Janssen Research & Development*

Epidemiology Study Protocol

A Multi-Country Prospective Multi-Drug Resistant Tuberculosis Patient Registry to Monitor Bedaquiline Safety, Utilization, and Emergence of Resistance

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NOTE

The outline of this template is consistent with the Guidelines for Good Pharmacoepidemiology Practices (GPP) and The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

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SYNOPSIS

Bedaquiline (BDQ, SIRTURO™) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). BDQ is indicated for use when an effective treatment regimen cannot otherwise be provided and should be administered by directly observed therapy (DOT). The safety and efficacy of BDQ for the treatment of drug-sensitive TB or for treatment of latent infection due to *Mycobacterium tuberculosis* has not been established. In addition, there are no data on the treatment with BDQ of extra-pulmonary TB (e.g., central nervous system). The safety and efficacy of SIRTURO™ for the treatment of infections caused by non-tuberculosis mycobacteria (NTM) has not been established, and the use of BDQ in these settings is not recommended.

Additionally, the World Health Organization (WHO) issued interim policy guidance on the use of BDQ in the treatment of MDR-TB and specified the essential treatment and management conditions for the use of BDQ. The interim policy guidance identified the need for collection of additional data to further evaluate the benefits and risks of BDQ treatment beyond data provided from the BDQ Phase II clinical development program. Specifically, the interim guidance identified the need to collect additional data from larger patient populations representative of the target population for BDQ treatment that would be able to yield results with high precision and generalizability to global populations with respect to efficacy, safety, and emergence of resistance to BDQ or to drugs in background regimen.

Janssen Research and Development LLC proposes the establishment of a prospective, multi-country MDR-TB registry to further assess the benefits and risks of BDQ by evaluating BDQ safety, effectiveness, and emergence of resistance, BDQ drug utilization, and adherence to WHO guidance in the use of BDQ in MDR-TB treatment. The following primary objectives were specifically chosen to address gaps in the currently available data informing BDQ benefits and risks:

- To describe the type of hospital or outpatient setting administering MDR-TB treatment
- To describe MDR-TB treatment delivery modalities, including treatment and management programs in place, administration of drug under closely monitored conditions, and consultation with experts in clinical management of MDR-TB and public health authorities such as national MDR-TB advisory groups within National TB Control Programs
- To describe the demographic and clinical characteristics of MDR-TB patients participating in the registry
- To describe MDR-TB treatment regimen utilization including dosages, duration, past treatment history, past medical history, concomitant medications used for conditions other than TB
- To measure adherence to WHO guidance in terms of selection of MDR-TB regimens and selection of patients for BDQ treatment
- To describe the indication for use of BDQ
- To measure extent to which patient informed consent is obtained for receipt of BDQ
- To describe BDQ and background drug susceptibility testing expressed as minimum inhibitory concentration (MIC) at baseline and for isolates from the last positive specimens
- To actively monitor adverse events using cohort event monitoring, including the monitoring for drug-drug interactions
- To actively monitor for mortality events using cohort event monitoring that includes collection of cause of death where available

- To estimate the relative risk of adverse events and mortality events by comparing event rates among BDQ-treated patients to respective event rates among patients not treated with BDQ, adjusting for potential imbalances in predictors of receiving BDQ for treatment, as well as predictors of mortality, assuming the availability of comparable populations
- To describe the following treatment outcomes separately for patients with MDR-TB and patients with non- MDR or MDR status not documented, as stipulated by the WHO revised definitions for resistant TB cases in 2013: cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated, and treatment success
- To compare the treatment outcomes of cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated, and treatment success between BDQ-treated patients and patients not treated with BDQ

The research design uses a prospective observational comparative cohort study of patients treated for MDR-TB in multiple countries included in the early adopter (WHO pilot) program. Patients are enrolled in the registry by their healthcare provider once the healthcare provider diagnoses a patient with MDR-TB (inception cohort for comparison) or decides to treat with BDQ (exposure cohort specifically identifying indication for use for BDQ). All patient follow-up data will be collected at each visit from the healthcare provider during the course of BDQ treatment and for an additional 24 months after the last BDQ dose unless the patient is lost to follow-up or has died. Similar follow-up will be conducted for MDR-TB patients not treated with BDQ. All patients newly diagnosed and treated for MDR-TB will be eligible for inclusion in the registry. All patients initiating BDQ treatment will be eligible for inclusion in the registry. All patients meeting the inclusion criteria and providing informed consent for participation in the study will be enrolled. The registry enrollment period will be open for 36 months with an additional 24 months of follow-up for safety assessment. This enrollment period should allow the enrollment of approximately 3000 MDR-TB patients treated with BDQ.

Data will be collected in an observational manner such that the management of the patient is determined by the patient and the caregiver and not influenced by the registry protocol. The registry will describe care as it is provided.

Relevant Institutional Review Board (IRB)/Ethics Committee (EC) and Health Authority (HA) approvals will be secured prior to initiating the study.

A separate statistical analysis plan and data collection form to meet the registry objectives will be submitted for review.

Analyses of MDR-TB drug susceptibility will use the total number of MDR-TB patients included in the registry. Proportions will describe the number of patients whose post-enrollment isolates exhibit at least 4-fold increase in BDQ MIC in comparison to baseline MIC, provided that the post-baseline MIC is >0.25 mg/mL based on phenotypic methods on solid or liquid media. Additional proportions will describe the number of patients with pre-XDR and XDR-TB.

ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
BDQ	Bedaquiline
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CRF	Case Report Form
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy Short-course
DS	Drug Susceptible
EC	Ethics Committee
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
FDA	United States Food and Drug Administration
GMS	Global Medical Safety
GPP	Good Pharmacoepidemiology Practices
HA	Health Authority
HIV-1	human immunodeficiency virus type 1
IRB	Institutional Review Board
MIC	Minimum inhibitory concentration
MDR-TB	Multi Drug Resistant Tuberculosis
NTM	Nontuberculosis mycobacterium
RMP	Risk Management Plan
SD	standard deviation
SPP	Specialty Pharmacy
SSCT	standard short-course therapy
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
TB	Tuberculosis
U.S.	United States
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB

1. INTRODUCTION

1.1. Background

On December 28, 2012 the United States (U.S.) Food and Drug Administration (FDA) granted Janssen Therapeutics, Division of Janssen Products, LP accelerated approval to SIRTURO™ (bedaquiline) tablets for the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) as part of combination therapy in adults. The European Commission granted conditional approval to SIRTURO™ in the European Union (EU) on March 6, 2014. Bedaquiline (BDQ) is also registered in the Russian Federation and South Korea, and is currently under review for approval in other countries worldwide.

