New drugs and regimens for the treatment of drug-resistant tuberculosis: a research and development case study
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Abstract

Two novel drugs, bedaquiline and delamanid, have recently become available to treat drug resistant tuberculosis (DR-TB) after many decades of little innovation in the field of DR-TB treatment. Despite evidence of improved efficacy and reduced toxicity of multi-drug regimens including the two agents, access to bedaquiline and delamanid has been very limited in many settings with a high burden of DR-TB and consistently poor treatment outcomes. Aside from regulatory, logistic, and cost barriers at country level, uptake of the novel agents was complicated by gaps in knowledge for optimal use in clinical practice after initial market approval. The main incentives of the current pharmaceutical research and development paradigm are structured around obtaining regulatory approval, which in turn requires efficacy and safety data generated by clinical trials. Recently completed and ongoing clinical trials did not answer critical questions of how to provide shorter, less toxic treatment DR-TB treatment regimens containing bedaquiline and delamanid and improve patient outcomes. Voluntary generation of evidence that is not part of this process – yet essential from a clinical or policy perspective – has been left to non-sponsor partners and researchers, often without collaborative efforts to improve post-regulatory approval access to life saving drugs. Additionally, these efforts are currently not recognized in the value chain of the research and development process, and there are no incentives to make this critical research happen in a coordinated way.

I. Introduction

Globally, tuberculosis (TB) is the leading cause of death from a single infectious agent, despite being an infectious disease that can be both prevented and successfully treated.[1] In 2017, 558,000 people were estimated to have developed rifampicin resistant tuberculosis (RR-TB, including multidrug-resistant TB, MDR-TB), yet only 160,684 (29%) of these individuals were diagnosed and even fewer started on appropriate treatment.[1] Only 55% of the 139,114 people enrolled on treatment were treated successfully[1] – a figure that has not changed significantly for decades.

It has been nearly six years since the World Health Organization (WHO) first recommended the novel drug bedaquiline (BDQ) for the treatment of some forms of MDR-TB in adults in June 2013.[2] In October 2014, the WHO recommended a second new anti-tuberculosis agent, delamanid (DLM), to treat MDR-TB.[3] These recommendations followed on conditional approvals for BDQ from the United States Food and Drug Administration (USFDA) in December 2012 and the European Medicines Agency (EMA) in March 2014; DLM was conditionally approved by the EMA in April 2014. Given the poor rates of treatment success and the high frequency of toxicities from conventional DR-TB regimens,[4] there was optimism that WHO recommendations and subsequent access to these therapeutic agents would significantly improve DR-TB treatment outcomes.[5,6]

In parallel to the more frequent release of normative RR-/MDR-TB guidance from the WHO, both the USFDA and the EMA have published recent positions on drug approval processes and agency regulatory decisions: the 'Framework for FDA's Real-World Evidence Program' was released in December 2018,[7] and the 'Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to Mycobacterium tuberculosis' was adopted by the EMA's Committee for Medicinal Products for Human Use (CHMP) in July 2017 and came into effect in February 2018.[8] The 21st Century Cures Act (Cures Act), signed into law by the United States Congress in December 2016, authorized 6 billion USD in funding primarily for the National Institutes of Health. Proponents of the Cures Act said it would streamline drug approval processes and bring treatments to consumers faster by easing the requirements put on drug companies looking for USFDA approval; opponents said it would allow drugs to be approved on weaker evidence, bypassing randomized controlled trials and bringing unsafe or ineffective treatments to market.[9] The EMA's adaptive pathways approach is a similar effort to improve timely medicine development and data generation which allows for early and progressive patient access to a medicine.[10] Both agencies acknowledge that only a few drug developers have made use of the updated guidance through submission of real world evidence, with very limited utility of submitted data towards additional regulatory approvals.

Despite the hope that accompanied regulatory approval, early access to bedaquiline and delamanid has been slow and problematic in most countries. The reasons for poor uptake are multifactorial and include programmatic, logistic, regulatory, and clinical barriers; more broadly, there is **a lack of correlation between Phase II/III trial design implemented in compliance with USFDA/EMA regulatory requirements and the clinical data required by physicians to provide optimal DR-TB management in programmatic settings**. This paper aims to analyze this gap through the lens of the current regulatory paradigm, including **the opportunity costs borne by public organizations in order to generate pragmatic data on the efficacy and safety of bedaquiline and delamanid** within novel treatment regimens, as well as this paradigm's non-traditional emphasis on **the role played by non-sponsor actors in research and development processes**.

II. Gaps in knowledge: data for regulatory approval versus clinical use

Bedaquiline, a diarylquinolone antimycobacterial agent with bactericidal activity developed by Janssen Therapeutics, received accelerated approval from the USFDA based on Phase IIb data generated by a randomized controlled trial (RCT) of multidrug backbone therapy with BDQ versus placebo for 24 weeks.[11] Results showed faster time to culture conversion, higher rates of culture conversion, and higher overall success with BDQ.[12] The Standardized Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB (STREAM) trial Stage 2 open label RCT – sponsored by the Union with funding from the United States Agency for International Development (USAID) – serves as the Phase III study for BDQ, with study results expected in 2022.[13] The first primary objective, a requirement of the USFDA, will assess the superiority of an all oral 40 week regimen with BDQ (Regimen C: 16 weeks BDQ/Lfx/Cfz/Pto/EMB/PZA/INH followed by 24 weeks BDQ/Lfx/Cfz/EMB/PZA) over the standardized 9-month shorter regimen recommended by the WHO in 2016 (Regimen B: 16 weeks Km/Mfx/Cfz/Pto/EMB/PZA/INH followed by 24 weeks Mfx/Cfz/EMB/PZA).[13,14] In addition to STREAM stage 2, bedaquiline is a component of several ongoing clinical trials (Table 1).

Delamanid, developed by Otsuka Pharmaceutical Japan, is the first in a new class of TB drugs called nitroimidazoles. The EMA based its conditional approval in 2014 on Phase IIb RCT data; results of the trial showed delamanid plus a background regimen conferred higher rates of culture conversion after two months (45.4%) than placebo plus a background regimen (29.6%).[15] In order to evaluate treatment outcomes, participants were then offered DLM for 24 weeks after a washout period; this observational study found higher rates of culture conversion, faster time to culture conversion, and higher overall success with 24 weeks versus 8 weeks of DLM.[15] In October 2017, the initial results of the Phase III trial for DLM were presented; Otsuka's Trial 213 added DLM or placebo for the first six months of the 24 month "optimized backbone regimen" at participating trial sites.[16] The main outcome was time to sputum culture conversion over the first six months of treatment. There was more rapid culture conversion in the DLM arm compared to those in the placebo arm (6 to 13 days), with a *p* value for the primary efficacy analysis of 0.056. While the safety and tolerability of the drug were well documented, the trial was not able to fully establish non-inferiority, the primary objective as specified in study protocols.[17] As with BDQ, delamanid continues to be studied in several ongoing clinical trials (Table 2).

STREAM Stage 2, which serves as the Phase III trial for bedaquiline, is sponsored by the Union and funded by the United States Agency for International Development (USAID); results are expected no earlier than June 2022. Janssen is accountable to the USFDA for the Phase III results under the regulations of accelerated approval[18]; the EMA also states the specific obligation to provide the final study report of the Phase III, albeit in a delayed timeline of the end of 2023 due to rapid changes in DR-TB management during the study period.[19] Bedaquiline continues to be investigated in at least nine Phase II and III trials – delamanid in at least five – with public actors as both primary sponsors and collaborators. In addition, academic institutions, National TB Programs, nonprofit organizations, and scientific consortiums are conducting retrospective and prospective observational studies to produce data on the safety and effectiveness of BDQ and DLM when used programmatically; these significant public investments will add to the body of evidence for policy guidance and provide much-needed guidance for clinicians on appropriate clinical use of the medicines.

