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Experiences in the introduction of bedaquiline pretomanid linezolid for drug-resistant tuberculosis in Kyrgyzstan

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ABSTRACT

Settings: In Kyrgyzstan, drug-resistant tuberculosis poses a significant challenge. Recognizing the potential of the BPaL regimen, the World Health Organization recommended its use for selected drug-resistant TB cases under operational research conditions in 2020.
Objective: This report presents experiences and results from the BPaL operational research under the LIFT-TB project in Kyrgyzstan.
Design: Prospective cohort study.
Results: From August 2021 to June 2022, 50 patients were enrolled, achieving an 84 % treatment success rate. Although adverse events affected 11 patients (34.3 %), primarily linked to linezolid use (39 [78 %] patients started on 1200 mg linezolid daily), no unexpected adverse events occurred, and management was appropriate. The operational research emphasized proper patient inclusion, highlighting the crucial roles of psychological counselling support and active drug safety monitoring.
Conclusion: With insights gained, Kyrgyzstan is now nationwide implementing the BPaLM/BPaL regimens for a broader drug-resistant TB patient group. The experiences, successes, and lessons from the BPaL operational research, along with the programmatic introduction, offer valuable guidance for global drug-resistant TB control strategies. This initiative becomes a resource for countries with similar drug-resistant TB burdens, promoting a collaborative global approach to address drug-resistant TB challenges.

1. Background

With a population of 7.1 million, Kyrgyzstan faces a significant burden of tuberculosis which stresses its health care resources and services [1,2]. Whilst overall notification and mortality rates decline, drug-resistant TB (DR-TB) remains a barrier. Conventional DR-TB treatment regimens, lasting 18 to 24 months with toxic adverse reactions, resulting in suboptimal treatment adherence and outcomes [3,4].

In recent years, the World Health Organization (WHO) has recommended shorter, injection-free DR-TB regimens with new and repurposed drugs [5–7]. The Kyrgyz National Tuberculosis Programme (NTP), supported by KNCV TB Foundation, under the 2015–19 USAID-funded Challenge TB project, introduced bedaquiline (Bdq) and delamanid (Dlm) containing regimens for rifampicin and/or multidrug-resistant TB (RR-/MDR-TB) cases. With the 9-month Shorter Treatment Regimen, success rates increased from 53% in 2016 to 72% in 2019

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(Fig. 1).

The TB Alliance's (TBA) Nix-TB trial demonstrated the efficacy and safety of the all-oral 6-month BPaL regimen (footnote[1]) in extensively drug-resistant TB (XDR-TB) (footnote[2]) and treatment-intolerant/non-responsive MDR-TB patients [8–9]. The regimen demonstrated a 90% favorable outcome rate, leading WHO to recommend it for use under operational research (OR) conditions in its 2020 DR-TB Treatment Guidelines [10].

2. BPaL introduction in Kyrgyzstan

2.1. International support

Introduction of BPaL in Kyrgyzstan has been a journey marked by dedication, collaboration, and numerous hurdles. The NTP, supported technically by the Kyrgyz-Netherlands Community of Volunteers (KNCV-KG) and KNCV and for laboratory-related matters by the International TB Research Center (ITRC), South Korea, introduced BPaL under OR conditions from 2021 onwards, under the "Leveraging Innovation for Faster Treatment of Tuberculosis (LIFT-TB)" project, jointly funded by TBA and the Korean International Cooperation Agency [11].

Support encompassed key components: developing the OR protocol, clinical guidelines, training materials and programmes; creating data collection forms and a REDCap database; providing comprehensive on-the-job training to doctors and nurses; patient counseling; and a robust monitoring and evaluation, backed by international technical assistance to national implementing partners. Notably, the local NGO received $207,000 for its activities from late 2021 to 2023. In comparison, the support to introduce new and re-purposed TB drugs under the "Challenge TB" project received $3.3 million from 2015 to 2019.

2.2. OR protocol and clinical guidelines

A generic BPaL OR guideline was developed in August 2020 by the KNCV global team and TBA [11]. This was adopted by the NTP, and used to develop a country-specific BPaL OR protocol, which the local Ethical Review Board approved in late 2020 [12]. KNCV and KNCV-KG initiated discussions with the Kyrgyzstan NTP and the MoH to navigate the regulatory landscape effectively for the OR to move forwards in the absence of specific regulations for OR conditions. The BPaL OR protocol was initially adopted as the national clinical guidelines for the treatment of pre-XDR-TB. All participants in the study gave informed consent.