BDQ has a novel mechanism of action (adenosine 5'-triphosphate [ATP] synthase inhibition), potent in vitro activity against both replicating and non-replicating bacilli, and significant bactericidal and sterilizing activity in the murine model of TB infection. It has been tested in vitro against multiple strains of *M. tuberculosis* and is equally active against drug susceptible (DS), $MDR_{H\&R}$ (resistant to isoniazid and rifampin only), pre-extensively drug resistant (XDR), and XDR strains of *M. tuberculosis* (Huitric 2007[13], Lounis 2012[19]). Due to its novel mode of action, BDQ defines a new class of anti-TB compounds. It is a diarylquinoline which is the first new anti-tuberculosis drug since 1998 (rifapentine received accelerated approval in the US on 22 June 1998). The distinct target and mode of action of BDQ minimizes the potential for cross-resistance with existing anti-TB drugs.

1.1.1. Epidemiology of MDR-TB

MDR-TB has been reported in all regions of the world. The true burden of the disease is likely to be underestimated due to limitations of survey data. The prevalence of drug-resistant TB is usually presented as the proportion of TB cases exhibiting resistance to anti-TB drugs rifampicin and isoniazid.

According to the World Health Organization (WHO) annual report on Global Tuberculosis Control (2013[27]), there were an estimated 450,000 (range 300,000 to 600,000) new cases of MDR-TB globally in 2012. Among patients with pulmonary TB notified in 2012, there were an estimated 300,000 (range 220,000 to 380,000) MDR-TB cases in 2012. India, China, the Russian Federation and South Africa carry nearly 60% of the estimated global burden of MDR-TB. Globally, an estimated 3.6% (95% CI: 2.1% to 5.1%) of new TB cases and 20.2% (95% CI: 13.3% to 27.2%) of retreatment TB cases have MDR-TB. At the country level, the proportion of MDR-TB cases among new cases and previously treated cases of TB ranged from 0 to 34.8% and from 0% to 68.6%,

respectively. The highest proportions of MDR-TB are found in countries in Eastern Europe and Central Asia (WHO 2013[27]).

The WHO estimates there were 76,400 (range 73,400 to 79,400) MDR-TB cases in the WHO European region among notified TB patients in 2012. The estimated proportion of TB cases that have MDR-TB was 16% among new TB cases and 45% among retreatment TB cases (WHO, 2013[27]). According to the European Centre for Disease Prevention and Control (ECDC) annual report on Tuberculosis Surveillance and Monitoring in Europe (2014[9]), there were 68,423 TB cases reported in the European Union (EU)/European Economic Area (EEA) countries in 2012. In 2012, MDR-TB was reported for 4.6% (range 0 to 25.5%) of TB cases with drug susceptibility test results in the EU/EEA Region. The prevalence of MDR-TB was 2.6% (range 0 to 20.5%) among new TB cases and 18.8% (range 0 to 50%) among previously treated cases (ECDC 2014[9]).

According to the Centers for Disease Control and Prevention (CDC) annual report on TB (CDC 2013[4]), there were 83 cases of MDR-TB reported in the U.S. in 2012. The proportion of MDR-TB was 1.1% in new TB cases and 2.9% in previously treated cases (CDC 2013[4]).

An increasing number of TB cases that are resistant to isoniazid and rifampicin plus a fluoroquinolone and at least one injectable second-line drug, known as extensively drug-resistant TB or XDR-TB, have been reported. XDR-TB has been documented in 92 countries globally. Surveillance data from 79 countries and territories revealed the average proportion of MDR-TB cases with XDR-TB was 9.6% (95% CI: 8.1% to 11%) (WHO 2013[27]). In the EU/EEA Region, the prevalence of XDR among MDR-TB cases tested for second-line drug susceptibility was 13.7% (range 0 to 50%) in 2012 (ECDC 2014[9]).

1.1.2. Demographics in MDR-TB

Males predominate among TB cases in most countries. However, analysis by the WHO suggested no overall association between MDR-TB and sex of the subject. Based on drug resistance surveillance data stratified by sex, the odds ratio of harbouring MDR-TB strains for female TB patients compared with male TB patients was 1.1 (95% confidence interval [CI]: 0.9-1.4) (WHO 2010[29]). In the 13 countries of Central and Eastern Europe, the frequency of MDR-TB was much higher in all age groups compared with the rest of the countries and peaked in young adulthood. In the other countries, frequency of MDR-TB declined linearly with age group (WHO 2010[29]).

1.1.3. Risk Factors for MDR-TB

The main risk factor for development of resistance among TB cases is incorrect TB treatment, usually associated with intermittent drug use, errors in medical prescription, poor patient adherence, and low quality of TB drugs (Matteelli 2014[21]). Many other risk factors for drug resistance and for MDR-TB have been identified in studies including previous TB treatment, irregular treatment, female sex, non-permanent residents, urban migration, urban residence, frequent travelers, younger age, lack of sewage in home, alcoholism plus smoking, and lung cavities (Caminero 2010[3]). A systematic review to determine risk factors associated with MDR-TB in Europe found previous TB treatment to be the strongest risk factor. The pooled risk of MDR-TB was 10 times higher in previously treated cases than never treated cases, with wide heterogeneity among studies. The analysis also found that patients with MDR-TB were more likely to be foreign born, younger than 65 years, male, and human immunodeficiency virus (HIV) positive (Faustini 2006[10]).

