RESEARCH PROPOSAL

(A SCIENTIFIC & TECHNOLOGICAL PROJECT)

Project Title (in Vietnamese)	
Nghiên cứu triển khai thí điểm theo dõi biến cố bất lợi trên bệnh nhân sử dụng phác đồ có bedaquilin tại 3 cơ sở trọng điểm trong Chương trình Chống Lao Quốc gia	
Project Title (in English)	
The pilot implementation of monitoring adverse events in patients treated with bedaquiline-containing treatment regimen at 3 sentinel sites in the Vietnam National Tuberculosis Control Program	
Duration	33 months

1. Overview of research-related situation and rationale for the research

1.1. Situation of research on bedaquilin in Vietnam and other countries

Bedaquilin (BDQ, also known as TMC207, R207910) is an anti-TB drug of diarylquinolin group - the first drug with a novel mechanism of action different from those anti-TB drugs which have been used and given approval by the US Food and Drug Administration (FDA) over the last 40 years [10]. The drug has prolonged terminate half-life, approximately 5.5 months.

This is the first drug which is indicated to use in combination with other anti-TB drugs for those patients diagnosed to have drug-resistant TB. BDQ was detected through the screening process of over 70,000 compounds having active inhibition of *Mycobacterium smegmatis* - a type of aerobic Gram (+) necrosis bacteria with rapid growth, often used in the model that causes TB in experiment conditions [16]. BDQ has a capability of inhibiting the biosynthesis of ATP (ATP synthase) - an enzyme necessary for the supply of energy to the TB bacteria. In addition, BDQ is capable to inhibit active replication of thoroughbred strains and multi-drug resistant *M. tuberculosis* [9]. Given such

different target of action and mechanisms that BDQ minimize the possibility of cross-resistance with other anti-TB drugs. Additionally, BDQ has affinity with bacterial ATP synthase 20,000 times higher than human ATP synthase, so that the target effect of the drug has a high selectivity. In December 2012, although the Phase III clinical trial was being conducted, FDA has approved the use of BDQ in combination regimen for treatment of multidrug-resistant tuberculosis (a regimen with minimum of 4 drugs) under accelerated approval Regulations [11]. However, FDA also requires that BDQ is indicated only for patients aged 18 and older, patients who do not respond to other treatment regimens and the need for close monitoring by health workers [11]. Recommended dosage is 400 mg BDQ with oral administration, once daily for 2 weeks, and then the dose is reduced to 200 mg, three times per week, with a 24-week duration of treatment. Nearly 15 months after the FDA's decision, on May 03, 2014, the European Medicines Agency (EMA) granted the marketing authorization for BDQ on its territory with strict indication limits similar to those of FDA [14]. On March 22, 2013, marketing authorization was given to BDQ in Russia. On March 21, 2014, marketing approval was given to BDQ in South Korea as a rare/orphan drug. BDQ has been circulated under the trade name of SIRTURO™.

From 2005 to 2012, there were 11 Phase I studies conducted to analyze such parameters as pharmacokinetics, pharmacodynamics, dosage, drug interactions and toxicity of BDQ with a total of 189 participants [9]. The safety of the dosage ranging 100 mg - 800 mg used alone and in combination with anti-TB regimens was studied. No deaths or serious adverse events were observed among those healthy volunteers. The majority of recorded adverse events included central nervous system disorders (24.3%) and digestive disorders (16.9%). Headache, dizziness, dry mouth, diarrhea, fatigue/malaise, increased blood uric acid levels and skin rashes were events recorded at most (with a frequency of 5% of subjects)[11]. No subjects using BDQ (alone or in combination with other anti-TB drugs) had QT interval greater than 500

milliseconds (ms) and no subjects had to stop taking the drug due to prolonged QT interval [9].

