Report of fatal and life-threatening adverse events during endTB post-marketing safety surveillance of new and repurposed TB drugs

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List of abbreviations

aDSM	Active TB Drug Safety Monitoring and management
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
Amk	Amikacin
Amx/Clv	Amoxicillin-clavulanate
Bdq	Bedaquiline
BMI	Body Mass Index
Cfz	Clofazimine
Clr	Clarithromycin
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
DRESS	Drug Rash with Eosinophilia and Systemic Symptom
E	Ethambutol
ECG	Electrocardiogram
endTB	Expand New Drug markets for TB
Eto	Ethionamide
H	Isoniazid
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
Imp/Cln	Imipenem/cilastatin sodium
IRD	Interactive Research and Development
Km	Kanamycin
Lfx	Levofloxacin
LLN	Low Limit of Normal
Lzd	Linezolid
MedDRA	Medical Dictionary for Regulatory Activities
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
Mpm	Meropenem
MRB	Medical Review Board
MSF	Médecins Sans Frontières
PAS	Para-Aminosalicylic Acid (sodium)
PIH	Partners In Health
Pto	Prothionamide
PV	Pharmacovigilance
R	Rifampicin
SAE	Serious Adverse Event
TB	Tuberculosis
Trd	Terizidone
TSH	Thyroid Stimulating Hormone
USAID	United States Agency for International Development
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

Introduction

During 2015-2019, the endTB (Expand New Drug markets for Tuberculosis) Consortium, comprising Médecins Sans Frontières (MSF), Partners In Health (PIH) and Interactive Research & Development (IRD), supported National Tuberculosis (TB) programs to introduce new and repurposed TB drugs (bedaquiline, delamanid, linezolid, clofazimine, etc.) in regimens to treat multidrug-resistant (MDR; defined here as resistance to isoniazid and rifampicin) and XDR (extensively drug-resistant; defined here as MDR with resistance to a second-line injectable and a fluoroquinolone) TB at sites in 17 countries: Armenia, Bangladesh, Belarus, Democratic People's Republic of Korea, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Vietnam, Haiti, South Africa, and Peru.

endTB conducted rigorous post-marketing safety surveillance for all patients (referred to as "endTB patients") who began regimens containing bedaquiline or delamanid over 2015-2019, through this initiative. The endTB post-marketing safety surveillance conformed to the "advanced" active TB Drug Safety Monitoring and Management (aDSM) package as defined by WHO (WHO/HTM/TB/2015.28). As post-marketing safety surveillance is not research, any patient treated as part of this initiative was included in the pharmacovigilance cohort.

The post-marketing safety surveillance was conducted in parallel with the endTB Observational Study (ClinicalTrials.gov Identifier: NCT03259269). The observational study was performed in endTB patients who further consented to participate in research; it collected additional data on effectiveness. More than 95% of the patients in the pharmacovigilance cohort consented to participate in the endTB Observational Study, meaning that the two cohorts are largely the same.

The pharmacovigilance process was the same for all patients, regardless of participation in the endTB Observational Study. Safety data collection started at time of first bedaquiline or delamanid dose in the frame of endTB. Patients were followed until the end of treatment or until the end of the project, whichever came first. Pharmacovigilance data were shared with the relevant stakeholders including National TB Programs, national PV/aDSM, WHO, and drug manufacturers, per applicable regulations or agreements. Periodic Safety Reports, which aggregated and summarized safety data approximately quarterly, are available on request from the MSF pharmacovigilance unit (PV unit). The PV unit was established in 2015 and hosted by MSF.

This report describes the pharmacovigilance procedures and all fatal and life-threatening SAEs reported in endTB patients and that occurred between 1 April 2015 and 31 March 2019.

Methods

Patients were monitored by local physicians and nurses according to national guidelines and the endTB clinical guidance monitoring schedule to ensure the early detection of any adverse events[1]. All clinicians were trained by the PV unit through e-learning and in person training on pharmacovigilance definitions and reporting requirements. The training curriculum included: principles of pharmacovigilance; recording of events; severity grading; distinguishing suspected unexpected serious adverse drug reaction

[1] endTB Consortium. endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 4.0; January 2018.

and serious adverse events from adverse events of special interest and other adverse events; establishing causality and expectedness; reporting to PV, regulatory authorities, and drug manufacturers; follow-up and closing of AEs; and management of AEs.

Ongoing support for reporting and direct communication and feedback was provided by the PV unit as well as other central and in-country endTB staff. Additional updates and training resources were also supplied as they were developed. Adverse events and comorbidities were managed by local clinicians with support from central consortium clinicians.

What is a Serious Adverse Event?

A Serious Adverse Event (SAE) was defined as any untoward medical occurrence that, at any dose and any time during or after endTB treatment[2]:

- Resulted in death (including death from TB progression),
- Was life-threatening; life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe,
- Required hospitalization or prolongation of hospitalization,
- Resulted in persistent or significant disability/incapacity; defined as a substantial to permanent disruption of the patient's ability to conduct normal life functions,
- Was a congenital anomaly or a birth defect,
- Was otherwise medically significant; medical and scientific judgment was exercised in deciding whether other situations were to be considered serious, such as important medical events that might not have been immediately life-threatening or resulting in death or hospitalization but might have jeopardized the patient or required intervention to prevent one of the other outcomes listed above.

How were serious adverse events reported and processed?

Clinicians were requested to report SAEs to the PV unit within 24 hours of awareness of the event, using a dedicated SAE reporting form (template available here). The SAE report included information on patient, drugs (TB and concomitant), description of SAE, severity (from grade 1 to 4 according to a standard grading scale; available here), relevant investigations, medical history, risk factors, causality per the reporter, and final action taken on drugs.

The case information from the report form was entered in the Pharmacovigilance database (Basecon®, Denmark). Each SAE term reported to the PV unit was coded using the Medical Dictionary for Regulatory Activities (MedDRA)[3] in the Pharmacovigilance database based on the reporter's exact language. Narrative summaries describe each SAE/all co-occurring SAEs in a single patient on a single date, during

[2] International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Step 4 version dated 27 October 1994.

[3] MedDRA, Medical Dictionary for Regulatory Activities (www.meddra.org).

treatment or follow-up. Quality control processes ensured coherence and consistency among source documents (such as SAE forms and lab results) shared by the sites, database contents, and the narratives.

The causality assessment from the central reviews were entered in the Pharmacovigilance database, and feedback and follow-up queries shared with the sites. Each SAE was followed-up until resolution or stabilisation and follow-up information was processed similarly as initial information.

Reporting of final action taken on TB drugs

The final action taken, defined as the decision to withdraw, maintain, or reduce the dose of each TB drugs in the regimen, was decided by the treating clinicians. The final action taken was the last action taken. For example, if drugs were interrupted for two weeks and then resumed at the same dose, the final action taken was recorded as "Dose maintained". The final action on TB drugs prescription varied depending on the nature of the adverse event and timing of the death (e.g., final action taken would be "Not applicable" in case of a sudden unexpected death as no action could be taken as a result of this serious event).

Causality assessment

The causal relationship between the SAE and each suspected (TB and non-TB) drug was evaluated according to the criteria in Table 1: Causality categories definition. This evaluation considered all other possible causal factors (e.g., medical history, risk factors, past drug use, concomitant procedures, TB progression).

The approach to causality assessment was very conservative and any adverse event was considered "related" to a drug unless that relationship could be definitively ruled out. No distinction between possibly, likely, certain was made; all were considered "related". In the absence of assessment, SAEs were considered to be "related" until and unless relatedness could be excluded. All SAEs were reported irrespective of causality and irrespective of ongoing exposure to any TB treatment.

Reported causality, risk factors and other causal factors displayed in this report included those identified by the sites and the central reviewers. Ruling out of all possible drug-related causes required concurrence among central reviewers and local reporters.

Table 1: Causality categories definition

Causality category	Description
Related	There is a reasonable possibility that the AE may be related to the drug(s). Elements in favour of a reasonable causal relationship include: • A favourable temporal relationship, • A positive dechallenge and/or rechallenge, • A plausible pharmacological/biological mechanism of action (whether proven or potential), • Previous knowledge of similar reaction with the drug(s), or • No other evident cause (e.g., previous disease, other drugs).
	There is insufficient information to evaluate the causal relationship between the AE and the exposure. Conservatively, the AE should be considered related to the drug(s) until a proper assessment is feasible (i.e., upon follow-up).

Causality category	Description
Not related	There is no reasonable possibility that the AE is related to the drug(s). This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE.