1.1.4. Main Treatment Options

The WHO-recommended treatment strategy for DS-TB is directly observed treatment short-course (DOTS). DOTS combines 5 elements: political commitment; microscopy services; drug supplies; surveillance and monitoring systems; and use of highly efficacious regimens with direct observation of treatment. The standard WHO chemotherapy treatment regimen for DS-TB consists of a 2-month intensive phase during which 4 drugs are administered once. or twice per week (isoniazid, rifampicin, pyrazinamide, and ethambutol), with a continuation phase of 4 months during which 2 drugs are administered (usually isoniazid and rifampicin) to which the mycobacterium has been demonstrated to be sensitive for 4 months (Chan 2002[6], Douglas 1999[8]). Streptomycin is also used as a first line drug to treat DS-TB, usually for retreatment of newly diagnosed cases that failed to complete the initial treatment course or are responding poorly to their first course of TB treatment.

MDR-TB is considered curable but cannot be adequately treated with the standard short-course therapy (SSCT) (Chan 2002[6], Douglas 1999[8]). MDR-TB therapy often requires extensive chemotherapy (up to 2 years of treatment) with a combination of less efficacious second line drugs, requires extensive supervision and treatment costs are extremely expensive. Most authorities recommend a regimen consisting of either 3 or 4 oral anti-TB drugs in combination with 1 injectable drug (Frieden 1999[12]).

1.1.5. Mortality and Morbidity

MDR-TB represents a major threat to global TB control. On average, these patients require a treatment duration of 2 years on average with the substantially more toxic and less potent second-line anti-TB drugs. Cure rates are lower and mortality higher than for DS TB, particularly if patients are coinfected with HIV. According to the latest WHO data, only 48% of the MDR-TB patients in the 2010 cohort of detected cases were successfully treated, reflecting high mortality rates and loss to follow-up (WHO 2013[27]).

Mortality and case fatality estimates are uncertain partly due to incomplete coverage of global drug resistance surveillance and the lack of direct measurements of MDR-TB deaths. An estimated 170,000 (range 102,000 to 242,000) deaths caused by MDR-TB occurred in 2012, including those with HIV infection (WHO 2013[27]). This high overall mortality reflects poor diagnostic and treatment capacity for MDR-TB globally. Even for patients that make it into good treatment programmes, overall mortality still exceeds 10%, with a range of 8% to 21% (Wells 2010[24]). Two independently conducted meta-analyses from 2009, each including approximately 30 studies in MDR-TB, found death as a reported outcome in 11% of treated patients (Johnston 2009[17], Orenstein 2009[22]). A more recent meta-analysis reflecting data from 9,153 individual patients reported a mortality rate of 15% (95% CI: 14.5% to 16%). Patients who died were significantly older, more likely to be HIV co-infected, with more extensive disease (defined as acid fast bacilli [AFB]-smear positive or cavities on chest x-ray if no information about AFB-smear), and/or had prior therapy (Ahuja 2012[1]).

1.1.6. Important Comorbidities Found in MDR-TB

Important comorbidities in patients with MDR-TB include HIV/AIDS, diabetes, and depression. Limited data are available on the incidence, prevalence, and mortality of these comorbidities in patients with MDR-TB. Therefore, the facts and figures presented in this section relate to DS-TB unless otherwise specified.

The WHO reports that 13% of the 8.6 million people who develop TB each year are HIV positive, equivalent to 1.1 million new TB cases among people living with HIV in 2012 (WHO 2013[27]). Persons who have both HIV and latent TB are 20 to 30 times more likely to develop active TB compared to those without HIV infection (CDC 2007[5]). Globally, 20% of TB patients with a documented HIV test result in 2012 were HIV positive. The highest rates of HIV coinfection in TB patients are in the African Region, where 43% of TB patients tested for HIV were coinfected, followed by the Region of the Americas (16%). In the WHO European region, 6.3% of TB patients tested for HIV were coinfected (WHO 2013[27]).

Globally in 2012, there were an estimated 0.32 million HIV-associated TB deaths (WHO 2013[27]). Based on treatment outcome data from 81 countries, accounting for 21% of the estimated global number of HIV-related TB cases, the death rate reported for HIV positive TB cases in 2009 was 20% compared with 3% among HIV-negative TB cases (WHO 2011[28]).

A review of TB and diabetes found that among the 10 highest burden TB countries in 2010, 11.4% of incident cases also had diabetes; by 2030 this figure is estimated to be 14.1% (Ruslami 2010[23]). Diabetes has been found to be associated with a 3.11 fold (95% CI: 2.27-4.26) increased risk of active TB among epidemiologic cohort studies. It has been estimated that comorbidity with diabetes occurs in 11% of TB cases in Mexico and 14.8% of incident TB cases in India (Jeon 2008[16]).

The prevalence of diabetes in most populations is 10% and the relative risk of TB varies from 3 to over 8 depending on the study population. In populations of India, the prevalence of diabetes in the TB population approaches 50% (Young 2009[31]). In a trial of a general medicine clinic in Spain, 69 (42%) of 163 diabetic patients had a positive tuberculin skin test indicating latent TB. Diabetic patients who need more than 40 units of insulin per day are twice as likely to develop active TB as those using lower doses, signifying a link with disease severity. Two trials have shown that diabetic patients are more likely to develop MDR-TB than those without diabetes; however, 4 trials in disparate settings showed no significant increased risk (Dooley 2009[7]). A retrospective study among Mexican and Mexican-American TB patients found that 31.6% of patients with MDR-TB reported diabetes. MDR-TB was significantly associated with diabetes (OR 2.1, 95% CI: 1.1-4.2) when adjusted for age, gender, drug and alcohol abuse in Texas and in Mexico (OR 1.80, 95% CI: 1.1-2.9) when adjusted for age and gender (Fisher-Hoch 2008[11]). In a cohort of 1407 patients with MDR-TB, 17% had comorbid diabetes mellitus (Kang 2013[18]).