BDQ and DLM both received conditional approval based on studies that looked at adding one drug to the 'standard of care' or an optimized background regimen. The evidence thus generated for regulators was focused on whether the drug was active against TB, not how it worked in a regimen with other anti-TB drugs. **Soon after approval, clinical management uncertainties arose as access to each drug increased through observational studies, compassionate use/clinical access programs, ongoing trials, and programmatic use**:

1. **Duration of use**: Phase II trial design limited the duration of the drug under investigation to 24 weeks, which was chosen for ease of endpoint analysis rather than the optimal duration to maximize treatment outcomes. Due to initial WHO guidance limiting the use of BDQ and DLM to 24 weeks based on available data (see Annexure A), clinicians were initially unable to prolong the duration for patients requiring extension of BDQ or DLM beyond 24 weeks due to resistance or intolerance to other second line medications, which could contribute to high rates of culture reversion and treatment failure.[20]
2. **Special populations**: children, adolescents, and pregnant women were excluded from eligibility in the Phase II trials. Otsuka's Trial 213 included a sub-trial with HIV positive individuals on antiretroviral therapy, while Janssen's C208/C209 only allowed HIV positive individuals with CD4 counts greater than 300 cells/µl; Phase III trials for both drugs include those with co-existing HIV infection. Despite an USFDA pregnancy category B rating for bedaquiline (animal studies fail to show a risk to the fetus), there is ongoing reluctance to use the drug in pregnancy, due to the lack of data and subsequent WHO recommendation for its use. The delay between adult and pediatric new drug investigations means most children and adolescents in need of novel MDR-TB drugs will not receive them.[21]
3. **Drug-drug interactions:** potential additive toxicities, most notably QT prolongation with BDQ, DLM, the fluoroquinolones, and clofazimine, were incompletely understood at the time of regulatory approval, leaving questions regarding the concurrent use of multiple QT prolonging agents, how to design an appropriate clinical monitoring schedule with electrocardiography, and whether patients should be hospitalized to initiate treatment. This concern, coupled with an excess death rate observed in the investigational arm of trial C208, led to the redefinition of pharmacovigilance requirements by the WHO in 2015 as active TB drug safety monitoring and management (aDSM) in order to strengthen the monitoring and management of patients on BDQ and DLM.[22] The additional investment required both at central and clinic level to establish and maintain this system are considerable and represent a risk management measure that covers for the uncertainties inherent to an EMA conditional approval or USFDA accelerated approval based on phase IIb data.
4. **Patient selection**: the phase II trials included patients with MDR-TB and both drugs received conditional approval for the treatment of MDR-TB. Despite this, the initial clinical use of BDQ and DLM was often restricted to patients with pre-XDR and XDR-TB, in part due to WHO guidance recommending use of the novel drugs only when an effective regimen containing four second-line drugs in addition to pyrazinamide could not be designed. The WHO graded the certainty of evidence for their initial BDQ recommendation as low (for efficacy) to very low (for safety).[23]

5. **Combination use**: similar to extension of BDQ or DLM, the phase II trials did not allow for concomitant use of the two drugs. For patients with severe patterns of resistance, with few treatment options remaining, the use of novel drugs in combination was a necessity for many patients, years prior to WHO's recommendation on combination use in 2017.[24-26]

The stepwise process of how TB clinical trials are done is time consuming, expensive, and problematic to interpret: years of tests in healthy volunteers, 2-week early bactericidal activity (EBA) trials, and 8-week serial sputum colony counting (SSCC) trials all preclude the start of a clinical trial (Table 1 and Table 2). Many working in the field of DR-TB over the past decade agree that the slow pace of clinical trial advancement, along with the urgency for new innovations in DR-TB treatment, appropriately justified rapid regulatory approval and access to BDQ and DLM coupled with the necessity for more extensive post-regulatory 'real world evidence' (RWE).[27] Balance between the two priorities depends on the current standard of care, and may thus shift over time: historically, DR-TB treatment regimens have been associated with such significant toxicities and poor treatment outcomes – and thus ongoing transmission of disease – that there was a need to push for rapidity. The conditional approval of bedaquiline based on Phase IIb data, while welcomed by the TB community, has led to a scientific dilemma for the sponsor of the ongoing Phase III trial: **national and international guideline updates are now challenging the trial standard of care, with the further risk that Janssen will have phase III outcomes of little added value for BDQ**. In the future, as the dangers of new drugs and regimens reduces, the acceptable balance of risk to patients and to sponsors will need to adapt accordingly.

III. Shifting opportunity costs: added value of post-approval programmatic trials

Organizations such as MSF are committed to guaranteeing their independence through maintaining a high level of private income from individual donors. Over 80% of all funds raised are used for supporting the organization's social mission; historically, funding has been allocated into interventions in stable, armed conflict, and internal instability contexts. The organization has been providing TB care and management for more than 40 years and is the largest non-governmental provider of DR-TB treatment. Thus, while the decision to take part in DR-TB clinical trials such as endTB and TB-PRACTECAL could be viewed as a natural progression of MSF's objectives, it was also a balance of investments, with both donor funding and operational costs being used to help improve the existing MDR-TB treatment outcomes at the expense of other field operations.

Using bedaquiline and delamanid, endTB's aims are to improve access through the following:

1. endTB observational study: expand use of the two drugs in 17 countries (at least 2600 patients) and study the results;
2. Remove policy and market barriers to making the drugs available in all 17 endTB countries;
3. endTB clinical trial: conduct a 7-country clinical trial (750 patients) to find shorter, safer MDR-TB treatment regimens;
4. endTB-Q clinical trial: conduct a 6-country clinical trial (500 patients) to find shorter, safer regimens to treat fluoroquinolone-resistant MDR-TB without injectables;

5. Share findings from the observation study and trials at the national and international level.

Partners In Health is the lead grantee for the Unitaid funding of endTB; the project's original term was 2015-2019 and its budget USD 60 million. Extension of the project through the end of 2022 was approved in September 2018, with Unitaid support of up to USD 81 million. The USD 21 million extension includes a new clinical trial, known as the endTB-Q trial, to develop a treatment regimen for patients with extensively drug-resistant TB (XDR-TB) and pre-XDR-TB. The breakdown of Unitaid funding for each of endTB's outputs, as well as additional MSF operational costs of the endTB project that are not covered by Unitaid, are listed in Table 3. For PIH and IRD, costs for endTB are primarily covered by Unitaid funds, with the existing standard of TB care in a country covered by other funding that is integrated into other TB programs.

Output	Timeline	Budget (USD)
endTB Observational Study	1 April 2015 – 31 March 2019	22,100,000
endTB Clinical Trial	1 April 2015 – 31 December 2022	26,900,000
endTB-Q Clinical Trial	1 April 2015 – 31 December 2022	14,400,000
Output 3 (increase uptake of new drugs) plus Output 4 (disseminate clinical and programmatic findings)	Output 3: 1 April 2015 – 31 March 2019 Output 4: 1 April 2015 – 31 December 2022	900,000
Shared organizational costs (staff, operations, audits)	1 April 2015 – 31 December 2022	17,000,000
	Subtotal	81,300,000
MSF operational costs, 2015-2018*		9,103,655
	TOTAL	90,403,655

**Estimate based on a percentage of operational budgets for MSF projects supporting the endTB observational study.*

Table 3: endTB project costs per expected output from Unitaid funding, 2015 – 2022, with additional MSF operational costs, 2015-2018.