Before conducting the randomized controlled clinical trial, a Phase 2a study (denoted as C202) was conducted with a total of 75 patients, including 45 patients using monotherapy with BDQ within 7 days at dose levels ranging from 25 mg to 400 mg [21]. In those dose levels, the dose of 400 mg/day was recognized to be effective in inhibiting bacteria equivalent to rifampicin 600 mg and isoniazid 300 mg with the same duration/course of drug use. None of the patients died within 7 days of dosing. Two patients in the group using 400 mg BDQ died during the follow-up period of TB treatment with a regimen containing isoniazid, rifampicin, pirazinamid, and ethambutol but none of those cases was found to be in association with the use of BDQ previously. The rate of adverse events in the group using BDQ and the group using other anti-TB drugs was balanced. However, there was a phenomenon of QT interval increase after drug use compared with baseline among patient groups, specifically as follows: group of patients receiving 400 mg BDQ (median QT interval increase: 24.5 ms), the group of patients receiving 100 mg BDQ (median QT interval increase: 10.1 ms), group of patients receiving 300 mg isoniazid (median QT interval increase: 15.8 ms), and group of patients receiving 600 mg rifampicin (median QT interval increase: 13.1 ms).

Two Phase IIb studies/trials have played a key role in providing data for priority approval process of BDQ at the pharmaceutical regulatory agencies, including a randomized controlled trial which was divided into two separate stages (denoted as C208 Stage 1 and as C208 Stage 2) and a single-arm, open label study which was denoted as C209. The key findings on the safety of BDQ was recorded from the Phase IIb study includes [27].

Mortality

In C208 Stage 1 study, 2 patients (8.7%) in BDQ group and 2 patients (8.3%) in placebo group died. No deaths occurred during the course of using BDQ.

Thirteen deaths were reported from C208 Stage 2 study: 10 patients (12.7%) in BDQ group and 3 patients (3.7%) in placebo group had serious adverse events leading to mortality (intention-to-treat [ITT] analysis). A case of death (alcohol poisoning) occurred while receiving BDQ. The median time since administration of last BDQ dose until death of nine remaining patients was 244 days. One of the 10 deaths in the BDQ group, and 1 out of 3 deaths in placebo group occurred after week 120. Among BDQ group, the most frequent cause of death reported by the investigators was TB (5 patients). For all the deaths due to tuberculosis, the final bacteria test outcome of patients was either failure in sputum culture conversion or relapse of TB. Causes of death for the remaining cases were varied. Researchers have reviewed all cases of serious adverse events leading to death to see if they were associated or less associated with BDQ/placebo. The reasons for the imbalance in deaths between the two arms were not identified.

16 out of 233 patients (6.9%) died in extended C209 study. 10 patients died in the whole process of treatment (3 of whom died from experiencing adverse drug events during treatment phase). 2 patients died during follow-up after completion of medication.

The cause of death due to tuberculosis developments was found with 5 cases, 1 case of congestive heart failure, 1 case of pneumonia, 1 case of renal failure, 1 case of hemoptysis, 1 case of respiratory failure, and 1 case of high blood pressure. The majority of deaths due to TB is caused by failure of sputum culture conversion or relapse. 4 deaths occurred during the period in which the subjects have withdrawn from the study, and all those 4 cases were assumed to have the cause of death related to tuberculosis. The researchers neither thought about nor suspected that BDQ was the cause of dead/fatal cases.

Frequently reported adverse events (AE):

The majority of AE cases (> 20%) were recorded during the treatment study stage. Findings from C208 Stage 1 and Stage 2 showed the incidence rates of AE in BDQ group were as follows: nausea - 35.3%, vomiting - 29.4%,

arthralgia - 20.6%, headache - 23.5 %, and hyperuricemia - 22.5%. Such symptoms as headache, nausea and arthralgia encountered in BDQ group were found at a higher level than that in placebo group (compared ratio was respectively 23.5% versus 11.4%, 35.3% versus 25.7%, and 29.4% versus 20.6%); the incidence of nausea and hyperuricemia was similar in both groups.

Most reports of AE observed in C209 study were similar in C208 study, for example, increased hyperuricemia (13.7%), arthralgia (12.4%), nausea (11.6%), vomiting (9%), and headache (9%).

Hepatic toxicity:

With in-depth analysis of C208 Stage 1 and Stage 2 trial, liver adverse events are defined by a higher level of liver disorders observed among patients in the group using BDQ than in the placebo group during the drug use stage/period (8.8% in BDQ group versus 1.9% in placebo group) and in the whole process/period of treatment (11.8% versus 6.7%). Adverse events that occurred in the liver during the BDQ using period was 11.6% in C209 study. No serious adverse events occurred during the stage/period for which indication of this drug was given.

