NHS England Evidence Review:

Bedaquiline (B), Pretomanid (Pa), Linezolid (L) +/-Moxifloxacin (M) (BPaLM/BPaL) for rifampicin resistant (RR) TB, multidrug resistant (MDR) TB or pre-extensively drug resistant (pre-XDR) TB

NHS England URN: 2310

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

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of bedaquiline, pretomanid, linezolid (BPaL) and of BPaL with moxifloxacin (BPaLM) compared to current standard care for the treatment of rifampicin resistant tuberculosis (RR TB), multidrug resistant (MDR TB) or pre-extensively drug resistant (pre-XDR TB).

Patients with RR TB are infected with tuberculosis (TB) bacterium that is resistant to rifampicin, and those with MDR TB are infected with bacterium that is resistant to both rifampicin and isoniazid. Pre-XDR TB is resistant to rifampicin (and may also be resistant to isoniazid) and is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin). The scope of this review does not include extensively drug-resistant (XDR) TB, which occurs when the TB bacterium is resistant to rifampicin, isoniazid, at least one fluroquinolone and at least one other 'Group A' drug (bedaquiline or linezolid). However, some older studies categorised people as having XDR TB using an earlier definition, and these may fall into the current pre-XDR TB category and so be eligible for inclusion.

The 6-to-9-month BPaLM regimen has been recommended by the World Health Organization (WHO) for patients with RR, MDR and pre-XDR TB. This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR TB).

Current standard treatment options for patients in whom fluroquinolone resistance has been excluded include a 9-month all-oral regimen for MDR/RR TB comprising the combined use of up to seven agents, most of which will be continued for at least 9 months.

Other treatment options include individualised treatment regimens with a total treatment duration of 18 to 20 months, which may be modified according to the patient's response to therapy.

Group A includes anti-TB medicines known as fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline and linezolid. All three medicines from Group A are generally used as part of the standard drug-resistant TB treatment regimens. In addition to the three medicines in Group A, one or two further medicines from Group B are added. If any medicines from Group A or B cannot be used or are not sufficient, further medicines from Group C may be added.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from BPaLM/BPaL more than others, as well as the treatment duration of the BPaLM/BPaL regimens used in the included studies.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of bedaquiline, pretomanid, linezolid (BPaL) and of BPaL with moxifloxacin (BPaLM) compared to current standard care (SC) for the treatment of rifampicin resistant tuberculosis (RR TB), multidrug resistant (MDR TB) or pre-extensively drug resistant (pre-XDR TB). The searches for evidence published since 1 January 2013 were conducted on 7 July 2023 and identified 357 references. Screening of titles and abstracts identified 14 potentially relevant references, which were assessed as full text papers.

Five papers were identified for inclusion (Nyang'wa et al 2022, Conradie et al 2020, Conradie et al 2022, Gomez et al 2021, Sweeney et al 2022). One paper reported the TB-PRACTECAL randomised controlled trial (RCT) (Nyang'wa et al 2022), which included people with RR TB at seven sites in Belarus, South Africa and Uzbekistan. Results for both the BPaLM (n=72) and BPaL (n=70) arms were compared against SC (n=73) at 72 weeks, with 108-week follow-up for some outcomes.

One paper reported the ZeNIX uncontrolled randomised trial (Conradie et al 2022), which included people with MDR TB, pre-XDR TB and XDR TB at four sites in South Africa, one in Georgia, one in Moldova, and five in Russia. Only data for those with MDR TB and pre-XDR TB are included in this report (n=106). One paper reported the Nix-TB study as a prospective case series (Conradie et al 2020), which took place at three sites in South Africa and included people with MDR TB (n=109) and (pre)XDR TB[1]. There was one economic evaluation associated with the TB-PRACTECAL study (Sweeney et al 2022) and one that was based on the Nix-TB trial (Gomez et al 2021).

In terms of clinical effectiveness:

- **Sputum culture conversion rates (critical outcome)**
  - *For RR TB:* One RCT provided low certainty evidence of a higher sputum conversion rate with BPaLM (88.5%) compared with SC (78.8%) for RR TB at 12 weeks (HR for time to conversion: 1.59, 95% CI 1.18 to 2.14) (statistical significance not reported), with a similar HR at 108 weeks follow-up (HR 1.49, 95% CI 1.10 to 2.01). One RCT provided moderate certainty evidence of a higher sputum conversion rate with BPaL (81.1%) compared with SC for RR TB at 12 weeks but very low certainty evidence of little difference between groups at 108 weeks (statistical significance not reported).
  - *For MDR TB/(pre)XDR:* One prospective case series reported very low certainty evidence of a 97.8% conversion rate after 16 weeks of BPaL treatment.
- **Unfavourable treatment outcome (critical outcome)**
  - *For RR TB:* One RCT provided moderate certainty evidence of a statistically significantly lower risk of an unfavourable status[2] in people with RR TB treated with BPaLM (23.6%) compared to SC (53.4%) at 72 weeks (RR 0.24, 95% CI 0.11 to 0.52), and moderate certainty evidence of a lower risk at 108 weeks (RR 0.19, 95% CI 0.08 to 0.51) (statistical significance not reported). One RCT provided moderate certainty evidence of a lower risk of an unfavourable status with BPaL compared to SC for RR TB at 72 weeks (BPaL: 34.4%; RR 0.47, 95% CI 0.28 to 0.80) and low certainty evidence of

[1] People described here as (pre)XDR TB were described in the Conradie et al 2020 study as having XDR TB. However, they meet the current WHO criteria for pre-XDR TB so were considered to meet the population criteria specified in the PICO for this review.

[2] Unfavourable status defined as a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis.

a lower risk at 108 weeks (RR 0.46, 95% CI 0.26 to 0.82, statistical significance not reported).

- *For MDR TB/pre-XDR TB:* Two uncontrolled studies provided very low certainty evidence that for people treated with BPAL, between 5% and 25%[3] of people with MDR TB or pre-XDR TB had an unfavourable outcome[4] at 6 months follow-up.

- **Treatment completion rates (critical outcome)**
  - *For RR TB:* One RCT provided low certainty evidence of a higher completion rate at 72 weeks in people with RR who received either BPaLM or BPaL compared with SC (statistical significance not reported). 20.8% of the BPaLM group and 26% of the BPaL group discontinued early, compared with 47.9% of the SC group.
  - *For MDR TB (pre)XDR TB:* One prospective case series provided very low certainty evidence of all surviving MDR/(pre)XDR TB patients completing treatment with BPaL, other than one patient who withdrew consent.
- **Quality of life (important outcome)**
  - None of the included studies reported this outcome.
- **Treatment failure and disease recurrence (important outcome)**
  - *For RR TB:* One RCT provided very low certainty evidence that no RR TB patients taking BPaLM, BPaL or SC failed treatment at 72 weeks, although 4% of those taking BPaL (and none on BPaLM or SC) had disease recurrence by 72 weeks.
  - *For MDR TB/(pre)XDR TB:* One prospective case series provided very low certainty evidence that < 2% treated with BPaL relapsed by six months.
- **Amplification of drug resistance (important outcome)**
  - *For MDR TB or pre-XDR TB treated with BPaL:* amplification of drug resistance was reported in 0.9% of patients at 6 months follow-up.

In terms of safety:

- Patients with at least one serious/≥ grade 3 adverse event
  - *For RR TB:* One RCT provided moderate certainty evidence of statistically significantly fewer people on BPaLM (19.4%) having at least one serious/≥ grade 3 adverse event compared with those receiving SC (58.9%) at 72 weeks, and moderate certainty evidence of fewer serious/≥ grade 3 adverse events among people treated with BPaL (21.7%) compared with SC (58.9%) at 72 weeks (statistical significance not reported). In terms of specific SAE or ≥ grade 3 AE, one RCT provided moderate certainty evidence that, at 72 weeks, hepatic disorders, QTcF prolongation, decreased creatinine renal clearance, and anaemia were all less common in people treated with either BPaLM or BPaL compared with those receiving SC, although similar rates of neutropaenia were reported in both BPaLM and SC groups (statistical significance not reported).
  - *For MDR/(pre)XDR TB:* One prospective case series provided very low certainty evidence that 17% of patients with MDR/ (pre)XDR TB treated with BPaL experienced at least one serious/≥ grade 3 adverse event during 6 months follow-up.
- Discontinuation due to adverse events

[3] Based on the linezolid 600mg/26-week arm only of Conradie et al 2022. Across all linezolid dosages, 19% of people with MDR TB had an unfavourable outcome.

[4] Unfavourable outcome defined as treatment failure (clinical or bacteriologic) or disease relapse in both Conradie et al 2020 and Conradie et al 2022.

- One RCT provided low certainty evidence that fewer people taking either BPaLM (6.9%) or BPaL (7.1%) discontinued by 72 weeks due to adverse events compared with those on SC (23.3%) (statistical significance not reported).

In terms of cost effectiveness:

- *RR TB*: One analysis estimated that BPaLM would save $80 to $997 per person and avert 0.7 to 1.3 Disability Adjusted Life Years (DALYs) per person in the countries included in the analysis. Savings with BPaL ranged from $112 to $1173 per person, but with fewer DALYs averted (0.0 to 0.4 DALYs per person). At a willingness-to-pay per DALY averted of 0.5 gross domestic product (GDP) per capita, BPaLM was the preferred regimen in all countries studied.
- *MDR/XDR TB*: One analysis reported that, compared with SC, the modelled incremental costs of BPaL ranged from $ -336,950 to $ −2,546,098. Corresponding DALYs averted ranged from 830 DALYs to 15,416 DALYs. Authors concluded that BPaL for XDR TB is likely to be cost saving in all study settings when pretomanid is priced at the Global Drug Facility list price, with increased savings and clinical benefits when BPaL treatment is extended to MDR TB treatment failure and treatment intolerant patients.

In terms of subgroups:

- One RCT reported that the proportion of RR TB patients with an unfavourable treatment outcome at 72 weeks (BPaLM vs SC) did not vary by age, sex, HIV infection, sputum smear status, the presence of cavities on chest radiographs, fluoroquinolone resistance, or country of recruitment. One prospective case series reported that people who were HIV positive had similar safety outcomes as those who were HIV negative, although the rate of grade 3 or 4 adverse events was slightly higher among people who were HIV positive.

Treatment duration of the BPaLM/BPaL regimen:

- Patients in one RCT had a 24-week BPaLM or BPaL regimen. One randomised uncontrolled trial gave patients 26 weeks of bedaquiline and pretomanid, but either 9 weeks or 26 weeks of linezolid. The prospective case series gave patients 26 weeks of bedaquiline and pretomanid, and linezolid for up to 26 weeks.

Limitations

Limitations in the certainty of the evidence from the RCT were its open-label design and factors associated with the numerical analysis due to early termination when it met the efficacy stopping rule. The analysis presented only includes patients who could have had a prespecified outcome event at the given time point, and the primary outcome (unfavourable treatment outcome at 72 weeks) was the only analysis to be reported using the full intention-to-treat (ITT) population – others used the modified ITT (mITT) population, which excluded people without microbiologically proven RR TB. It is possible that early discontinuations in the SC arm of the RCT led to a lower proportion of people in that group achieving a favourable outcome at the end of follow-up. Changes in the SC treatment regimen over time (in line with international recommendations) occurred and earlier comparator treatments may have been more toxic than those currently in use. In line with current WHO guidelines, most people on standard care received at least two Group A drugs. Statistical significance was not reported in the form of p values, and although the RCT presented confidence intervals around effect estimates, the authors noted that the confidence intervals for BPaL compared with standard care should not be used to infer relative treatment effects as they were not adjusted for multiplicity.

The ZeNix and TB-Nix studies did not compare the BPaL regimens against SC, so the certainty of evidence from these studies is limited by the lack of comparative data and their small size. In addition, only the primary outcome from the ZeNix study was available separately for people with MDR/pre-XDR TB, so evidence from other outcomes could not be incorporated into this review. None of the clinical effectiveness studies took place in the UK, and results may not be generalisable to the UK/NHS setting.

Limitations introducing uncertainty into the cost effectiveness evidence include the application of short-term (72 month/ 6 month) trial outcome data to 20-year or lifetime horizons and for different countries' populations, and the small numbers of people in the TB-PRACTECAL and TB-Nix studies. Uncertainty and variation in the cost of treatment could also be considered as limitations.

Conclusion

The studies identified for this review provide moderate to very low certainty evidence that in patients with RR TB, BPaLM/BPaL may improve unfavourable clinical outcomes, reduce treatment discontinuation, and reduce grade 3 or 4 serious adverse events compared to standard care at up to 108 weeks follow-up. Higher rates of sputum culture conversion were seen at 12 weeks for people with RR TB taking BPaLM or BPaL than for those receiving standard care. For people with MDR/(pre)XDR TB, 97.8% had culture conversion by 16 weeks. The shorter duration of the 26-week BPaL/M regimen is an additional benefit compared with the standard treatment regimens that may last from 9 to 20 months. Cost effectiveness modelling suggests that treatment with BPALM/BPAL may be cost effective compared to standard care and may even be cost saving overall, although it is uncertain to what extent the cost effectiveness outcomes can be generalisable to the NHS in England.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the clinical effectiveness of BPaLM/BPaL compared with standard of care?
2. In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the safety of BPaLM/BPaL compared with standard of care?
3. In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the cost effectiveness of BPaLM/BPaL compared with standard of care?
4. From the evidence selected, are there any subgroups of patients that may benefit from BPaLM/BPaL more than the wider population of interest?
5. From the evidence selected, what was the treatment duration of the BPaLM/BPaL regimen?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on [insert date.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Five papers were identified for inclusion (Nyang'wa et al 2022, Conradie et al 2020, Conradie et al 2022, Gomez et al 2021, Sweeney et al 2022). Table 1 provides a summary of these included studies and full details are given in Appendix E.