TB-PRACTECAL, which receives funding from the Dutch National Postcode Lottery, smaller private donors, and MSF Netherlands, differentiates the total budget of 29,300,000 Euros (USD 33,150,000) into project costs of 22,700,000 Euros and support costs of 6,600,000 Euros. Project costs include staff in the field, drugs, medical and laboratory supplies, clinical monitoring, logistical costs, and trial monitoring; support costs are mostly human resources within MSF and collaborating institutions that do not work in the field (e.g. central statisticians).

IV. Responding to the need for clinically relevant evidence on the use of novel drugs

Organizations such as Médecins Sans Frontières (MSF) and Partners In Health (PIH), as well as individual countries and research institutions, recognized that programmatic **trials to generate clinical evidence optimizing use of the newer drugs were necessary**. As public sector knowledge and experience with MDR-TB was accumulating over two decades, it was broadly recognized that despite ambitious goals and large institutional investments, treatment outcomes were not noticeably improving; even prior to the accelerated approval of bedaquiline, countries and partner organizations alike noted with concern and frustration that ongoing substantial financial investments could take place without further effect. At the same time, Treatment Action Group (TAG) was negotiating with Otsuka and Janssen to work together towards combination use of the two novel drugs, but no agreement was reached; this led to the feeling that "if MSF didn't do a trial of new regimens with the two new drugs available for DR-TB treatment, no one else would."[28] Trials at the time were only looking at adding one drug to the conventional longer regimen, without a significant reduction in toxicities, rather than investigating new regimens. Longer regimens were using multiple drugs, some of which were likely ineffective; usually with one agent only available in intramuscular or intravenous formulation; and with uncertainty as to the optimal combination. Lastly, there was growing awareness that the current 20-24-month duration of treatment was probably too long, yet there was no evidence on what a shorter duration could be and whether the novel drugs would allow treatment shortening. Thus, the question for organizations like MSF and PIH was not one of relevance, but rather how they could engage in clinical trials in order to design new fully oral, shorter MDR-TB treatment regimens that could markedly improve treatment outcomes. **At the time, the minimal consideration of the design of such a trial to generate data of regulatory value reflected a broad lack of participation of public sector actors in clinical research and development.**

The endTB partnership between MSF, PIH, Interactive Research and Development (IRD), collaborators, and financial partner Unitaid went one step further in design of the endTB trial by having specific workstreams to address access to BDQ and DLM, including revision of national guidelines; efforts to increase transparency of drug pricing; and support on regulatory components (e.g. drug registration) at country level. Additional innovations with endTB to generate the best evidence for clinical practice, rather than for regulatory approval or impact on policy, included:

- *Trial design*: electing to use a multi-arm multi-stage (MAMS) framework for conducting a large, flexible platform trial under a single protocol to speed the evaluation of new regimens and improve the success in identifying effective regimens;
- *Regimen construction*: providing the most efficacious regimen at the initial diagnosis of MDR/RR-TB using innovative principles of regimen design[29], in contrast to incremental change in regimen design based on the severity of drug resistance;
- *Individual drug selection*: prioritize the most efficacious second line drugs whenever possible.

Other groups are also innovating:

1. TB-PRACTECAL (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen[s]): a multi-centre, open label, multi-arm, randomised, controlled, phase II-III trial evaluating short treatment regimens containing BDQ and pretomanid in combination with existing and re-purposed anti-TB drugs;[30]
2. The TRUNCATE-TB trial (Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-sensitive TB): evaluates a strategy, not a drug or regimen, comprising treatment for 2 months with a regimen predicted to have enhanced sterilizing activity, monitoring closely after completion, and retreating those that relapse with a standard 6-month regimen;[31]
3. The EDCTP-funded PanACEA consortium (Pan-African Consortium for the Evaluation of Anti-tuberculosis Antibiotics): innovative phase study designs of a '14+14' phase IIA SMART (Sequential, Multiple Assignment, Randomized Trial) trial and the novel STEP design (the Phase IIC Selection Trial with Extended Post-treatment follow-up) to close the gap between Phase II and Phase III studies and predict the success rate of the new regimens in a future phase III study;[32]
4. The South African Department of Health: South Africa has been a site for several of the pivotal DR-TB trials and has contributed to an estimated 60% of global BDQ use[33] through a progressive stance toward the implementation of innovative diagnostics and regimens[34]; strong collaborations with academic institutions and partners; and publication of programmatic BDQ observational cohort data.[35,36]

The lack of coordination amongst trialists, partners, and countries involved in generating post-regulatory approval data for BDQ and DLM has led to a loss of efficiencies, including several competing prioritizations of research questions,[37-39] inconsistent data quality with variable outcome measurements, and inconsistent support for regional research collaborations. Perhaps most important is how and when the real-world evidence being generated is used by national TB programs and the WHO to produce progressive DR-TB management guidelines. In many countries, regulatory approval has demonstrated limited power to affect change if not followed by WHO recommendations; even with WHO guidance, the language of 'conditional approval' and 'low certainty in the estimates of effect' may be a contributing factor which has led to slow uptake of the newer drugs.[40] Despite this, there are commonalities amongst post-approval clinical research initiatives that are worth highlighting: the decision to study a regimen or regimens, rather than a single drug; the choice of less rigid, innovative trial designs (MAMS, 14+14) to reduce the gap between Phase II and Phase III trials and reduce the time for study completion and availability of results; including individual drugs that have not received regulatory approval into trial regimens; and allowing the use of interim data for policy guidance consideration, such as the sharing of DLM data from the endTB observational study with Otsuka and WHO.

It can be argued that the balance between drug access through regulatory approval versus policy recommendation is a false dichotomy, since the key is good quality data: **both RWE and RCTs can and should contribute to regulatory approval, the quality of evidence in WHO recommendations, and interpretation by clinicians and programs. However, the traditional motivations of industry, regulators, and sponsor-led trials primarily to determine**

market entry can be different from clinical research initiatives to optimize use of new agents. Additionally, the pathway towards regulatory approval of a DR-TB drug is better defined than the framework necessary to receive normative body policy guidance. For the Phase III trial of DLM, the primary trial endpoint of time to sputum culture conversion differed from the WHO defined outcomes of interest in clinical care (cure, completion, failure, lost from treatment, death). As an international public health agency tasked with providing leadership on health policy for member states, the WHO also has an informal role in defining paths for research in order to generate strong evidence for policy guidance.

V. Placing the debate in the larger new regulatory paradigm

As previously mentioned, the approvals of delamanid and bedaquiline were based on phase IIb trial data; the regulatory pathways that enabled such a decision are the Accelerated Approval in the United States, created in 1992,[41] and the Conditional Approval in Europe, created in 2006.[42] The stated underlying principles of these two pathways are the same: they are meant to accelerate the marketing of medicines for unmet medical needs and enable the treatment of debilitating or life-threatening conditions. This is premised upon the belief that the benefits for patients of accessing these medicines at an earlier stage of development outweigh the potential risks associated with their early use. The conditional approval is usually based on surrogate or intermediary endpoints rather than on final clinical outcomes; as such, the approval is granted under the condition that confirmatory trials will be conducted that will definitively establish the conditional approval assessment outcome and related safety and efficacy profile assumptions. An example of a surrogate endpoint from TB clinical trials is the use of time to sputum culture conversion as a proxy of a successful treatment outcome. Such surrogate endpoints usually occur much earlier in the course of treatment and can therefore considerably shorten the time for clinical results to be analyzed and submitted for review. Their capacity to accurately predict the desired outcome varies and constitutes the main challenge when relying on surrogate outcomes for a regulatory decision. Moreover, since conditional approval is based on phase II trials, the assessment is also limited by the size of the study population.