DS-TB treatment failure is more common among patients with diabetes and mortality is increased. A trial in Egypt reported a 3.9 times increased risk of treatment failure in patients with diabetes compared to those without. In an Indonesian trial, 22.2% of patients with diabetes had positive sputum cultures at 6 months following treatment compared to 6.9% among controls. In a descriptive case-control study, treatment failure or death was observed in 41% of patients with TB and diabetes mellitus compared to only 13% of those with TB alone. Other trials have found up to a 6.5-6.7 times increased risk of death among diabetics, and 1-year all-cause mortality rate of 17.6% among diabetic patients compared to 7.7% among non-diabetic controls (Dooley 2009[9]). A systematic

review of the impact of diabetes on outcomes of TB treatment found patients with diabetes have a risk ratio of death during TB treatment of 1.89 (95% CI: 1.52-2.36) (Baker 2011[2]).

The prevalence of depression and other psychiatric disorders is high among patients with TB. Prevalence varies depending on the study population and criteria used to define depression. High rates have been observed in India, with a reported prevalence in 1 trial of 49%. A survey of hospitalised TB patients in South Africa reported a prevalence of 68%. Lower rates have been reported in Nigeria, with 1 trial reporting an overall prevalence of depression in TB patients to be 27.7%, including 21.5% with mild depression and 6.2% with moderate depression (Issa 2009[15]). Another trial in Nigeria reported the prevalence of depression to be 45.5% in TB patients and 13.4% in non-tuberculosis controls (Ige 2011[14]). In a cross-sectional survey of pulmonary TB patients in the Philippines, 16.8% of study participants were classified as having depression (Masumoto 2014[20]).

High rates of relapse and poor outcomes among patients with depression have been observed due to poor medication compliance (Issa 2009[15]).

1.1.7. Concomitant Medication(s) in MDR-TB

Concomitant medications observed in patients with HIV/AIDS and MDR-TB include antiretroviral (ARV) therapy. Concomitant medications observed in the treatment of diabetes among patients infected with MDR-TB include insulin, sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors. Concomitant medications observed in the treatment of depression among patients infected with MDR-TB include selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors.

1.1.8. Bedaquiline

BDQ is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary MDR-TB. BDQ is indicated in the U.S. for use when an effective treatment regimen cannot otherwise be provided and should be administered by DOT. Additionally, the World Health Organization (WHO) has issued guidance on the treatment of MDR-TB with BDQ. The safety and efficacy of BDQ for the treatment of DS-TB or for treatment of latent infection due to *Mycobacterium tuberculosis* has not been established. In addition, there are no data on the treatment with BDQ of extra-pulmonary TB (e.g., central nervous system), and the safety and efficacy of SIRTURO™ for the treatment of infections caused by non-tuberculous mycobacteria

(NTM) has not been established. Therefore, use of BDQ in these settings is not recommended.

1.2. Overall Rationale for the Study

A post marketing requirement relative to the accelerated approval of bedaquiline by the U.S. FDA included the development of a patient registry for BDQ-treated patients. Additionally, the WHO issued interim policy guidance on the use of BDQ in the treatment of MDR-TB identified the need for collection of additional data to further evaluate the benefits and risks of BDQ treatment beyond data provided from the BDQ Phase II clinical development program. Specifically, the interim guidance identified the need to collect additional data from larger patient populations representative of the target population for BDQ treatment that would be able to yield results with high precision and generalizability to global populations with respect to efficacy, safety, and emergence of resistance to BDQ or to drugs in background regimen.

Janssen Research and Development LLC proposes the establishment of a prospective, multi-country MDR-TB registry to further assess the benefits and risks of BDQ by evaluating BDQ safety, effectiveness, and emergence of resistance, BDQ drug utilization, and adherence to WHO guidance on the use of BDQ in MDR-TB treatment.

1.3. STUDY OBJECTIVES

1.3.1. Primary Objectives:

The following primary objectives were specifically chosen to address gaps in the currently available data informing BDQ benefits and risks:

- To describe the type of hospital or outpatient setting administering MDR-TB treatment
- To describe MDR-TB treatment delivery modalities, including treatment and management programs in place, administration of drug under closely monitored conditions, and consultation with experts in clinical management of MDR-TB and public health authorities such as national MDR-TB advisory groups within National TB Control Programs
- To describe the demographic and clinical characteristics of MDR-TB patients participating in the registry
- To describe MDR-TB treatment regimen utilization including dosages, duration, past treatment history, past medical history, concomitant medications used for conditions other than TB
- To measure adherence to WHO guidance in terms of selection of MDR-TB regimens and selection of patients for BDQ treatment

- To describe the indication for use of BDQ
- To measure extent to which patient informed consent is obtained for receipt of BDQ
- To describe BDQ and background drug susceptibility testing expressed as minimum inhibitory concentration (MIC) at baseline and for isolates from the last positive specimens
- To actively monitor adverse events using cohort event monitoring, including the monitoring for drug-drug interactions
- To actively monitor for mortality events using cohort event monitoring that includes collection of cause of death where available
- To estimate the relative risk of adverse events and mortality events by comparing event rates among BDQ-treated patients to respective event rates among patients not treated with BDQ, adjusting for potential imbalances in predictors of receiving BDQ for treatment, as well as predictors of mortality, assuming the availability of comparable populations
- To describe the following treatment outcomes separately for patients with MDR-TB and patients with non- MDR cases or MDR status not documented, as stipulated by the WHO revised definitions for resistant TB cases in 2013: cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated, and treatment success
- To compare the treatment outcomes of cured, treatment completedtreatment failed, died, lost to follow-up, not evaluated, and treatment success between BDQ-treated patients and patients not treated with BDQ