Role of the PV unit

All SAEs were immediately and individually reviewed by a medically qualified person at the level of PV unit to evaluate its expectedness (i.e., identify whether the information is in line with the current knowledge on the product's adverse reactions in terms of nature and severity) and to assess the causal relationship between the SAE and the TB regimen. After initial review by the PV unit, all reports were reviewed by central medical referents from MSF-PIH-IRD as well as external medical reviewers when required. The reporting physicians and central and external medical reviewers were trained to evaluate potential causal relationships according to the definitions in Table 1.

The PV unit convened medical reviews of all suspected unexpected serious adverse drug reactions by the Medical Review Board (MRB), fatal and non-fatal. The MRB comprised clinicians with extensive experience in MDR-TB management as well as specialists in related domains (i.e., cardiology, electrophysiology). All deaths in the cohort were scrutinized carefully. Verbal "autopsies" were performed at the sites with the support of the MRB, PV unit and central medical referents from MSF-PIH-IRD. This entailed a retrospective chart review of the evolution, risk factors, available labs/investigations, and determination of possible causes of death.

The MRB recommended risk minimization actions as required for example avoiding specific drugs in individual patients or groups of patients. MRB decisions were documented and archived in the MSF electronic document repository system and in the Pharmacovigilance database. Significant safety issues were communicated to the relevant stakeholders without delay, within maximum 3 calendar days, and included advice on management and prevention of future events.

Fatal/life-threatening SAE reporting and classification

Site clinicians reported the SAEs as life-threatening or fatal. Fatal SAEs were defined as AEs with an outcome recorded as "Fatal". Life-threatening SAEs were defined as AEs with a seriousness recorded as "Life-threatening". The PV unit discussed cases with the sites, notably causality and the seriousness; neither the causality reported by the site, nor the seriousness label given by the site (e.g., life-threatening) was changed unless the local clinicians agreed. The criteria to establish seriousness were reported as listed in the definition of serious adverse events above and the severity (grades 1 to 4) were recorded as separate parameters in both the SAE report form and the database. A grade 4 SAE was likely to be considered immediately life-threatening, but a severity grade 4 was not necessarily systematically indicative of a life-threatening experience (e.g., grade 4 creatine kinase elevation). By convention, all fatal SAEs were graded as 4[4].

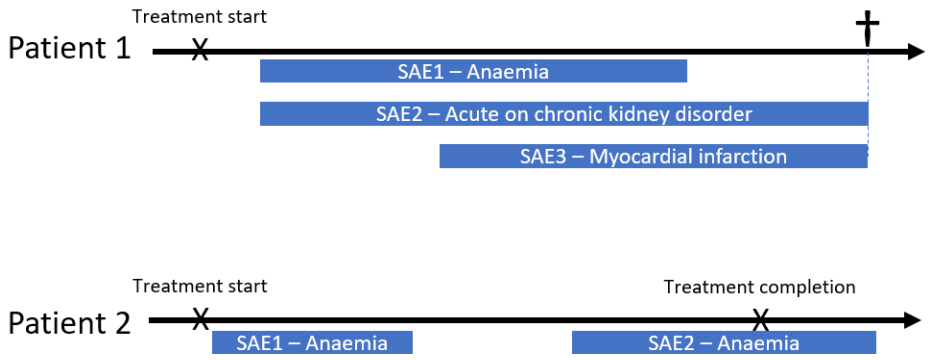
[4] MSF Severity grading scale version 5.0; date, 14-Nov-2016. Main sources: Division of Microbiology and Infectious Diseases (DMID) Severity Grading Scale Nov-2007 and Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 14-Jun-2010.

If multiple SAEs contributed to death, then all were reported as fatal SAEs (Figure 1, Patient 1, acute on chronic kidney disorder and myocardial infarction both fatal).

A single patient could experience more than one occurrence of the same SAE (Figure 1, Patient 2; 2 separated episodes of anaemia) or different SAEs (Figure 1, Patient 1, concomitant anaemia and acute on chronic kidney disorder).

A single safety occurrence could also involve multiple SAE terms (Figure 1, Patient 1, all 3 SAEs are reasons for hospitalisation).

Figure 1: Examples of situations including multiple SAE



For this report, the SAE terms were subsequently manually classified into categories (e.g., Tuberculosis, Death of undetermined causes, Sudden deaths) after review of the case narratives. The classification of all deaths and life-threatening events was made by two experienced central endTB physicians with support from the PV unit. During the manual review, the fatal or life-threatening SAE could be classified differently than the reporter's verbatim and MedDRA Preferred Term if the underlying cause was deemed different (e.g., anaemia in a person infected by malaria was classified as malaria whereas anaemia in the context of end stage lung damage from TB was classified as Tuberculosis).

Specifically, "Sudden deaths" referred to cases where deaths occurred rapidly (i.e., within few minutes) and unexpectedly in an otherwise stable patient. "Death of undetermined causes" referred to cases where the cause of death could not be reasonably assessed, and the death was unwitnessed.

Details of all the terms included in each category are available in Annex 1. Full case narratives are available in Annex 2 and Annex 3 (these are not available in electronic form on the endTB website, please contact endTB for more information).

Results

There was a total of 967 serious adverse events (SAEs) reported during the project from 1 April 2015 to 31 March 2019 in 621 patients in the endTB cohort of 2,906 patients exposed to bedaquiline (1,686 patients), delamanid (760 patients), or combination/sequential use of bedaquiline and delamanid (460 patients). Cohort characteristics are shown in Table 2.

Table 2: Cohort characteristics

Patient characteristics (N= 2906)	
Median age at registration [interquartile range]	35 [27-47]
Male	64%
Body mass index <18.5	42%
Co-morbidities	
Diabetes mellitus	14%
HIV infection	14%
Hepatitis B serology positive	4%
Hepatitis C serology positive	11%
At least one co-morbidity other than HIV	9%
Disease characteristics	
Past TB treatments	
No prior TB treatment	15%
Received prior TB treatment only with first line TB drugs	17%
Received prior TB treatment with second line TB drugs	67%
Extra-pulmonary disease	1%
Radiographic findings	
Bilateral disease	66%
Cavitary disease	47%
Resistance profile	
RR/MDR-TB without injectable or fluoroquinolone resistance	20%
RR/MDR-TB without second-line drug susceptibility results	11%
RR/MDR-TB with injectable resistance	13%
RR/MDR-TB with fluoroquinolone resistance	23%
RR/MDRTB with injectable and fluoroquinolone resistance	28%
No results for RR/MDR	6%
Drugs comprising the baseline treatment regimen	
Bedaquiline only	58%
Delamanid only	26%
Bedaquiline **and** Delamanid	16%
Linezolid	80%
Clofazimine	72%
Cycloserine or Terizidone	64%
Moxifloxacin or Levofloxacin	64%
Pyrazinamide	58%
Prothionamide or Ethionamide	42%
Kanamycin, Capreomycin or Amikacin	39%
P-Aminosalicylic Acid	24%
Imipenem/Cilastatin or Meropenem	15%

Serious Adverse Events with Fatal Outcome

A total of 273 patients experienced 317 SAEs with fatal outcomes (Table 3). The number of patients is less than the total sum of SAEs because 38 patients experienced fatal episodes that were described with two or more adverse events term (e.g., "Respiratory failure" and "Right ventricular failure"). Patients who experienced adverse events with fatal outcomes were mainly males (61%; 166/273), aged in years between 13 and 89 years old (average 43, median (standard deviation) 41 (±15); missing in 11 patients), and had body mass indexes (BMI) in kg/m^2 of between 9.9 and 39.8 (average 17.7, median (standard deviation) 16.9 (±4.2); missing in 56 patients).

The largest proportion (48%; 132/273) experienced events likely caused by advanced TB disease (category "Tuberculosis"). This was recorded in various ways: as respiratory failure (56 fatal SAEs in 56 patients) or disease progression (14 SAEs in 14 patients), but also cardiopulmonary failure (13 SAEs in 13 patients), dyspnoea (11 SAEs in 11 patients), or haemoptysis (5 SAEs in 5 patients) (full list in Annex 1).

The next most frequent category of death was due to undetermined causes (21 SAEs in 21 patients), sudden deaths (19 SAEs in 18 patients), hepatic failures (16 SAEs in 11 patients), renal failures (16 SAEs in 11 patients), myocardial infarctions (15 SAEs in 12 patients), cardiac failures (13 SAEs in 10 patients), and neoplasms (13 SAEs in 12 patients). Sudden deaths, deaths of undetermined cause, and hepatic failures are discussed in dedicated sections; details for the other categories can be found in Table 2, Annex 1 and Annex 2. (NB: Annex 2 is not available in electronic form on the endTB website, please contact endTB for more information).