Assessment of liver function according to Temple's corollary (equivalent to the highest AST or ALT level which are 3-fold the upper limit of normal (3xULN), not coincided with elevated bilirubin with 2-fold the upper limit of normal (2xULN)) in C208 Stage 2 study showed that the percentage experiencing AE in patients using BDQ was higher than that in the placebo group (9 patients (8.8%) compared with 4 patients (3.8%)). Approximately 50% of patients using BDQ regimens had abnormal liver functions evaluated against Temple's corollary during the period of using BDQ. Three patients (with a history of liver enzyme elevations in the evaluation against Temple's corollary), were recorded with occurrence of liver adverse events and had to stop using prolonged BDQ. Two of those 3 patients had occurrence of liver adverse events and hesitated to withdrawal from the study, while 1 patient had elevated liver enzymes at the time before treatment and one case had occurrence of adverse

events on the background/baseline of hepatitis B. Assessment of elevated liver enzymes according to Temple's corollary on patients involved in C209 study revealed that a total of 22 patients (9.4%) were seen with elevated liver enzymes, including 9 patients who were recorded with elevated liver enzymes throughout TB treatment course, and 13 patients with elevated liver enzymes during the phase of using BDQ in a combination.

Two patients were observed to have elevated liver enzymes on the principle of Hy's Law (ALT or AST >3xULN with accompany of elevated bilirubin 2xULN upward) although those two cases were not in concomitant use with another drug causing liver toxicity or alcohol.

A patient in BDQ group of C208 Stage 2 study was found with the sign of elevated enzymes during 24 weeks of treatment with BDQ, at week 84 and throughout process of follow-up. Experts assessed the statement that hepatotoxicity in this patient was complicated due to TB background treatment regimen and alcohol abuse by patients. This patient died at week 98 due to septic shock with peritonitis and was commented by researchers that the death was unrelated to treatment drug. One patient in C209 study showed the sign of elevated liver enzymes level at week 32, after completion of 58 days of treatment. Researchers commented that this adverse event was not related to BDQ and it is very probable that it is related to background regimen. Experts assessed that this bad condition was due to the use of background regimen with 4 drugs which are highly toxic to the liver (levofloxacin, protionamid, pyrazinamide, and ethambutol) although the cause of BDQ drug use in combination was not completely eliminated. This patient had recovered at week 48.

Cardiovascular toxicity:

In both Stage 1 and Stage 2 of C208 study, the mean QT interval adjusted by formula F (QTcF) was prolonged in 2 groups - BDQ group and control group, but more occurrence was observed in BDQ group, and the mean increase in BDQ group was evaluated immediately after the first treatment day onwards.

The largest mean QTcF increase at the time prior to medication during the first 24 weeks of treatment in BDQ group was 15.4ms (at week 24) and 7.7ms in placebo group (at week 20). In the group of patients using BDQ, the mean variations in QTcF compared to the reference values had equivalence between the 5^{th} hour after medication (equivalent period in maximum BDQ concentration in blood: Tmax) with the time immediately before dosing, suggesting that there was no relation between the maximum BDQ concentration in blood (Cmax) and QTcF interval. After the end of the period for indication of BDQ (week 24), the elevation of QTcF interval tended to gradually reduce. One patient in BDQ group in the study had QTcF value >500ms. This case is said to coincide with an adverse event of hypokalemia. QTcF value which was over 450 ms and increased from 30-60ms and> 60ms was recognized to have happened more in BDQ group compared with that in placebo group.

The mean QTcF interval recorded from patients in C209 study increased during treatment course with BDQ, with mean increase >10ms compared to reference values from week 8 to week 24 of treatment course. After week 24 (corresponding to the end of treatment course with BDQ), the mean value of QTcF gradually decreased. There were no clinically relevant changes or consistent changes over time upon recording other ECG indexes (electrocardiography - ECG). 2 patients involved in treatment clearly showed QTcF >500ms, and both of them had corresponding value QTcF >60ms compared to initial level and clofazimin contained in background treatment regimen. One of those 2 patients with level 2 hypokalemia at the time of the QTcF increase.