2. OVERVIEW OF STUDY DESIGN

2.1. Study Design

The research design uses a prospective observational comparative cohort study of patients treated for MDR-TB in multiple countries included in the early adopter (WHO pilot) program. A case of tuberculosis is one in which a health worker (clinician or other medical practitioner) has diagnosed TB. MDR-TB is defined as TB caused by *Mycobacterium tuberculosis* resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs. Patients are enrolled in the registry by their healthcare provider once the healthcare provider diagnoses a patient with MDR-TB (inception cohort for comparison) or decides to treat with BDQ (exposure cohort specifically identifying indication for use for BDQ). All patient follow-up data will be collected at each visit from the healthcare provider during the course of BDQ treatment and for an additional 24 months after the last BDQ dose unless the patient is lost to follow-up or has died. Similar follow-up will be conducted for MDR-TB patients not treated with BDQ. Two options are under evaluation for the recruitment of MDR-TB patients not treated with BDQ. The first option under consideration is to include patients who are eligible for BDQ, but refuse BDQ at sites where BDQ is available. The second

option under consideration is the use of a stepwise cluster wedge design to enroll patients at centers who would be eligible for BDQ, but do not have access. The method for selecting MDR-TB patients not treated with BDQ will depend on how BDQ is made available in the early adopter countries. All patients newly diagnosed and treated for MDR-TB will be eligible for inclusion in the registry. Additionally, all patients initiating BDQ treatment will be eligible for inclusion in the registry regardless of the indication for use. All patients meeting the inclusion criteria and providing informed consent for participation in the study will be enrolled. The registry enrollment period will be open for 36 months with an additional 24 months of follow-up for safety assessment. This enrollment period should allow the enrollment of approximately 3000 MDR-TB patients treated with BDQ.

Data will be collected in an observational manner such that the management of the patient is determined by the patient and the caregiver and not influenced by the registry protocol. The registry will describe care as it is provided.

Relevant Institutional Review Board (IRB)/Ethics Committee (EC) and Health Authority (HA) approvals will be secured prior to initiating the study.

2.2. Study Design Rationale

The prospective observational comparative cohort design of the registry was chosen to specifically meet the study objectives. Prospective data collection not only facilitates characterization of clinics treating MDR-TB patients and how care is delivered, as well as patients being treated, but also facilitates active pharmacovigilance via real-time identification and reporting of adverse events, including deaths. By including MDR-TB patients as well as all patients treated with BDQ, the study is able to assess the indication for BDQ use, as well as how BDQ is used. By including patients treated with BDQ and MDR-TB patients not treated with BDQ, the study is able to provide an assessment of the relative risk of adverse events and deaths for BDQ relative to the observed risk among similar MDR-TB patients. The study design also provides for drug sensitivity testing over time for MDR-TB patients as well as the possibility of collecting samples for future drug sensitivity testing. The registry design was chosen due to the limited data on BDQ utilization and treatment outcomes (clinical and microbiologic) as well as the limited information on treatment outcomes for other MDR-TB treatments. Patients will be treated at a limited number of healthcare sites under the early adopter program (WHO pilot sites) which facilitates targeting healthcare providers who treat MDR-TB with educational material on the importance of enrolling patients in the registry.

3. STUDY POPULATION

3.1. Patient Selection

3.1.1. Inclusion Criteria

The study population will be drawn from the population of all patients treated for MDR-TB in multiple countries. All patients newly diagnosed with MDR-TB as well as all patients newly treated with BDQ at participating sites will be eligible for inclusion in the registry. All patients meeting registry inclusion criteria will be eligible for inclusion in the registry provided they submit the necessary informed consent for participation.

3.1.2. Exclusion Criteria

No specific exclusion criteria will be applied in this study other than those scenarios that follow from the inclusion criteria.

3.1.3. Data Source(s)

3.1.3.1. Healthcare Providers

Data for the registry will be gathered by healthcare providers treating patients MDR-TB at participating centers that evaluate, diagnose and treat patients with MDR-TB. Data will be recorded at patient enrollment and at each subsequent patient visit.

4. STATISTICAL METHODS

4.1. Sample Size and Study Precision

The three year enrollment period of the registry is estimated to result in an enrollment of 3000 to 5000 BDQ-treated patients.

A cohort of 3000 patients gives a 95% probability of identifying an adverse event with an incidence rate of 1:1000.

Based on the sample size estimates below, a registry of 1000 BDQ-exposed patients would have 95% power to detect a Relative Risk of 2 assuming alpha = 0.05 and a 1:1 ratio of BDQ-exposed patients to unexposed patients for events that occur with a frequency of at least 3%.

Power and Sample Size for Adverse Events Occurring with a Frequency of at Least 3%

	Relative Risk						
Exposed	**1.5**	**2**	**3**	**4**	**5**	**7**	**10**
0	0.049985	0.049985	0.049985	0.049985	0.049985	0.049985	0.049985
100	0.133214	0.252768	0.559428	0.828643	0.961157	0.999754	1.000000
200	0.190756	0.414883	0.844041	0.986772	0.999721	1.000000	1.000000
300	0.243884	0.552078	0.952777	0.999299	0.999999	1.000000	1.000000
400	0.294233	0.663681	0.987120	0.999970	1.000000	1.000000	1.000000
500	0.342210	0.751574	0.996745	0.999999	1.000000	1.000000	1.000000
600	0.387925	0.819043	0.999224	1.000000	1.000000	1.000000	1.000000
700	0.431400	0.869774	0.999824	1.000000	1.000000	1.000000	1.000000
800	0.472639	0.907271	0.999961	1.000000	1.000000	1.000000	1.000000
900	0.511649	0.934588	0.999992	1.000000	1.000000	1.000000	1.000000
1,000	0.548449	0.954244	0.999998	1.000000	1.000000	1.000000	1.000000

4.2. Measurements

Janssen is currently collaborating with the WHO to outline a comprehensive list of data elements and definitions as well as data collection instruments.

4.2.1. Exposure Definition and Measures

Exposure to MDR-TB regimens will be determined by documentation by the healthcare provider. The initiation date of MDR-TB treatment for each patient will be the drug initiation date as reported by the healthcare provider. The discontinuation date for each drug exposure will be defined as the date the drug was stopped as reported by the healthcare provider. Duration of exposure will be based on initiation and discontinuation dates for each drug. Switches from one drug to another will be captured and time on drug will be defined by the exposure periods.

4.2.2. Outcome Definitions and Measures

The registry is designed to observe several aspects of MDR-TB treatment such as drug utilization characteristics, treatment outcomes (clinical and microbiologic), and safety outcomes (adverse events and mortality). All study outcomes will be documented by the healthcare provider and will be reported up to 24 months after discontinuation of MDR-TB treatment.