One paper reported the TB-PRACTECAL RCT (Nyang'wa et al 2022), which included people with RR TB. This was conducted in two stages, with stage 1 randomising patients to one of four different treatment arms (Standard of Care (SC), BPaLM, BPaL and BPaL + clofazimine) and stage 2 randomising patients to BPaLM or SC. Both the BPaLM and BPaL arms were compared against SC at 72 weeks, so results for both regimens are included in this review.

One paper reported results from the ZeNIX uncontrolled randomised trial (Conradie et al 2022), which included people with MDR TB, pre-XDR TB and XDR TB. Only data for those with MDR TB and pre-XDR TB are included in this report. One paper reported results from the Nix-TB study as a prospective case series (Conradie et al 2020). There was one economic evaluation associated with the TB-PRACTECAL study (Sweeney et al 2022) and one that was based on the Nix-TB trial (Gomez et al 2021).

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Nyang'wa et al 2022 RCT (TB-PRACTECAL) 7 sites in Belarus, South Africa and Uzbekistan	• 303 patients with RR TB included in stage 2 prespecified analysis for BPaLM vs SC • N in safety population: BPaLM: n=151 BPaL n=123 SC n=152 • N in ITT population: BPaLM: n=72 BPaL n=70 SC n=73 • Subgroups: age, sex, country, HIV status, cavity present, previous TB treatment, smear positivity, smoking, fluoroquinolone resistance, isoniazid resistance	**Intervention** BPaLM • B 400 mg/d for 2 weeks, followed by 200 mg 3 times per week for 22 weeks • Pa 200 mg/d for 24 weeks • L 600 mg/d for 16 weeks, followed by 300 mg/d for 8 weeks • M 400 mg/d for 24 weeks There was also a BPaL arm (without moxifloxacin) randomised in stage 1 with follow-up until week 72. **Comparison:** SC (9 to 20 month regimen) Locally accepted SC, closely aligned to WHO guidelines.	**Critical outcomes** • Sputum culture conversion at 12 weeks and 108 weeks • Unfavourable treatment outcome at 24, 72 and 108 weeks (72 weeks for ITT) • Treatment completion rates (early discontinuation at 72 weeks) **Important outcomes** Reported at 72 weeks • Treatment failure and disease recurrence • SAE • AE • Discontinuation due to AE • Deaths during treatment • Specific AE: hepatic disorder, prolonged QTcF, creatinine renal clearance, anaemia, neutropaenia, optic neuropathy
Conradie et al 2022 Randomised uncontrolled trial (ZeNix) South Africa (4 sites), Georgia (1 site), Moldova (1 site) and	181 patients with: • MDR TB (n=21) • Pre-XDR TB (n=85) • XDR TB (n=75, not in scope) • Patients split into 4 different L groups (see Intervention) • Subgroups: primary outcome available for pre-	**Intervention** BPaL • B (200 mg/d for 8 weeks, followed by 100 mg/d for 18 weeks) • Pa (200 mg daily for 26 weeks). • L (either 1200 mg/d or 600 mg/d for either 26 weeks or 9 weeks.	**Critical outcome** • Unfavourable treatment outcome at 26 weeks **Important outcomes** • Treatment failure and disease recurrence – reported by authors as 'unfavourable treatment outcome'

Study	Population	Intervention and comparison	Outcomes reported
Russia (5 sites)	XDR TB and MDR TB patients.	**Comparison** None	
Conradie et al 2020 Prospective case series (Nix-TB) South Africa (3 sites)	109 patients with: • MDR TB: n=38 • XDR TB[5]: n=71 Subgroups: primary outcome available stratified by TB type, HIV status and linezolid dosing	**Intervention** BPaL • B 400 mg/d for 2 weeks then 200 mg 3 times a week for 24 weeks • Pa 200 mg/d for 26 weeks • L 1200 mg/d for up to 26 weeks[6] **Comparison** None	**Critical outcomes** • Sputum culture conversion rates (up to 16 weeks) • Unfavourable treatment outcome at 6 months • Treatment completion rates (26 weeks) **Important outcomes** Reported at 6 months • Treatment failure and disease recurrence) • AE • AE grade 3 or 4 • Deaths • Specific AE: peripheral neuropathy, optic neuritis, myelosuppression, anaemia, aminotransferase increases, hepatic AE, QTcF increases
Sweeney et al 2022 CEA with Markov model, based on TB-PRACTECAL outcomes India, Georgia, Philippines and South Africa	Total people with RR TB • India: 49,945 • South Africa: 10,233 • Philippines: 5,952 • Georgia: 284 % on short/long SC regimens • India: 96%/4% • South Africa: 74%/26% • Philippines: 99%/1% • Georgia: 31%/69%	**Intervention** BPaL and BPaLM arms as described for TB-PRACTECAL Assumed duration: 24 weeks **Comparison** WHO-recommended short and long SC regimens in Philippines, South Africa, Georgia and India Assumed duration: 36 weeks (short regimen) and 80 weeks (long regimen)	**Important outcomes** Cost effectiveness
Gomez et al 2021 CEA with Markov model, based on Nix-TB outcomes South Africa, Philippines and Georgia	Two scenarios: 1. Patients with MDR TB who have failed or are intolerant to their MDR TB treatments 2. Patients with XDR TB MDR intolerant/failure: 10% of all patients with MDR TB MDR/RR TB incidence per 100,000 • South Africa: 21 (14-30) • Philippines: 26 (12-45) • Georgia: 15 (11-18)	**Intervention** BPaL (6 months) **Comparison** Standardised recommendations for XDR TB regimens (18 months)	**Important outcomes** Cost effectiveness

Abbreviations

AE: adverse events; B: bedaquiline; BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; CEA: cost-effectiveness analysis; HIV: human immunodeficiency virus; ITT: intention-to-treat; L: linezolid; M: moxifloxacin; MDR: multidrug-resistant TB; Pa: pretomanid; QTcF: QT interval calculated with Fridericia's formula; RCT: randomised controlled trial; RR TB:

[5] Those defined in the paper as having XDR TB in this study meet the pre-XDR eligibility criteria defined in the PICO in Appendix A. In this report they are described as (pre)XDR TB.

[6] The first 44 patients started on linezolid at 600 mg twice daily, and the remaining 65 started on 1200 mg daily.

Study	Population	Intervention and comparison	Outcomes reported
rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; TB: tuberculosis; WHO: World Health Organization; XDR TB: extensively drug resistant TB			

5. Results

In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the clinical effectiveness and safety of BPaLM/BPaL compared with standard of care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Sputum culture conversion rates **Certainty of evidence:** Very low to Moderate	Sputum culture conversion rates are an important outcome to patients as sputum culture negativity is an indicator that a patient is non-infectious and could potentially be discharged from hospital. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to sputum culture conversion rates in people with RR TB treated with either BPaL or BPaLM (Nyang'wa et al 2022), and in people with MDR TB (pre)XDR TB[7]treated with BPaL (Conradie et al 2020). **At 12 weeks follow-up** *BPaLM vs SC* • One RCT (Nyang'wa et al 2022) reported a higher conversion rate among people treated with BPaLM (85/96, 88.5%) compared with SC (78/99,78.8%); p not reported. HR for time to conversion favoured BPaLM: 1.59 (95% CI 1.18 to 2.14). RD adjusted for site was 9.2% higher with BPaLM (95% CI –1.6% to 20.1%); p not reported; RR adjusted for site was 1.12 (95% CI 0.99 to 1.27); p not reported. (**LOW**) *BPaL vs SC* • One RCT (Nyang'wa et al 2022) reported a higher conversion rate among people treated with BPaL (73/90 81.1%) compared with SC (78/99,78.8%); p not reported. HR for time to conversion not reported. RD adjusted for site was 3.9% higher with BPaL (95% CI –8.0% to 15.9%); p not reported; RR adjusted for site was 1.04 (95% CI 0.90 to 1.20); p not reported. (**MODERATE**) **At 16 weeks follow-up** • One prospective case series (Conradie et al 2020) reported that 30/31 (96.8%) of people with MDR TB and 61/62 (98.4%) of people with (pre)XDR TB (overall cohort: 91/93, 97.8%) treated with BPaL had sputum culture conversion. (**VERY LOW**) **At 108 weeks follow-up** *BPaLM vs SC* • One RCT (Nyang'wa et al 2022) reported HR for time to conversion adjusted for site as: 1.49 (95% CI 1.10 to 2.01). 91[8] people on BPaLM converted compared to 85 on SC (denominators unclear). No p value reported. (**LOW**) *BPaL vs SC* One RCT (Nyang'wa et al 2022) reported HR for time to conversion adjusted for site as: 1.05 (95% CI 0.77 to 1.44). 82 people on BPaL converted compared to 85 on SC (denominators unclear). No p value reported. (**VERY LOW**)

[7] People described here as (pre)XDR TB were described in the Conradie et al 2020 study as having XDR TB. However, they meet the current WHO criteria for pre-XDR TB so were considered to meet the population description in the PICO for this review.
[8] Actual number of people converting is larger than total N for 108 weeks; this is assumed to include the larger cohort.

Outcome	Evidence statement
	For BPaLM vs SC: one RCT provided low certainty evidence of a higher sputum conversion rate with BPaLM compared with SC for RR TB at 12 weeks and at 108 weeks (statistical significance not reported). **For BPaL: one RCT provided moderate certainty evidence of a higher sputum conversion rate with BPaL compared with SC for RR TB at 12 weeks but very low certainty evidence of little difference between groups at 108 weeks (statistical significance not reported). One prospective case series reported very low certainty evidence of a 97.8% conversion rate in people with MDR or (pre)XDR TB after 16 weeks of BPaL treatment.**
Unfavourable treatment outcome **Certainty of evidence:** Very low to Moderate	This outcome is important to patients as it provides an indication of how effective and tolerable the treatment regimen is. It is a composite measure which may include death, treatment failure, treatment discontinuation, loss to follow-up or recurrence of tuberculosis. In total, one RCT (Nyang'wa et al 2022), one arm of a prospective randomised uncontrolled trial (Conradie et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to unfavourable treatment outcome in people with RR TB, MDR TB or (pre)XDR TB. **At 26 weeks/6 months follow-up** • One randomised uncontrolled trial (Conradie et al 2022) reported that, across all four arms with different linezolid dosages, 4/21 (19.0%) people with MDR TB and 4/83 (4.8%) people with pre-XDR TB treated with BPaL had an unfavourable treatment outcome[9]. In the 600mg/26-week linezolid dosage arm specifically, 1/4 (25%) people with MDR TB and 2/22 (9.1%) people with pre-XDR TB had an unfavourable outcome. (**VERY LOW**) • One prospective case series (Conradie et al 2020) reported that 3/38 (7.9%) people with MDR TB and 8/71 (11.3%) people with (pre)XDR TB (11/109 (10.1%) overall) treated with BPaL had an unfavourable treatment outcome. (**VERY LOW**) **At 72 weeks follow-up** *BPaLM vs SC* • One RCT (Nyang'wa et al 2022) reported an unfavourable status[10] in *statistically significantly* fewer people with RR TB treated with BPaLM (17/72, 23.6%) compared with 39/73 (53.4%) receiving SC (RD: -30% (96.6% CI –46% to –14%)[11]. The RR adjusted for site gave a lower risk of an unfavourable status with BPaLM for the mITT population (RR 0.24, 0.11 to 0.52). No p values reported. (**MODERATE**) *BPaL vs SC* • One RCT (Nyang'wa et al 2022) reported an unfavourable status in 24/70 (34.3%) of people with RR TB treated with BPaL compared with 39/73 (53.4%) receiving SC (RD: -19% (95% CI –36% to –2%). The RR adjusted for site gave a lower risk[12] of an unfavourable status with BPaL for the mITT population (RR 0.47, 0.28 to 0.80). No p values reported. (**MODERATE**)

[9] Unfavourable outcome defined as treatment failure (clinical or bacteriologic) or disease relapse in both Conradie et al 2020 and Conradie et al 2022.

[10] Unfavourable status defined as a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis.

[11] Nyang'wa et al 2022 state that: *"A noninferiority margin of 12 percentage points as the upper boundary of the confidence interval was determined to be a reasonable clinical and public health trade-off limit, given the benefits of a shorter treatment duration, decreased pill burden and regimen cost, and the all-oral nature of the investigational regimens."* This was assumed to indicate clinical and statistical significance.

[12] Nyang'wa et al 2022 note that *"Confidence intervals for the BPaLC group and BPaL group as compared with the standard-care group are two-sided and were not adjusted for multiplicity and should not be used to infer relative treatment effects."* Results were therefore not described as statistically significant even if the 95% confidence interval excluded no effect.