The majority (66%; 210/317) of the fatal events were considered not related to any anti-TB drugs by both the reporting physician and the central reviewers. These are cases where all the reviewing clinicians agreed there was a clear cause of death that was unrelated to anti-TB drugs.

For 107 SAEs (34%; 107/317) in 88 patients, one or more drugs were considered by the reporter or the central reviewers to be possibly related. Other causal factors in these cases included ancillary/non-TB drugs for 31 SAEs, co-morbidities for 59 SAEs, and other causal factors in 26 SAEs. A quarter (23%; 64/273) of patients were not receiving bedaquiline or delamanid at the time of the SAE.

Table 3 describes all fatal SAEs in a summarized format. MedDRA preferred terms were grouped in categories; full list of terms included in each category is available in Annex 1. Case narratives of all patients are presented in Annex 2. (NB: Annex 2 is not available in electronic form on the endTB website, please contact endTB for more information).

Table 3: Summary of fatal serious adverse events reported between 01-Apr-2015 and 31-Mar-2019 in endTB patients exposed to bedaquiline or delamanid by SAE term classification (classified manually into categories)

SAE term classification°	#Patients	#SAEs	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs§								#SAEs related to§		
			Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Tuberculosis	132	143	21	11	31	11	2	11	11	11	2	4	11	6	87	25
Death of undetermined cause	21	21	0	0	2	11	6	18	7	15	1	9	16	4	13	6
Sudden death	18	19	4	1	5	8	7	12	3	7	2	2	4	6	11	5
Hepatic failure	11	16	5	3	8	10	0	10	12	7	3	7	12	8	5	4
Renal failure	11	16	5	5	15	3	4	8	4	6	1	1	9	9	13	2
Myocardial infarction	12	15	5	2	6	4	4	4	1	5	1	0	1	4	13	5
Cardiac failure	10	13	5	1	6	6	0	6	5	5	2	1	5	4	8	3
Neoplasm	12	13	2	3	6	0	1	0	0	1	0	0	1	1	5	2
Sepsis	6	8	2	2	3	0	0	0	0	0	0	0	0	0	5	0
Pneumonia	5	5	0	0	1	0	0	0	0	0	0	0	0	0	2	1
Gastrointestinal haemorrhage	4	4	2	2	4	2	1	3	0	3	0	0	4	1	4	1
Gastrointestinal infection	4	4	0	0	0	1	1	1	2	2	0	0	2	0	4	0
HIV	3	4	0	0	1	0	0	0	0	0	0	0	0	2	4	3
Injury	4	4	2	0	2	0	0	0	0	0	0	0	0	0	4	2
Malaria	1	3	0	0	0	3	0	3	0	3	0	0	3	1	0	0
Opportunistic infection	2	3	0	1	1	0	1	0	1	1	0	1	1	2	3	2
Cerebrovascular accident	2	2	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Intestinal ischaemia	1	2	0	2	2	0	0	0	0	0	0	0	0	2	2	0
Pancytopenia	2	2	0	1	2	0	1	1	1	0	0	1	1	1	1	2
Pyelonephritis	1	2	0	0	0	0	0	0	1	1	0	0	0	0	2	0
Seizure	2	2	1	1	1	0	0	0	0	0	0	0	0	0	1	1
Adrenal insufficiency	1	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1
Anaemia	1	1	0	1	1	0	0	0	0	0	1	0	0	0	1	0
Cardiomyopathy	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Coma	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SAE term classification°	#Patients	#SAEs	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs§								#SAEs related to§		
			Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Complete heart block & prolonged QT	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Coronary artery insufficiency	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperbilirubinaemia	1	1	0	1	1	0	1	1	0	0	0	1	1	1	1	1
Hyperglycaemia	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0
Homicide	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Meningitis	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	1
Multiorgan failure	1	1	0	0	0	0	1	1	1	1	0	0	1	1	0	0
Pancreatitis acute	1	1	0	0	0	0	1	1	0	1	0	0	1	0	0	0
Progressive multifocal leukoencephalopathy	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Respiratory infection from food aspiration	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Suicide	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Thrombosis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

§Considered possibly related by the reporting physician and/or the central reviewers.

°Details of the MedDRA preferred terms available in the Annex 1.

Life-threatening Serious Adverse Events

Fifty-one patients experienced 60 life-threatening non-fatal SAEs. Eight patients experienced more than one life-threatening SAE (e.g., "Anaemia" and "Thrombocytopenia"). Life-threatening SAEs occurred mainly in males (67%; 34/51) between 18 and 76 (median 48) years of age. Reported BMIs were between 10.9 and 29.0 (median 19.0) kg/m^2.

The most frequently reported life-threatening events were "Anaemia" (7 SAEs in 7 patients) and "QT prolongation" (7 SAEs in 7 patients). The next most frequent categories were: tuberculosis (5 SAEs in 4 patients), linezolid-induced bone marrow suppression (4 SAEs in 3 patients), renal failure (4 SAEs in 4 patients), hepatic failure (3 SAEs in 3 patients), and hypokalaemia (3 SAEs in 3 patients). Details for the other categories can be found in Table 3, Annex 1 and Annex 3. (NB: Annex 3 is not available in electronic form on the endTB website, please contact endTB for more information).

Twenty-two (37%) of the life-threatening events were considered not related to any anti-TB drugs by both the reporting physician and the central reviewers. For 38 SAEs (63%) in 36 patients, one or many drugs were considered possibly related by the reporter or the central reviewers. Other causal factors in these cases included ancillary/non-TB drugs for 13 SAEs, co-morbidities for 18 SAEs, and other causal factors in 7 SAEs. Table 4 summarizes all life-threatening SAEs. MedDRA preferred terms were grouped into categories as detailed in the Methods; full list of MedDRA terms included in each category is available in Annex 1. Case narratives of all patients are presented in Annex 3. (NB: Annex 3 is not available in electronic form on the endTB website, please contact endTB for more information).

Table 4: Summary of life-threatening non-fatal serious adverse events reported between 01-Apr-2015 and 31-Mar-2019 in endTB patients exposed to bedaquiline or delamanid by SAE term classification (classified manually into categories)

SAE term classification°	#Patients	#SAEs	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs§								#SAEs related to§		
			Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Anaemia	7	7	1	0	4	0	0	1	5	3	0	0	2	3	2	1
Electrocardiogram QT prolonged	7	7	2	2	6	5	2	6	1	3	1	0	2	2	3	0
Tuberculosis	4	5	0	0	1	0	1	1	1	1	0	0	1	1	3	0
Linezolid-induced bone marrow suppression	3	4	1	0	3	0	0	1	4	2	0	1	1	2	1	0
Renal failure	4	4	2	1	4	0	0	0	0	0	0	1	0	1	2	0
Hepatic failure	3	3	0	1	1	2	2	3	3	1	1	0	3	0	2	1
Hypokalaemia	3	3	0	1	2	0	0	0	0	0	0	1	2	2	1	0
Allergic reaction	2	2	0	0	1	0	0	0	0	0	0	1	0	0	1	0
Complete heart block & prolonged QT	1	2	0	2	0	0	1	0	0	0	0	0	0	0	2	0
Hyperglycaemia	2	2	0	0	0	0	0	0	0	0	0	0	0	1	2	0
Hypoglycaemia	2	2	0	0	1	0	0	0	0	2	0	0	0	2	2	0
Myocardial infarction	2	2	1	0	1	2	0	2	1	1	0	1	1	0	2	1
Vomiting	2	2	1	0	1	1	1	0	1	0	0	0	1	1	1	0
Alcohol abuse	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Appendicitis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiac failure	1	1	0	1	1	0	0	0	0	0	0	0	1	0	1	1
Cholecystitis, acute	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Diabetes	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Gastrointestinal infection	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypophosphataemia	1	1	0	0	1	0	0	0	0	0	0	0	0	1	1	0
Neoplasm	1	1	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Opportunistic infection	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Orthostatic syncope	1	1	0	0	0	0	1	0	1	0	0	1	1	0	0	0
Pancytopenia	1	1	0	0	1	0	0	0	1	0	0	0	0	0	1	1
Pericarditis	1	1	0	1	1	0	0	0	0	0	0	0	1	0	1	0

SAE term classification°	#Patients	#SAEs	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs§								#SAEs related to§		
			Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Psychotic disorder	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0
Systemic inflammatory response syndrome	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Tachyarrhythmia	1	1	0	0	0	0	1	0	0	0	0	0	0	1	1	0

§Considered possibly related by the reporting physician and/or the central reviewers.
°Details of the MedDRA preferred terms available in the Annex 1.

