from treatment	Skripconoka et al 2013	6	Direct	C	The authors define treatment default as meaning that treatment was interrupted for more than two consecutive months for any reason without medical approval. Skripconoka et al 2013 reported a treatment default rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 15/192 (7.8%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 58/229 (25.3%), p<0.001. Treatment default may lead to recurrent symptoms and possibly fatal progression, so avoiding it is likely to be of high value to patients. This study may indicate that more patients have defaulted from treatment with courses of delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months, compared with delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months. However, short-term treatment was only received by those who completed the first of two studies reported by Skripconoka et al 2013, but did not enter the second one. The authors report no data comparing these participants with those who entered the second study. If they had more severe TB (perhaps making their initial response to delamanid less marked) or had a worse prognosis for some other reason such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse results. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes, and mean the former may not be the cause of the latter.

II. Delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Cure	Chang et al 2018	5	Direct	C	The authors do not define cure. Chang et al 2018 reported a cure rate after delamanid 100mg twice daily for "one to two months", then 200mg daily of 9/11 (82%). Cure is of very high value to patients. The small size of this study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.

III. Bedaquiline and delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Cure	Guglielmetti et al 2018	5	Direct	C	The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months. Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Cure is of very high value to patients. The small size of this case series and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
Sputum culture conversion	Guglielmetti et al 2018	5	Direct	C	Sputum culture conversion is the disappearance of TB from cultures of sputum. Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Sputum culture conversion indicates a higher probability of cure, so is of high value to patients. The small size of this case series and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
Prolongation of the corrected QT interval of more than 500 ms	Guglielmetti et al 2018	5	Direct	C	Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid. Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/3 (67%). Prolongation of the corrected QT interval may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients The small size of this case series and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.

IV. Bedaquiline and delamanid sequential use in multi-drug resistant tuberculosis (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Cure	Guglielmetti et al 2018	5	Direct	C	The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months. Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/2 (100%). Cure is of very high value to patients. This case series provides little reliable information on the relationship between use of bedaquiline and/or delamanid, and outcomes. Both participants were "exposed" to a combination of bedaquiline and delamanid for at least 30 days; exposure was defined as the sum of the duration of concomitant treatment and, for the patients receiving sequential treatment, the duration of a washout period for one drug after stopping it, while taking the other drug. Bedaquiline washout was 180 days and delamanid washout was 5 days. Two aspects of the paper make interpretation difficult. First, it is not clear the extent to which the washout period should be regarded as part of treatment as specified in the PICO. The prescribing physician had withdrawn bedaquiline, so the patient was no longer being actively treated with it. Notwithstanding the long half-life of bedaquiline, tissue concentrations were falling and its effect diminishing. It is unclear whether inclusion of washout periods is a reliable way of assessing the effect of sequential prescription of the two drugs of interest. Second, for one participant, the reported duration of exposure to both drugs was 109 days, less than bedaquiline's washout period, which appears incompatible with the authors' definition of total exposure. So it is unclear if the authors applied their definitions consistently. For these reasons, it is unclear if the participants fall within the scope of the PICO. These issues, the small size of the study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
Sputum culture conversion	Guglielmetti et al 2018	5	Direct	C	Sputum culture conversion is the disappearance of TB from cultures of sputum. Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 1/1 (100%). One participant had negative sputum culture at the start of treatment, so the denominator is 1, not 2. Sputum culture conversion indicates a higher probability of cure, so is of high value to patients. This case series provides little reliable information on the relationship between use of bedaquiline and/or delamanid, and outcomes. Both participants were "exposed" to a combination of bedaquiline and delamanid for at least 30 days; exposure was defined as the sum of the duration of concomitant treatment and, for the 4 patients receiving sequential treatment, the duration of a washout period for one drug after stopping it, while taking the other drug. Bedaquiline washout was 180 days and delamanid washout was 5 days. Two aspects of the paper make interpretation difficult. First, it is not clear the extent to which the washout period should be regarded as part of treatment as specified in the PICO. The prescribing physician