Outcome	Evidence statement
	At 108 weeks follow-up *BPaLM vs SC* • One RCT (Nyang'wa et al 2022) reported the unadjusted RD for an unfavourable status for people with RR TB (ITT population) as -50.0% (95% CI -69.2% to -30.9%), and a RR of 0.19 (95% CI 0.08 to 0.51). No p values reported. (**MODERATE**) *BPaL vs SC* • One RCT (Nyang'wa et al 2022) reported the unadjusted RD for an unfavourable status for people with RR TB as -33.6% (95% CI -55.2% to -12.0%), and a RR of 0.46 (95% CI 0.26 to 0.82). No p values reported. (**LOW**) **For BPaLM vs SC: one RCT provided moderate certainty evidence of a *statistically significantly* lower risk of an unfavourable status in people with RR TB treated with BPaLM compared to SC at 72 weeks, and moderate certainty evidence of a lower risk at 108 weeks (statistical significance not reported).** **For BPaL: two uncontrolled studies provided very low certainty evidence that between 5% and 25%[13] of people with MDR TB or pre-XDR TB had an unfavourable outcome at 6 months follow-up. One RCT provided moderate certainty evidence of a lower risk of an unfavourable status with BPaL compared to SC for RR TB at 72 and low certainty evidence of a lower risk at 108 weeks (statistical significance not reported).**
Treatment completion rates **Certainty of evidence:** Very low to Low	Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of treatment failure and drug resistance. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to treatment completion rates in people with RR TB treated with either BPaL or BPaLM (Nyang'wa et al 2022), and in people with MDR TB and (pre)XDR TB treated with BPaL (Conradie et al 2020). **At 6 months follow-up** • One prospective case series reported that 1/71 (1.4%) people with (pre)XDR TB treated with BPaL withdrew their consent to continue in the study (1/109, 0.9% of the whole cohort). Excluding 7 people who died and 2 who relapsed, authors reported that *"All surviving participants completed 26 weeks (including two who extended to 39 weeks) of treatment with allowable interruptions of up to 35 consecutive days, and none had the regimen permanently discontinued."* (**VERY LOW**) **At 72 weeks follow-up** *BPaLM vs SC* • One RCT (Nyang'wa et al 2022) reported fewer people with RR TB discontinuing BPaLM early (15/72, 20.8%) compared with those on SC (35/73, 47.9%). Statistical significance not reported (**LOW**). Of those who discontinued, 0/15 in the BPaLM group did so due to adherence issues, compared with 3/35 (8.6%) in the SC arm. Statistical significance not reported. (**VERY LOW**) *BPaL vs SC* • One RCT (Nyang'wa et al 2022) reported fewer people with RR TB discontinuing BPaL early (18/70 (26%) compared with those on SC 35/73 (47.9%) (**LOW**). Of those who discontinued, 2/18 (11.1%) in the BPaL group did

[13] Based on the linezolid 600mg/26-week arm only of Conradie et al 2022. Across all linezolid dosages, 19% of people with MDR TB had an unfavourable outcome.

Outcome	Evidence statement
	so due to adherence issues, compared with 3/35 (8.6%) in the SC arm. Statistical significance not reported. (**LOW**) **One prospective case series provided very low certainty evidence of all surviving MDR/(pre)XDR TB patients completing treatment with BPaL at 6 months follow-up, other than one who withdrew consent. One RCT provided low certainty evidence of a higher completion rate at 72 weeks in people with RR who received either BPaLM or BPaL compared with SC (statistical significance not reported).**
Important outcomes	
Quality of life **Certainty of evidence:** Not reported	Quality of life (QOL) is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. **None of the included studies reported this outcome.**
Treatment failure and disease recurrence **Certainty of evidence:** Very low	This outcome is important to patients because it can result in further treatment being required which will impact on patient satisfaction as well as any potential drug side effects from further treatment. There is also a negative public health impact associated with treatment failure. This is a composite outcome, as the terms treatment failure and disease recurrence are used interchangeably in some studies. In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) provided evidence relating to treatment failure and disease recurrence. **At 6 months follow-up** One prospective case series (Conradie et al 2020) reported that 1/38 (2.6%) people with MDR TB and 1/71 (1.4%) people with (pre)XDR TB treated with BPaL (2/109, 1.8% overall) relapsed at 6 months. (**VERY LOW**) **At 72 weeks follow-up** *BPaLM vs SC* • No RR TB patients treated with either BPaLM (0/72) or SC (0/73) failed treatment at 72 weeks in the RCT. (**VERY LOW**) • No RR TB patients treated with either BPaLM (0/72) or SC (0/73) had disease recurrence at 72 weeks in the RCT. (**VERY LOW**) **At 72 weeks follow-up** *BPaL vs SC* • No RR TB patients treated with either BPaL (0/70) or SC (0/73) failed treatment at 72 weeks in the RCT. (**VERY LOW**) • 3 RR TB patients treated with BPaL (3/72, 4.2%) and none on SC (0/73) had disease recurrence at 72 weeks in the RCT. (**VERY LOW**) **For people with MDR/(pre)XDR TB, one prospective case series provided very low certainty evidence that < 2% relapsed by six months. One RCT provided very low certainty evidence that no RR TB patients taking BPaLM, BPaL or SC failed treatment at 72 weeks, although 4% of those taking BPaL (and none on BPaLM or SC) had disease recurrence by 72 weeks.**
Amplification of drug resistance **Certainty of evidence:** Very low	This is an important outcome to patients as increased levels of drug resistance may results in changes to their treatment regimen and longer treatment duration. In total, one prospective case series (Conradie et al 2020) provided evidence relevant to the PICO-specific population of people with MDR TB and pre-XDR TB.

Outcome	Evidence statement
	At 6 months follow-up: • 1/109 (0.9%) people treated with BPaL had a change in bedaquiline resistance gene Rv0678, from wild type at baseline to a 138-139insG variant in the late isolate. **(VERY LOW)** **For people with pre-XDR TB or MDR TB treated with BPaL, amplification of drug resistance was reported in 0.9% of patients at 6 months follow-up.**
Safety	

Safety outcomes
 	
Certainty of evidence:
 	
Very low to Moderate
	Safety of BPaL/BPaLM is important to patients as it allows comparison of treatment approaches.
	
	In total, one RCT (Nyang'wa et al 2022) and one prospective case series (Conradie et al 2020) reported safety outcomes for people with RR TB, MDR TB and pre-XDR TB.
	
	At 6 months follow-up
	
	• One prospective case series (Conradie et al 2020) reported that all patients with MDR/(pre)XDR TB experienced at least one AE (109/109, 100%) **(VERY LOW)**
	  ○ Peripheral neuropathy was reported by 88/109 (80.7%).
	  ○ Optic neuritis was reported by 2/109 (1.8%).
	  ○ 52/109 (47.7%) had myelosuppression, 40/52 (76.9%) of whom had anaemia (36.7% of all patients).
	  ○ Aminotransferase increases were reported in 17/109 (15.6%), of whom 12 had ALT elevation and 11 had AST elevation to > 3x ULN.
	  ○ 8/109 (7.3%) patients had hepatic AE leading to regimen interruption (then resumed).
	  ○ No patients had QTcF > 480 msec.
	• One prospective case series (Conradie et al 2020) reported that 62/109 (56.9%) patients with MDR/(pre)XDR TB experienced at least one grade 3 or 4 AE and 19/109 (17.4%) had at least one grade 3 or 4 SAE. There were 6/109 (5.5%) deaths. **(VERY LOW)**
	
	At 72 weeks follow-up
	
	BPaLM vs SC
	
	• One RCT (Nyang'wa et al 2022) reported that *statistically significantly* fewer people with RR TB treated with BPaLM (14/72, 19.4%) had at least one SAE or AE of at least grade 3 compared with those receiving SC (43/73 (58.9%). RD: -40% (96.6% CI -55% to -24%). No p value reported. (**MODERATE**)
	• In terms of specific SAE/grade ≥3 AE, one RCT (Nyang'wa et al 2022) reported:
	  ○ A lower incidence of hepatic disorders in people with RR TB on BPaLM (3/72, 4.2%) compared with those on SC (8/73, 11.0%).
	  ○ QTcF prolongation was reported by fewer people with RR TB on BPaLM (1/72, 1.4%) compared with those on SC (10/73, 13.7%).
	  ○ Rates of decreased creatinine renal clearance were lower among people taking BPaLM (1/72, 1.4%) compared with SC (5/73, 6.8%).
	  ○ Rates of anaemia were also lower in those taking BPaLM (2/72, 2.8%) compared with SC (6/73, 8.2%).
	  ○ Similar rates of neutropaenia were reported in both groups (BPaLM: 3/72, 4.2%) vs SC: 2/73, 2.7%).
	  ○ No patients in either group reported optic neuropathy. (**MODERATE**)
	• Fewer people with RR TB taking BPaLM discontinued due to AE (5/72, 6.9%) compared with those on SC (17/73, 23.3%). Statistical significance not reported. (**LOW**)
	• No RR TB patients taking BPaLM (0/72) had died by 72-week follow-up, compared with 7/73 (9.6%) on SC (4 considered to be treatment-related, 0 TB-related). (**LOW**)

Outcome	Evidence statement

	At 72 weeks follow-up
	
	BPaL vs SC
	
	• One RCT (Nyang'wa et al 2022) reported that fewer people with RR TB treated with BPaL (15/69, 21.7%) had at least one SAE or AE of at least grade 3 compared with those receiving SC (43/73 (58.9%). RD: -37% (95% CI -52% to -22%). No p value reported. (**MODERATE**)
	• In terms of specific SAE/grade ≥3 AE, one RCT (Nyang'wa et al 2022) reported:
	  ○ A lower incidence of hepatic disorders in people with RR TB on BPaL (2/69, 2.9%) compared with those on SC (8/73, 11.0%).
	  ○ No RR TB patients on BPaL had QTcF prolongation (0/69, 0%) compared with those on SC (10/73, 13.7%).
	  ○ Rates of decreased creatinine renal clearance were lower among people taking BPaL (2/69, 2.9%) compared with SC (5/73, 6.8%).
	  ○ Rates of anaemia were lower in those taking BPaL (1/69, 1.4%) compared with SC (6/73, 8.2%).
	  ○ No patients on BPaL reported neutropaenia (0/69, 0%) compared with two patients on SC: 2/73, 2.7%).
	  ○ No patients in either group reported optic neuropathy. (**MODERATE**)
	• Fewer people with RR TB taking BPaL discontinued due to AE (5/70, 7.1%) compared with those on SC (17/73, 23.3%). Statistical significance not reported. (**LOW**)
	• One RR TB patient taking BPaL (1/70, 1.4%) had died by 72-week follow-up (not treatment-related or TB-related), compared with 7/73 (9.6%) on SC (4 considered to be treatment-related, 0 TB-related (**MODERATE**)
	
	At 108 weeks follow-up[14]
	
	BPaLM vs SC
	
	• One RCT (Nyang'wa et al 2022) reported a *statistically significantly*[15] lower incidence of patients with at least one SAE or AE of at least grade 3 in the BPaLM group compared with those receiving SC (RD adjusted for randomisation site: -35.3%, 96.6% CI -56.2% to -14.3%). P not reported. (**MODERATE**)
	
	Other time points
	
	One RCT (Nyang'wa et al 2022) reported similar numbers of people with RR TB who experienced an AE of any grade by the date of study termination (duration not defined) either on BPaLM (142/151, 94.0%), BPaL 120/122 (98.4%) or SC 145/150 (96.7%).
	
	One prospective case series provided very low certainty evidence that all patients with MDR/ (pre)XDR TB treated with BPaL experienced at least one AE during 6 months follow-up, the most common being peripheral neuropathy or myelosuppression, and 19/109 (17.4%) had at least one grade 3 or 4 SAE.
	
	One RCT provided moderate certainty evidence of *statistically significantly* fewer people on BPaLM for RR TB having at least one SAE or AE of at least grade 3 compared with those receiving SC at either 72 weeks or 108 weeks follow-up, and moderate certainty evidence of fewer SAE or AE of at least grade 3 among people with RR TB treated with BPaL compared with SC at 72 weeks (statistical significance not reported).
	
	One RCT provided low certainty evidence that fewer people taking either BPaLM or BPaL discontinued by 72 weeks due to adverse events compared with those on SC (statistical significance not reported). The RCT provided low to moderate certainty evidence of a higher number of treatment-related deaths

[14] This outcome was not reported for the BPaL group.

[15] This result was reported with a 96.6% confidence interval and met the study definition of statistically significant.

Outcome	Evidence statement
	among people with RR TB on SC compared with either BPaLM or BPaL (statistical significance not reported). **In terms of specific SAE or ≥ grade 3 AE, one RCT provided moderate certainty evidence that, at 72 weeks, hepatic disorders, QTcF prolongation, decreased creatinine renal clearance, and anaemia were all less common in people treated with either BPaLM or BPaL compared with those receiving SC, although similar rates of neutropaenia were reported in both BPaLM and SC groups (statistical significance not reported).**
Abbreviations AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; MDR: multidrug-resistant TB; mITT: modified ITT; QTcF: QT interval calculated with Fridericia's formula; RCT: randomised controlled trial; RD: risk difference; RR: risk ratio; RR TB: rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; ULN: upper limit of normal range; XDR TB: extensively drug resistant TB	

In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the cost effectiveness of BPaLM/BPaL compared with standard of care?

Outcome	Evidence statement
Cost effectiveness	In total, two analyses provided evidence for the cost effectiveness of BPaLM/BPaL compared to SC. One analysis (Sweeney et al 2022) applied treatment effects from TB-PRACTECAL (Nyang'wa et al 2022) to data for people with RR TB in India, South Africa, the Philippines and Georgia. The analysis used a Markov model with a 20-year time horizon and a provider's perspective, with costs reported in 2019 USD and a 3% discount rate. One analysis (Gomez et al 2021) applied treatment effects from Nix TB (Conradie et al 2020) to data for people with MDR/XDR TB in South Africa, the Philippines and Georgia. The analysis used a Markov model with a lifetime horizon (treatment outcomes modelled for 5 years but costs and included until death) and a provider's perspective, with costs reported in 2018 USD and a 3% discount rate. The analysis was presented for two scenarios: 1) XDR TB patients, 2) XDR TB and people with MDR TB who have failed or are intolerant to their MDR TB treatments. Only scenario 2 is considered here. **RR TB:** • One analysis (Sweeney et al 2022) estimated that BPaLM would save $80 to $997 per person and avert 0.7 to 1.3 DALYs per person in the countries included in the analysis. Savings with BPaL ranged from $112 to $1173 per person, but with fewer DALYs averted (0.0 to 0.4 DALYs per person). • The authors calculated that, at a willingness-to-pay per DALY averted of 0.5 GDP per capita, BPaLM is the preferred regimen in all countries studied. **MDR/XDR TB**: • One analysis (Gomez et al 2021) reported that, compared with SC, incremental costs of BPaL ranged from $ -336,950 (-337,480 to -336,420)[16] in Georgia to $ −2,546,098 (-2,542,254 to -2,549,942) in the Philippines. Corresponding DALYs averted ranged from 830 DALYs (819 to 841) in Georgia to 15,416 DALYs (15,214 to 15,618) in South Africa. • Authors concluded that BPaL for XDR-TB is likely to be cost saving in all study settings when pretomanid is priced at the Global Drug Facility list price, with

[16] The meaning of the numbers in brackets is not clear in the Gomez et al 2021 study.