In recent years, **attempts to broaden the scope of these regulatory pathways and generalize the use of their underlying concepts to any new potential drug development have emerged**. In 2012, a multi-stakeholder NEWDIGS (New Drug Development Paradigms Initiative) collaboration hosted by the Massachusetts Institute of Technology's (MIT) Center for Biomedical Innovation proposed the concept of Adaptive Licensing (AL).[43] The collaboration regrouped experts from the leading regulatory agencies (EMA, USFDA, Health Canada, etc.), academia (Harvard, MIT) and large pharmaceutical companies (BMS, Novartis, Astra Zeneca, J&J, amongst others). AL is a flexible approach to drug regulation underpinned by an iterative data generation process: an initial approval is delivered with a number of restrictions due to the limited available data at the moment of submission. The scope of the approval evolves as more data on the safety and efficacy profile of the medicine becomes available. The same core group came back together in 2015 arguing that AL as a regulatory pathway is better adapted to the growing therapeutic "niche" markets characterized by small target populations, and would result in shorter

time-to-patient and a shorter and thus cheaper R&D process. The potential benefit of shortening time to market and lowering overall R&D costs addresses the major complaints that pharmaceutical companies have had with the current R&D and regulatory processes in recent decades. Real world data (RWD) and the resulting RWE are already in use by some regulators (e.g. USFDA, EMA) in post-marketing monitoring. The major change introduced by AL is the possibility of using this type of data and evidence as a complement to the traditional RCTs to support regulatory decisions such as a new indication or use in additional patient categories. There are many voices that oppose this new regulatory paradigm: critics question the quality of RWD or the scientific value of unorthodox clinical study designs; the level of uncertainty and subsequent risk to patients associated with earlier market access; and the role the pharmaceutical industry is playing in promoting this paradigm.

From the perspective of access for patients in MSF's care to long awaited new therapies in areas of unmet medical need, we believe that innovative R&D and regulatory approaches need to be maintained and further developed. However, **MSF's experience as an implementer of a number of clinical trials and observational studies that have included bedaquiline and/or delamanid has revealed a number of flaws and missed opportunities that are not covered in the existing literature around AL**. For both molecules, the R&D processes and early regulatory approvals broadly follow the principles of AL. The post marketing phase was characterised by mandatory phase 3 trials as part of the conditional approval processes sponsored by applicant companies, along with a number of trials and non-controlled studies financed and implemented by different actors. All of these studies, both randomized controlled and observational, have sequentially been advancing current knowledge on the safety profile of BDQ and DLM and how best to integrate them into treatment protocols. In December 2018, WHO made substantial changes to the current DR-TB treatment guidelines based on a meta-analysis of a mix of RCTs and RWE, not all of which were part of the approved clinical development plans.[44]

VI. Discussion and conclusions

Below, we examine how AL is fundamentally changing the R&D, regulatory, and benefit assessment frameworks and highlight three areas which require closer attention. This examination combines MSF's experience as an implementer of clinical trials and observational studies; the EMA experience with the Adaptive Pathways pilot project (2014-2016)[1], arguably the most accomplished example of the use of AL concepts in real-world settings; and the broader literature on regulatory affairs.

1. **The growing disconnects between the Marketing Authorisation (MA) process and clinical needs**.

[1] https://www.ema.europa.eu/en/documents/report/final-report-adaptive-pathways-pilot_en.pdf

"Because clinical trials are necessary to obtain regulatory approval in the United States, they are a high priority to companies. It was noted by a number of workshop participants that the prioritization of clinical research questions by companies seeking regulatory approval is distinctly different from the priorities of society in general, which may prioritize the comparison of two commonly used therapies. This divergence between the priorities of society and industry is notable as the nation discusses how to address the current gaps in clinical research and medical decision making."

This statement from the workshop "Transforming Clinical Research in the United States" – organized by the Forum on Drug Discovery, Development and Translation (United States Institute of Medicine of the National Academies) – perfectly summarizes the divergence in priorities between industry and "society." It is reasonable to assume that industry will seek the most efficient (shortest and least onerous) way to achieve marketing authorization; the role expected from the regulator is to reach a middle ground where this imperative of financial efficiency of the predominant profit-based development model is balanced by the public health imperatives of society, which should be represented and defended by the regulator. Recent MSF experience with clinical research has highlighted the reality that regardless of the choice of candidate drug, the regulatory process that determines the clinical development plan doesn't necessarily result in studies that answer the needs of society, patients, and clinicians. **A well-designed trial that could answer predetermined criteria, successfully reach pre-approved endpoints, and lead to a favorable regulatory decision may still fail to answer questions that practitioners involved in day-to-day care would consider as essential.** Management of DR-TB, with the introduction of BDQ and DLM, is a perfect example of this disconnect. **The result is a gap that sponsors have no incentive to fill, as it is not part of their legal commitment to the regulator.**

The approvals of both BDQ and DLM provide an insight into the practical functioning of a regulatory model where post marketing evidence built both on smaller, "smarter," and less expensive controlled trials by sponsor(s) and/or non-sponsors together with RWE by non-sponsors completes the missing pieces of the evidentiary puzzle. In that sense, AL seems to better acknowledge that clinical development oriented towards a regulatory approval cannot possibly answer all the questions, and this unfulfilled role leaves room for practitioners and society to compensate for these gaps after the initial limited market entry.

2. **Formalised pre-marketing process versus a hazy post-marketing landscape: pushing responsibilities and costs out of the well-defined framework of the marketing authorization process**.

   The current regulatory paradigm has been characterized by a critical, "magic" moment when regulatory approval moves a drug from being an uncertain investigational product to becoming a safe and effective drug that can be dispensed with confidence. It is also the magic moment from the industry's perspective when a product moves from being a cost burden to a financial asset earning profits. This "magic" moment still exists

with AL; the difference is that it occurs at an earlier stage in the case of AL and results in an approval that: 1) has a greater number of strings attached to it in terms of use restrictions; 2) requires society to acknowledge and accept a greater risk and put in place measures to manage it; and 3) leaves an unclear post-marketing phase in terms of roles and responsibilities, especially when it comes to collecting and processing RWD. In the case of DR-TB, BDQ and DLM were granted accelerated/conditional approvals based on studies that didn't answer all clinical questions; MSF and other non-sponsor actors felt obliged to close this evidentiary gap by conducting additional studies on the drugs within novel regimens. As we have seen in the first part of this case study, these additional studies were not coordinated with sponsors, regulators, or between non-sponsors. None of these efforts, as valuable as they turned out to be, was part of a formal process with well-defined roles and responsibilities.

Earlier access to an incompletely characterized drug, with the incumbent need for additional data and enhanced monitoring, does not only change the timing in the product lifecycle where the medicine hits the market. It also operates as a *de facto* task shifting: a certain amount of evidence, based on controlled and/or uncontrolled studies, is generated by actors that in the traditional regulatory model offered little or no contribution to the regulatory process. Although AL proponents seem to acknowledge the role of non-sponsors, they do not propose a formal framework for it to be fully integrated in the earlier phases of the regulatory process. Furthermore, AL principles mention nothing about the operational burden associated with the use of treatments necessitating higher levels of control and monitoring: this burden falls entirely on the shoulders of health systems and the non-sponsor actors conducting additional research. MSF and other treatment providers' use of BDQ and DLM outside of clinical trials came with considerable human and financial resource costs to ensure full compliance with the safety monitoring required for the responsible integration of these medicines in treatment protocols. Therefore, the question is not only about the willingness of patients and practitioners to assume a higher risk, but also about the capacity of the system to manage this risk and take up the extra costs that this management requires.