The OR's primary objectives were: to evaluate BPaL's effectiveness by assessing the end of treatment outcome amongst BPaL treated patients; and to evaluate BPaL's safety by determining the rates of adverse events (AE).

Subsequently new clinical guidelines for BPaL utilization were

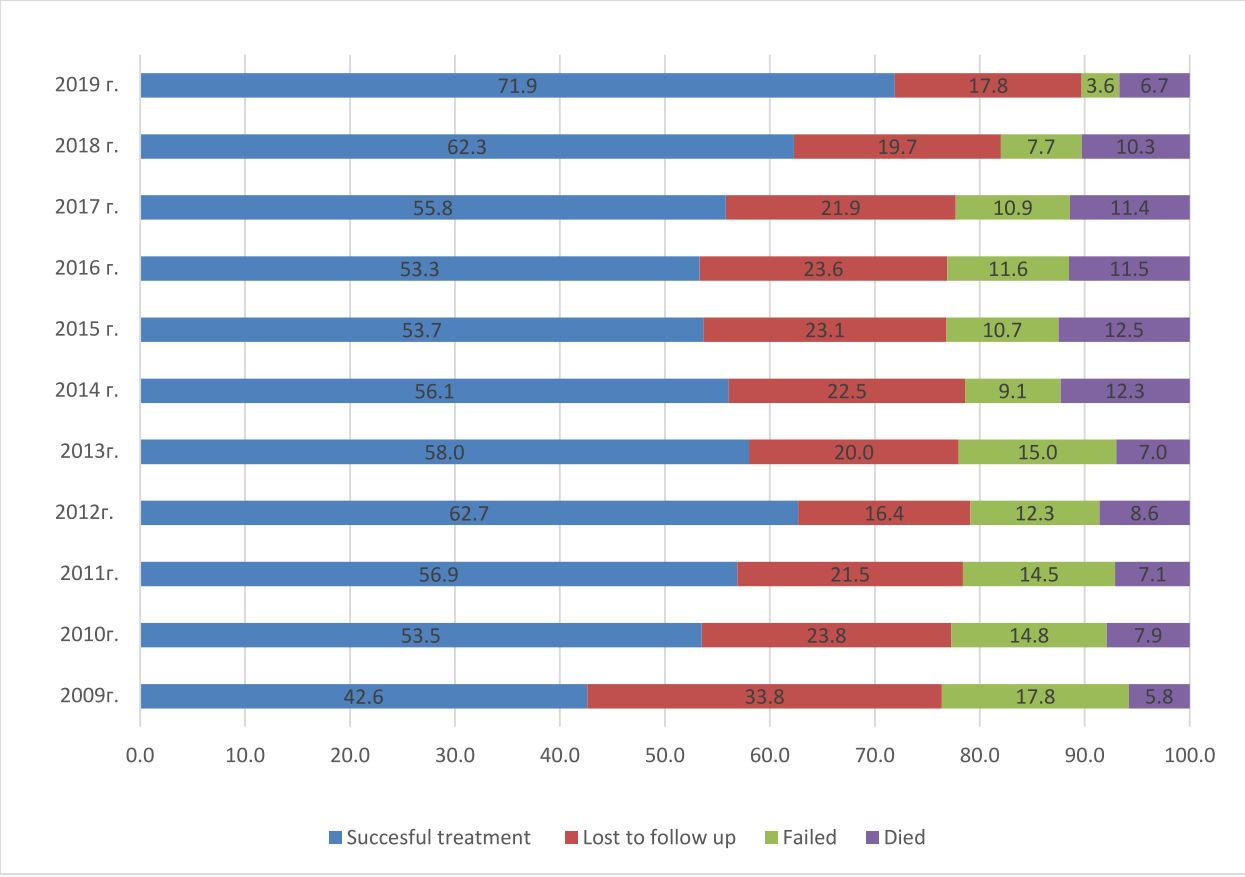

Fig. 1. Treatment outcomes of DR-TB in Kyrgyzstan, 2009 – 2019.

[1] The BPaL regimen contains bedaquiline, pretomanid, and linezolid. Pretomanid is a new nitroimidazole developed by the TBA, approved in August 2019 by the US Food & Drug Administration, and by the Committee for Medicinal Products for Human Use of the European Medicines Agency in March 2020, in combination with Bdq and Lzd as part of the 6-months all-oral BPaL regimen treatment regimen for XDR-TB or treatment-intolerant/non-responsive MDR-TB patients.