Serious Adverse Events by category

Sudden deaths

Eighteen (18) deaths in the cohort were classified as sudden deaths, 10 in males and 8 in females. They ranged in age from 20 to 74 (median: 42), and BMI from 14.4 to 25.9 (median: 17.6) kg/m^2.

These patients had received multiple TB medications considered as potentially QT-prolonging including clofazimine (16 patients), delamanid (11), bedaquiline (9), levofloxacin (8), and moxifloxacin (6). Two patients received concomitant bedaquiline and delamanid. Seven (7) patients received 2 of these potentially QT-prolonging TB medications, 8 patients received 3, and 3 patients received 4. Other TB medications received by these patients included pyrazinamide (14 patients), cycloserine (14), linezolid (11), PAS (9), prothionamide (5), capreomycin (5), ethionamide (5), amikacin (4), amoxicillin/clavulanate (4), imipenem/cilastatin (3), isoniazid (1), terizidone (1), and ethambutol (1).

These patients had received concomitant non-TB medications considered by the clinicians and central reviewers to be directly or indirectly linked with their deaths. These included fluconazole (3 patients), metoprolol (3), propranolol (2), bisoprolol (1), amiodarone (1), lopinavir/ritonavir (1), metronidazole (1), multi-vitamin (Iberet folic) (1), dimenhydrinate (1), ondansetron (1), pregabalin (1), flupentixol (1), domperidone (1) and melitracen (1). In 6 patients, up to 5 concomitant non-TB drugs with known cardiac effects had been prescribed. These included 6 cases for whom a beta-blocker was prescribed without a clear cardiac indication as well as 1 prescription of amiodarone without reported indication.

All ECGs considered difficult to interpret were reviewed by external cardiologists; their input included in the case narratives (Annex 2, NB: Annex 3 is not available in electronic form on the endTB website, please contact endTB for more information). In most cases, no evidence of QT prolongation was documented prior to death (13/18; 72%) or during TB treatment (11/18; 61%).

In two cases of sudden death, QTcF greater than 500 ms was documented prior to death. The first case (16524) was a frail young man (24 years old) without known risk factors except for fluctuating blood glucose. An underlying previously undetected heart condition was suspected, and patient received furosemide, carvedilol and bisoprolol for 1 day before his sudden demise. On that day, 10 hours before his cardiac arrest, his QTcF was measured at 536 msec.

The second case (16219) was an older male (50 years old) diabetic with probable ischemic heart disease and fluctuating electrolytes. Multiple ECGs on taken 12-14 days before his death showed QTcF greater than 500 msec, but this resolved before the day of his death.

Four other individuals (13225, 10484, 11364, 14533) had documented mild QTcF prolongation (450-480 ms) in the latest reported ECGs prior to sudden death taken between 1 day to 5 months before the death; concomitant risk factors in these deaths included low electrolytes, uncontrolled diabetes over 10 years, and polypharmacy.

In another sudden death case (14533), right bundle branch block, without QTcF prolongation, was documented.

A review of the sudden deaths narratives by an external electrophysiologist indicated additional risk factors that may have contributed to some of these fatal SAEs: low electrolytes or high TSH (not necessarily "abnormal"), and polypharmacy. While cardiac arrhythmia cannot be excluded, patients

suffered from other important comorbidities, notably alcoholism, uncontrolled diabetes mellitus, hypothyroidism. Alternative causes of death included: pulmonary embolism, acute stroke, myocardial infarction, hypo/hyperglycemia, hepatic failure (decompensated alcoholic cirrhosis), suspected suicide, TB progression, and sepsis.

Deaths of undetermined cause

When a death occurred at home and was unwitnessed by medical staff, or if the patient suffered from very severe, complex, and multiple medical conditions, it was not possible to assess the actual cause of death and therefore these deaths were classified as deaths of undetermined cause. Twenty-one (21) deaths in the cohort were classified in this category: 16 in males and 5 in females. These individuals ranged in age from 17 to 87 (median 53.5) years. Median BMI was 19.0 (range: 14.1, 31.2) kg/m^2.

The majority occurred at home and no autopsy was performed (17 deaths) or information on whether an autopsy was performed was not known to the reporter (4 deaths). Since the patients were at home, there was generally very little medical data or documentation at the time of the death for the medical committee to determine a cause of death. However most (18) cases, had detailed baseline and monthly follow-up information.

All patients received at least one potentially QT-prolonging TB medication (bedaquiline, delamanid, clofazimine, levofloxacin or moxifloxacin); 4 patients received 2 of these medications, 15 patients received 3, and 1 patient received 4. Other potentially QT-prolonging concomitant medications included quetiapine, amitriptyline, chlorprothixene, citalopram, cotrimoxazole, furosemide, and glimepiride. One patient had been exposed to up to 7 QT-prolonging TB and non-TB medications.

As with the sudden deaths, the last available ECG was normal in most (13/21; 62%) of these patients. Two patients (14924, 12634) who died of undetermined causes had a documented QTcF of greater than 500 ms.

Potential causes of death, significant comorbidities or risk factors were present for most (18/21; 86%). These included: severe malnutrition with BMI <17 (6 patients), electrolyte imbalance (5), advanced age >70 years old (4), severe anaemia (3), HIV (3), suspected TB progression (2), possible hepatic failure (2), suspected myocardial infarction (2), uncontrolled diabetes (2), renal failure (2), arrhythmia (1), suspected rheumatoid arthritis with renal involvement (1), congestive heart failure (1), gastrointestinal haemorrhage (1), very poor TB prognosis (1), suspected sepsis (1), sequelae from TB (such as COPD) (1), probable suicide (1), hypovolemic shock following gastroenteritis (1), possible homicide/head trauma (1), hypertension (1), untreated hepatitis B (1), alcoholism (1).

Given the absence of a definite cause of death, most (18/21; 86%) cases were conservatively deemed related to all TB drugs given at the time of the death, and notably the QT-prolonging TB and non-TB drugs: arrhythmia was considered possible to probable depending on the case. Other effects, suspected to be directly or indirectly caused by other TB drugs, such as hepatotoxicity, psychiatric effects or electrolyte wasting, were also highlighted in the assessment of the individual cases. In 3 cases, where the reporter strongly suspected sepsis, hypovolemic shock and myocardial infarction, respectively, the deaths were deemed unlikely to be drug related.

Fatal & Life-threatening cardiac events summary (excluding sudden deaths)

Twenty-three patients experienced 28 cardiac SAEs: cardiac failure (14 SAEs in 11 patients), electrocardiogram QT prolonged (7 patients with 7 SAEs), complete heart block & QT prolongation (1 patient with 3 SAEs), cardiomyopathy (1 patient with 1 SAE), pericarditis (1 patient with 1 SAE), tachyarrhythmia (1 patient with 1 SAE), coronary artery insufficiency (1 patient with 1 SAE). Sixteen (16) SAEs were fatal and 12 were deemed life-threatening (severity grade 3, 1 SAE; grade 4, 11 SAEs). These events occurred in 18 male and 5 female patients with ages ranging from 20 to 84 years old (median 44), and median BMI of 17.7 (range 13.8 and 23.3) kg/m^2.

Cardiac failure was the most common SAE. It commonly related to a pre-existing chronic condition; in 6 patients (13582, 12353, 13135, 11760, 13562, 14791), it was thought to be an exacerbation of chronic heart failure related to advanced pulmonary TB. One patient (11927) had a pre-existing diagnosis of alcoholic cardiomyopathy. Another patient (15272) died from cardiac failure related to aortoiliac occlusive disease from atherosclerosis.

QT prolongation was often documented in patients who were experiencing tachycardia (11667, 11836, 12707, 12693), but it was often unclear if it was related to the QT prolongation. One patient (15680) experienced shortness of breath and chest pain. Another patient (10529) experienced bradycardia which was thought to be unrelated to QT prolongation. QT prolongation generally resolved quickly when QT prolonging drugs were suspended.