II. Delamanid for more than six months in multi-drug resistant tuberculosis (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					had withdrawn bedaquiline, so the patient was no longer being actively treated with it. Notwithstanding the long half-life of bedaquiline, tissue concentrations were falling and its effect diminishing. It is unclear whether inclusion of washout periods is a reliable way of assessing the effect of sequential prescription of the two drugs of interest. Second, for one participant, the reported duration of exposure to both drugs was 109 days, less than bedaquiline's washout period, which appears incompatible with the authors' definition of total exposure. So it is unclear if the authors applied their definitions consistently. For these reasons, it is unclear if the participants fall within the scope of the PICO. These issues, the small size of the study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.
Prolongation of the corrected QT interval of more than 500 ms	Guglielmetti et al 2018	5	Direct	C	Prolongation of the corrected QT interval of more than 500ms is an electrocardiographic abnormality associated with bedaquiline and delamanid. Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 0/2 (0%). Prolongation of the corrected QT interval may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients This case series provides little reliable information on the relationship between use of bedaquiline and/or delamanid, and outcomes. Both participants were "exposed" to a combination of bedaquiline and delamanid for at least 30 days; exposure was defined as the sum of the duration of concomitant treatment and, for the patients receiving sequential treatment, the duration of a washout period for one drug after stopping it, while taking the other drug. Bedaquiline washout was 180 days and delamanid washout was 5 days. Two aspects of the paper make interpretation difficult. First, it is not clear the extent to which the washout period should be regarded as part of treatment as specified in the PICO. The prescribing physician had withdrawn bedaquiline, so the patient was no longer being actively treated with it. Notwithstanding the long half-life of bedaquiline, tissue concentrations were falling and its effect diminishing. It is unclear whether inclusion of washout periods is a reliable way of assessing the effect of sequential prescription of the two drugs of interest. Second, for one participant, the reported duration of exposure to both drugs was 109 days, less than bedaquiline's washout period, which appears incompatible with the authors' definition of total exposure. So it is unclear if the authors applied their definitions consistently. For these reasons, it is unclear if the participants fall within the scope of the PICO. These issues, the small size of the study and the lack of controls make it difficult to draw conclusions from this study relevant to this review's research questions.

9 Literature Search Terms

PICO I: Bedaquiline use for over 6 months

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People aged 18 years and above with multi-drug resistant TB (MDR TB) or extensively drug resistant TB (XDR TB).
I – Intervention Which intervention, treatment or approach should be used?	Bedaquiline for more than 6 months in combination with other TB drugs
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Bedaquiline for less than 6 months in combination with other TB drugs • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) *Important to decision-making:* • Cost effectiveness
Assumptions / limits applied to search	
The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Standard Exclusion criteria: • Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane. • Studies not available in the English language • Studies published more than 10 years ago • Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents • Case reports	

PICO II: Delamanid use for over 6 months

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People aged 18 years and above with multi-drug resistant TB (MDR TB) or extensively drug resistant TB (XDR TB).
I – Intervention Which intervention, treatment or approach should be used?	Delamanid for more than 6 months in combination with other TB drugs
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Delamanid for less than 6 months in combination with other TB drugs • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) *Important to decision-making:* • Cost effectiveness
Assumptions / limits applied to search	
The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Standard Exclusion criteria: • Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane. • Studies not available in the English language • Studies published more than 10 years ago • Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents • Case reports	

PICO III: Bedaquiline and delamanid combined use for over 6 months

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People aged 18 years and above with multi-drug resistant TB (MDR TB) or extensively drug resistant TB (XDR TB).
I – Intervention Which intervention, treatment or approach should be used?	Bedaquiline and delamanid for more than 6 months together in combination with other TB drugs
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Bedaquiline and delamanid for less than 6 months together in combination with other TB drugs for treating multi-drug resistant TB • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) *Important to decision-making:* • Cost effectiveness
Assumptions / limits applied to search	
The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Standard Exclusion criteria: • Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane. • Studies not available in the English language • Studies published more than 10 years ago • Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents • Case reports	

PICO IV: Bedaquiline and delamanid sequential use

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People aged 18 years and above with multi-drug resistant TB (MDR TB) or extensively drug resistant TB (XDR TB)
I – Intervention Which intervention, treatment or approach should be used?	Bedaquiline (for at least 6 months) then delamanid (for at least 6 months) in sequence with other TB drugs for treating multi-drug resistant TB
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Bedaquiline for at least 6 months in combination with other TB drugs for treating multi-drug resistant TB • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) *Important to decision-making:* • Cost effectiveness

Assumptions / limits applied to search

The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team.

Standard Exclusion criteria:

- Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane.
- Studies not available in the English language
- Studies published more than 10 years ago
- Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents
- Case reports

PICO V: Delamanid and bedaquiline sequential use

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People aged 18 years and above with multi-drug resistant TB (MDR TB) or extensively drug resistant TB (XDR TB)
I – Intervention Which intervention, treatment or approach should be used?	Delamanid (for at least 6 months) then bedaquiline (for at least 6 months) in sequence with other TB drugs for treating multi-drug resistant TB
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Delamanid for at least 6 months in combination with other TB drugs for treating multi-drug resistant TB • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) *Important to decision-making:* • Cost effectiveness
Assumptions / limits applied to search	
The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Standard Exclusion criteria: • Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane. • Studies not available in the English language • Studies published more than 10 years ago • Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents • Case reports	