[2] Using the pre-2021 WHO definition of XDR-TB, which was MDR-/RR-TB plus resistance to FQ and/or any of the second-line injectable agents (SLI).

developed, endorsed by the MoH after review by its Center for Evidence Based Medicine, with the Minister of Health approving them in early 2021 [13].

2.3. Training materials

Parallel efforts in knowledge dissemination were equally crucial. KNCV worked with the NTP to develop BPaL training materials, and to integrate them into the curricula of prominent medical institutions in Kyrgyzstan. With this integration into the country's Medical Education curricula, future healthcare professionals, including doctors, nurses, pharmacists, and laboratory staff, will be equipped with the necessary skills to administer and monitor BPaL effectively, and ensure sustainable implementation of BPaL-based regimens.

2.4. Laboratory training

ITRC, with the Kyrgyz National TB Reference Laboratory, conducted training on phenotypic drug susceptibility testing (pDST) for the new drugs in mid-November 2022.

2.5. Advocacy

It was crucial to build trust amongst the local healthcare professionals on this innovative regimen early. Barriers in trust were surmounted by enlisting expert involvement and fostering transparent communication channels. This collaborative approach was instrumental in garnering stakeholder support and cooperation.

Nonetheless, challenges emerged. Skepticism from key figures, both healthcare professionals and community activists, within the "TB community" cast shadows on the BPaL use. Doctors used to the 18–24 months regimens, containing many drugs, did not initially trust that the 6-month BPaL regimen with only 3 drugs, was so effective. They felt justified when they saw the high numbers of AEs with BPaL in comparison with the long regimens. But the OR had a fully functioning aDSM system, unlike under usual programmatic conditions. Community activists worried about "experimentation on people" caused by the lack of knowledge about the BPaL trials elsewhere and the strict conditions under which the OR was conducted. Overcoming these obstacles necessitated additional training and communications. The involvement of a seasoned local DR-TB treatment expert played a pivotal role in gaining the trust and support of the central TB consilia [3], leading to enrollment of the first patients in August 2021. The OR was initiated at the Kara-Balta MDR-TB Hospital and the National TB Center.

2.6. Pretomanid supply

Securing a reliable supply of Pa proved to be a formidable task. Supply chain disruptions and uncertainties surrounding the United Nations Development Programme (UNDP) position as the principal recipient of Kyrgyzstan's Global Fund (GF) grant, posed significant obstacles to the OR initiation. Early on, KNCV took proactive measures with the NTP, by engaging with the pharmaceutical company Mylan, (now Viatris), to facilitate a donation of Pa to allow the OR activities to start. A donation and importation of 50 Pa patient courses followed in July 2021. Subsequent deliveries of 50 Pa patient courses through the GF/UNDP in August 2021 marked another step forward. Important partnerships amongst the key stakeholders were fostered along the way that facilitated future access to crucial Pa supplies.

Ongoing efforts to enroll patients faced further challenges after the MoH's December 2021 decentralization decision, which led to a reluctance from the regional TB consilia. KNCV's on-the-job training accelerated enrolment, with monitoring visits and additional training leading to successful outcomes. All 50 patients of the planned OR cohort were enrolled by 11 June 2022.

In December 2021, the MOH approved a national scale-up plan for BPaL under programmatic conditions. Starting in January 2022, the country expanded treatment services to 7 sites. The momentum persisted with the WHO's "Rapid Communication for programmatic use of BPaL" in May 2022, reinforcing the country's commitment to TB treatment innovation [14]. From August to September 2022, 24 DR-TB and pre-XDR-TB patients had been enrolled onto BPaL under programmatic conditions. However, the warehouse rented for TB (including DR-TB) and HIV drugs, went up in flames on 22 June 2022. All TB drugs and laboratory reagents imported in UNDP's last delivery of spring 2022, including 32 Pa patient courses, were destroyed.

Although there was no impact on the treatment of patients already enrolled onto BPaL as their full treatment course was ensured, due to the resultant potential future Pa stock-out, the NTP stopped enrolment of "new" patients onto BPaL under programmatic conditions from 28 September 2022. Following further discussions in October 2022, UNDP/GF placed an urgent procurement request for BPaL and BPaLM, which began to arrive from March 2023, allowing NTP to restart enrolment at end of March 2023.