Fatal & Life-threatening hepatic failures and hyperbilirubinaemia

Eleven patients experienced fatal hepatic failure reported as 16 SAEs (one patient experienced 3 SAEs and 3 patients experienced 2 SAEs). There were 8 males and 3 females. The median age was 38 (range 27 to 66) and median BMI 19.5 (range 15.6 to 27.4) kg/m^2. One additional patient (15543) experienced hyperbilirubinaemia and pancytopenia.

These patients received multiple TB medications, most of which can be considered as potentially hepatotoxic including clofazimine (11), linezolid (10), bedaquiline (8), cycloserine (6), capreomycin (5), delamanid (4), levofloxacin (4), pyrazinamide (4), amoxicillin-clavulanate (2), ethionamide (2), moxifloxacin (2), PAS (2), amikacin (1), ethambutol (1), imipenem/cilastatin (1) and prothionamide (1). Linezolid was considered possibly related in 7 (64%) cases, bedaquiline in 6 (55%) and clofazimine in 5 (45%), cycloserine and levofloxacin each in 4 (36%), pyrazinamide and capreomycin in 3 (27%) cases.

In four (4/11; 36%) patients (11911, 11977, 12045, 13412), excess alcohol was reported as related. Clinicians reported hepatitis C infection as a contributing cause in 2/11 (18%) patients (15081, 10874) experiencing a fatal hepatic failure. One patient (15081) was suffering from severe liver cirrhosis due to chronic hepatitis C when starting TB treatment. In one patient (11280), a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was suspected.

For four patients (14953, 15100, 10874, 13142) hepatic failure was characterized by hyperbilirubinaemia; one additional patient (15543) experienced hyperbilirubinaemia with mild transaminitis and pancytopenia. All five were HIV-positive. Advanced HIV, ARV drugs (nevirapine, zidovudine, ritonavir, raltegravir) or cotrimoxazole were reported as contributing factors. These patients had in common low CD4 counts, severe and extensive forms of TB (four with XDR-TB, two with TB meningitis) and four with hepatitis C co-infection. One hypothesis after review of these narrative suggests that these patients may have suffered from undiagnosed CMV septicaemia.

Three additional patients experienced hepatic failure considered as life-threatening by the reporting clinician. In the first (11809), excessive alcohol, hepatitis C infection, comorbidities, opiate use and infiltrative TB were listed as contributing factors. In the second (12008), hepatitis C infection, decompensated diabetes and hypertension were listed as contributing factors. In the third (15349), hepatitis C infection was listed as a contributing factor.

Fatal & Life-threatening myelosuppression

Eleven patients in the cohort experienced 14 SAEs classified as "Anaemia" or "Linezolid-induced bone marrow suppression". There was 1 patient with 4 SAEs. Thirteen SAEs were considered life-threatening by the reporter, and one was fatal. All patients experienced anaemia (11 patients), but some also experienced thrombocytopenia (3 patients) and leukopenia (2 patients). These events occurred in 8 male and 3 female patients with median age 51 (range 18 to 59) years and median BMI 20.1 (range 13.1 and 25.3 kg/m^2).

Linezolid was considered related in all 8 (73%) patients who received it; this judgement was often made after suspension of linezolid and subsequent resolution of the SAE. Five patients discontinued linezolid, including 3 patients for whom all the other drugs in the regimen were also stopped and 1 patient who stopped linezolid and isoniazid. One patient (11162) tolerated a reduced dose of linezolid.

Relevant comorbidities included HIV (4 patients), chronic HCV (2), hereditary spherocytosis anaemia (1), iron-deficiency anaemia (1), chronic kidney disease (1) and kidney stone related anaemia/bleeding (1). Co-suspected non-TB drugs included antiretroviral drugs (4), cotrimoxazole/dapsone (3), and warfarin (1). Some patients were thought to suffer nutrition issues or alcohol use/abuse.

The fatal SAE occurred in a patient (13627) with previous diagnosis of hereditary spherocytosis who developed anaemia and then pancytopenia in the third month of treatment. He was not taking linezolid. The SAE was thought to be related to imipenem and amoxicillin-clavulanate, which had been recently added to strengthen the TB regimen.

Discussion

This report describes SAEs that occurred during treatment of a cohort of patients with highly drug-resistant TB, many of whom have a history of severe disease and multiple failed courses of previous treatment with second-line TB drugs. In this cohort, it was common for patients to start treatment, often as a last resort, with very severe and advanced TB disease. Death from complications of TB was the most frequent fatal SAE. Death may have been due to progressive respiratory failure or massive haemoptysis from resistant TB that failed to respond to treatment, but also from TB-related complications that are often experienced by a patient with poor clinical or nutritional conditions. The high frequency of these types of fatal SAEs speaks to the importance of early diagnosis and treatment of MDR- and XDR-TB.

Many of the patients who experienced fatal or life-threatening SAEs have important co-morbidities such as diabetes, HIV and hepatitis C. Fortunately, the start of regular visits to the MDR-TB clinic may be an opportunity to improve follow-up and management of these chronic conditions. While TB clinicians may not feel confident in the management of other diseases, it is important to integrate these into the MDR-TB clinic workflow.

For patients with diabetes, regular monitoring of blood glucose and periodic haemoglobin A1c monitoring and adjustment of diabetic medications or referral to an endocrinologist will decrease progression of conditions that share a drug adverse effect and disease pathology like peripheral nephropathy or acute kidney failure. In patients with risk factors for hepatotoxicity, such as chronic viral hepatitis or alcoholism, attention to monitoring of liver enzymes and careful prescribing of only essential drugs is strongly advised. Finally, in patients with advanced HIV disease, a wide range of infections should be considered as part of the differential diagnosis of an SAE—CMV, albumin and prothrombin time testing may be helpful.

Polypharmacy is common in the treatment of MDR- and XDR-TB patients. They often take a large number of drugs: TB drugs, drugs to treat other co-morbid chronic conditions, and drugs to manage AEs. While clinicians were often concerned about the AE profile of new TB drugs like bedaquiline and delamanid, it is important to remember that many other TB drugs have well-known side effects that can be life-threatening. For example, linezolid is an important TB drugs but was possibly the cause of multiple instances of life-threatening bone marrow suppression (anaemia, thrombocytopenia or pancytopenia). QT prolongation can be caused by other TB drugs, such as clofazimine or moxifloxacin, as well as many non-TB drugs. It is important to think broadly about all TB drugs that the patient is receiving.

MDR- and XDR-TB patients often receive many non-TB drugs that are unfamiliar to TB clinicians. Some might be prescribed by the TB clinicians themselves to treat side effects or co-morbidities. Some might be prescribed by other specialists who are unfamiliar with TB. Either way, prescription of unfamiliar non-TB drugs can contribute dangerous polypharmacy. TB clinicians need to regularly review all prescriptions, even those from other specialists, and carefully consider if they are effective and necessary. One common example is the prescription of beta-blockers to treat physiological tachycardia, which is both unnecessary and potentially interactive with other drugs with cardiac effects.

Finally, even in patients with advanced TB disease, severe SAEs can often be managed successfully with appropriate monitoring and protocols. For example, there is no doubt that severe QT prolongation can happen in patients receiving MDR-TB treatment. When this was detected with ECG monitoring, however, generally the contributing drugs could be identified and TB treatment could be continued without recurrence of the SAE. Similarly, regular monitoring of electrolytes, complete blood counts, liver function tests, renal function, BMI, albumin, and other clinical conditions can mitigate the negative effects of most SAEs.

In conclusion, fatal and life-threatening SAEs are a challenge in the treatment of this type of MDR-/XDR-TB patient. This report reports on the frequency of SAEs during the longer treatment regimens used for MDR-/XDR-TB. Although drawing causal inference about specific drugs and risk factors is beyond the scope of this report, it does describe comorbidities and concomitant medications that could contribute to the frequency and severity of these events. There are still many gaps in identifying risk factors for SAEs, assigning causality to one or more drugs, and assessing the safety of regimen combinations. The extensive, rigorous pharmacovigilance monitoring of this very large cohort identified no signals of new safety risks for the TB drugs examined. Nevertheless, there may be rare drug reactions that were not detected through the pharmacovigilance monitoring.

It is crucial for TB programs to rapidly diagnose and treat these patients; delays in appropriate treatment leads to patients in poor clinical condition and SAEs that are more difficult to manage. Clinicians should learn to manage non-TB chronic conditions like diabetes, HIV and hepatitis C; to engage with other specialists when possible; and to be vigilant of SAEs that can be caused by a wide range of TB and non-TB drugs. Ongoing pharmacovigilance in MDR-TB treatment, as well as randomized control studies that compare drugs or drug regimens, are crucial to add to the evidence presented in this report so that MDR-/XDR-TB treatment can be as effective and safe as possible.