Study outcome definitions will include:

- Medical indication for BDQ treatment as reported by the healthcare provider
- Frequency of use of expert medical consultation in MDR-TB treatment with BDQ
- Drug susceptibility of MDR-TB isolates (Pre-XDR, XDR) and drug susceptibility to BDQ based on MIC reported

- Laboratory location and type performing susceptibility testing as well as type of test performed
- Past treatment history, past medical history, prior medications utilization, and health care site of treatment
- Use of DOT for drug administration
- Adverse events including deaths over the course of MDR-TB therapy recorded using WHO guidance for pharmacovigilance of medicines used in the treatment of tuberculosis (WHO 2012[25])
- Comorbidities prior to initiating MDR-TB therapy as well as over the course of therapy
- Concomitant medications prior to initiating MDR-TB therapy as well as over the course of therapy
- Reason for discontinuation of MDR-TB therapy
- Change in TB background regimen (Y/N)
- Cavities on chest x-ray
- Acid fast bacilli-smear ≥ 1+ (Y/N)

The following definitions will be used for treatment outcomes among MDR-TB cases (WHO, 2013[30]):

- Cured: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a].
- Treatment Completed: Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a].
- Treatment Failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:
    - Lack of conversion[b] by the end of the intensive phase[a], *or*
    - Bacteriological reversion[b] in the continuation phase after conversion[b] to negative, *or*

- Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, *or*
- Adverse drug reactions (ADRs).

- Died: A patient who dies for any reason during the course of treatment.

- Lost to Follow-Up: A patient whose treatment was interrupted for 2 consecutive months or more.

- Not Evaluated: A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)

- Treatment Success: The sum of cured and treatment completed

[a] For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the program. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for *Cured*, *Treatment completed* and *Treatment failed* start to apply.

[b] The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining *Treatment failed*, reversion is considered only when it occurs in the continuation phase.

The following definitions will be used for treatment outcomes among non MDR cases or MDR status not documented (WHO 2013[30]):

- Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

- Treatment Completed: A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

- Treatment Failed: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
- Died: A TB patient who dies for any reason before starting or during the course of treatment.
- Lost to Follow-Up: A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for which the treatment outcome is unknown to the reporting unit.
- Treatment success: the sum of cured and treatment completed.

Appropriate use of BDQ encompasses aspects of drug utilization such as whether or not treatment was initiated in an eligible patient at the earliest opportunity, the patients' treatment history, medical history, concomitant medication use, type of facility dispensing treatment, whether lab confirmation is documented, indication for use (i.e., drug resistant versus drug sensitive versus latent infection versus extra-pulmonary versus non-tuberculosis mycobacteria infections), documentation of treatment outcome (clinical and microbiologic). Safety data will include the collection of adverse events, serious and non-serious, concomitant medications, and concurrent diseases/diagnoses which may impact the reported event or its resolution; data on deaths will be collected along with attribution. Treatment adherence will be measured by the percent of prescribed doses taken as directly observed therapy. Adherent will be defined as taking greater than 80% of prescribed doses. Non-adherent will be defined as taking 80& or fewer of the prescribed doses.

4.2.2.1. Adverse Events

An AE is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment (WHO 2012[25]).

A treatment-emergent AE (TEAE) will be defined as any new AE reported or any worsening of an existing condition on or after the first dose of BDQ drug, and up to and including 30 days after last BDQ dose.

Seriousness of AE will be graded per the following (WHO 2012[25]):

- Not serious
- Results in hospitalization (caused or prolonged)
- Results in permanent disability
- Results in congenital abnormality
- Is life-threatening
- Results in death

Serious AEs are those AEs that are graded in any seriousness category other than the "Not Serious" category.

Relation of AEs (e.g., whether there is a reasonable possibility that the study drug caused the event) using the following requirements (WHO 2012[25]):

- Probable: the event is an identifiable clinical or laboratory phenomenon; the time elapsed between the administration of the drug and the occurrence of the event is plausible; the event cannot be explained by concurrent disease or any other drug or chemical; the patient recovered within a plausible length of time following withdrawal of the drug; rechallenge did not occur, or the result is unknown.

- Possible: the time elapsed between the administration of the drug and the occurrence of the event is plausible; the outcome of withdrawal of the suspect medicine is not known, and/or the medicine might have been continued and the final outcome is not known; and/or there might be no information on withdrawal of the medicine; and/or the event could be explained by concomitant disease or use of other drugs or chemicals; and/or there might be no information on the presence or absence of other medicines.

- Unrelated (Unlikely): the event occurred with a duration to onset that makes a causal effect improbable with the drug being considered and/or; the event commenced before the first administration of the drug; and/or the drug was withdrawn and this made no difference to the event when, clinically, recovery would be expected; and/or it is strongly suggestive of a non-causal relationship if the drug was continued and the event resolved.

The following will be used for grading the severity of AEs following WHO (WHO 2012[25]):

- Mild

- Moderate
- Severe

Severity does not have the same meaning as seriousness. The degree of severity reflects the intensity of the event. A patient can experience a severe event that is not serious, e.g. pruritus.

4.2.3. Potential Confounders and Effect Modifiers

Potential confounders and effect modifiers will be collected and used to describe the cohort. Patient factors will include demographics, comorbidities and concomitant medications that might influence MDR-TB treatment use.

- Age
- Sex
- Weight or BMI
- Ethnicity
- Length of TB infection
- Evidence of cavitary disease on chest X-RAY
- Depression
- HIV/AIDS
- Diabetes
- Cardiovascular risk factors for QT prolongation, electrolyte abnormalities and arrhythmia (including medications)
- Hepatic risk factors (alcohol use, history of liver disease, chronic hepatitis)
- TB drug susceptibility to Isoniazid and rifampin, as well as pre-XDR/XDR
- Prior treatment with TB therapy
- Prior adherence to TB therapy
- Concomitant TB therapy administered with BDQ

- Substance use

4.2.4. Length of Follow-up

Each patient will be followed for 24 months from the discontinuation of MDR-TB therapy, until death, or loss to follow-up within the cohort, whichever occurs first. Time varying variables will be recorded at each patient visit.