Outcome	Evidence statement
	increased savings and clinical benefits when BPaL treatment is extended to MDR TB treatment failure and treatment intolerant patients.

Abbreviations
BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; DALY: disability-adjusted life year; GDP: gross domestic product; MDR TB: multidrug-resistant TB; RR TB: rifampicin-resistant TB; SC: standard care; USD: US dollars; XDR TB: extensively drug resistant TB

From the evidence selected, are there any subgroups of patients that may benefit from BPaLM/BPaL more than the wider population of interest?

Outcome	Evidence statement
Unfavourable treatment outcome by subgroup	One RCT (Nyang'wa et al 2022) reported subgroup analyses in patients with RR TB for unfavourable treatment outcome at 72 weeks as the RD (96.6% CI) for BPaLM vs SC: • Sex (F vs M): -29.3% (-53.9% to -4.6%) vs -42.9% (-63.1% to -22.8%) • Country (S Africa vs Uzbekistan): -7.6% (-42.2% to 27.0%) vs -41.7% (-61.1% to -22.3%); Belarus not calculable • HIV status (negative vs positive): -44.7% (-61.3% to -28.1%) vs -11.4% (-48.5% to 25.6%) • Cavity present (absent vs present): -38.8% (-66.7% to -11.0%) vs -37.7% (-56.4% to -19.0%) • Previous TB treatment (no vs yes): -30.1% (-50.7% to -9.5%) vs -47.6% (-70.9% to -24.2%) • Smear positivity (negative vs positive): -53.4% (-82.2% to -24.6%) vs -31.5% (-50.1% to -12.9%) • Current smoker (no vs yes): -31.6% (-50.7% to -12.5%) vs not calculable • Fluoroquinolone resistance (sensitive vs resistant): -45.3% (-63.7% to -26.9%) vs -17.3% (-45.1% to 10.5%) • Isoniazid resistance (sensitive vs resistant): -46.7% (-115.7% to 22.4%) vs -37.2% (-53.6% to -20.8%) **One RCT reported that the proportion of RR TB patients with an unfavourable treatment outcome at 72 weeks (BPaLM vs SC) did not vary by age, sex, HIV infection, sputum smear status, the presence of cavities on chest radiographs, fluoroquinolone resistance, or country of recruitment.**
Adverse events results by HIV status	One prospective case series (Conradie et al 2020) reported AE results for the combined population of MDR TB and (pre)XDR TB for people who were HIV positive vs those who were HIV negative: • AE: 53/53 (100%) vs 56/56 (100%) • AE leading to death: 3/53 (5.7%) vs 3/56 (5.4%) • SAE: 10/53 (18.9%) vs 9/56 (16.1%) • Grade 3 or 4 AE: 27/53 (50.9%) vs 35/56 (62.5%) **One prospective case series reported that people who were HIV positive had similar safety outcomes as those who were HIV negative, although the rate of grade 3 or 4 AE was slightly higher among people who were HIV positive.**

Abbreviations
AE: adverse events; BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; CI: confidence interval; F: female; HIV: human immunodeficiency virus; M: male; MDR: multidrug-resistant TB; RCT: randomised controlled trial; RD: risk difference; RR TB: rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; TB: tuberculosis; XDR TB: extensively drug resistant TB

From the evidence selected, what was the treatment duration of the BPaLM/BPaL regimen?

Outcome	Evidence statement
Treatment duration	Patients in one RCT (Nyang'wa et al 2022) had a 24-week BPaLM or BPaL regimen. Both the randomised uncontrolled trial (Conradie et al 2022) and the prospective case series (Conradie et al 2020) gave patients 26 weeks of bedaquiline and pretomanid, but either 26 weeks or 9 weeks of linezolid (in Conradie et al 2022) or linezolid for up to 26 weeks (Conradie et al 2020).
Abbreviations BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; RCT: randomised controlled trial	

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of BPaLM/BPaL compared to current standard care (SC) for the treatment of RR TB, MDR TB and pre-XDR TB. The critical outcomes of interest were sputum culture conversion rates, unfavourable treatment outcome and treatment completion. Important outcomes were quality of life, treatment failure and disease recurrence, amplification of drug resistance, safety outcomes and cost effectiveness.

Evidence was available from one RCT (TB-PRACTECAL, Nyang'wa et al 2022), one arm of a prospective randomised uncontrolled trial (ZeNix, Conradie et al 2022, n=106 in scope, 45 of whom were in the linezolid 600mg/26-week dosage arm), one prospective case series (Nix-TB, Conradie et al 2020, n=109), and two cost effectiveness analyses (one that used treatment effects from TB-PRACTECAL, and one based on the results of Nix-TB). The RCT enrolled people with RR TB in a two-stage process. Stage 1 randomised patients to SC, BPaLM, BPaL or BPaL+clofazimine, and Stage 2 randomised patients to BPaLM or SC. Results for both BPaLM (n=72) and BPaL (n=70) arms were compared with SC (n=73) at 72 weeks, with some outcomes also available at 108 weeks. The two uncontrolled studies reported at 26 weeks/6 months for people with MDR TB, pre-XDR TB and XDR TB. Only data for people with MDR TB and pre-XDR TB are included in this report. Patients described as having XDR TB in the Nix-TB trial had pre-XDR TB under the current definition so were deemed to be in scope for this review.

The RCT TB-PRACTECAL took place at seven sites in Belarus, South Africa and Uzbekistan. The randomised uncontrolled trial ZeNix took place at four sites in South Africa, one in Georgia, one in Moldova, and five in Russia. The prospective case series Nix-TB took place at three sites in South Africa. Both economic evaluations took data from the clinical studies and applied them to populations in South Africa, the Philippines and Georgia, with the Sweeney et al 2022 study also including India. None of the clinical effectiveness studies took place in the UK and none of the cost-effectiveness analyses modelled the UK/NHS scenario. Therefore, results may not be generalisable to the UK. Population differences such as the number of people with HIV and differences in provider costs led to large variation by country in the cost effectiveness studies, suggesting that the cost effectiveness of BPaL(M) treatment in the UK would be different from that estimated by the included studies.

The critical outcomes sputum culture conversion rate and treatment completion rate were both reported by two studies (one RCT and one prospective case series). The critical outcome unfavourable treatment outcome was reported by three studies (one RCT, one prospective case series, and one randomised uncontrolled trial that had four different dosages of linezolid, one of which was 600mg for 26 weeks). The important outcomes treatment failure/disease recurrence and safety were both reported by two studies (one RCT and one prospective case series). One prospective case series reported the important outcome amplification of drug resistance. Although this outcome was also reported by the uncontrolled randomised trial for the cohort as a whole, data were not available separately for the in-scope MDR/pre-XDR TB patients.

None of the studies reported the important outcome quality of life.

A limitation in the certainty of the evidence from the RCT is the impact of early termination when the efficacy stopping rule was met. The analysis presented only includes patients who could have had a prespecified outcome event at the given time point (i.e. 72 weeks, 108 weeks). The trial's primary outcome (unfavourable treatment outcome at 72 weeks) was the only analysis to be reported using the full intention-to-treat (ITT) population – others used the modified ITT (mITT) population, which excluded people without microbiologically proven RR TB. Those

excluded from the mITT population would still have been in scope for this review as they could be assumed to have had suspected/functional RR-TB.

Although the RCT presented confidence intervals around effect estimates, the authors noted that the confidence intervals for BPaL compared with SC were *"two-sided and were not adjusted for multiplicity and should not be used to infer relative treatment effects."* Results were therefore not described as statistically significant even if the 95% confidence interval excluded no effect. No P values were presented for any of the analyses, and it is not possible to infer statistical significance for the majority of the results (other than those reported with 96.6% confidence intervals, which met the study definition of statistically significant). For the primary outcome (for the comparison of BPaLM versus SC), the authors stated that *"A noninferiority margin of 12 percentage points as the upper boundary of the confidence interval was determined to be a reasonable clinical and public health trade-off limit, given the benefits of a shorter treatment duration, decreased pill burden and regimen cost, and the all-oral nature of the investigational regimens."* This was interpreted as implying clinical and statistical significance. Minimal clinically important differences were not available for any other outcomes.

Another limitation in the certainty of the evidence from the RCT was its open-label design. Although lack of blind measurement of objective outcomes such as sputum culture conversion rate should not have been affected by knowledge of treatment group allocation, treatment completion rates could have been adversely affected (and any consequent impact on compliance may affect all efficacy outcomes). It is possible that early discontinuations in the SC arm of the RCT led to a lower proportion of people in that group achieving a favourable outcome at the end of follow-up. In the mITT population, 61% of these discontinuations were due to adverse events. However, 25% were due to withdrawal of consent. The trial authors noted that the difference between SC and BPaLM/BPaL groups was less pronounced when early discontinuations were excluded from the per protocol analysis set. Changes in the SC treatment regimen over time (in line with international recommendations) occurred and earlier comparator treatments may have been more toxic than those currently in use. In line with current WHO guidelines, most people on standard care received at least two Group A drugs.

The ZeNix and TB-Nix studies did not compare the BPaL regimens against SC, so the certainty of evidence from these studies is limited by the lack of comparative data and their small size. In addition, only the primary outcome from the ZeNix study was available separately for people with MDR/pre-XDR TB, so evidence from other outcomes could not be incorporated into this review. Whilst the ZeNix study documented reasons for people being excluded/lost to follow-up at different stages of the study, it is not clear how many people were screened for possible inclusion in the TB-Nix study, and what proportion of those were included.

The cost effectiveness of BPaLM/BPaL compared to SC was reported by two analyses, based on the treatment effects from the TB-PRACTECAL and Nix-TB studies, respectively, applied to populations in India (one analysis), and in South Africa, the Philippines and Georgia (both analyses). These both used a healthcare provider perspective, and a time horizon of either 20 years or a lifetime. Limitations introducing uncertainty include the application of short-term (72 month/ 6 month) trial outcome data to 20-year or lifetime horizons and for different countries' populations, and the small numbers of people in the TB-PRACTECAL and TB-Nix studies. The authors of the Gomez et al 2021 analysis also reported that the use of linezolid in both the active and comparator arms of their analysis meant that they could not quantify the impact of adverse events on either disability-adjusted life years or costs. Uncertainty and variation in the cost of treatment could also be considered as limitations of the economic evaluations (partly due to uncertainty about the number of people resistant or susceptible to fluoroquinolones in TB-PRACTECAL and due to cost estimates in the Gomez et al 2021 study).

Although both studies used the provider perspective costs in the UK may be different, so the cost of the intervention compared to standard care may not be generalisable to the UK NHS setting. There was also large variation in cost estimates for different countries, which introduces uncertainty about generalisability to the NHS in England.

7. Conclusion

This evidence review includes one RCT, one arm of a prospective randomised uncontrolled trial, one prospective case series and two economic analyses. These studies provided data comparing BPaLM/BPaL to standard care for the treatment of RR TB, MDR TB and pre-XDR TB for the critical outcomes of sputum culture conversion rates, unfavourable treatment outcome and treatment completion. RR TB patients treated with BPaLM or BPaL had higher sputum culture conversion rates compared with standard care at 12 weeks, although statistical significance was not reported. For people with MDR/(pre)XDR TB, 97.8% had culture conversion by 16 weeks.

Statistically significantly fewer RR TB patients had an unfavourable outcome at 72 weeks with BPaLM compared with standard care, and fewer patients on BPaL than on standard care had an unfavourable outcome (statistical significance not reported, but the risk ratio indicated a large effect). Between 5% and 25% of people with MDR TB or pre-XDR TB had an unfavourable outcome at 6 months follow-up.

Fewer people with RR TB treated with either BPaLM or BPaL discontinued early compared with those receiving standard care, but statistical significance was not reported. There were no discontinuations due to adherence issues in the BPaLM group, two in the BPaL group and three in the standard care group. For people with MDR/pre-XDR, all surviving patients completed treatment with BPaL at six months follow-up.

There was also evidence for the important outcomes of treatment failure and disease recurrence, amplification of drug resistance, safety outcomes and cost effectiveness. No RR TB patients taking BPaLM, BPaL or SC failed treatment at 72 weeks in the RCT, although 4% of those taking BPaL (and none on BPaLM or SC) had disease recurrence by 72 weeks. The prospective case series reported treatment relapse at six months for two people treated with BPaL, and amplification of drug resistance was identified in one of these patients.

Statistically significantly fewer people with RR TB treated with BPaLM had at least one serious adverse event or adverse event of at least grade 3 compared with those receiving standard care at 72 and 108 weeks, with similar results for BPaL although statistical significance was not reported. At 72 weeks, there was a lower incidence of hepatic disorders among people on BPaLM or BPaL than on standard care, and considerably fewer people with QTcF prolongation. There was low certainty evidence of a marked difference in discontinuations due to adverse events: 7% of people on BPaL/M compared to 23% of those in the standard care arm (statistical significance not reported).