The proportion experiencing serious adverse events according to MedDRA Query classification for Torsades de Pointes/ increase of QT interval prolongation was low (<5%) and almost equal/balance between the two groups of patients - BDQ group as well as placebo group during the BDQ indicated treatment course, and the entire regimen-based treatment course of the patients (results of the analysis in both Stage 1 and Stage 2 of C208 study). C209 study

also provided similar results. All adverse events reported in C208 study were classified as level 1 in the taxonomy of the severity of the adverse events and no events were considered as serious or treatment for BDQ group as well as placebo group needed to be stopped. There was an adverse event recorded at level 3 (ECG QT prolongation) in C209 study, and this was a serious adverse event that BDQ use needed to be stopped. No reports mentioned Torsades de Pointes or severe ventricular arrhythmias.

The World Health Organization (WHO) commented that data on the safety and long-term efficacy of BDQ in the treatment of drug-resistant TB is still very limited. The co-infections such as HIV/AIDS and liver disorders – as well as impacts of alcohol and accompany drug use and the risk of occurrence of serious adverse events in patients have not been evaluated. Experts of the World Health Organization ranked the level of evidence about the safety of BDQ at low levels [22]. However, under pressure from the drug-resistant TB which is on an increasingly complicated trend around the world, FDA as well as some other regulatory agencies approved the marketing authorization of BDQ although safety data of the new drug gained from a Phase II clinical trial only. WHO specially encourages accelerating the Phase 2I clinical trial - to provide more adequate information on the efficacy and safety of drugs, as well as actively implement pharmacovigilance surveillance methods to create a more comprehensive data system, provide the basis for making policies on BDQ use in the future.

In June, 2013, WHO announced the interim policy guidance for the use of BDQ in combination with regimens of drug-resistant TB, with the following main principles [22]:

1. ***Treatment must be closely monitored for effectiveness of medication*** *(with treatment and management protocols to be approved by competent national regulatory agencies.*
2. ***Strict condition for patient admission****: Special caution is needed when bedaquiline is used in persons aged 65 years and older, and in adults*

living with HIV, and use of the drug in pregnant women and children is not advised

3. ***Patient informed consent obtained*** *after the patient has been explained about the potential risks and benefits of this therapy*.
4. ***Adherence to recommendations of WHO****: adherence to the principles of designing a WHO-recommended MDR-TB, especially with addition of 4 second-line drugs, which still exists. BDQ alone should not be introduced into a regimen in which the other companion drugs are known or believed to be ineffective*
5. ***Active pharmacovigilance and proper management of adverse drug reactions****: active pharmacovigilance methods should be put in place to ensure the early detection and appropriate handling of adverse drug reactions and potential drug interactions.*

1.2. Rationale for conducting the research

1.2.1. Epidemiology of drug-resistant TB in Viet Nam and the rationale to pilot BDQ use in treatment of drug-resistant TB patients

According to WHO report, Viet Nam is ranked the 12th out of 22 countries with high TB burden and ranked the 14th out of 27 countries with high burden of MDR-TB worldwide [23]. According WHO epidemiological review of situation of tuberculosis disease in Viet Nam in January 2013, TB incidence rate decreased by 2.6%/year; prevalence decreased by 4.4%/year and TB death rate dropped by 4.6%/year. However, Viet Nam still needs much effort to be able to achieve the goals of the National Strategy for TB prevention and control by 2020, with a Vision to 2030 which was approved by the Prime Minister in 2014. The 4th survey of drug-resistant TB conducted in 2011 showed that the proportion of MDR-TB among new patients and TB retreatment patients were 4% and 23.3% respectively compared with 2.7% and 19% respectively in 2004. Based on data of pulmonary tuberculosis patients registering treatment annually, it is estimated that there will be about 5,100 MDR-TB patients in Viet Nam each

year. Using predictive TIME model shows that Viet Nam needs more effort in diagnosis and treatment in order to control drug-resistant TB.