10 Search Strategy

We searched PubMed, Embase and Cochrane Library, limiting the search to papers published in English between 1 January 2008 and 19 December 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 19 December 2018

Embase search:

1 drug resistant tuberculosis/ or extensively drug resistant tuberculosis/ or multidrug resistant tuberculosis/
2 *Tuberculosis/
3 (((multi* or extensive*) adj2 drug resistan*) and (tb or tuberculosis)).ti,ab.
4 (mdr-tb or mdrtb or xdr-tb or xdrtb).ti,ab.
5 (drug resistan* adj5 (tb or tuberculosis)).ti,ab.
6 (tb or tuberculosis).ti.
7 1 or 2 or 3 or 4 or 5 or 6
8 bedaquiline/ or delamanid/
9 (bedaquiline or sirturo or tmc207).mp.
10 (delamanid or deltyba or opc-67683).mp.
11 8 or 9 or 10
12 7 and 11
13 (exp animals/ or nonhuman/) not human/
14 12 not 13
15 conference*.pt.
16 14 not 15
17 limit 16 to (english language and yr="2008 -Current")

References from the PWG supplied by in the PPP		Paper selection decision and rationale if excluded
1	Achar, J., Hewison, C., Cavalheiro, A., Skrahina, A., Cajazeiro, J., Nargiza, P., Herboczek, K., Rajabov, A., Hughes, J., Ferlazzo, G., Seddon, J. and du Cros, P. (2017). Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis. Emerging Infectious Diseases, 23(10), pp.1711-1713.	This is a study in children and adolescents. It is out of the scope of this review, but included in the review of bedaquiline and delamanid in children and adolescents.
2	Guglielmetti, L., Barkane, L., Le Dû, D., Marigot-Outtandy, D., Robert, J., Veziris, N., Yazdanpanah, Y., Kuksa, L., Caumes, E. and Fréchet-Jachym, M. (2018). Safety and efficacy of exposure to bedaquiline−delamanid in multidrug-resistant tuberculosis: a case series from France and Latvia. European Respiratory Journal, 51(3), p.1702550	Included
3	Ferlazzo, G., Mohr, E., Laxmeshwar, C., Hewison, C., Hughes, J., Jonckheere, S., Khachatryan, N., De Avezedo, V., Egazaryan, L., Shroufi, A., Kalon, S., Cox, H., Furin, J. and Isaakidis, P. (2018). Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. The Lancet Infectious Diseases, 18(5), pp.536-544	Excluded. No participant in this study had reported results for more than six months' combination treatment with bedaquiline and delamanid, as specified in the PICO.

11 Evidence Selection

- Total number of publications reviewed: 84
- Total number of publications considered potentially relevant: 6
- Total number of publications selected for inclusion in this briefing: 6

12 References

British National Formulary. https://bnf.nice.org.uk/treatment-summary/tuberculosis.html (accessed 7 January 2019).

Chahine EB, Karaoui LR, Mansour H 2014. Bedaquiline: a novel diarylquinoline for multidrug-resistant tuberculosis. *Annals of Pharmacotherapy* 48: 107-15.

Chang KC Leung E C-C, Law W-S, Leung W-M, Tai L-B, Lee S-N, Lam F-M, Chau C-H, Mok T Y-W, Yew W-W, Leung C-C 2018. Early experience with delamanid-containing regimens in the treatment of complicated multidrug-resistant tuberculosis in Hong Kong. *Eur Respir J* 51: 1800159.

Guglielmetti L, Jaspard M, Le Dû D, Lachatre M, Marigot-Outtandy D, Bernard C, Veziris N, Robert J, Yazdanpanah Y, Caumes E, Fréchet-Jachym M for the French MDR-TB Management Group 2017. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Resp J* 49: 1601799.

Guglielmetti L, Barkane L, Le Dû D, Marigot-Outtandy D, Robert J, Veziris N, Yazdanpanah Y, Kuksa L, Caumes E, Fréchet-Jachym M 2018. Safety and efficacy of exposure to bedaquiline−delamanid in multidrug-resistant tuberculosis: a case series from France and Latvia. *Eur Resp J* 51: 1702550.

Kuksa L, Barkane L, Hittel N, Gupta RI 2017. Final treatment outcomes of multidrug- and extensively drug-resistant tuberculosis patients in Latvia receiving delamanid-containing regimens. *Eur Respir J* 9; 1701105.

NHS England. Clinical Commissioning Policy: Bedaquiline and Delamanid for defined patients with MDR-TB and XDR-TB. www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/f04pa-bedaquiline-delamanid-oct15.pdf (accessed 4 January 2019).

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Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, Cirule A, Leimane V, Kurve A, Levina K, Geiter LJ, Manissero M, Wells CD 2013. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Resp J* 41:1393-1400.