The risk of bias for the comparison of BPaLM/BPaL to standard care was unclear. Limitations which reduced the certainty in the outcomes include the RCT's open-label design and factors associated with the numerical analysis due to its early termination for meeting the efficacy stopping rule. The analysis presented only includes patients who could have had a prespecified outcome event at the given time point (i.e. 72 weeks, 108 weeks) and early discontinuations in the standard care arm may have contributed to the lower proportion of that group achieving a favourable outcome. Statistical significance was not reported in the form of p values, and although the RCT presented confidence intervals around effect estimates, the authors noted that the confidence intervals for BPaL compared with standard care should not be used to infer relative treatment effects. The ZeNix and TB-Nix studies did not compare the BPaL regimens against SC, so the certainty of evidence from these studies is limited by the lack of comparative data and their small size.

No data were reported for quality of life.

Subgroup data from the RCT indicated that that the proportion of RR TB patients with an unfavourable treatment outcome at 72 weeks (BPaLM vs SC) did not vary by age, sex, HIV infection, sputum smear status, the presence of cavities on chest radiographs, fluoroquinolone resistance, or country of recruitment. At six months, people in the prospective case series who were HIV positive had similar safety outcomes as those who were HIV negative, although their rate of grade 3 or 4 adverse events was slightly higher.

The studies identified for this review provide moderate to very low certainty evidence that in patients with RR TB, BPaLM/BPaL may improve unfavourable clinical outcomes, reduce treatment discontinuation, and reduce grade 3 or 4 serious adverse events compared to standard care at up to 108 weeks follow-up. The shorter duration of the 26-week BPaL/M regimen is an additional benefit compared with the standard treatment regimens that may last from 9 to 20 months. Cost effectiveness modelling suggests that treatment with BPALM/BPAL may be cost effective compared to standard care and may even be cost saving overall, although it is uncertain to what extent the cost effectiveness outcomes can be generalisable to the NHS in England.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the clinical effectiveness of BPaLM/BPaL compared with standard of care?
2. In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the safety of BPaLM/BPaL compared with standard of care?
3. In people with suspected, functional or confirmed RR, MDR- or pre-XDR TB, what is the cost effectiveness of BPaLM/BPaL compared with standard of care?
4. From the evidence selected, are there any subgroups of patients that may benefit from BPaLM/BPaL more than the wider population of interest?
5. From the evidence selected, what was the treatment duration of the BPaLM/BPaL regimen?

P –Population and Indication	Patients with suspected, functional or confirmed rifampicin-resistant (RR)-TB, multidrug-resistant (MDR)-TB or pre-extensively drug-resistant (pre-XDR) TB [Rifampicin-resistant (RR) TB occurs when the TB bacterium is resistant to the antibiotic (anti-TB drug) rifampicin. Multidrug-resistant (MDR) TB is when the TB bacterium is resistant to rifampicin and isoniazid. Pre-extensively drug-resistant (pre-XDR) TB is a form of TB that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).] [Extensively drug-resistant (XDR) TB when it is defined as when the TB bacterium is resistant to rifampicin, isoniazid, at least one fluroquinolone and at least one other 'Group A' drug (bedaquiline or linezolid), is not in scope]. [The definitions relating to the categorisation of drug-resistant TB have undergone multiple revisions over the last decade, in line with respective updates to the WHO guidelines. The preceding definitions, taken from the updated 2022 WHO guidelines, represent the current definitions. From 2013 to 2020, the definition of MDR TB as defined by the WHO remained 'resistance to at least both isoniazid and rifampicin'; this is unchanged (WHO, 2013). From 2013 to 2020, the definition of XDR TB as defined by the WHO was 'resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance (WHO, 2013). Pre-XDR TB was only defined by the WHO as a distinct entity for the first time in January 2021, with the definition stated as above (WHO, 2022). Therefore, there may be patients categorised as XDR TB using the 2013 definitions, who would fall into the current pre-XDR TB category, and should not be excluded from this review] Particular subgroups of interest: homeless individuals, people living with HIV, adolescents, patients with extrapulmonary TB.

I – Intervention	Bedaquiline and linezolid and pretomanid (BPaL) +/ - moxifloxacin (BPaLM) [Typical doses as per WHO 2022 Guidelines are Bedaquiline: 400mg once daily for 2 weeks, then 200mg 3 times per week afterwards OR 200mg daily for 8 weeks, then 100mg daily; Pretomanid: 200mg once daily; Linezolid: 600mg once daily (dose adjustments are permitted); Moxifloxacin: 400mg once daily (applicable to BPaLM only 6-9 months] [From WHO 2022 Guidance which recommends the dosing of component drugs for BPaLM/BPaL as above. The dosing information for moxifloxacin is only relevant for the BPaLM regimen. Dose modifications for bedaquiline, moxifloxacin and pretomanid are not permitted. It is preferred to continue linezolid at the full dose for the entire duration; however, the dose of linezolid can be reduced to 300 mg or can be discontinued (and restarted when possible) if there is significant toxicity (depending on the severity of specific adverse events or serious adverse events) associated with linezolid, including optic neuritis, peripheral neuropathy or myelosuppression. Dose modification of linezolid should be avoided if possible in the first 9 weeks of therapy.]
C – Comparator(s)	Standard of care regimen [Current standard treatment options for patients in whom fluroquinolone resistance has been excluded include a 9-month all-oral regimen for MDR/RR TB comprising the combined use of seven agents, most of which will be continued for at least 9 months. Other treatment options include individualised treatment regimens with a total treatment duration of 18–20 months suggested for most patients, but this may be modified according to the patient's response to therapy (often continuing for 15–17 months after culture conversion.]
O – Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. <u>*Critical to decision-making:*</u> • **Sputum culture conversion rates** *Sputum culture conversion rates are an important outcome to patients as sputum culture negativity is an indicator that a patient is non-infectious and could potentially be discharged from hospital*. • **Unfavourable treatment outcome** *This outcome is important to patients as it provides an indication of how effective and tolerable the treatment regimen is. It is a composite measure which may include death, treatment failure, treatment discontinuation, loss to follow-up or recurrence of tuberculosis*.

	• **Treatment completion rates** *Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. If a treatment has adherence challenges, it can increase the risk of treatment failure and drug resistance*. [Examples include, but not limited to: o Missed doses (observed by research staff review of medication/returned medication) o Self-reported adherence measures (e.g., questionnaire methods) o Interview methods] *<u>Important to decision-making:</u>* • **Quality of life** *Quality of life (QOL) is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy.* [There are no validated TB-specific QOL tools available. However, examples of quality-of-life tools that have been used to measure QOL in patients with TB include but are not limited to: o EUROHIS-QOL 8-item index o SF-36 o EQ-5D o The abbreviated WHO Quality of scale WHOQOL-BREF] • **Treatment failure and disease recurrence** *This outcome is important to patients because it can result in further treatment being required which will impact on patient satisfaction as well as any potential drug side effects from further treatment. There is also a negative public health impact associated with treatment failure. This is a composite outcome, as the terms treatment failure and disease recurrence are used interchangeably in some studies.* • **Amplification of drug resistance** *This is an important outcome to patients as increased levels of drug resistance may results in changes to their treatment regimen and longer treatment duration.* **<u>Safety</u>**

	Safety of BPaL/BPaLM is important to patients as it allows comparison of treatment approaches. [Examples include, but not limited to: • Frequency of adverse events • Frequency of serious adverse events • Adverse events leading to discontinuation • Treatment related adverse events – e.g., including but not limited to: prolongation of the QTc interval, hepatic side effects, cytopaenias, peripheral neuropathy, optic neuritis.] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2013 to 7 July 2023

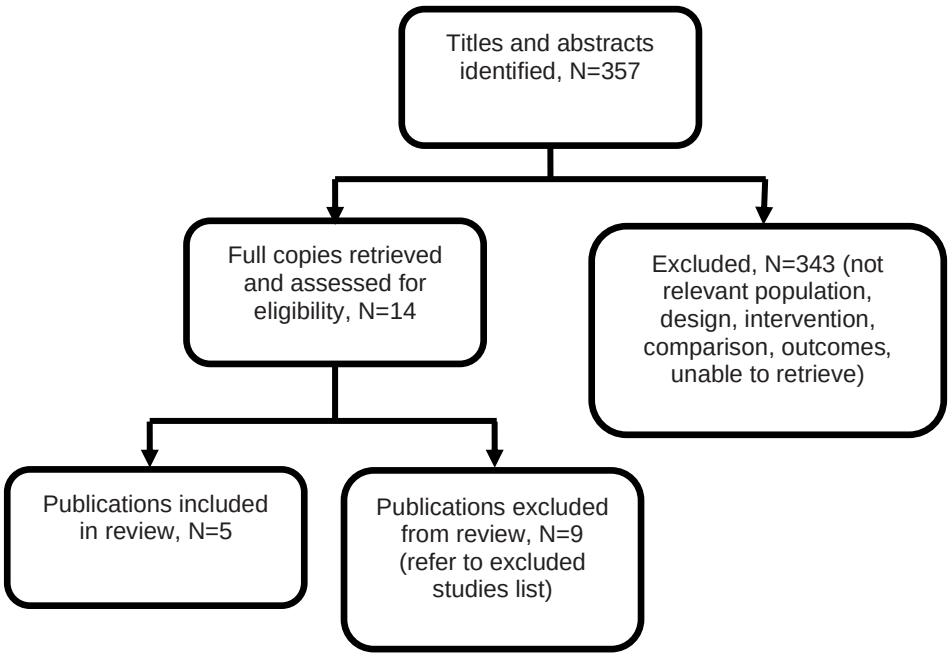
Medline search strategy 7 July 2023

1	tuberculosis/ or tuberculosis, pulmonary/ or exp tuberculosis, multidrug-resistant/
2	(tuberculosis or tb).ti,kf.
3	(rrtb or rr-tb or mdrtb or mdr-tb or xdrtb or xdr-tb or prexdr or pre-xdr or ((resistan* or intoleran*) adj2 (tuberculosis or tb))).ti,ab,kf.
4	1 or 2 or 3
5	Diarylquinolines/ and Linezolid/ and Nitroimidazoles/
6	(((bedaquiline or sirturo or diarylquinoline*) and (linezolid or zyvox) and (pretomanid or dovprela or nitroimidazole*)) or (bpal or bpalm)).ti,ab,kf.
7	5 or 6
8	4 and 7
9	limit 8 to (english language and yr="2013 -Current")