The National Tuberculosis Control Program (NTP) has piloted the MDR-TB management program in Ho Chi Minh City since 2009 and now has expanded to 41 of the 63 provinces/cities across the country (10 treatment and 31 satellite provinces). Diagnosis of multidrug-resistant tuberculosis is mainly based on Xpert MTB/RIF test - a new method of molecular biology test, certified by WHO for use in diagnosis of drug-resistant TB since 2012. The length of hospital stay for treatment of MDR-TB ranges from 2 to 4 weeks, depending on the points of treatment, and then the patient will be transferred to directly observed treatment (DOT) at Commune Health Station (CHS) or the District anti-TB Team. As of December 2014, there was a cumulative total of approximately 4,000 patients with MDR-TB treatment admitted to the program. In Viet Nam, results of MDR-TB treatment for patient cohorts in 2009, 2010, 2011 showed that our successful treatment rate was higher (70%) compared to the global average rate (48%) but mortality and drop-out rates remained relatively high due to the undesirable/side effects and prolonged treatment time (18-24 months), while treatment failure rate is about 7%, equivalent to approximately 250 patients who are currently having no follow-up/next treatment options. Results of "The 4th National drug-resistant TB survey in 2011" also shows that 16.7% of patients with MDR-TB had additional resistance to fluoroquinolone (pre-XDR, pre-XDR-TB) and 5.6% MDR-TB patients had extensively drug-resistant tuberculosis (XDR-TB). With this rate, the number of patients with pre-XDR-TB and XDR-TB is about 850 each year. However, at present, the NTP has no standard treatment regimens and guidelines for management of those patients with pre-XDR and XDR-TB.

Based on the evidence showing the benefits of new BDQ drug brought to patients, Viet Nam has committed to becoming one of the first countries in the world to use new BDQ drug for treatment of drug-resistant TB in the condition of an exploratory/investigational study of the NTP. With the support of WHO,

three workshops were held in April 2013, February, 2014 and November, 2014 in Viet Nam to introduce the development process and results of drug trials of BDQ in the world. Viet Nam currently is having adequate conditions to start using BDQ soon. It is expected that pilot will be conducted in three pilot sites of Lung Hospital in Hanoi, Can Tho Hospital of Tuberculosis and Lung Diseases, and Pham Ngoc Thach Hospital (Ho Chi Minh City).

1.2.2. The need for conducting research on monitoring adverse events of BDQ

Currently, BDQ still in the process of Phase III clinical trial. In order to have pilot drug use in patients, monitoring efficacy and safety of drugs is required. Effectiveness of BDQ will be evaluated in the study entitled ***"Exploring the use of bedaquilin in treatment regimens for XDR-TB and pre-XDR-TB in Viet Nam"*** conducted by the NTP. This study was approved by the IRB of the Ministry of Health on June 30, 2015. Parallel to this study, the National Center of Drug Information and Adverse Drug Reactions Monitoring (National DI & ADR Center) collaborated with the NTP in conducting the research ***"The pilot implementation of monitoring adverse events in patients treated with bedaquilin-containing treatment regimen at 3 sentinel sites in the Vietnam National Tuberculosis Control Program".*** Research will explore the adverse events occurring during treatment with BDQ – containing regimens and determine related risk factors. Those two studies will be conducted simultaneously and serves as an important base for benefit - risk analysis of BDQ in drug-resistant TB treatment. Data on safety from the study also provides important information to serve updating, revising WHO recommendations and guidelines on BDQ use in particular and anti-TB drugs in general.

2. Research objectives

General objective:

To investigate adverse events (AE) in patients using BDQ-containing regimen for treatment of drug-resistant TB in some sentinel sites through the active surveillance program.

Specific objectives:

1. To explore/investigate adverse events occurring in patients using BDQ for treatment of drug-resistant TB in three sentinel sites and cardiovascular adverse events of BDQ regimen.

2. To analyze factors influencing occurrence of adverse events in patients using BDQ for treatment of drug-resistant TB in three sentinel sites.

3. To evaluate impacts of adverse events on efficacy for treatment of drug-resistant TB.

3. Research activities

- Conducting surveys on characteristics of patients with treatment of drug-resistant TB enrolled in the study. Study targets include:

  - Patient's characteristics: age, sex, history of TB treatment, lesion location, clinical condition (alcohol, tobacco addiction, drug addiction, cachexia), companion diseases (CVD, liver disease, HIV infection, diabetes ...)
  - Characteristics of treatment: treatment history, treatment regimens, duration of treatment, maintenance/follow-up treatment status, treatment outcomes.

- Exploring adverse events occurring during the course of treatment with BDQ regimen. Study targets include:

  - Number of AEs in general, number of AEs/patient, occurrence frequency of each type of AE, number of AE by types of BDQ regimens, the time since the start of treatment until the occurrence of AE, severity of AE, handing of AEs (stop medication, symptom-based treatment, changing regimen or no further interventions).
  - Number of cardiovascular AEs, specific number of AE by each type (QTc interval prolongation >500 ms, Torsades de pointes, ventricular arrhythmias), Number of cardiovascular AEs in each type of BDQ regimens, the time since the start of treatment until the occurrence of AE, severity of AE, handling of AEs (stop medication, symptom-

based treatment, changing regimen or no further interventions), mean QTc interval during the process of treatment of patients corresponding to each BDQ treatment regimen/type.