4.3. Analyses

4.3.1. Descriptive Analysis

Frequencies, proportions, and rates will be determined as appropriate based on each study objective.

4.3.2. Specific Comparisons

The observed rates of adverse events and death among BDQ-treated patients will be compared with the observed rates of adverse events and death among patients with similar clinical characteristics, but not treated with BDQ.

4.4. Statistical Analysis Plan

4.4.1. Analysis of Baseline Characteristics

Baseline characteristics including demographics, country of origin, medical history, susceptibility of baseline MDR-TB isolates to BDQ and TB background regimen drugs, and use of medications at cohort entry will be described. The analysis will report the frequency distribution (number and percentage of patients) for categorical variables and descriptive statistics (median, mean, standard deviation [SD]) for continuous variables.

4.4.2. Analysis of Study Objectives

4.4.2.1. Descriptive Analyses

This analysis will describe and summarize the prescribing and utilization of MDR-TB treatments, as well as patient treatment outcomes (clinical and microbiologic), and TB isolate susceptibility. MDR-TB treatment will be summarized by patient demographics and clinical characteristics (comorbidities and concomitant medications). In addition, the details of MDR-TB treatment will be described including indication of use, dose, frequency, duration of use, usage with TB background regimen, and susceptibility of concomitant TB treatment regimens. Patients treated with BDQ outside of the MDR-TB indication will be summarized by patient demographics and clinical characteristics including indications of use, frequency, duration of use, usage with TB background regimen, and susceptibility of concomitant TB treatment regimens. Additionally,

treatment outcomes will be described separately for MDR-TB cases and non MDR cases or MDR status not documented (WHO, 2013[30]).

Proportions and 95% confidence intervals will be estimated separately for BDQ-treated patients and non-BDQ-treated patients for each study objective.

Additionally the following treatment outcomes will be estimated separately for patients with MDR-TB for BDQ-treated patients and non-BDQ-treated patients: cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated, and treatment success.

Analyses of MDR-TB drug susceptibility will use the total number of MDR-TB patients included in the registry. Proportions will describe the number of subjects whose post-enrollment isolates exhibit at least 4-fold increase in BDQ MIC in comparison to baseline MIC, provided that the post-baseline MIC is >0.25 mg/mL based on phenotypic methods on solid or liquid media. Additional proportions will describe the number of patients with pre-XDR and XDR-TB.

4.4.2.2. Analysis of Adverse Events

Incidence rates of adverse events will be calculated for the BDQ and non-BDQ treated cohorts. Additional descriptive analyses will include incidence rates of adverse events of interest for BDQ treated patients and non-BDQ treated patients calculated by dividing the total number of each adverse event by the total person-exposure time and expressed as the number of events per person-year, and 95% confidence intervals.

Relative risk rates and 95% confidence intervals will be calculated and appropriate stratified analyses will be conducted for each adverse event, including death. Poisson regression models will be used to adjust for potential confounders based on baseline clinical characteristics and patient demographics. Adjustments for imbalances between the treatment groups will be applied using accepted methods based on sample size availability and the observed overlap of key patient characteristics. If the sample size is adequate, propensity score methods may be used to adjust for imbalances between the 2 treatment groups before receiving the BDQ treatment or other MDR-TB therapy. Adjustment methods will be determined *a priori* to any comparative analysis with respect to safety outcomes.

4.5. Evaluation of Appropriateness of Comparison Study

The evaluation of appropriateness of a comparison of BDQ-exposed patients with non-BDQ-treated MDR-TB patients will be based on the consistency of the clinical

experience of the 2 cohorts. This assessment will be conducted based on distribution of propensity scores for receipt of BDQ or other treatment regimens.

The evaluation of clinical experience will assess the patients' clinical and demographic characteristics in relation to receipt of BDQ and other MDR-TB regimens. Information will be captured on the patients' clinical and demographic characteristics that could be predictive of treatment appropriateness. This information will be incorporated into multivariate model to identify a group of patients with similar characteristics to the BDQ cohort but treated with other MDR-TB treatments. All patients will be assigned a propensity score ranging from 0 to 1 that represents the fitted probability of receiving BDQ. The scores from non-BDQ-treated patients will be plotted against those for BDQ-treated patients. Overlap in the cohorts based on sample size estimates of approximately 750 patients per treatment group in the propensity space must exist for a comparison of safety events between the two groups. An epidemiologist trained in propensity score estimation and matching methodology will make this assessment on the epidemiological validity of a comparison between the 2 treatment cohorts.

4.6. Data Quality Assurance and Validation Procedures

The registry will be managed by INC Research and will utilize the INC Research Coordinating Center (RCC). INC Research will develop the case report form (CRF) with input from Janssen as well as from INC Research's data management team, biostatistician, epidemiologist, and Project Manager as relevant. Concurrent with the development of the CRF, INC Research will draft CRF completion guidelines for review by the INC Research registry team and Janssen and CRF Completion Guidelines.

INC Research's RCC is staffed with Central Monitoring Associates with varied backgrounds ranging from patient care experience in nursing, to clinically oriented research as study coordinators, call center nurses, or safety specialists, to backgrounds in data management, research project administration, or regulatory document administration. All Central Monitoring Associates undergo extensive training regarding 21 CFR Part 50, 54, 56, 312, 314, the principles of International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and INC Research standard operating procedures (SOPs).

Staff of the RCC at INC Research are experienced in working directly with both patients and HCPs via telephone and email. Dedicated Central Monitoring Associates will be designated for this registry; however, all Central Monitoring Associates in the RCC are cross-trained on all projects to provide maximum coverage.

A National Coordinator from INC Research will review CRFs for accuracy, identifying missing data and resolving any inconsistencies and transfer key coded data to the RCC within 24 hours or data receipt. Additionally, the National Coordinator will maintain CRFs as well as participant enrollment records and ongoing assessments.

INC Research will use Oracle Clinical RDC Onsite electronic CRFs (eCRFs) to process the data for the registry.