3. **Accounting for societal contribution.**
   It is clearly incorrect to assume that the product sponsor is bearing the full burden of product development in the new regulatory paradigm, yet the fiction that they are persists. The regulatory process acts as the gatekeeper that allows a product to transition to its profit-making phase; entry to this phase constitutes the reward for the sponsor's investment in the development of a product.

   Health technology assessment (HTA) bodies are increasingly using economic metrics that factor in the public health value of new medicines when negotiating the price with a product sponsor. Yet, the contribution of non-sponsor actors in the generation of evidence on the safety and effectiveness profiles of the candidate medicines are not factored into this calculation, despite what they may add to the medicine's marketable value. The increased share of the development costs now shouldered by non-sponsor actors needs to be reflected in the sharing of benefits such

as lower prices. Higher implementation costs incurred by health systems that result from the need for enhanced monitoring when a product is released earlier in development also need to be factored into the pricing equation.

The current absence of a formal channel to integrate the societal contribution to drug development makes it extremely challenging to fully quantify. A number of publications have already emphasized the tremendous role played by publicly funded institutions in the R&D processes that led to the approval of flagship medicines; in most cases, this contribution was not acknowledged by the formal regulatory and health technology processes, let alone given a financial value. If societal contributions were planned for from the outset as an integral part of the development process, it would be much easier to track the investment of resources. AL may facilitate this process as it allows, in principle, for a wider consultation at early stages of drug development. However, EMA's Adaptive Pathways experience was limited to consultations mostly involving patient groups, not independent clinicians from the field; ultimately, these discussions are consultative in nature, since they do not identify patients, clinicians and health structures as full contributors to the development process. As part of the Adaptive Pathways pilot project, HTA agencies were included early in regulatory discussions with the sponsor. However, these agencies have not yet been sensitized to the role of non-sponsor stakeholders in the development process and the potential extra implementation costs associated with an early use of drugs that are shouldered by health systems. The lack of accounting for the costs borne by non-sponsors renders the assessment of HTAs incomplete and biased in favor of industry sponsors.

There seems to be a general acknowledgement in the medical R&D world that we are **moving increasingly towards a collaborative model of drug development**, where costs and risks are shared among a number of stakeholders. Therefore, it is imperative that regulatory authorities capture this plurality, alter their processes in a manner that formally integrates the inputs and contributions of all stakeholders, and acknowledge the participation of independent clinical practitioners and healthcare organizations from the outset. The inclusion of a public-health driven voice early on in the regulatory process should increase the likelihood that the clinical development process will better reflect the needs of patients and practitioners and therefore of society as a whole. In the event where sponsors are not able or willing to conduct some of the decided studies, non-sponsor organizations willing to take them up will do so in a fully acknowledged and coordinated manner. This also applies to post marketing studies and RWE when early access regulatory pathways are being pursued. Enabling a robust quantification of the societal contribution to drug development, pre- and post-marketing, will strengthen an evidence-based argument to challenge the pervasive discourse that presents the profit-driven sector as principally responsible for both medical research and its source of funding. The quantification of societal contribution will also be used as a strong leverage when considering the balance of rights to these medicines, such as moving away from exclusive rights towards collective rights to use.

For tuberculosis, it is not clear if there will be another unique situation of urgency that prompted the creation of the endTB and TB-PRACTECAL trials. If countries are slow to adopt the WHO 2019 guideline recommendations of all oral regimens for MDR-TB, and the results of the two trials are significantly delayed, there may be an increased need for data on the use of new 'salvage regimens' for patients that have acquired resistance to either BDQ, DLM, or both newer drugs. The paucity of actors pursuing clinical trials and programmatic observational studies for DR-TB, along with significant TB R&D funding gaps and limited RCT data, will also contribute to the need for consortiums amongst academic institutions, implementing partners, and countries to build on earlier investments in R&D and ongoing capacity development. Thus, it is likely that future TB R&D needs will only increase the concurrent necessity for clarity in R&D processes. Nonetheless, the development timeline for bedaquiline and delamanid can teach us crucial lessons that will assist with solutions going forward:

- There is a need for a clearer framework of what a 'regulatory pathway' for drugs and regimens means for regulatory approval, incorporation into WHO guidance, and post-approval efficacy and safety monitoring;
- The role of WHO in driving innovation should be clarified. In contrast to the role WHO plays as an RCT implementer for Ebola vaccine trials, WHO has historically had much less of a role in the clinical development of TB drugs; at what point should WHO be involved in the DR-TB clinical trial process, or should they be largely excluded aside from observer status until trial results are known;
- Efforts should be made to define the principles of regimen design, standardize primary outcome measurements, and ensure multicentre site participation for post-approval studies;
- Mechanisms should be identified to have ongoing dialogue between drug sponsors, regulatory agencies, partners, and trialists to optimize timely, high quality, real world evidence.

VII. Annexure: evolution of World Health Organization guidance on bedaquiline and delamanid

Subsequent to the WHO interim guidance on BDQ in June 2013, the 20th WHO Expert Committee on essential medicines recommended the inclusion of bedaquiline and delamanid in the anti- tuberculosis (TB) medicines section of the WHO Model List of Essential Medicines (EML) in May 2015.[45] One month earlier, Janssen and the United States Agency for International Development (USAID) agreed to provide BDQ for free to 30,000 MDR-TB patients in over 100 low- and middle-income countries over a four year period through the Stop TB Partnership's Global Drug Facility (GDF).[46] In May 2018, Janssen amended its agreement with USAID to extend the Bedaquiline Donation Program until March 2019 by committing to donate up to 30,000 additional courses of BDQ.[47] No further comprehensive guidance on the use of BDQ was released by the WHO from June 2013 until December 2018, although several documents were produced in the interim to address clinical need or the emergence of new data from programmatic use of the drug:

1. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis, March 2017 – the conditional recommendation to use BDQ in patients in whom a four-drug regimen (plus PZA) cannot be constructed for resistance or intolerance or for those who do not qualify for the shorter regimen remained unchanged after an assessment of newly available programmatic data[23]
2. Frequently asked questions document to accompany the GDG Report, March 2017[48]
3. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis, September 2017 – recommended that clinicians and national TB programs can decide to use BDQ and DLM in combination or extension beyond 24 weeks for patients with extensive resistance or intolerance with limited treatment options[24]
4. WHO Rapid Communication: Key changes to treatment of multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB), August 2018 – the grouping of TB medicines recommended for use in longer MDR-TB regimens are revised based on the latest evidence about the balance of effectiveness to safety. Group A drugs now include bedaquiline, the later generation fluoroquinolones levofloxacin and moxifloxacin, and linezolid.[49]

In March 2019, the WHO released their consolidated DR-TB treatment guideline update, which reiterated the emphasis on all oral treatment regimens for a majority of patients diagnosed with MDR/RR-TB; a strong recommendation for inclusion of BDQ in longer MDR-TB regimens as a core Group A drug; and the use of BDQ for patients aged 6-17 years.[37] At the time of the guideline update, BDQ had been used programmatically for 28,746 patients, with 56,506 courses ordered from GDF.[50]

After DLM's conditional approval in 2014, the WHO released guidance on its use in children and adolescents between the ages of 6-17 years in October 2016.[51] Recommendations for off-label use of BDQ in September 2017 also applied to DLM.[24] The final Trial 213 data were released in late November 2017 by Otsuka to the WHO and the EMA in compliance with EMA regulatory requirements. The WHO undertook a rapid review of this evidence and issued a position statement on the use of DLM in January 2018, which concluded that while the safety profile of DLM is favorable, DLM should only be added to a longer MDR-TB regimen when it cannot be composed according to WHO guidelines.[52] The Rapid Communication from WHO in December 2018 categorized DLM as a Group C drug.[49] This grouping was upheld in the Mach 2019 consolidated WHO guidelines, with the drug now recommended in children from 3 years of age.[38] At the time of the guideline update, DLM had been used programmatically for only 2,291 patients, with 11,020 courses ordered from GDF.[50]

VIII. References

1. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0 IGO.
2. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim guidance. WHO/HTM/TB/2013.6. Geneva, Switzerland: WHO, 2013.

3. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. WHO/HTM/TB.2014.23. Geneva, Switzerland: WHO, 2014.
4. Ahuja S D, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012; 9: e1001300.
5. Zumla A, Schito M, Maeurer M. Advancing the portfolio of tuberculosis diagnostics, drugs, biomarkers and vaccines. Lancet Infect Dis 2014; 14: 267–269.
6. Sharma A, Hill A, Kurbatova E, van der Walt M, et al. Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. Lancet Infect Dis 2017; 17: 707–715.
7. U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program, December 2018. https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf (accessed 5 January 2019).
8. European Medicines Agency. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to Mycobacterium tuberculosis, July 2017. https://www.ema.europa.eu/en/addendum-note-guidance-evaluation-medicinal-products-indicated-treatment-bacterial-infections (accessed 5 January 2019).
9. U.S. Food and Drug Administration. The 21st Century Cures Act, December 2016. https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/21stcenturycuresact/default.htm (accessed 5 January 2019).
10. European Medicines Agency. Adaptive pathways. https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways (accessed 5 January 2019).
11. Diacon A, Pym A, Grobusch M, et al, for the TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014; 371: 723–32.
12. Belard S, Heuvelings CC, Janssen S, Grobusch MP. Bedaquiline for the treatment of drug-resistant tuberculosis. Expert Rev Anti Infect Ther 2015; 13: 535–53.
13. National Institutes of Health, U.S. National Library of Medicine, ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02409290 (accessed 5 January 2019).
14. WHO. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update: October 2016 revision. Geneva: World Health Organization, 2016. https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/ (accessed 5 January 2019).
15. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug resistant pulmonary tuberculosis. New Engl J Med 2012; 366: 2151–60.

16. TB Online. Phase III clinical trial results at the 48th Union world conference on lung health: implications for the field. Available from: http://www.tbonline.info/posts/2017/11/25/phase-iii-clinical-trial-results-48th-union-world-/ (accessed 5 January 2019).
17. Von Groote-Bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multi-drug resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med 2019;7:249-59.
18. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/204384Orig1s000ltr.pdf (accessed 9 April 2019).
19. https://www.ema.europa.eu/en/documents/procedural-steps-after/sirturo-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf (accessed 9 April 2019).
20. Hewison C, Bastard M, Khachatryan N, et al. Is 6 months of bedaquiline enough? Results from the compassionate use of bedaquiline in Armenia and Georgia. Int J Tuberc Lung Dis 22(7):766-772.
21. McKenna L, Mingote LR. Paediatric study of bedaquiline remains an "open issue." European Respiratory Journal 2016 48: 956-957; DOI: 10.1183/13993003.00628-2016.
22. WHO. Active tuberculosis drug-safety monitoring and management (aDSM): framework for implementation. Geneva: World Health Organization, 2015.
23. WHO. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: a review of available evidence (2016). Geneva: World Health Organization, 2017.
24. WHO. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization, 2017.
25. Ferlazzo G, Mohr E, Laxmeshwar C, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet Infec Dis 2018. https://doi.org/10.1016/S1473-3099(18)30100-2.
26. Migliori GB, Pontali E, Sotglu G, et al. Combined Use of Delamanid and Bedaquiline to Treat Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: A Systematic Review. Int J Mol Sci. 2017 Feb 7;18(2).
27. Sherman R, Anderson S, Dal Pan G, et al. Real World Evidence – What Is It and What Can It Tell Us? New Engl J Med 2016; 375: 2293-97.
28. (F Varaine, personal communication, December 2018).
29. Brigden G, Nyang'wa B-T, du Cros P, et al. Principles for designing future regimens for multidrug-resistant tuberculosis. Bull World Health Organ. 2014 Jan 1;92(1):68-74.
30. TB-PRACTECAL (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen[s]). https://www.newtbdrugs.org/pipeline/trials/tb-practecal (accessed 5 January 2019).

31. TRUNCATE-TB trial (Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-sensitive TB). https://clinicaltrials.gov/ct2/show/NCT03474198 (accessed 5 January 2019).
32. PanACEA consortium (Pan-African Consortium for the Evaluation of Anti-tuberculosis Antibiotics). http://www.edctp.org/news/panacea-consortium-kicks-new-clinical-trials-programme-accelerate-tb-drug-evaluation/ (accessed 5 January 2019).
33. Drug-resistant TB Scale Up treatment Action Team (DR-TB STAT) Country Updates. http://drtb-stat.org/country-updates/ (accessed 5 January 2019).
34. https://www.msf.org.za/stories-news/press-releases/south-africa-new-revolution-tb-treatment-injection-falls (accessed 5 January 2019).
35. Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018. http://dx.doi.org/10.1016/ S2213-2600(18)30235-2.
36. Zhao Y, Fox T, Manning K, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug resistant tuberculosis: a retrospective cohort study. Clin Infect Dis 2018 Aug 24. doi: 10.1093/cid/ciy727.
37. WHO. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization, March 2019.
38. Tiberi S, du Plessis N, Walzl G, et al. Tuberculosis: progress and advances in development of new drugs, treatment regimens, and host-directed therapies. Lancet Infect Dis 2018. http://dx.doi.org/10.1016/ S1473-3099(18)30110-5.
39. Mitnick C, Rodriguez C, Hatton M, et al. Programmatic Management of Drug-Resistant Tuberculosis: An Updated Research Agenda. PLoS ONE 11(5): e0155968. Doi:10.1371/journal.pone.0155968.
40. Cox V, Brigden G, Crespo RH, et al. Global programmatic use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2017; 22(4):407-412.
41. https://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm313768.htm (accessed 9 April 2019).
42. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (accessed 9 April 2019).
43. https://newdigs.mit.edu/mit-newdigs-janus-program-workshop-payerhta-adaptive-pathways (accessed 9 April 2019).
44. The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB Treatment – 2017. Treatment correlates of successful outcomes of pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018;392:821-34.
45. WHO. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee 2015. Geneva: World Health Organization, 2015. https://www.who.int/selection_medicines/committees/expert/20/en/ (accessed 5 January 2019).
46. https://www.usaid.gov/what-we-do/global-health/tuberculosis/technical-areas/bedaquiline-donation-program (accessed 5 January 2019).
47. Johnson & Johnson and USAID Bedaquiline Donation Program: May 2018 Update.
48. WHO. Frequently asked questions about the use of bedaquiline according to the WHO guidelines and evidence from its early use in selected countries. Geneva: World Health Organization, 2017.

49. WHO. WHO Rapid Communication: Key changes to treatment of multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB). Geneva: World Health Organization, August 2018.
50. Drug-resistant TB Scale Up treatment Action Team (DR-TB STAT) Country Updates. http://drtb-stat.org/country-updates/ (accessed 5 January 2019).
51. WHO. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents, interim policy guidance. Geneva: World Health Organization, October 2016. https://www.who.int/tb/publications/Delamanid_interim_policy/en/ (accessed 5 January 2019).
52. WHO. WHO position statement on the use of delamanid for multidrug-resistant tuberculosis: expedited review of the phase III clinical trial data of delamanid added to an optimized background MDR-TB regimen. Geneva: World Health Organization, January 2018. https://www.who.int/tb/publications/2018/Position_Paper_Delamanid/en/ (accessed 5 January 2019).