Appendix C Evidence selection

The literature searches identified 357 references. These were screened using their titles and abstracts and 14 references were obtained in full text and assessed for relevance. Of these, 5 references are included in the evidence summary. The remaining 9 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Nyang'wa B-T, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. NEJM. 2022; 387(25): 2331-43.	Included
Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. NEJM. 2020;382(10):893-902.	Included
Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. NEJM. 2022;387(9):810-23.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Gils T, Lynen L, de Jong BC, Van Deun A, Decroo T. Pretomanid for tuberculosis: a systematic review. Clinical Microbiology and Infection.2022;28(1):31-42.	Only 1 of the included studies had bedaquiline (B), linezolid (L) and pretomanid (Pa) (BPaL); (Conradie et al 2020, already selected for inclusion in this review). No additional outcomes of interest.
Haley CA, Schechter MC, Ashkin D, Peloquin CA, Cegielski JP, Andrino BB, et al. Implementation of BPaL in the United States: Experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant TB disease. Clinical Infectious Diseases.2023. DOI: 10.1093/cid/ciad312	RCT evidence available for discontinuations due to non-adherence.
Hewison C, Khan U, Bastard M, Lachenal N, Coutisson S, Osso E, et al. Safety of treatment regimens containing bedaquiline and delamanid in the endTB Cohort. Clinical Infectious Diseases. 2022;75(6):1006-13.	Intervention not in scope. No data presented for the BPaL or BPaL + moxifloxacin (BPaLM) regimens
Li H, Salinger DH, Everitt D, Li M, Del Parigi A, Mendel C, et al. Long-term effects on QT prolongation of pretomanid alone and in combinations in patients with tuberculosis. Antimicrobial Agents and Chemotherapy. 2019;63(10).	Models QTc from 8 studies. Only 1 of the 8 studies used BPaL (Conradie et al 2020, already selected for inclusion in this review)
Mallick JS, Nair P, Abbew ET, Van Deun A, Decroo T. Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review. JAC-Antimicrobial Resistance. 2022;4(2):dlac029.	Only 1 of the 13 included studies was BPaL (Conradie et al 2020, already selected for inclusion in this review)
Mulder C, Rupert S, Setiawan E, Mambetova E, Edo P, Sugiharto J, et al. Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis. BMJ Global Health. 2022;7(1).	Budget/cost analysis not cost-effectiveness analysis (e.g. no cost per Disability Adjusted Life Year), and population was extensively drug resistant tuberculosis (XDR TB) (insufficient information to determine whether this included pre-XDR TB or just XDR TB).
Nguyen TVA, Cao TBT, Akkerman OW, Tiberi S, Vu DH, Alffenaar JWC. Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis. Expert Review of Clinical Pharmacology. 2016;9(8):1025-37.	Intervention not in scope: systematic review of bedaquiline, but not BPaL pr BPaLM.
Oelofse S, Esmail A, Diacon AH, Conradie F, Olayanju O, Ngubane N, et al. Pretomanid with bedaquiline and linezolid for drug-resistant TB: a comparison of prospective cohorts. International Journal of Tuberculosis and Lung Disease. 2021;25(6):453-60.	This study uses Conradie et al 2020 (already selected for inclusion in this review) and reports comparative results for treatment with BPAL vs B/L based treatment. Therefore, the comparator is not 'standard of care' for pre-XDR TB, which would have been rifampicin, isoniazid, flouroquinolone or injectable e.g. amikacin.
Solans BP, Imperial MZ, Olugbosi M, Savic RM. Analysis of dynamic efficacy endpoints of the Nix-TB Trial. Clinical Infectious Diseases. 2023;76(11):1903-10.	Pharmacokinetic study. Direct studies reporting outcomes of interest available.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Nyang'wa B-T, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. NEJM. 2022; 387(25): 2331-43. **Study location** 7 sites in Belarus, South Africa and Uzbekistan **Study type** RCT (TB-PRACTECAL) **Study aim (stage 2)** To evaluate the safety and efficacy of a 24-week regimen containing BPaLM for the treatment of rifampin-resistant tuberculosis. **Study dates** Jan 2017 – March 2021 (enrolment terminated early for benefit)	**Inclusion criteria** Patients ≥15 years old with TB (confirmed by positive sputum smear) with resistance to rifampin (RR TB) **Exclusion criteria** Pregnancy; ALT or AST level >3 x ULN; QTcF >450 msec, structural heart disease, or suspected resistance to bedaquiline, pretomanid, or linezolid. **Total sample size** N=552 randomised at start of Stage 1 (includes 126 in BPaLC, not in scope N=303 included in stage 2 prespecified analyses (for BPaLM and SC) **No. of participants in each treatment group (safety population)** BPaLM: n=151 BPaL n=123 SC n=152 **No. of participants in each treatment group (ITT population,**	**Interventions** BPaLM: • B 400 mg/d for 2 weeks, followed by 200 mg 3 times per week for 22 weeks • Pa 200 mg/d for 24 weeks • L 600 mg/d for 16 weeks, followed by 300 mg/d for 8 weeks • M 400 mg/d for 24 weeks BPaL: As above but without M **Comparator** SC: locally accepted SC, closely aligned to WHO guidelines. **(9 to 20 month regimen)** Most received at least 2 Group A drugs (95% had fluroquinolones, 77% had linezolid, 76% had bedaquiline	**Critical outcomes** **Sputum culture conversion rates** mITT population at 12 weeks, n/N (%) • BPaLM: 85/96 (88.5%) • BPaL: 73/90 (81.1%) • SC: 78/99 (78.8%) HR for culture conversion at 12 weeks (BPaLM vs SC): 1.59 (95% CI 1.18 to 2.14) N who converted by 108 weeks (denominators unclear): BPaLM: n=91 BPaL: n=82 SC n=85 HR for culture conversion adjusted for site at 108 weeks (BPaLM vs SC): 1.49 (95% CI 1.10 to 2.01) HR for culture conversion adjusted for site at 108 weeks (BPaL vs SC): 1.05 (95% CI 0.77 to 1.44) RD adjusted for site for BPaLM vs SC (mITT, 12 weeks): 9.2% (95% CI –1.6% to 20.1%) RD adjusted for site for BPaL vs SC (mITT, 12 weeks): 3.9% (95% CI –8.0% to 15.9%) RR adjusted for site for BPaLM vs	This study was appraised using the Cochrane RoB 1 checklist for RCTs. 1. Low 2. Low 3. High 4. Unclear 5. Unclear 6. Unclear 7. Unclear **Other comments** This was conducted in two stages, with stage 1 randomising patients to one of four different treatment arms (SC, BPaLM, BPaL and BPaLC) and stage 2 randomising patients to BPaLM or SC. Both the BPaLM and BPaL arms were compared against SC at 72 weeks **Subgroup analyses** Subgroup analyses for unfavourable treatment outcome (composite) at 72 weeks, mITT, RD (96.6%) for BPaLM vs SC: Age 18 to < 45: -33.0% (-50.9% to -15.0%) Age 45 to <65: -48.7% (-82.7% to -14.6%) Sex Female: -29.3% (-53.9% to -4.6%) Male: -42.9% (-63.1% to -22.8%)

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	received at least one dose and completed 72-week follow-up) BPaLM: n=72 BPaL n=70 SC n=73 **No. of participants in each treatment group (mITT population (received at least one dose and completed 72-week follow-up but excluded those who did not have microbiologically proven RR TB)** BPaLM: n=62 BPaL n=60 SC n=66 **Baseline characteristics** Median age (range) BPaLM: 35 (17-71) BPaL: 35 (15-72) SC: 37 (18-71) Male, n(%) BPaLM 85/151 (56.3) BPaL: 65/123 (52.8) SC: 96/152 (63.2) Smear positivity, n(%) BPaLM 91 (60.3) BPaL: 77 (63) SC: 98 (64.5) Cavitation on chest radiography, n(%) BPaLM 80 (53.0)		SC (mITT, 12 weeks): 1.12 (95% CI 0.99 to 1.27) RR adjusted for site for BPaL vs SC (mITT, 12 weeks): 1.04 (95% CI 0.90 to 1.20) **Unfavourable treatment outcome** Analysis at 72 weeks, ITT, n/N(%) • BPaLM: 17/72 (23.6%) • BPaL: 24/70 (34.3%) • SC: 39/73 (53.4%) RD for BPaLM vs SC: -30% (96.6% CI -46% to –14%) RD for BPaL vs SC: -19% (95% CI -36% to -2%) Analysis at 72 weeks, mITT, n/N(%) • BPaLM: 7/62 (11.3%) • BPaL: 14/60 (23.3%) • SC: 32/66 (48.5%) Unadjusted RD for BPaLM vs SC at 72 weeks, mITT: -37% (96.6% CI -53% to -22%) Unadjusted RD for BPaL vs SC at 72 weeks, mITT: -25% (95% CI -41% to -9%) Unadjusted RD for BPaLM (n=33) vs SC (n=37) at 108 weeks, mITT: -50.0% (95% CI -69.2% to -30.9%) Unadjusted RR for BPaLM vs SC at 108 weeks, mITT: 0.19 (95% CI 0.08 to 0.51) Unadjusted RD for BPaL (n=35) vs SC (n=37) at 108 weeks, mITT: -33.6% (95% CI -55.2% to -12.0%) Unadjusted RR for BPaL vs SC at 108 weeks, mITT: 0.46 (95% CI 0.26 to 0.82)	Country Belarus: not calculable S Africa: -7.6% (-42.2% to 27.0%) Uzbekistan: -41.7% (-61.1% to -22.3%) HIV status Negative: -44.7% (-61.3% to -28.1%) Positive: -11.4% (-48.5% to 25.6%) Cavity present Absent: -38.8% (-66.7% to -11.0%) Present: -37.7% (-56.4% to -19.0%) Previous TB treatment No: -30.1% (-50.7% to -9.5%) Yes: -47.6% (-70.9% to -24.2%) Smear positivity Negative: -53.4% (-82.2% to -24.6%) Positive: -31.5% (-50.1% to -12.9%) Current smoker No: -31.6% (-50.7% to -12.5%) Yes: not calculable Fluoroquinolone resistance Sensitive: -45.3% (-63.7% to -26.9%) Resistant:-17.3% (-45.1% to 10.5%) Isoniazid resistance Sensitive: -46.7% (-115.7% to 22.4%) Resistant: -37.2% (-53.6% to -20.8%) **Source of funding** Supported by Medecins sans Frontieres. The TB Alliance donated the first batch of pretomanid before it was commercially available.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	BPaL: 74 (60.2) SC: 95 (62.5) Fluoroquinolone-resistant TB, n/N(%) BPaLM 32/134 (23.9) BPaL: 25/104 (24.0) SC: 32/131 (24.4) Authors state that baseline demographic characteristics were "balanced among the trial groups with follow-up for 72 weeks, although the mITT SC group had a higher proportion of female patients and patients with smear-positive and cavitary disease than the investigational groups"		Additional reporting for mITT RD adjusted for site for BPaLM vs SC (72 weeks): -39.3% (96.6% CI –55.3% to –23.2%) RD adjusted for site for BPaL vs SC (72 weeks): -25.4% (95% CI –41.7% to –9.1%) RR adjusted for site for BPaLM vs SC (72 weeks): 0.24 (96.6% CI 0.11 to 0.52) RR adjusted for site for BPaL vs SC (72 weeks): 0.47 (95% CI 0.28 to 0.80) RD adjusted for site for BPaLM vs SC (108 weeks): -50.6% (95% CI –-71.5% to -29.8%) RD adjusted for site for BPaL vs SC (108 weeks): -34.3% (95% CI –-56.0% to -12.6%) RR adjusted for site for BPaLM vs SC (108 weeks): 0.20 (95% CI 0.07 to 0.55) RR adjusted for site for BPaL vs SC (108 weeks): 0.45 (95% CI 0.24 to 0.82) **Treatment completion rates** Early discontinuation at 72 weeks, ITT, n/N(%) • BPaLM: 15/72 (20.8%) • BPaL: 18/70 (25.7%) • SC: 35/73 (47.9%) Adherence issues (leading to early discontinuation) at 72 weeks, ITT, n/n who discontinued (%)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• BPaLM: 0/15 (0%) • BPaL: 2/18 (11.1%) • SC: 3/35 (8.6%) **Important outcomes** **Treatment failure and disease recurrence** ITT population at 72 weeks Treatment failure BPaLM: 0/72 (0%) BPaL: 0/70 (0%) SC: 0/73 (0%) Disease recurrence at 72 weeks BPaLM: 0/72 (0%) BPaL: 3/70 (4.3%) SC: 0/73 (0%) **Safety** n/N with ≥ 1 SAE (or grade ≥ 3 AE) within 72 weeks BPaLM: 14/72 (19.4%) BPaL: 15/69 (21.7%) SC: 43/73 (58.9%) RD (BPaLM vs SC): -40% (96.6% CI –55% to -24%) RD (BPaL vs SC): -37% (95% CI –52% to -22%) n/N with hepatic disorder, grouped, BPaLM: 3/72 (4.2%) BPaL: 2/69 (2.9%) SC: 8/73 (11.0%) n/N with QTcF prolongation BPaLM: 1/72 (1.4%) BPaL: 0/69 (0%) SC: 10/73 (13.7%)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			n/N with creatinine renal clearance decreased BPaLM: 1/72 (1.4%) BPaL: 2/69 (2.9%) SC: 5/73 (6.8%) n/N with anaemia BPaLM: 2/72 (2.8%) BPaL: 1/69 (1.4%) SC: 6/73 (8.2%) n/N with neutropaenia BPaLM: 3/72 (4.2%) BPaL: 0/69 (0%) SC: 2/73 (2.7%) n/N with optic neuropathy BPaLM: 0/72 (0%) BPaL: 0/69 (0%) SC: 0/73 (0%) n/N with an AE of any grade BPaLM: 142/151[17] (94.0%) BPaL: 120/122 (98.4%) SC: 145/150 (96.7%) Discontinuation due to AE at 72 Weeks: n/N BPaLM: 5/72 (6.9%) BPaL: 5/70 (7.1%) SC: 17/73 (23.3%) Deaths during treatment BPaLM: 0/72 BPaL: 1/70 (1.4%) (seizure, not treatment-related or TB-related) SC: 7/73 (9.6%) (4 of which were considered to be treatment-related:	

[17] N is the 'as treated population up to 18 March 2021'.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			suicide, acute pancreatitis, sudden death, sudden cardiac death; 0 thought to be TB-related)	
Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. NEJM. 2022;387(9):810-23. **Study location** South Africa (4 sites), Georgia (1 site), Moldova (1 site) and Russia (5 sites) **Study type** Randomised uncontrolled trial (ZeNix) **Study aim** To investigate the efficacy and safety of different doses of linezolid in the bedaquiline–pretomanid–linezolid regimen for highly drug-resistant tuberculosis. **Study dates** Enrolled between November 2017 and December 2019	**Inclusion criteria** **Patients** ≥ 14 years old (≥18 years in Russia and Moldova) with documented positive sputum culture or molecular test for **TB** within 3 months before screening. • XDR TB (not in scope): resistance to rifampin, a fluoroquinolone, and an aminoglycoside. • Pre-XDR TB: resistance to rifampin plus resistance to either a fluoroquinolone or an aminoglycoside. • MDR TB: resistant to rifampin (with or without resistance to isoniazid) and did not respond to treatment or for which a second-line regimen had been discontinued because of side effects 6 months or more before enrolment.	**Intervention** **BPaL** • B (200 mg/d for 8 weeks, followed by 100 mg/d for 18 weeks) • Pa (200 mg daily for 26 weeks). • L (either 1200 mg/d or 600 mg/d for either 26 weeks or 9 weeks. Dose could be reduced in a stepwise manner (1200 mg, 600 mg, 300 mg, or 0 mg) in response to adverse events. **Comparator** None	**Critical outcomes** **Unfavourable treatment outcome** Reported at 26 weeks L 1200mg 26 weeks • MDR TB: 0/5 • Pre-XDR TB: 1/18 (5.6%) L 1200mg 9 weeks • MDR TB: 1/6 (16.7%) • Pre-XDR TB: 0/22 L 600mg 26 weeks • MDR TB: 1/4 (25%) • Pre-XDR TB: 2/22 (9.1%) L 600mg 9 weeks • MDR TB: 2/6 (33.3%) • Pre-XDR TB: 1/21 (4.8%) Across all doses of L • MDR TB: 4/21 (19.0%) • Pre-XDR TB: 4/83[19] (4.8%) **Important outcomes** **Treatment failure and disease recurrence** Reported by authors as 'unfavourable treatment outcome'	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. No 9. Unclear 10. Yes **Other comments** ZeNix trial: only 106/181 (58.6%) participants were in scope. Results only presented where available for in-scope participants separately (restricted to primary outcome). **Subgroup analyses** Results are reported separately for pre-XDR TB and MDR TB patients. **Source of funding** Supported by the TB Alliance with funding from Australia Department of Foreign Affairs and Trade; Bill and Melinda Gates Foundation; Federal Ministry of Education and Research of Germany; Irish Aid; Netherlands Ministry of Foreign Affairs; UK Department of Health; UK Foreign, Commonwealth and Development Office; US Agency for International