- The mortality rate of patients in the study (disease-related deaths, drug-related deaths or non-identified cause).

- Analyzing factors influencing occurrence of adverse events. Study targets include:

- Analysis of factors influencing occurrence of adverse events: age, gender, history of TB treatment, lesion location, clinical condition, companion diseases, HIV status, treatment time, treatment regimens; effects of the use of drugs to some specific AEs (e.g. hepatotoxicity, nephrotoxicity ...).

- Assessing the impact of adverse events on treatment efficacy of drug resistant TB. The study targets include: determining the percentage/proportion of patients not maintaining treatment (death, drop-out, changing regimen) because of occurrence of adverse events affecting the therapeutic effect; analysis of impacts/influences of adverse event occurrence on patients' treatment effectiveness, presented through sputum culture conversion, lung lesions on X-rays and clinical outcomes of the patient; (Data on sputum examination, radiology and clinical results are retrieved directly from eTB Manager software).

4. Methods

Research methodology: Observational study (cohort event monitoring *means* longitudinal monitoring of patients over time through recoding information about adverse events and other information of the patient during the treatment using the designated data collection form).

Study sites and selection criteria of facilities involved in the study

- Treatment facilities using BDQ regimens must be selected by the Research team and the National Therapeutic Council
- Facilities should ensure DOT monitoring (of BDQ) as applied to other anti-TB drugs.

- Doctors have much experience in MDR-TB treatment
- Ability to perform and understanding of ECG to analyze the results of the QTc interval.
- Uninterrupted supply sources of approved second-line drugs.
- Laboratory capacity allows monitoring and management of drug adverse events, performing routine bacterial culture and antimicrobial susceptibility testing when required.
- Patients are admitted to hospital when necessary.
- Patients have access to the specific counselling services
- Each approved treatment facility will have a nominated responsible doctor, and another healthcare worker to assist with treatment monitoring.

On the above-mentioned basis, a decision was made by the NTP on execution of a pilot study big centers for treatment of drug-resistant TB in the country, namely Lung Hospital in Hanoi, Pham Ngoc Thach Hospital (Ho Chi Minh City) and Can Tho Hospital of Tuberculosis and Lung Diseases. Those are facilities with rich experience in management drug-resistant TB, with relatively good treatment outcomes and having sufficient clinical and laboratory infrastructure for follow-up and treatment of patients. Those three facilities are also implementing pharmacovigilance with both proactive and passive methods. The pilot of BDQ use at these facilities have received the participation consent of the hospital leaders with the aim to provide more treatment options for drug-resistant TB patients.

Sample size and sampling methods for the research

A total of 100 adult patients with severe drug-resistant pulmonary TB, pre-XDR, and XDR-TB (meeting selection criteria) will be enrolled in this study. All safety evaluations at the time of registration must be done and be checked and evaluated by the researchers before administering drugs to the patients. Results gained from before, during and at completion of treatment of all 100 patients will be recorded and reported in the study.

Estimated number of patients at each site:

- Pham Ngoc Thach Hospital: 50 patients
- Ha Noi Hospital of Lung Diseases: 30 patients
- Can Tho Hospital of Tuberculosis and Lung Diseases: 20 patients

Subjects and methods of patient selection

The following groups of subjects are put into consideration for inclusion in BDQ containing treatment regimen:

- *Pre-XDR-TB with resistance to quinolones (Pre XDR/quinolone)*: MDR-TB patients (simultaneously resistant to rifampicin and isoniazid) and have resistance to fluoroquilnolon drugs (ofloxacin and/or levofloxacin and/or moxifloxacin) who are confirmed by results of antimicrobial susceptibility testing.
- *Pre-XDR-TB with resistance to second-line anti-TB injectables (Pre-XDR/injectables*): Those MDR-TB patients have resistance to kanamycin and/or amikacin and/or capreomycin.
- *XDR-TB patients (XDR)*: patients with multidrug-resistant TB (MDR-TB) having resistance to quinolones and at least one of second-line anti-TB injectables (Cm, Km, Amk) are confirmed by antimicrobial susceptibility.
- *Multidrug-resistant TB patients being given treatment but are intolerant or resistant to many drugs in group 4*
    - Intolerance of one or more second-line anti-TB drugs in the standard regimen.
    - Multidrug-resistant Tuberculosis: MDR-TB patients having resistance to 2 anti-drugs in group 4 as classified 4 by WHO (Cs, Pto/Eto, PAS) are confirmed by antimicrobial susceptibility testing.