To enable the team to collect data while on the phone with HCPs, paper copies of the CRF, suitable for hand-written completion will also be available to reporters who prefer to complete a paper form, via access from the registry website. Paper forms can be sent to the registry via mail or electronically. Once received by the registry, the data from these forms will be entered into the system by the central monitoring team or the reporters who will have direct access to the data entry system.

Occasionally, HCPs provide patient medical records in lieu of completed CRFs. The registry will review the medical records and transcribe information onto the appropriate CRFs.

Simple on-line checks will be displayed for the Central Monitoring Associates at point of entry, reducing the need for queries. The data management team will perform additional data review of the more complex checks and raise queries with the central monitoring team as required in the EDC system.

Quality measures included in the registry include monitoring of all incoming and outgoing calls to capture the following information:

- Time and date of call
- Contact type
- Name and position of site personnel making call
- Topic of call (e.g., protocol question, technical assistance, medical information)
- Resolution of call (e.g., completed, next steps, triage)
- Additional comments and questions from the HCP

The database used enables the RCC to categorize calls by contact type, reason for calls, etc. The RCC database enables fast, accurate reporting on the total number of calls

received and made daily, weekly, or monthly or, for example, report on the types of calls or reasons for the calls by contact type.

Calls conducted by the Central Monitoring Associates to the national coordinators facilitate enrollment and retention by minimizing reporter burden in all aspects of the registry.

Additional data quality efforts are focused on minimizing reporter burden through the following approaches:

- Streamlining data collection with simple and concise CRFs that focus on the endpoints of interest as specified in the protocol
- Providing multiple options for submitting data such as phone, fax, or mail and allowing the reporter to select his/her preferred method of communication
- Providing the HCP with information for verification, where applicable, rather than recreating the data at a given contact

Central Monitoring Associates who are intimately involved in the registry handle the query process. The same Central Monitoring Associates who conduct the calls also manage the query resolution process. To assure data quality INC Research has developed a process that proves to be both efficient and effective. The Central Monitoring Associate from the RCC establishes a rapport with the HCPs at first contact and maintains this relationship throughout the data collection and query resolution processes.

A standard query follow-up regimen of four attempts is used at two-week intervals using phone, fax, mail and/or e-mail as appropriate for query resolution. If no further information is obtained on an otherwise evaluable case, the discrepant data fields may be left blank or identified as “Unknown” as appropriate. However, some cases may be flagged as “Lost to Follow-Up” or “Not Valid” if critical data required to evaluate the case is missing or unknown.

5. STUDY LIMITATIONS

The proposed study is based on analysis of prospective cohort data provided by healthcare providers treating patients with BDQ. The following limitations should be considered:

The registry may include bias related to the observational nature of the data and potential lack of data due to loss to follow-up or essential data not collected as routine fields.

These studies are also subject to real-world prescribing practices that may not provide sufficient patient numbers to meet study goals of ascertainment within a reasonable timeframe. Additionally, participation in the registry may influence prescribing of BDQ in routine patient care.

Allocation of treatment is not subject to randomization. Patients will likely be channeled to treatment based on several measured and unmeasured characteristics and based on treatment guidelines. This potentially introduces associations between exposures and outcomes that are confounded.

6. ETHICAL ASPECTS

6.1. Privacy of Personal Data

Confidentiality of patient records will be maintained at all times. All analyses of data will be performed using appropriately de-identified data without access to personal identifying information. All study reports will contain aggregate data only and will not identify individual patients or physicians. Medical record abstraction, if available, will only be performed after receiving a waiver of authorization from the relevant data holder's privacy board and approval from an Institutional Review Board (IRB). At no time during the study will the sponsor receive patient identifying information.

6.2. Informed Consent

Each subject must give written consent according to local requirements after the nature of this research study has been fully explained. The informed consent form (ICF) must be signed before any study-related data is collected. The ICF used must be approved by the reviewing IRB and acceptable to JRD. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and JRD policy. The collection and processing of personal data from subjects enrolled in this study will be limited to data necessary to fulfill the objectives of the study. Sample data and corresponding relevant clinical data will be made non-identifiable by the removal of personal identifiers.

A subject may withdraw their consent for this research study through the contact information given on the Informed Consent. JRD will not use the collected data upon receipt of such a request. However, data that have already been processed will be retained by JRD to avoid compromising data analysis.

7. ADMINISTRATIVE REQUIREMENTS

7.1. Adverse Event Reporting

This study is based on aggregate analyses, and the sponsor will report aggregate findings as study reports. Due to the prospective design of this study, in instances where an HCP identifies adverse events or serious adverse events, regardless of causality, the events will be captured by staff at the RCC during the registry data collection process, and an AE form will be forwarded to the Sponsor for review and to be entered to the Sponsor's Safety database. The events will be reported as individual case safety reports under timelines as appropriate per company standard operating procedures.

7.2. Special Situations

In addition to adverse events, the following categories of data are considered to be 'special situations' and also require reporting to Global Medical Safety (GMS), whereby processing and reporting are determined in accordance with national reporting requirements for each marketed product in a particular country or territory:

- Drug exposure during pregnancy (maternal and paternal)
- Exposure to a Janssen medicinal product from breastfeeding
- Overdose of a Janssen medicinal product
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product (e.g., occupational exposure)
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a Janssen medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product
- Off-label use of a Janssen medicinal product

7.3. Study Completion/Termination

7.3.1. Study Completion

The study will be completed three years after registry start. Interim analyses will be conducted to check the number of BDQ-treated patients captured in the registry. Updates on patient accrual and timelines for study completion will be provided annually as part of the Interim Report. A descriptive report on patient counts and the safety profile with respect to study objectives will be prepared in alignment with the PSUR schedule.

7.3.2. Study Termination

JRD has the right to close study sites, e.g. in case of non-compliance with protocol, IRB guidelines, Sponsor procedures and ICH guidelines.

7.3.3. Dissemination and Communication of Study Results

Study results will be disseminated and communicated through the final study report. Study progress will be provided in Interim Reports for BDQ-containing products. Additionally, findings of potential scientific or public health importance will be disseminated through conference presentations or journal articles as appropriate.

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