[19] In the pre-XDR group: 2/85 were unassessable.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Exclusion Criteria HIV infection and a CD4+ cell count of less than 100 per cubic mm; a risk of arrhythmia; ALT and AST > 3 x ULN; or peripheral neuropathy of grade 3 or higher at baseline; previously received any of the three trial drugs or delamanid for 2 weeks or more before enrolment. **Total sample size** N=181 randomised XDR TB (not in scope): n=75 (41%) Pre-XDR TB: n=85 (47%) MDR TB: n=21 (12%) **No. of participants in each treatment group** L 1200mg 26 weeks MDR: 5/45 (11%) Pre-XDR: 19/45 (42%) L 1200mg 9 weeks MDR: 6/46 (13%) Pre-XDR: 22/46 (48%) L 600mg 26 weeks MDR: 4/45 (9%) Pre-XDR: 22/45 (49%) L 600mg 9 weeks			Development; and UK Research and Innovation Medical Research Council.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	MDR: 6/45 (13%) Pre-XDR: 22/45 (49%) **Baseline characteristics[18]** Median age: 36 years (IQR 30-44) Male: 122/181 (67%) Cavitation on chest radiography: 112 (62%)			
Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. NEJM. 2020;382(10):893-902. **Study location** South Africa (3 sites) **Study type** Open-label, single-group study (prospective case series) (Nix-TB) **Study aim** To evaluate the safety, tolerability, efficacy, and pharmacokinetics of this BPaL. **Study dates**	**Inclusion criteria** Patients ≥ 14 years old with pulmonary XDR TB or MDR TB (culture or molecular test) and drug resistance (phenotypic/genotypic test). • XDR-TB: resistance to isoniazid, rifamycin, a fluoroquinolone and an injectable within 3 months prior to screening) • MDR TB: documented non-response to treatment with an available regimen for 6 months or more prior to enrolment, or inability to continue a second-line drug	**Intervention BPaL:** • B: 400 mg/d for 2 weeks then 200 mg 3 times a week for 24 weeks • Pa 200 mg/d for 26 weeks • L 1200 mg/d for up to 26 weeks[20] (with dosage adjustment depending on tolerability or toxicity) **Comparator** None	Critical outcomes **Sputum culture conversion rates** Reported at 16 weeks • Overall cohort: 91/93 (97.8%) • MDR TB:30/31 (96.8%) • (pre)XDR TB: 61/62 (98.4%) **Unfavourable treatment outcome** Reported at 6 months, n/N (%) • Overall: 11/109 (10.1%) • MDR TB: 3/38 (7.9%) • (pre)XDR TB: 8/71 (11.3%) **Treatment completion rates** • Withdrew consent: 1 ((pre)XDR TB) • Death: 7 (1 MDR TB, 6 (pre)XDR TB) • Relapse: 2 (1 MDR TB, 1 (pre)XDR TB)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments** Planned enrolment of up to 200 patients stopped after 109 patients when ZeNix started recruiting. Those defined in the paper as having XDR TB in this study meet the pre-XDR eligibility criteria defined in Appendix A. In this report they are described as (pre)XDR TB. Sputum culture conversion rates extrapolated from graph.

[18] Baseline characteristics only available for whole population, not separately for eligible MDR TB and pre-XDR TB patients.

[20] The first 44 patients started on linezolid at 600 mg twice daily, and the remaining 65 started on 1200 mg daily.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Enrolment April 2015 - November 2017	regimen due to documented drug intolerance. **Exclusion Criteria** Grade 3 or 4 peripheral neuropathy **Total sample size** N=109 XDR TB: n=71 MDR TB: n=38 **Baseline characteristics** Median age (range): 35 years (17 to 60) Male: 57/109 (52%) Cavities present on chest radiograph: 92/109 (84.4%)		*"All surviving participants completed 26 weeks (including two who extended to 39 weeks) of treatment with allowable interruptions of up to 35 consecutive days, and none had the regimen permanently discontinued."* **Important outcomes** **Treatment failure and disease recurrence** 2/109 (1.8%) relapsed at up to 6 months (1/38 (2.6%) MDR TB, 1/71 (1.4%) (pre)XDR TB) **Amplification of drug resistance** 1/109 (0.9%)[21] **Safety** • At least one AE: 109/109 (100%) • AE grade 3 or 4: 62/109 (56.9%) SAE: 19/109 (17.4%) • Peripheral neuropathy: 88/109 (80.7%) • Optic neuritis: 2/109 (1.8%) • Myelosuppression: 52/109 (47.7%), 40/52 (76.9%) of whom had anaemia (36.7% overall) • Aminotransferase increases: 17/109 (15.6%) (12 had ALT elevation and 11 had AST elevation to > 3x ULN)	**Subgroup analyses** Efficacy results were reported to be consistent regardless of HIV status and L dosing schedule. AE reported by HIV status (combined MDR/(pre)XDR TB), n/N (%), (negative vs positive): • AE: 53/53 (100%) vs 56/56 (100%) • AE leading to death: 3/53 (5.7%) vs 3/56 (5.4%) • SAE: 10/53 (18.9%) vs 9/56 (16.1%) • Grade 3 or 4 AE: 27/53 (50.9%) vs 35/56 (62.5%) **Source of funding** TB Alliance (Global Alliance for TB Drug Development); UK Department for International Development; UK Department of Health; Bill and Melinda Gates Foundation; US Agency for International Development; Directorate General for International Cooperation of the Netherlands; Irish Aid; Australia Department of Foreign Affairs and Trade; Federal Ministry for Education and Research of Germany; Medical Research Council; National Research Foundation of South Africa

[21] The authors describe one patient who had a relapse 'One of these SNPs produced a change in the bedaquiline resistance gene Rv0678, from wild type at baseline to a 138-139insG variant in the late isolate. The bedaquiline MIC was elevated in the late isolate (4 μg per milliliter, as compared with 0.5 μg per milliliter at baseline).'

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Hepatic AE leading to regimen interruption (then resumed): 8/109 • QTcF: max mean increase was 10 msec and no patient had an increase > 480 msec. • Deaths: 6/109 (5.5%)	
Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. PLOS Global Public Health. 2022;2(12):e0001337. **Study location** India, Georgia, Philippines and South Africa **Study type** CEA with Markov model, based on TB-PRACTECAL (Nyang'wa et al 2022) **Study aim** To estimate the incremental cost-effectiveness of BPaL with and without moxifloxacin (BPaLM) or clofazimine (BPaLC) compared with the current mix of long and short SC regimens to treat RR TB, from the provider perspective. **Study dates** N/A	Total people with RR TB India: 49,945 South Africa: 10,233 Philippines: 5,952 Georgia: 284 % on short/long SC regimens: India: 96%/4% South Africa: 74%/26% Philippines: 99%/1% Georgia: 31%/69%	**Interventions** BPaL and BPaLM arms as described for TB-PRACTECAL (Nyang'wa et al 2022). Assumed duration: 24 weeks Per-protocol population used. **Comparators** WHO-recommended short and long SC regimens in Philippines, South Africa, Georgia and India Assumed duration: 36 weeks (short regimen) and 80 weeks (long regimen)	**Important outcomes** **Cost effectiveness** Incremental costs per person (compared with SC) Philippines BPaL: -$251 BPaLM: -$204 South Africa BPaL: -$1,173 BPaLM - $997 India BPaL: -$112 BPaLM: -$80 Georgia BPaL: -$983 BPaLM: - $904 Incremental DALYs averted per person (compared with SC) Philippines BPaL: 0.0 DALYs BPaLM: 0.8 DALYs South Africa BPaL: 0.2 DALYs BPaLM 0.8 DALYs India	Appraisal with a checklist is not required for cost effectiveness studies. **Other comments** This study used the treatment success rates from TB-PRACTECAL and applied it to TB cohorts in four countries. The exact number of people in each cohort is not clear. The analysis used a Markov model with a time horizon of 20 years. The mean age of patients was assumed to be 35 (comparable with TB-PRACTECAL cohort). Healthcare resource use costs (from the provider's perspective) were estimated from a range of country-specific sources. Costs were reported in 2019 USD, with those from earlier years being inflated using the United States gross domestic product (GDP) deflator. DALY weights for each health state came from the GBD database, with a DALY weight of 0.053 for 'post-TB' state. Costs and DALYs were discounted at 3% in the base case.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			BPaL: 0.0 DALYs BPaLM: 0.7 DALYs Georgia BPaL: 0.4 DALYs BPaLM: 1.3 DALYs Authors calculated that, in the countries studied, BPaLM would save $80 to $997 [22] per person and avert 0.7 to 1.3 DALYs per person. The authors presented cost-effectiveness acceptability curves which show that, at a willingness-to-pay per DALY averted of 0.5 GDP per capita, BPaLM is the preferred regimen in all countries.	**Source of funding** Supported by Medecins sans Frontieres.
Gomez GB, Siapka M, Conradie F, Ndjeka N, Garfin AMC, Lomtadze N, et al. Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines. BMJ Open. 2021;11(12):e051521. **Study location** South Africa, Georgia and the Philippines	**Population** Two scenarios modelled: 1. Patients with XDR TB 2. Patients with MDR-TB who have failed or are intolerant to their MDR TB treatments (assumed to be 10% of all patients with MDR TB) MDR/RR TB incidence per 100,000 South Africa: 21 (14-30)[23] Philippines: 26 (12-45)	**Interventions** BPaL (6 months) **Comparators** Standardised recommendations for XDR TB regimens (18 months)	**Important outcomes** **Cost effectiveness** **Results for MDR TB intolerant/failure and XDR TB cohort** Incremental costs compared with SC[24] South Africa: $ −2,539,419 (−2,594,548 to –2,484,290)[25] Georgia: $−336,950 (−337,480 to –336,420) Philippines: $ −2,546,098	Appraisal with a checklist is not required for cost effectiveness studies. **Other comments:** This study used the treatment success rates from Nix-TB and applied it to TB cohorts in three countries. The exact number of people in each cohort is not clear. The analysis used a Markov model with a lifetime horizon. Treatment outcomes were modelled for 5 years but costs and consequences relevant to the economic evaluation were

[22] Sweeney et al (2022) report this as $80 to $904 in the text of the publication, but $80 to $997 in Table 2
[23] Gomez et al (2021) do not state the meaning of the numbers in brackets.
[24] Incremental costs per person not reported, and unclear from paper how many people the model included.
[25] Gomez et al (2021) do not describe what the numbers in brackets mean.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type CEA using Markov cohort model **Study aim** To estimate cost and benefits of BPaL for treatment of a cohort of diagnosed patients with XDR TB (with and without the inclusion of MDR TB failure and intolerant patients) in three settings adopting a lifetime horizon and a health sector perspective. **Study dates** N/A	Georgia: 15 (11-18)		(−2,542,254 to –2,549,942) Total DALYs averted, compared with SC South Africa: 15,416 DALYs (15,214 to 15,618) Georgia: 830 DALYs (819 to 841) Philippines: 6,574 DALYs (6,482 to 6,667)	included until death. The average age of patients was 35 (range 17 to 60). Healthcare resource use costs (from the provider's perspective) were estimated from a range of country-specific sources. Costs were reported in 2018 USD, with those from earlier years being inflated using the United States gross domestic product (GDP) deflator. DALY weights for each health state came from the GBD database. Costs and effects were discounted at 3%. **Source of funding** TB Alliance and Bill & Melinda Gates Foundation.