ANNEX 1 – Supplementary tables

Table 5: Full description of fatal serious adverse events reported between 01-Apr-2015 and 31-Mar-2019 in endTB patients exposed to bedaquiline or delamanid by SAE term classification and MedDRA Preferred Term

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Tuberculosis	132	143	_	21	11	31	11	2	11	11	11	2	4	11	6	87	25
Respiratory failure	56	56	254	8	1	11	2	0	3	3	2	0	2	4	1	33	7
Disease progression	14	14	138	1	1	2	2	0	2	1	2	0	0	2	1	7	3
Cardiopulmonary failure	13	13	268	2	1	4	2	0	2	2	2	2	0	2	1	11	4
Dyspnoea	11	11	86	0	0	2	1	1	1	0	1	0	0	0	0	7	2
Haemoptysis	5	5	94	0	0	0	0	0	0	0	0	0	0	0	0	4	0
Pulmonary embolism	5	5	68	1	2	2	0	0	0	0	0	0	0	0	1	2	1
Respiratory distress	5	5	315	1	0	0	0	0	0	0	0	0	0	0	0	5	0
Pulmonary haemorrhage	4	4	427	0	2	2	0	0	0	0	0	0	0	0	0	3	1
Anaemia	2	2	72	1	0	1	0	0	0	1	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease	2	2	116	1	1	1	0	0	0	0	0	0	0	0	0	2	2
Pneumothorax	2	2	107	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Pulmonary tuberculosis	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Acute kidney injury	1	1	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Acute respiratory failure	1	1	17	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Asphyxia	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aspiration	1	1	59	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Bone tuberculosis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cachexia	1	1	124	0	1	1	0	0	0	1	0	0	1	0	0	1	0
Cardiac failure congestive	1	1	233	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Cardio-respiratory arrest	1	1	455	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Chronic respiratory failure	1	1	179	1	1	1	0	0	0	0	0	0	0	0	0	1	1
Cor pulmonale acute	1	1	312	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Electrolyte imbalance	1	1	301	1	0	1	1	0	1	1	1	0	0	1	0	0	0
Empyema	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Gastrointestinal disorder	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	0	0
General physical health deterioration	1	1	63	1	0	0	1	0	1	1	1	0	1	1	0	0	0
Meningitis tuberculous	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Post procedural pulmonary embolism	1	1	245	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Renal failure	1	1	4	1	1	1	0	0	0	0	0	0	0	0	0	1	0
Right ventricular failure	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Tuberculoma of central nervous system	1	1	360	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Tuberculosis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ventricular extrasystoles	1	1	0	0	0	0	1	1	0	0	1	0	0	0	0	0	0
Weight decreased	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Death of undetermined cause	21	21	_	0	0	2	11	6	18	7	15	1	9	16	4	13	6
Death	16	16	178	0	0	2	10	5	16	6	13	1	9	14	3	9	5
Dyspnoea	1	1	0	0	0	0	1	0	1	0	1	0	0	1	0	1	0
Hypovolaemic shock	1	1	168	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Myocardial infarction	1	1	112	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Respiratory failure	1	1	0	0	0	0	0	1	1	1	1	0	0	1	0	0	0
Sepsis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Sudden death	18	19	_	4	1	5	8	7	12	3	7	2	2	4	6	11	5
Sudden death	9	9	135	1	0	1	6	2	6	1	3	0	1	1	4	5	2
Arrhythmia	2	2	148	2	1	2	1	1	1	0	0	0	0	0	1	1	0
Death	2	2	238	0	0	0	0	2	2	1	2	1	0	2	0	2	1
Cardiac arrest	1	1	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0
Cardio-respiratory arrest	1	1	46	0	0	0	0	1	1	0	1	0	0	0	0	1	1
Electrocardiogram QT prolonged	1	1	0	1	0	1	1	0	1	0	0	0	0	0	0	0	0
Respiratory distress	1	1	51	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Respiratory failure	1	1	342	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sudden cardiac death	1	1	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Hepatic failure	11	16	_	5	3	8	10	0	10	12	7	3	7	12	8	5	4
Hepatic failure	4	4	168	1	1	2	3	0	3	4	2	0	2	3	2	2	2
Acute hepatic failure	3	3	172	1	0	1	2	0	1	2	2	0	0	2	1	2	1
Cardiogenic shock	1	1	0	0	1	1	0	0	1	1	1	0	1	1	0	0	0
Chronic hepatic failure	1	1	301	0	0	0	1	0	0	0	0	0	0	0	0	1	1
Death	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	0	0
Hepatic encephalopathy	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
Hepatitis	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	0	0
Hyperbilirubinaemia	1	1	0	1	0	1	1	0	1	1	0	1	1	1	1	0	0
Metabolic acidosis	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	0	0
Respiratory failure	1	1	0	0	1	1	0	0	1	1	1	0	1	1	0	0	0
Septic shock	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Renal failure	11	16	_	5	5	15	3	4	8	4	6	1	1	9	9	13	2
Acute kidney injury	8	8	158	3	2	7	2	2	4	3	3	1	0	5	5	5	1
Anaemia	1	1	663	0	0	1	0	0	1	1	0	0	0	1	0	1	0
Arrhythmia	1	1	72	0	0	1	0	1	1	0	1	0	0	1	1	1	0
Hyperkalaemia	1	1	69	0	0	1	0	1	1	0	1	0	0	1	1	1	0
Hyponatraemia	1	1	20	1	1	1	0	0	0	0	0	0	0	0	1	1	0
Multiple organ dysfunction syndrome	1	1	43	0	0	1	0	0	0	0	0	0	1	0	0	1	0
Renal failure	1	1	19	1	1	1	0	0	0	0	0	0	0	0	1	1	0
Renal impairment	1	1	0	0	1	1	0	0	0	0	1	0	0	1	0	1	1
Respiratory failure	1	1	668	0	0	1	1	0	1	0	0	0	0	0	0	1	0
Myocardial infarction	12	15	_	5	2	6	4	4	4	1	5	1	0	1	4	13	5
Myocardial infarction	9	9	275	2	1	2	2	2	2	1	3	1	0	1	2	8	3
Acute myocardial infarction	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0
Arrhythmia	1	1	15	0	0	0	0	1	0	0	1	0	0	0	1	1	1
Cardiopulmonary failure	1	1	146	1	0	1	1	0	1	0	1	0	0	0	0	1	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Cor pulmonale	1	1	308	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Ejection fraction decreased	1	1	16	1	0	1	0	0	0	0	0	0	0	0	0	1	1
Myocardial ischaemia	1	1	95	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Cardiac failure	10	13	_	5	1	6	6	0	6	5	5	2	1	5	4	8	3
Cardiac failure	3	3	0	2	0	2	1	0	1	1	1	1	1	1	2	2	0
Cardiac failure acute	2	2	341	0	0	0	0	0	1	0	1	0	0	0	0	2	1
Cardiac failure congestive	2	2	36	1	1	2	1	0	1	0	1	0	0	1	2	2	2
Cardiac arrest	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	0	0
Cor pulmonale	1	1	0	1	0	1	1	0	1	1	0	1	0	1	0	1	0
Decreased appetite	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	0	0
Leriche syndrome	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0
Pancytopenia	1	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