2.7. Oversight, monitoring, and evaluation

Oversight and support were provided by a multidisciplinary team of TB experts from the NTP, KNCV, WHO Regional Office for Europe, and TBA, ensuring comprehensive patient management and treatment adherence. Supervision and monitoring missions, on-the-job training and mentoring, were conducted by teams from NTP and KNCV, with video DOT utilized at the outpatient level.

2.8. Data collection and database

A set of standardized data collection forms were developed and implemented by all countries of the LIFT-TB project. Data was inputted into a customized REDCap database and analyzed.

3. Progress and results

3.1. Enrolment

From August 2021 to June 2022, a total of 99 patients with pre-XDR-TB or MDR-TB treatment non-response/intolerance, underwent screening for enrolment. Of these 99 patients, 50 (51 %) were deemed eligible and successfully enrolled into the BPaL OR patient cohort (Table 1).

In the absence of a rapid pre-treatment DST test for the BPaL drugs, an important reason for a screened patient being deemed ineligible for entry into the OR cohort was prior exposure to Bdq, Dlm, and Lzd, with the potential challenge of resistance to any of the BPaL drugs (Table 1). Among the 49 patients who underwent screening and had a reason noted for why they were not enrolled, 18 (37 %) had had prior exposure to Bdq and/or Lzd for more than 4 weeks. This will become an important consideration for future use of BPaL-based regimens, as many countries, including Kyrgyzstan, have used Bdq, Dlm and Lzd widely in recent years to treat DR-TB.

The TB expert committee also rejected 22 (45 %) patients due to extended lung damage [4]. This was discussed further and reversed as a rejection reason in the latter stages of the OR. The National TB Expert Committee also excluded 2 patients due to relative

[3] A "consilium" is the local term for a local TB Expert group / committee that is empowered to review and approve the treatment of a patient, in this case related to the patient's eligibility to be enrolled into the BPaL OR.

[4] As per the country's definition "extended lung disease" meant presence of bilateral cavities or extensive parenchymal damage on chest x-ray.

Table 1
Screening, enrolment, outcomes, and safety monitoring of BPal OR patient cohort.

Screening and enrolment	Number of patients
Number of patients screened	**99**
Enrolled	**50 (50.9%)**
Culture positive at baseline	29 (58%)
Not Enrolled	**49 (49.1%)**
Previous exposure to Bdq and Lzd > 4 weeks	18 (36,7%)
Relative contraindications	2 (4,1 %)
Refused to sign ICF	7 (14,3 %)
TB expert committee rejected due to extended lung damage	22 (44,9%)
Treatment outcomes	**N=50**
Cured	38 (76.0%)
Treatment Completed	5 (10.0%)
Treatment failures	2 (4.0%)
Died	3 (6.0%)
Lost To Follow Up	2 (4.0%)
Treatment Success	**43 (86.0%)**
Safety monitoring	**N=50**
Number of patients with AESI	11 (22%)
o Peripheral neuropathy	10 (91%)
o Serious adverse events, with the discontinuation of Lzd	4 (40%)
o Hepatotoxicity	1(9%)
Number patients with > 1 AESI	3 (27,2%)

ICF Informed Consent Form AESI Adverse Event of Special Interest.

contraindications, such as haemoglobin levels below 8 g/dL or Grade 3 or 4 peripheral neuropathy.

3.2. Treatment outcomes

Treatment success was 86 % (43 / 50; Table 1). Two patients failed treatment, 2 were lost to follow up, and 3 died. The deaths were not linked to the DR-TB disease directly or AE – 1 committed suicide, 1 died of food poisoning, and 1 died of pre-existing chronic cardiac disease. Patients witnessed the positive outcomes of BPaL, which led to patients outside of the OR demanding to be treated with BPaL.

3.3. Safety monitoring and management

Rigorous safety monitoring and effective management practices were seen as crucial for the introduction of the BPaL OR. A comprehensive framework was established to proactively monitor and address potential adverse events, ensuring patient well-being and minimizing risks associated with the treatment.

Adverse events of special interest were documented in 11 patients (22 %). Peripheral neuropathy was reported in 10 patients (91 %), of whom 4 experienced serious adverse events, leading to Lzd discontinuation (Table 1). Hepatotoxicity occurred in 1 patient (9 %). While these events highlight challenges [(footnote5)], no unexpected AEs were observed, with those that did occur being mainly expected potential AEs of Lzd, and all were managed appropriately. Thirty-three patients had their daily Lzd dose reduced from 1200 mg to 600 mg, with nine patients having a further reduction to 300 mg. Four patients stopped the regimen, with one stopping Lzd alone. With the starting dose of 1200 mg Lzd being reduced to 600 mg daily, the overall benefit-risk profile should become even more promising.