Abbreviations

AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; B: bedaquiline; BPAL: bedaquiline, pretomanid, and linezolid; BPaLC: BPaL+clofazimine; BPaLM: BPAL+ moxifloxacin; CEA: cost-effectiveness analysis; CI: confidence interval; DALY: disability-adjusted life year; GBD: Global Burden of Disease study; HIV: human immunodeficiency virus; HR: hazard ratio; IQR: interquartile range; ITT: intention-to-treat; JBI: Joanna Briggs Institute; L: linezolid; M: moxifloxacin; MDR TB: multidrug-resistant TB; mITT: modified ITT; Pa: pretomanid; QTcF: QT interval calculated with Fridericia's formula; RCT: randomised controlled trial; RD: risk difference; RoB 1: Cochrane's risk of bias tool (version 1); RR: risk ratio; RR TB: rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; TB: tuberculosis; ULN: upper limit of normal range; USD: US dollars; WHO: World Health Organization; XDR TB: extensively drug resistant TB

Appendix F Quality appraisal checklists

Cochrane RoB 1 tool for RCTs

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Sputum culture conversion rates (1 RCT and 1 prospective case series)									
Sputum culture conversion rates at 12 weeks (benefit indicated by more events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	96	99	BPaLM vs SC 85/96 (88.5%) vs 78/99 (78.8%) HR (BPaLM vs SC): 1.59 (95% CI 1.18 to 2.14) RD adjusted for site for BPaLM vs SC: 9.2% (95% CI –1.6% to 20.1%) RR adjusted for site for BPaLM vs SC: 1.12 (95% CI 0.99 to 1.27)	Critical	Low
Sputum culture conversion rates at 12 weeks (benefit indicated by more events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	90	99	BPaL vs SC 73/90 (81.1%) vs 78/99 (78.8%) HR: not reported RD adjusted for site for BPaL vs SC: 3.9% (95% CI –8.0% to 15.9%) RR adjusted for site for BPaL vs SC: 1.04 (95% CI 0.90 to 1.20)	Critical	Moderate
Patients with sputum culture conversion rates at 16 weeks (benefit indicated by more events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series Conradie et al 2020	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	93	None	Overall cohort: 91/93 (97.8%) MDR TB:30/31 (96.8%) (pre)XDR TB: 61/62 (98.4%)	Critical	Very low
Sputum culture conversion rates at 108 weeks (benefit indicated by more events): BPaLM vs SC for RR TB									
1 RCT	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	Not reported	Not reported	N who converted: BPaLM: n=91	Critical	Low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Nyang'wa et al 2022							SC n=85 HR for culture conversion adjusted for site (BPaLM vs SC): 1.49 (95% CI 1.10 to 2.01)		
Sputum culture conversion rates at 108 weeks (benefit indicated by more events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[6]	Not reported	Not reported	N who converted: BPaL: n=82 SC n=85 HR for culture conversion adjusted for site (BPaL vs SC): 1.05 (95% CI 0.77 to 1.44)	Critical	Very low
Unfavourable treatment outcome (1 RCT, 1 randomised uncontrolled trial and 1 prospective case series)									
Unfavourable treatment outcome at 26 weeks (defined as treatment failure (clinical or bacteriologic) or disease relapse) (benefit indicated by fewer events): BPaL for pre-XDR TB and MDR TB									
1 randomised uncontrolled trial Conradie et al 2022	Serious limitations[5]	Serious indirectness[4]	Not applicable	Not calculable	106	None	L 1200mg 26 weeks • MDR TB: 0/5 • Pre-XDR TB: 1/18 (5.6%) L 1200mg 9 weeks • MDR TB: 1/6 (16.7%) • Pre-XDR TB: 0/22 L 600mg 26 weeks • MDR TB: 1/4 (25%) • Pre-XDR TB: 2/22 (9.1%) L 600mg 9 weeks • MDR TB: 2/6 (33.3%) • Pre-XDR TB: 1/21 (4.8%) Across all doses of L • MDR TB: 4/21 (19.0%) • Pre-XDR TB: 4/83 (4.8%)	Critical	Very low
Unfavourable treatment outcome at 6 months (defined as treatment failure (clinical or bacteriologic) or disease relapse) (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series Conradie et al 2020	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	Overall cohort: 11/109 (10.1%) MDR TB: 3/38 (8.0%) (pre)XDR TB: 8/71 (11.**3**%)		Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Unfavourable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	72	73	BPaLM vs SC 17/72 (23.6%) vs 39/73 (53.4%) RD for BPaLM vs SC: -30% (96.6% CI –46% to –14%) RR adjusted for site for BPaLM vs SC: 0.24 (96.6% CI 0.11 to 0.52)	Critical	Moderate
Unfavourable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	70	73	BPaL vs SC 24/70 (34.3%) vs 39/73 (53.4%) RD for BPaL vs SC: -19% (95% CI -36% to -2%) RR adjusted for site for BPaL vs SC: 0.47 (95% CI 0.28 to 0.80)	Critical	Moderate
Unfavourable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 108 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	33	37	Unadjusted RD for BPaLM vs SC: -50.0% (95% CI -69.2% to -30.9%) Unadjusted RR for BPaLM vs SC: 0.19 (95% CI 0.08 to 0.51)	Critical	Moderate
Unfavourable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 108 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[7]	35	37	Unadjusted RD for BPaL vs SC: -33.6% (95% CI -55.2% to -12.0%) Unadjusted RR for BPaL vs SC: 0.46 (95% CI 0.26 to 0.82)	Critical	Low
Treatment completion rates (1 RCT and 1 prospective case series)									
Withdrawal during treatment up to 26 weeks (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	Withdrew consent Overall cohort: 1/109 (0.9%) MDR TB: 0/38 (0%) (pre)XDR TB: 1/71 (1.4%)	Critical	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Conradie et al 2020							Death Overall cohort: 7/109 (6.4%) MDR TB: 1/38 (2.6%) (pre)XDR TB: 6/71 (8.5%) Relapse Overall cohort: 2/109 (1.8%) MDR TB: 1/38 (2.6%) (pre)XDR TB: 1/71 (1.4%) *"All surviving participants completed 26 weeks (including two who extended to 39 weeks) of treatment with allowable interruptions of up to 35 consecutive days, and none had the regimen permanently discontinued."*		
Early discontinuation at 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	72	73	BPaLM vs SC 15/72 (20.8%) vs 35/73 (47.9%)	Critical	Low
Early discontinuation at 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	70	73	BPaL vs SC 18/70 (25.7%) vs 35/73 (47.9%)	Critical	Low
Adherence issues (leading to early discontinuation) at 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Serious imprecision[9]	72	73	n/n who discontinued (%) BPaLM vs SC 0/15 (0%) vs 3/35 (8.6%)	Critical	Very low
Adherence issues (leading to early discontinuation) at 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	70	73	n/n who discontinued (%) BPaL vs SC 2/18 (11.1%) vs 3/35 (8.6%)	Critical	Low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Nyang'wa et al 2022									
Treatment failure and disease recurrence (1 RCT and 1 prospective case series)									
Treatment failure at 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Serious imprecision [10]	72	73	BPaLM vs SC 0/72 (0%) vs 0/73 (0%)	Important	Very low
Treatment failure at 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Serious imprecision [10]	70	73	BPaL vs SC 0/70 (0%) vs 0/73 (0%)	Important	Very low
Disease recurrence at 6 months (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series Conradie et al 2020	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	Relapse Overall cohort: 2/109 (1.8%) MDR TB: 1/38 (2.6%) (pre)XDR TB: 1/71 (1.4%)	Important	Very low
Disease recurrence at 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Serious imprecision [10]	72	73	BPaLM vs SC 0/72 (0%) vs 0/73 (0%)	Important	Very low
Disease recurrence at 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Serious imprecision [11]	70	73	BPaL vs SC 3/70 (4.3%) vs 0/73 (0%)	Important	Very low
Amplification of drug resistance (1 prospective case series): BPaL for (pre)XDR TB and MDR TB									
Change in bedaquiline resistance gene at 6 months (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	1/109 (0.9%)	Important	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Conradie et al 2020									
Safety (1 RCT and 1 prospective case series)									
SAE grade 3 or 4 within 6 months (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series Conradie et al 2020	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	19/109 (17.4%)	Important	Very low
Patients with at least 1 SAE (or grade ≥ 3 AE) within 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	72	73	BPaLM vs SC 14/72 (19.4%) vs 43/73 (58.9%) RD (BPaLM vs SC): -40% (96.6% CI -55% to -24%) • Hepatic disorder, grouped 3/72 (4.2%) vs 8/73 (11.0%) • QTcF prolongation 1.4/72 (1%) vs 10/73 (13.7%) • Creatinine renal clearance decreased 1/72 (1.4%) vs 5/73 (6.8%) • Anaemia 2/72 (2.8%) vs 6/73 (8.2%) • Neutropaenia 3/72 (4.2%) vs 2/73 (2.7%) • Optic neuropathy 0/72 (0%) vs 0/73 (0%)	Important	Moderate
Patients with at least 1 SAE (or grade ≥ 3 AE) within 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	69	73	BPaL vs SC: 15/69 (21.7%) SC: 43/73 (58.9%) RD (BPaL vs SC): -37% (95% CI -52% to -22%) • Hepatic disorder, grouped, 2/69 (2.9%) vs 8/73 (11.0%)	Important	Moderate

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
							• QTcF prolongation 0/69 (0%) vs 10/73 (13.7%) • Creatinine renal clearance decreased 2/69 (2.9%) vs 5/73 (6.8%) • Anaemia 1/69 (1.4%) vs 6/73 (8.2%) • Neutropaenia 0/69 (0%) vs 2/73 (2.7%) • Optic neuropathy 0/69 (0%) vs 0/73 (0%)		
Patients with at least 1 SAE (or grade ≥ 3 AE) within 108 weeks (benefit indicated by lower risk): BPaLM vs SC for RR TB (BPaL vs SC not reported)									
1 RCT Nyang'wa et al 2022	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	33	37	RD adjusted for randomisation site, BPaLM vs SC -35.3% (96.6% CI -56.2% to -14.3%)	Important	Moderate
At least one AE within 6 months (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series Conradie et al 2020	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	109/109 (100%) • Peripheral neuropathy: 88/109 (80.7%) • Optic neuritis: 2/109 (1.8%) • Myelosuppression: 52/109 (47.7%), 40/52 (76.9%) of whom had anaemia (36.7% overall) • Aminotransferase increases: 17/109 (15.6%) (12 had ALT elevation and 11 had AST elevation to > 3x ULN) • Hepatic AE leading to regimen interruption (then resumed): 8/109 • QTcF > 480 msec: 0/109	Important	Very low
AE grade 3 or 4 within 6 months (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	62/109 (56.9%)	Important	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Conradie et al 2020									
Patients with an AE (of any grade) (at study termination, duration not clear) (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	151	150	BPaLM vs SC 142/151 (94.0%) vs 145/150 (96.7%)	Important	Low
Patients with an AE (of any grade) (at study termination, duration not clear) (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	122	150	BPaL vs SC 120/122 (98.4%) vs 145/150 (96.7%)	Important	Low
Discontinuation due to AE within 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	72	73	BPaLM vs SC 5/72 (6.9%) vs 17/73 (23.3%)	Important	Low
Discontinuation due to AE within 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	70	73	BPaL vs SC 5/70 (7.1%) vs 17/73 (23.3%)	Important	Low
Deaths within 6 months (benefit indicated by fewer events): BPaL for (pre)XDR TB and MDR TB									
1 prospective case series Conradie et al 2020	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	109	None	6/109 (5.5%)	Important	Very low
Deaths during treatment within 72 weeks (benefit indicated by fewer events): BPaLM vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[8]	No serious indirectness	Not applicable	Serious imprecision[9]	72	73	BPaLM vs SC 0/72 vs 7/73 (4 of which were considered to be treatment-related: suicide, acute pancreatitis, sudden death, sudden cardiac death; 0 thought to be TB-related)	Important	Low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BPaL(M)	SC	Result		
Deaths during treatment within 72 weeks (benefit indicated by fewer events): BPaL vs SC for RR TB									
1 RCT Nyang'wa et al 2022	Serious limitations[8]	No serious indirectness	Not applicable	Not calculable	70	73	BPaL vs SC BPaL: 1/70 (1.4%) (seizure, not treatment-related or TB-related) vs 7/73 (9.6%) (4 of which were considered to be treatment-related: suicide, acute pancreatitis, sudden death, sudden cardiac death; 0 thought to be TB-related)	Important	Moderate

Abbreviations
AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPAL: bedaquiline, pretomanid, and linezolid; BPaLM: BPAL+ moxifloxacin; CI: confidence interval; HR: hazard ratio; MDR TB: multidrug-resistant TB; pre-XDR TB: meeting WHO definition for pre-extensively drug resistant TB; (pre)XDR TB: described by trial authors as XDR TB but meeting the PICO scope for pre-XDR TB; QTcF: QT interval calculated with Fridericia's formula; RCT: randomised controlled trial; RD: risk difference; RR: risk ratio; RR TB: rifampicin-resistant TB; SAE: serious adverse events; SC: standard care; TB: tuberculosis; ULN: upper limit of normal range; WHO: World Health Organization; XDR TB: extensively drug resistant TB

Footnotes

1 Risk of bias: serious limitations due to lack of blinding of patients and clinicians and potential for early withdrawals leading to poorer performance in SC arm.
2 Serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference upper threshold.
3 Risk of bias: serious limitations as unclear whether consecutive patients were enrolled or whether there was complete inclusion of eligible patients.
4 Indirectness: serious indirectness due to no comparison across treatment arms.
5. Risk of bias: serious limitations as baseline data presented for whole cohort not by country/site.
6 Very serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower and upper thresholds.
7 Serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold.
8 Risk of bias: serious limitations due to a lack of any statistical analysis or summary statistic.
9 Imprecision: serious imprecision due to 0 events in the intervention arm.
10 Imprecision: serious imprecision due to 0 events in both the intervention and the comparator arm.
11 Imprecision: serious imprecision due to 0 events in the comparator arm

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance or significance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals. As an example, it might include a general reduction in symptoms, less pain or improved breathing. Effects identified as statistically significant are not always clinically significant, because the effect is small or the outcome is not important. For example, if a treatment might lower blood pressure but there may be no evidence that this leads to an important clinical outcome, such as a lower risk of stroke or heart attack.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention (sometimes called 'usual care') or a dummy intervention (placebo). The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.

Term	Definition
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
Disability-adjusted life yar (DALY)	A measure of the impact of a disease or injury in terms of healthy years lost.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Follow-up	Observation over a period of time of a person, group or defined population to observe changes in health status, or health- and social care-related variables.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least one dose of a study drug.
Markov modelling	A decision-analytic technique that characterises the prognosis of a group by assigning group members to a fixed number of health states and then modelling transitions among the health states.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Outcomes	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Depending on the intervention, outcomes could include changes in knowledge and behaviour related to health or in people's health and wellbeing, the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, symptoms or situation.
PICO (population, intervention, comparison and outcome) framework	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing two treatments found that one seems to be more effective than the other, the p value is the probability of obtaining these results by chance.

Term	Definition
	By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. However, a statistically significant difference is not necessarily clinically significant. For example, drug A might relieve pain and stiffness statistically significantly more than drug B. But, if the difference in average time taken is only a few minutes, it may not be clinically significant. See Minimal clinically important difference. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance. See P value.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.
Time horizon	The time period over which the main differences between interventions in effects and the use of resources in health and social care are expected to be experienced, taking into account the limitations of the supporting evidence.

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