Right ventricular failure	1	1	648	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Neoplasm	12	13	_	2	3	6	0	1	0	0	1	0	0	1	1	5	2
Adenocarcinoma gastric	1	1	79	1	0	1	0	0	0	0	0	0	0	0	1	1	1
Anaemia	1	1	14	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Breast cancer	1	1	14	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Cervix carcinoma	1	1	500	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gallbladder cancer	1	1	477	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Hepatocellular carcinoma	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Hodgkin's disease	1	1	287	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lung cancer metastatic	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Neurofibrosarcoma	1	1	156	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Non-small cell lung cancer stage IIIA	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Pancoast's tumour	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0
Plasma cell myeloma	1	1	0	0	1	1	0	1	0	0	1	0	0	1	0	0	0
Respiratory failure	1	1	393	0	0	0	0	0	0	0	0	0	0	0	0	1	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Sepsis	6	8	_	2	2	3	0	0	0	0	0	0	0	0	0	5	0
Sepsis	3	3	134	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Burn infection	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Haemolysis	1	1	64	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Klebsiella sepsis	1	1	97	1	1	1	0	0	0	0	0	0	0	0	0	1	0
Lymphoma	1	1	49	1	1	1	0	0	0	0	0	0	0	0	0	1	0
Septic shock	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Pneumonia	5	5	_	0	0	1	0	0	0	0	0	0	0	0	0	2	1
Pneumonia	2	2	233	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Pneumonia aspiration	1	1	375	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Post procedural pneumonia	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Septic shock	1	1	233	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal haemorrhage	4	4	_	2	2	4	2	1	3	0	3	0	0	4	1	4	1
Gastrointestinal haemorrhage	3	3	29	1	2	3	1	1	3	0	2	0	0	3	1	3	1
Hepatorenal syndrome	1	1	6	1	0	1	1	0	0	0	1	0	0	1	0	1	0
Gastrointestinal infection	4	4	_	0	0	0	1	1	1	2	2	0	0	2	0	4	0
Gastroenteritis	4	4	101	0	0	0	1	1	1	2	2	0	0	2	0	4	0
HIV	3	4	_	0	0	1	0	0	0	0	0	0	0	0	2	4	3
HIV infection	2	2	0	0	0	1	0	0	0	0	0	0	0	0	0	2	1
Anaemia	1	1	99	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Gastroenteritis	1	1	85	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Injury	4	4	_	2	0	2	0	0	0	0	0	0	0	0	0	4	2
Alcohol poisoning	2	2	127	2	0	2	0	0	0	0	0	0	0	0	0	2	1
Road traffic accident	1	1	371	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Overdose	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Malaria	1	3	_	0	0	0	3	0	3	0	3	0	0	3	1	0	0
Anaemia	1	1	149	0	0	0	1	0	1	0	1	0	0	1	1	0	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Malaria	1	1	149	0	0	0	1	0	1	0	1	0	0	1	0	0	0
Multiple organ dysfunction syndrome	1	1	152	0	0	0	1	0	1	0	1	0	0	1	0	0	0
Opportunistic infection	2	3	_	0	1	1	0	1	0	1	1	0	1	1	2	3	2
Central nervous system infection	1	1	48	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Encephalitis	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Gastritis	1	1	34	0	0	0	0	1	0	1	1	0	1	1	1	1	1
Cerebrovascular accident	2	2	_	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Cerebrovascular accident	2	2	190	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Intestinal ischaemia	1	2	_	0	2	2	0	0	0	0	0	0	0	0	2	2	0
Intestinal ischaemia	1	1	129	0	1	1	0	0	0	0	0	0	0	0	1	1	0
Metabolic acidosis	1	1	129	0	1	1	0	0	0	0	0	0	0	0	1	1	0
Pancytopenia	2	2	_	0	1	2	0	1	1	1	0	0	1	1	1	1	2
Pancytopenia	2	2	28	0	1	2	0	1	1	1	0	0	1	1	1	1	2
Pyelonephritis	1	2	_	0	0	0	0	0	0	1	1	0	0	0	0	2	0
Hypoglycaemic coma	1	1	295	0	0	0	0	0	0	1	1	0	0	0	0	1	0
Pyelonephritis acute	1	1	324	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Seizure	2	2	_	1	1	1	0	0	0	0	0	0	0	0	0	1	1
Generalised tonic-clonic seizure	1	1	260	1	1	1	0	0	0	0	0	0	0	0	0	1	1
Seizure	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adrenal insufficiency	1	1	_	1	1	1	0	0	0	0	0	0	0	0	1	1	1
Adrenal insufficiency	1	1	67	1	1	1	0	0	0	0	0	0	0	0	1	1	1
Anaemia	1	1	_	0	1	1	0	0	0	0	0	1	0	0	0	1	0
Anaemia	1	1	0	0	1	1	0	0	0	0	0	1	0	0	0	1	0
Cardiomyopathy	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Cardiomyopathy	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Coma	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Coma	1	1	79	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Complete heart block & prolonged QT	1	1	_	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Atrioventricular block complete	1	1	118	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Coronary artery insufficiency	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Coronary artery insufficiency	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperbilirubinaemia	1	1	_	0	1	1	0	1	1	0	0	0	1	1	1	1	1
Hyperbilirubinaemia	1	1	0	0	1	1	0	1	1	0	0	0	1	1	1	1	1
Hyperglycaemia	1	1	_	0	0	1	0	0	0	0	0	0	0	1	0	1	0
Hyperglycaemic hyperosmolar nonketotic syndrome	1	1	28	0	0	1	0	0	0	0	0	0	0	1	0	1	0
Homicide	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Victim of homicide	1	1	228	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Meningitis	1	1	_	0	1	1	0	0	0	0	0	0	0	0	0	1	1
Meningitis streptococcal	1	1	280	0	1	1	0	0	0	0	0	0	0	0	0	1	1
Multiorgan failure	1	1	_	0	0	0	0	1	1	1	1	0	0	1	1	0	0
Multiple organ dysfunction syndrome	1	1	20	0	0	0	0	1	1	1	1	0	0	1	1	0	0
Pancreatitis acute	1	1	_	0	0	0	0	1	1	0	1	0	0	1	0	0	0
Pancreatitis acute	1	1	403	0	0	0	0	1	1	0	1	0	0	1	0	0	0
Progressive multifocal leukoencephalopathy	1	1	_	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Progressive multifocal leukoencephalopathy	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Respiratory infection from food aspiration	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory tract infection	1	1	278	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Suicide	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Completed suicide	1	1	715	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Thrombosis	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Thrombosis	1	1	404	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*Days between the start date of the TB regimen including Bdq/Dlm and the onset date of the event.