4. Future directions

In December 2022, WHO issued updated DR-TB treatment guidelines in which BPaL-based regimens (BPaLM and BPaL) were recommended for use under programmatic conditions for RR-/MDR-TB patients and pre-XDR-TB patients respectively [15]. Following the delivery of 30 courses of Pa in mid-March 2023, enrolment of patients onto BPaL under programmatic conditions restarted at the end of March 2023. In July 2023, updated National TB Treatment Guidelines, including the BPaL-based regimens) were approved [16]. The BPaL-based regimens were now recognized as the NTP's standardized DR-TB treatment options, and widespread adoption and seamless incorporation into the nationwide healthcare system could occur. Forty and 200 Pa patient courses arrived in-country in June and July-August 2023 respectively. These factors combined to allow for the introduction of BPaLM under programmatic conditions alongside BPaL in June 2023. As of 1 July 2024, 93 patients had been enrolled on BPaLM and 46 on BPaL under programmatic conditions.

The sustained availability of Pa remains crucial for the continuity and success of implementation of the BPaL-based regimens. Looking ahead, Pa procurement has been aligned with the GF's strategy (Table 2). With the wide use of the new and repurposed DR-TB drugs in Kyrgyzstan, it is also crucial that adequate laboratory capacity for Bdq, Lzd, and Dlm or Pa pDST is in place across the whole country quickly to allow for the correct regimen selection for patients as access to treatment increases across the country.

Kyrgyzstan's transformative journey highlights the power of collaboration, innovation, and patient-centric strategies in public health (Fig. 2). Overcoming enrolment challenges and embracing comprehensive patient management, the adoption of BPaL-based regimens shows the significance of adaptable and patient-focused healthcare strategies. Kyrgyzstan's move towards BPaL-based regimens holds immense promise to revolutionize DR-TB patient care, improve treatment outcomes, and alleviate the overall DR-TB burden. This strategic shift aligns with Kyrgyzstan's goal of eliminating TB as a public health concern by 2030.

5. Conclusions

The results of Kyrgyzstan's BPaL OR show comparable successful treatment results as those seen in the earlier Nix, ZeNix and TB-PRACTECAL clinical trials. Although AE were common, no unexpected ones were seen. Most AE were related to Lzd use; however, they were managed appropriately, often with reduction or discontinuation of Lzd dose alone. As demonstrated by the Zenix trial, reduction from Lzd 1200 mg to 600 mg daily is expected to decrease the AE, but monitoring and swift management of any AE that arises remains crucial. Both primary objectives of the OR were achieved.

Strict and correct patient selection, based on the required DST information, intensive follow-up, and psychosocial counselling, are crucial to maintain the high treatment successes seen in the OR. With implementation of the BPaL OR, Kyrgyzstan gained access to Pa in 2021 – two years earlier than would have been otherwise expected, with programmatic use of Pa starting in 2022 and having adapted national guidelines

Table 2
Global Fund/UNDP procurement plan for Kyrgyzstan, 2023 to 2026.

Year	**2023**	**2024**	**2025**	**2026**
MDR-/RR-TB & FQ res	**1,030**	**1,020**	**1,020**	**1,020**
BPaLM	270	330	390	420
STR (9 months)	5	5	5	5
STR – children up to 25 kg	5	5	5	5
mSTR *	140	140	140	170
mSTR - children up to 25 kg*	10	10	10	10
Individualised treatment regimens	600	530	470	410
% of patients treated with individualised regimens	**58 %**	**52 %**	**46 %**	**40 %**
pre-XDR-TB & XDR-TB	**170**	**180**	**180**	**180**
To be treated with BPaL	110	110	110	110

mSTR modified Shorter Treatment Regimen.

[5] Note that at the start of the OR, patients were started on Lzd 1200mg daily from Day 1 of treatment (39 [78] of the OR cohort). Following the WHO recommendations of 2022, the starting dose was reduced to 600mg daily.