IX. Tables

BDQ Trials	Phase	Description	Sponsor (Funding Source*)	Number enrolled#	Study Start Date	Primary Completion Date	Study Completion Date
IMPAACT 1025/1026S	IV	Pharmacokinetic properties of antiretroviral therapy, tuberculosis drugs, and hormonal contraception during pregnancy and postpartum in HIV positive and HIV negative women	NIAID Collaborator: NICHD	1786	March 2003	September 2020	September 2020
ACTG 5267	I	Safety, tolerability, and effect of single-dose BDQ and efavirenz in healthy volunteers	NIAID	37	December 2009	December 2010	December 2010
NCT01012284	I	Safety, tolerability, and effect of single-dose BDQ in patients with moderate hepatic impairment	Tibotec BVBA	16	January 2010	January 2011	January 2011
TMC207-CL002	I	Open-label trial to evaluate PK interaction between rifapentine or rifampicin and single-dose BDQ in healthy volunteers	TB Alliance (GATB)	32	March 2010	May 2010	May 2010
TMC207-CL001	II	Dose ranging trial to evaluate the EBA, safety, tolerability, and PK of BDQ in smear positive pulmonary TB	TB Alliance	68	April 2010	August 2010	September 2010

C208/C209	IIb	Open-label trial with 6 months of BDQ in addition to a background regimen for smear-positive pulmonary MDR-TB	Janssen Pharmaceuticals	241	September 2009	March 2011	January 2013
NC-001	IIa	Evaluation of EBA for different combinations of BDQ, moxifloxacin, pretomanid, and pyrazinamide for pulmonary DS-TB	TB Alliance	85	October 2010	May 2011	August 2011
NCT01341184	I	Evaluation of effect of rifampin or rifabutin on single dose PK of BDQ in healthy volunteers	NIAID Collaborator: CWRU	33	October 2011	May 2012	May 2012
NC-003	IIa	Evaluation of EBA, safety, and tolerability of combinations of BDQ, clofazimine, pretomanid, and pyrazinamide for newly diagnosed DS-TB	TB Alliance	105	October 2012	April 2013	May 2013
USFDA accelerated approval December 2012							
NC-005	IIb	Open-label trial to evaluate efficacy, safety and tolerability of combinations of BDQ, moxifloxacin, pretomanid, and pyrazinamide during 8 weeks of treatment in newly diagnosed smear positive pulmonary DS-TB or MDR-TB	TB Alliance	60 (MDR)	October 2014	February 2016	February 2018
Janssen Japan Trial	II	Open-label, single-arm, multi-center trial to explore safety, efficacy, and PK of BDQ for pulmonary MDR-TB	Janssen Pharmaceuticals	6	February 2015	November 2018	November 2018
NiX-TB	III	Study of BDQ, pretomanid, and linezolid in XDR-TB and MDR-TB for 6 months with option of 9 months	TB Alliance	109	March 2015	February 2019	October 2021
NeXT-5001	II/III	Open label RCT of 6-9 month fully oral shorter regimen with BDQ, linezolid, levofloxacin, ethionamide/high dose isoniazid, and pyrazinamide	UCT Collaborators: South African universities	300	October 2015	January 2019	January 2019
STREAM Stage 2	III	Comparison of a 6- and 9-month BDQ based regimen against the WHO and 'Bangladesh' regimen	IUATLD (USAID) Collaborators: MRC, ITM, LSHTM, Rede TB	530	April 2016	April 2021	June 2022
C211 (Pediatric)	II	Evaluate PK, safety, tolerability, and activity of BDQ in combination with MDR-TB therapy for HIV uninfected children and adolescents	Janssen Pharmaceuticals	60	May 2016	March 2021	July 2025

DELIBERATE (ACTG 5343)	II	Study of drug-drug interactions and combined QT effects of bedaquiline and delamanid	NIAID	84	August 2016	January 2019	January 2021
Expand New Drugs for TB (endTB)	--	Non-interventional, prospective, observational cohort study to examine the safety and efficacy of BDQ and delamanid used individually in routine, multidrug regimens for treatment of MDR-TB	PIH Collaborators: MSF-F, HMS, IRD, Epicentre	2600	February 2016	September 2020	September 2020
TASK-002	I	Randomized, open-label, cross-over study comparing the bioequivalence of BDQ administered in whole tablet form versus BDQ administered in crushed (experimental) form in healthy adult volunteers	IMPAACT	24	November 2016	December 2016	January 2017
endTB	III	Open-label, non-inferiority, multi-country RCT evaluating the efficacy and safety of new combination regimens for MDR-TB treatment	MSF-F (Unitaid) Collaborators: PIH; HMS; Epicentre; ITM; Ministries of Health	750	December 2016	September 2020	April 2021
TB-PRACTECAL	II-III	Multi-centre, open-label, multi-arm RCT evaluating short treatment regimens containing BDQ and pretomanid in combination with existing and re-purposed drugs for pulmonary MDR-TB treatment	MSF-N (Government of Netherlands, private donors) Collaborators: LSHTM; TB Alliance; UCL; DNDi; STPHI; eResearch; WHO; THINK; Ministries of Health; LSTM	630	January 2017	June 2020	March 2021
InDEX	IV	RCT comparing treatment success of a gene-derived individualized drug-resistant tuberculosis regimen to a standard tuberculosis regimen based on South African National Tuberculosis guidelines	CAPRISA	448	June 2017	June 2021	December 2021
P1108 (DAIDS ID 11884)	I-II	Evaluate the safety, tolerability, and pharmacokinetics of BDQ to treat MDR-TB in HIV-infected and HIV uninfected infants, children, and adolescents	NIAID	72	August 2017	March 2020	January 2022
ZeNiX-TB	III	Evaluate the efficacy, safety, and tolerability of various doses and durations of linezolid plus BDQ and pretomanid after 26 weeks of	TB Alliance	180	November 2017	April 2021	January 2022

		treatment for either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB					
SimpliciTB	II-III	Treatment for MDR-TB with BDQ, pretomanid, moxifloxacin, and pyrazinamide for 26 weeks or 6 months	TB Alliance	450	July 2018	March 2020	January 2022
BCH_PPK003	--	Observational, prospective cohort study to establish population PK models of each anti-tuberculosis drug in children by nonlinear mixed effect modeling	Beijing's Children Hospital Collaborators: Shandong University; Robert Debré Hospital; Rennes University Hospital	800	July 2018	October 2026	December 2026
BEAT TB	III	Open label, multi-centre, randomized controlled trial to compare efficacy and safety of 6 months BDQ, DLM, LZD, CFZ compared to the South African 9-month standard of care for RR-TB treatment.	Wits Health Consortium (USAID) Collaborators: Regents of University of California; University of Cape Town; PHRU	85	August 2019	March 2023	March 2023

*If different from the trial sponsor as a complementary or complete source of funding.

#Or estimated participant enrollment if the trial is planned or ongoing.