Table 6: Full description of life-threatening non-fatal serious adverse events reported between 01-Apr-2015 and 31-Mar-2019 in endTB patients exposed to bedaquiline or delamanid by SAE term classification and MedDRA Preferred Term

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Anaemia	7	7	_	1	0	4	0	0	1	5	3	0	0	2	3	2	1
Anaemia	7	7	128	1	0	4	0	0	1	5	3	0	0	2	3	2	1
Electrocardiogram QT prolonged	7	7	_	2	2	6	5	2	6	1	3	1	0	2	2	3	0
Electrocardiogram QT prolonged	7	7	63	2	2	6	5	2	6	1	3	1	0	2	2	3	0
Tuberculosis	4	5	_	0	0	1	0	1	1	1	1	0	0	1	1	3	0
Bronchospasm	1	1	0	0	0	0	0	1	1	1	1	0	0	1	0	1	0
Infectious pleural effusion	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Pneumothorax	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pyopneumothorax	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory failure	1	1	50	0	0	1	0	0	0	0	0	0	0	0	1	1	0
Linezolid-induced bone marrow suppression	3	4	_	1	0	3	0	0	1	4	2	0	1	1	2	1	0
Anaemia	2	2	154	1	0	2	0	0	1	2	1	0	1	1	1	1	0
Bone marrow failure	1	1	350	0	0	0	0	0	0	1	1	0	0	0	0	0	0
Thrombocytopenia	1	1	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0
Renal failure	4	4	_	2	1	4	0	0	0	0	0	0	1	0	1	2	0
Acute kidney injury	1	1	0	0	0	1	0	0	0	0	0	0	1	0	1	0	0
Azotaemia	1	1	115	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Chronic kidney disease	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Renal failure	1	1	28	1	0	1	0	0	0	0	0	0	0	0	0	1	0
Hepatic failure	3	3	_	0	1	1	2	2	3	3	1	1	0	3	0	2	1
Hepatic failure	1	1	0	0	1	1	0	1	1	1	0	0	0	1	0	0	0
Hepatitis	1	1	213	0	0	0	1	0	1	1	1	0	0	1	0	1	1
Hepatotoxicity	1	1	57	0	0	0	1	1	1	1	0	1	0	1	0	1	0
Hypokalaemia	3	3	_	0	1	2	0	0	0	0	0	0	1	2	2	1	0
Hypokalaemia	3	3	4	0	1	2	0	0	0	0	0	0	1	2	2	1	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Allergic reaction	2	2	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0
Anaphylactic shock	1	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0
Hypersensitivity	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Complete heart block & prolonged QT	1	2	_	0	2	0	0	1	0	0	0	0	0	0	0	2	0
Electrocardiogram QT prolonged	1	1	118	0	1	0	0	1	0	0	0	0	0	0	0	1	0
Syncope	1	1	118	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Hyperglycaemia	2	2	_	0	0	0	0	0	0	0	0	0	0	0	1	2	0
Hyperglycaemia	2	2	72	0	0	0	0	0	0	0	0	0	0	0	1	2	0
Hypoglycaemia	2	2	_	0	0	1	0	0	0	0	2	0	0	0	2	2	0
Hypoglycaemia	2	2	147	0	0	1	0	0	0	0	2	0	0	0	2	2	0
Myocardial infarction	2	2	_	1	0	1	2	0	2	1	1	0	1	1	0	2	1
Cardiac pseudoaneurysm	1	1	433	0	0	0	1	0	1	1	0	0	1	1	0	1	0
Myocardial infarction	1	1	185	1	0	1	1	0	1	0	1	0	0	0	0	1	1
Vomiting	2	2	_	1	0	1	1	1	0	1	0	0	0	1	1	1	0
Hypovolaemic shock	1	1	50	0	0	1	1	1	0	0	0	0	0	1	1	1	0
Vomiting	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Alcohol abuse	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Alcoholic psychosis	1	1	459	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Appendicitis	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Appendicitis	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiac failure	1	1	_	0	1	1	0	0	0	0	0	0	0	1	0	1	1
Cardiac failure congestive	1	1	7	0	1	1	0	0	0	0	0	0	0	1	0	1	1
Cholecystitis, acute	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Cholecystitis infective	1	1	476	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Diabetes	1	1	_	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Diabetic ketoacidosis	1	1	174	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Gastrointestinal infection	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SAE term classification MedDRA Preferred Term	#Patients	#SAEs	Mean time-to-onset*	Final action taken: Drug withdrawn			#SAEs possibly related to TB drugs								#SAEs related to		
				Bdq	Dlm	Other TB drug	Bdq	Dlm	Cfz	Lzd	Mfx/ Lfx	Imp/ Cln	Injectables	Other	Non-TB drugs	Co-morbidities	Other
Hypovolaemia	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypophosphataemia	1	1	_	0	0	1	0	0	0	0	0	0	0	0	1	1	0
Hypophosphataemia	1	1	43	0	0	1	0	0	0	0	0	0	0	0	1	1	0
Neoplasm	1	1	_	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Intestinal obstruction	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0
Opportunistic infection	1	1	_	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Respiratory failure	1	1	79	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Orthostatic syncope	1	1	_	0	0	0	0	1	0	1	0	0	1	1	0	0	0
Syncope	1	1	0	0	0	0	0	1	0	1	0	0	1	1	0	0	0
Pancytopenia	1	1	_	0	0	1	0	0	0	1	0	0	0	0	0	1	1
Pancytopenia	1	1	14	0	0	1	0	0	0	1	0	0	0	0	0	1	1
Pericarditis	1	1	_	0	1	1	0	0	0	0	0	0	0	1	0	1	0
Pericarditis	1	1	0	0	1	1	0	0	0	0	0	0	0	1	0	1	0
Psychotic disorder	1	1	_	0	0	1	0	0	0	0	0	0	0	1	0	0	0
Psychotic disorder	1	1	93	0	0	1	0	0	0	0	0	0	0	1	0	0	0
Systemic inflammatory response syndrome	1	1	_	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Systemic inflammatory response syndrome	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Tachyarrhythmia	1	1	_	0	0	0	0	1	0	0	0	0	0	0	1	1	0
Tachyarrhythmia	1	1	27	0	0	0	0	1	0	0	0	0	0	0	1	1	0

*Days between the start date of the TB regimen including Bdq/Dlm and the onset date of the event.

Table 7: Serious events reported with a fatal outcome (data lock point 31-Mar-2019): by frequency of event term used

Fatal SAE (MedDRA Preferred Term)	Numbers of SAEs
Respiratory failure	61
Death	19
Disease progression	14
Cardiopulmonary failure	14
Dyspnoea	12
Myocardial infarction	10
Sudden death	9
Acute kidney injury	9
Anaemia	7
Respiratory distress	6
Gastroenteritis	5
Haemoptysis	5
Pulmonary embolism	5
Arrhythmia	4
Sepsis	4
Pulmonary haemorrhage	4
Hepatic failure	4
Septic shock	3
Multiple organ dysfunction syndrome	3
Cardiac failure	3
Cardiac failure congestive	3
Pancytopenia	3
Gastrointestinal haemorrhage	3
Acute hepatic failure	3
Chronic obstructive pulmonary disease	2
Pulmonary tuberculosis	2
Pneumonia	2
Cardiac failure acute	2
Alcohol poisoning	2
Right ventricular failure	2
Cor pulmonale	2
Cardio-respiratory arrest	2
Pneumothorax	2
Cardiac arrest	2
Renal failure	2

Fatal SAE (MedDRA Preferred Term)	Numbers of SAEs
Cerebrovascular accident	2
Metabolic acidosis	2
HIV infection	2
Hyperbilirubinaemia	2
Seizure	1
Pneumonia aspiration	1
Neurofibrosarcoma	1
Electrocardiogram QT prolonged	1
Pyelonephritis acute	1
Electrolyte imbalance	1
Coma	1
Empyema	1
Pancreatitis acute	1
Encephalitis	1
Progressive multifocal leukoencephalopathy	1
Gallbladder cancer	1
Burn infection	1
Gastritis	1
Meningitis streptococcal	1
Acute respiratory failure	1
Aspiration	1
Gastrointestinal disorder	1
Overdose	1
Cardiomyopathy	1
Plasma cell myeloma	1
General physical health deterioration	1
Post procedural pneumonia	1
Generalised tonic-clonic seizure	1
Bone tuberculosis	1
Haemolysis	1
Renal impairment	1
Asphyxia	1
Central nervous system infection	1
Hepatic encephalopathy	1
Acute myocardial infarction	1
Ventricular extrasystoles	1
Meningitis tuberculous	1

Fatal SAE (MedDRA Preferred Term)	Numbers of SAEs
Victim of homicide	1
Completed suicide	1
Cervix carcinoma	1
Myocardial ischaemia	1
Hepatorenal syndrome	1
Non-small cell lung cancer stage IIIA	1
Chronic hepatic failure	1
Pancoast's tumour	1
Hodgkin's disease	1
Cardiogenic shock	1
Sudden cardiac death	1
Cor pulmonale acute	1
Adenocarcinoma gastric	1
Coronary artery insufficiency	1
Tuberculoma of central nervous system	1
Post procedural pulmonary embolism	1
Chronic respiratory failure	1
Atrioventricular block complete	1
Hyponatraemia	1
Adrenal insufficiency	1
Hypovolaemic shock	1
Decreased appetite	1
Intestinal ischaemia	1
Breast cancer	1
Klebsiella sepsis	1
Respiratory tract infection	1
Leriche syndrome	1
Road traffic accident	1
Lung cancer metastatic	1
Cachexia	1
Lymphoma	1
Ejection fraction decreased	1
Malaria	1
Thrombosis	1
Hyperglycaemic hyperosmolar nonketotic syndrome	1
Tuberculosis	1
Hyperkalaemia	1

Fatal SAE (MedDRA Preferred Term)	Numbers of SAEs
Hypoglycaemic coma	1
Weight decreased	1
Hepatitis	1
Hepatocellular carcinoma	1
Total	**317**

Table 8: Non-fatal events of any severity grade defined by the reporter as immediately life-threatening (data lock point 31 March 2019)

Life-threatening SAE (MedDRA Preferred Term)	Numbers of SAEs
Anaemia	9
Electrocardiogram QT prolonged	8
Hypokalaemia	3
Respiratory failure	2
Syncope	2
Hypoglycaemia	2
Hyperglycaemia	2
Bone marrow failure	1
Pneumothorax	1
Intestinal obstruction	1
Bronchospasm	1
Cardiac failure congestive	1
Hypovolaemic shock	1
Cardiac pseudoaneurysm	1
Pancytopenia	1
Cholecystitis infective	1
Pyopneumothorax	1
Chronic kidney disease	1
Systemic inflammatory response syndrome	1
Diabetic ketoacidosis	1
Hypovolaemia	1
Alcoholic psychosis	1
Infectious pleural effusion	1
Hepatic failure	1
Myocardial infarction	1
Hepatitis	1
Pericarditis	1
Hepatotoxicity	1
Psychotic disorder	1
Thrombocytopenia	1
Renal failure	1
Vomiting	1
Azotaemia	1

Life-threatening SAE (MedDRA Preferred Term)	Numbers of SAEs
Anaphylactic shock	1
Tachyarrhythmia	1
Appendicitis	1
Hypophosphataemia	1
Acute kidney injury	1
Hypersensitivity	1
Total	**60**