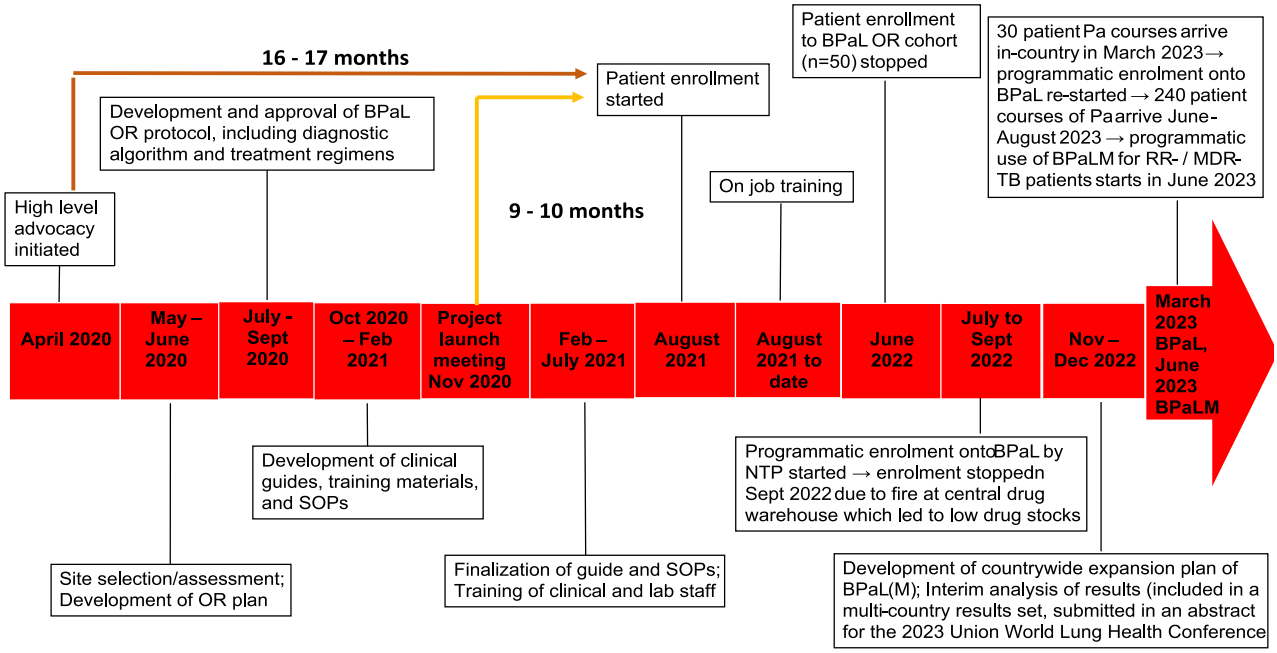

Fig. 2. Timeline of BPaL OR and Programmatic Introduction of BPaL-based regimens in Kyrgyzstan, 2020 – 2023.

by 2023. By investing in the innovative DR-TB treatment approach offered by the BPaL-based regimens, Kyrgyzstan can improve treatment outcomes for DR-TB patients, reduce the burden of DR-TB to both patients and the country, and accelerate progress towards TB elimination, and improvement of the health and well-being of its citizens.

Insights gleaned from the challenges, successes and lessons learnt from the BPaL OR and the programmatic introduction of BPaL-based regimens in Kyrgyzstan, can inform DR-TB control strategies worldwide, serve as a valuable resource for countries with similar DR-TB burdens, and foster a global collaborative approach to tackling DR-TB.

CRediT authorship contribution statement

B. Myrzaliev: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation. **M. Ahmatov:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation. **A. Duishekeeva:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation. **A. Kulzhabaeva:** Writing – review & editing, Writing – original draft, Supervision, Project administration. **A. Kadyrov:** Writing – review & editing, Writing – original draft, Supervision, Project administration. **A. Toktogonova:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation. **G. Abdulaeva:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Data curation. **D.F. Wares:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **V. Mirtskhulava:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **M. Mbenga:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation. **A. Slyzkyi:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **S. Foraida:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **M. Diachenko:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition. **S. Juneja:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **G. Turdumambetova:** Writing – review & editing, Writing – original draft, Supervision. **A. Musaeva:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **A. Gebhard:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: KNCV TB Foundation reports financial support was provided by Korean International Cooperation Agency. KNCV TB Foundation reports financial support was provided by TB Alliance. None reports a relationship with None that includes:. None has patent None pending to None. S Foraida, M Diachenko, and S Juneja are either staff of or consultant to TB Alliance, who developed the drug, pretomanid. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

All authors contributed equally.

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