BDQ: bedaquiline; DLM: delamanid; LZD: linezolid; CFZ: clofazimine; NIAID: National Institute of Allergy and Infectious Diseases; NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development; PK: pharmacokinetics; GATB: Global Alliance for TB Drug Development; EBA: early bactericidal activity; MDR-TB: multidrug-resistant tuberculosis; DS-TB: drug sensitive tuberculosis; CWRU: Case Western Reserve University; TB Alliance: Global Alliance for TB Drug Development; RCT: randomized, placebo-controlled trial; UCT: University of Cape Town; STREAM: Standardized Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB; IUATLD: International Union Against TB and Lung Disease; MRC: Medical Research Council; ITM: Institute of Tropical Medicine; LSHTM: London School of Hygiene and Tropical Medicine; ACTG: AIDS Clinical Trials Group; IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network; endTB: Evaluating Newly Approved Drugs for MDR-TB; MSF-F: Médecins Sans Frontières-France; PIH: Partners In Health; HMS: Harvard Medical School; MSF-N: MSF-Netherlands; UCL: University College London; DNDi: Drugs for Neglected Diseases Initiative; STPHI: Swiss Tropical and Public Health Institute; WHO: World Health Organization; THINK: TB and HIV Investigative Network; LSTM: Liverpool School of Tropical Medicine; InDEX: Individualized M(X)DR-TB Treatment Strategy Study; CAPRISA: Centre for the AIDS Programme of Research in South Africa; XDR-TB: extremely drug-resistant tuberculosis; pre-XDR-TB: pre-extremely drug-resistant tuberculosis; PHRU: Perinatal Research Unit of the University of WItswatersrand.

Table 1: Selected recently completed and ongoing trials testing bedaquiline as a single drug or as part of a multi-drug regimen for drug resistant tuberculosis. The table does not include planned trials, trials evaluating diagnostics, or pre-clinical trials; the Phase III trial for bedaquiline is listed in red.

DLM Trials	Phase	Description	Sponsor (Funding Source*)	Number enrolled#	Study Start Date	Primary Completion Date	Study Completion Date
--	Pre-clinical	Investigated the properties of OPC-67683 against TB in vitro and in mice	Otsuka Pharmaceuticals	--	--	--	2006
--	Pre-clinical	Investigated the sterilizing activity of OPC-67683 against drug-tolerant TB in the Bactec model	Otsuka Pharmaceuticals	--	--	--	2007
NCT00401271	IIa	Evaluate the safety, efficacy and PK of four oral doses of DLM in patients with uncomplicated, smear-positive pulmonary TB	Otsuka Pharmaceuticals	54	November 2006	March 2007	March 2007
204	II	Multi-center RCT to evaluate safety and efficacy of DLM at 100 mg BD, 200 mg BD or placebo for 56 days with an optimized background regimen to treat MDR-TB	Otsuka Pharmaceuticals	481	April 2008	June 2010	October 2010
208	II	Multi-center, uncontrolled, open-label trial extended the administration of DLM for an additional 6 months among MDR-TB patients who completed Trial 204	Otsuka Pharmaceuticals	213	March 2009	September 2011	September 2011
NCT01131351	II	Multi-center, uncontrolled, open-label dose escalation trial to evaluate the safety and tolerability, PK, and efficacy of oral DLM when administered BD to MDR-TB patients refractory to treatment with an optimized background regimen of anti-TB medications	Otsuka Pharmaceuticals	10	February 2010	May 2011	May 2011
213	III	Safety and efficacy of delamanid or placebo for 6 months in combination with optimized background regimen for 18-24 months	Otsuka Pharmaceuticals	511	September 2011	May 2014	June 2016
232 (Pediatric)	II	Pharmacokinetic and safety trial of delamanid to determine the appropriate dose for pediatric MDR-TB HIV negative patients	Otsuka Pharmaceuticals	37	June 2013	December 2017	December 2017
233 (Pediatric)	II	Safety, efficacy, and pharmacokinetic study of delamanid in pediatric patients with MDR-TB	Otsuka Pharmaceuticals	37	July 2013	February 2020	February 2020
EMA conditional approval April 2014							
MDR-END	II/III	Compares efficacy of a treatment regimen including delamanid, linezolid, levofloxacin,	Seoul National University Hospital	238	January 2016	June 2021	June 2021

		and pyrazinamide for 9-12 months with a control arm of a standard treatment regimen including injectables for 20-24 months for treatment of quinolone sensitive MDR-TB	Collaborators: Korean University Hospitals; Korean Institute of TB; NMC-S; KCDC; Korean University				
Expand New Drugs for TB (endTB)	--	Non-interventional, prospective, observational cohort study to examine the safety and efficacy of bedaquiline and delamanid used individually in routine, multidrug regimens for treatment of MDR-TB	PIH Collaborators: MSF-F, HMS, IRD, Epicentre	2600	February 2016	September 2020	September 2020
DELIBERATE (ACTG 5343)	II	Study of drug-drug interactions and combined QT effects of bedaquiline and delamanid	NIAID	84	August 2016	January 2019	January 2021
endTB	III	Open-label, non-inferiority, multi-country RCT evaluating the efficacy and safety of new combination regimens for MDR-TB treatment	MSF-F (Unitaid) Collaborators: PIH, HMS; Epicentre; ITM; Ministries of Health	750	December 2016	September 2020	April 2021
InDEX	IV	RCT comparing treatment success of a gene-derived individualized drug-resistant tuberculosis regimen to a standard tuberculosis regimen based on South African National Tuberculosis guidelines	CAPRISA	448	June 2017	June 2021	December 2021
IMPAACT 2005 (Pediatric)	I/II	Evaluation of pharmacokinetics, safety, and tolerability of delamanid in combination with an optimized background regimen for MDR-TB in HIV-infected and HIV-uninfected children with MDR-TB	NIAID	48	January 2018	January 2021	May 2022
NCT03678688	I/II	Evaluate the safety, tolerability, pharmacokinetics, and efficacy of multiple oral doses of OPC-167832 in subjects with uncomplicated, smear-positive DS-TB (Stage 2 with DLM)	Otsuka Pharmaceuticals Collaborator: Bill and Melinda Gates Foundation	125	October 2018	December 2020	December 2020
PHOENIx	III	Compare efficacy and safety of 26 weeks of DLM versus 26 weeks of isoniazid for preventing confirmed or probable active TB during 96 weeks of follow-up among high-risk household contacts of adults with MDR-TB	NIAID Collaborator: NICHD	5610	June 2019	June 2025	June 2025

BEAT TB	III	Open label, multi-centre, randomized controlled trial to compare efficacy and safety of 6 months BDQ, DLM, LZD, CFZ compared to the South African 9-month standard of care for RR-TB treatment.	Wits Health Consortium (USAID) Collaborators: Regents of University of California; University of Cape Town; PHRU	85	August 2019	March 2023	March 2023

*If different from the trial sponsor as a complementary or complete source of funding.

DLM: delamanid; BDQ: bedaquiline; LZD: linezolid; CFZ: clofazimine; PK: pharmacokinetics; RCT: randomized, placebo-controlled trial; BD: twice daily; MDR-TB: multidrug-resistant tuberculosis; NMC-S: National Medical Center, Seoul; KCDC: Korean Center for Disease Control and Prevention; NIAID: National Institute of Allergy and Infectious Diseases; endTB: Evaluating Newly Approved Drugs for MDR-TB; MSF-F: Médecins Sans Frontières-France; PIH: Partners In Health; HMS: Harvard Medical School; ITM: Institute of Tropical Medicine; InDEX: Individualized M(X)DR-TB Treatment Strategy Study; CAPRISA: Centre for the AIDS Programme of Research in South Africa; IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network; National Institutes of Health; NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development; PHRU: Perinatal Research Unit of the University of WItswatersrand.

Table 2: Selected recently completed and ongoing trials testing delamanid as a single drug or as part of a multi-drug regimen for drug resistant tuberculosis. The table does not include planned trials, trials evaluating diagnostics, or trials for treatment of TB infection; the Phase III clinical trial for delamanid is listed in red.