World Health Organization 2016. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: a review of available evidence.

World Health Organization 2018. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB).

Xavier AS, Lakshmanan M 2014. Delamanid: A new armor in combating drug-resistant tuberculosis. *Pharmacol Pharmacother* 5: 222–224.

13 Appendix

Chart illustrating the flow of patients reported by Skripconoka et al 2013.

Source: Figure 2, Skripconoka et al 2013

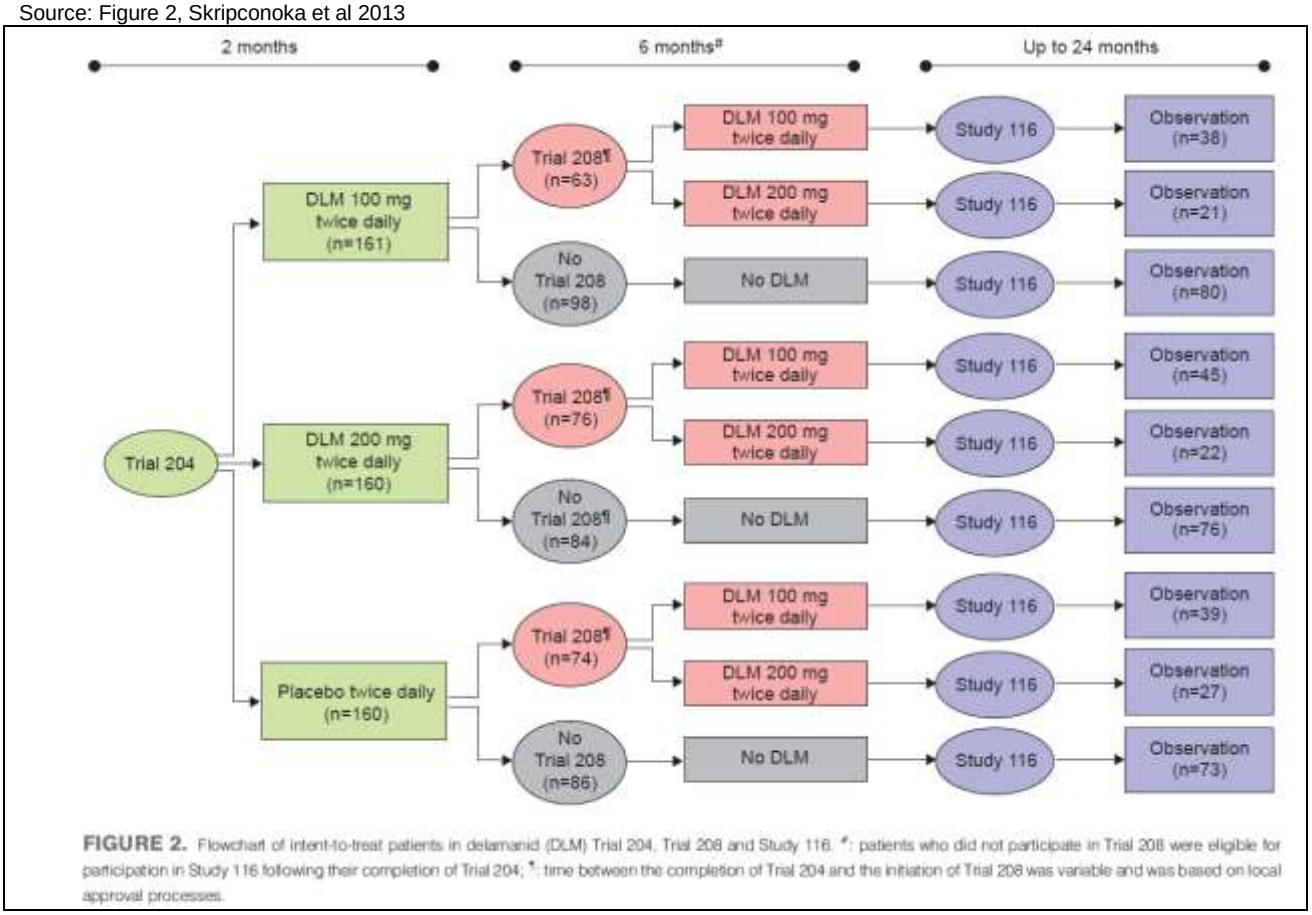

FIGURE 2. Flowchart of intent-to-treat patients in delamanid (DLM) Trial 204, Trial 208 and Study 116. #: patients who did not participate in Trial 208 were eligible for participation in Study 116 following their completion of Trial 204; ¶: time between the completion of Trial 204 and the initiation of Trial 208 was variable and was based on local approval processes.