The selection of patients is done by checking all inclusion/exclusion criteria when conducting screening and registration. Eligibility checklist must be stored with the source documentation at study sites. If there are any inclusion criteria which are not satisfied, the subject will not be enrolled in the study.

Selection criteria

One in 4 types of subjects is included in BDQ-containing treatment regimen (regimen and specific duration of treatment are presented in Annex 3)

Exclusion criteria

- Patients who refused to sign commitment for treatment. Patients who decided not to get involved in treatment after being given proper counseling about the risks - benefits of BDQ
- Children under 18 years of age
- Pregnant women
- Women who are giving breast-feeding to their babies
- High risk of cardiovascular complications: Patients with a QT interval >500ms, with a history of arrhythmias, torsades de pointes or ventricular arrhythmias or have severe coronary artery disease.
- Extrapulmonary tuberculosis.

Due to safety-related issues, the subjects should be considered carefully before being admitted to the study:

- Patients over 65 years of age
- Patients with liver disease or liver damage/lesions shown by indicators of liver function test abnormalities, e.g. SGOT (AST) or SGPT (ALT)> 2 times of the upper limit of normal values.
- Patients with renal insufficiency, serum creatinine> 2 times of the upper limit of normal value in a state of non-dehydration; in cases of dehydration, serum creatinine should be <2 times of the upper limit of normal values after oral administration or intravenous transfusion.
- Patients with a history of skeletal muscle disease, amylase and lipase levels/indicators in initial tests are higher than normal limits
- HIV infection.

Data collection methods

Data of BDQ adverse events and other information of each patient will be collected using two types of tools/instruments:

- ***Paper-based toolkit (Annex 1):***
  - ***Form 1: Patient's initial information Form***, including demographic information, lesion location, history of TB treatment, clinical status, companion diseases, the initial tests, health-related adverse events before start of treatment, history of drug use (within 30 days), companion drugs, indicated anti-tuberculosis in the regimen.
  - ***Form 2: for gathering information about reported adverse events or changes of medications during the treatment***: including the following information about changing medications or doses of anti-TB treatment drugs, information about types of adverse events, occurrence date, severity/measures for handling events, information on current drug use, companion drugs, and drugs suspected of causing adverse events.

  Paper-based data (original copies of Form 1 and Form 2) will be periodically sent to the National DI & ADR Center once a month (the 30th day every month). Also, the staff at the facility should fill information in the adverse events management table (Form 3), to be stored in the in-patient/out-patient medical records of the patients, serving as a basis to monitor the entire process of adverse event occurrence. Copies of Form 1 will be under management and retention by staff at the facility throughout the research process.

- ***Electronic Toolkit***:

- The paper-based data of Form 1 will be entered into eTB Manager software. Some of preliminary information fields are already available on eTB Manager when patients are admitted for drug-resistant TB treatment will be directly retrieved.
- Reports being sent to the National DI & ADR Center should ensure the following deadlines (by dates updated in eTB Manager system):

+ Report of serious adverse events causing fatality or life-threatening for patients: to be sent as soon as possible but no later than 3 working days from the time of adverse event occurrence.
+ Report of remaining serious adverse events: to be sent as soon as possible but no later than 7 working days from the time of from the time of adverse event occurrence.
+ Report of non-serious adverse events: to be collected and sent monthly, before the 25th day of the month.
    - All data will be exported as excel.xls. or excel.xml. Files. Then, the received data will be cleaned and processed by the Center.

Research quality control and assurance

The research quality control and assurance will be carried out through the following steps: 1) training for data collectors, 2) setting up operations at the facility, 3) supervision and technical support for the facility during the process of data collection, 4) data management at the National DI & ADR Center, 5) evaluation of the causal relationship between the event and the drug use, and 6) data cleaning and processing.

1) Training on utilization of data collection toolkit for the staff of 3 facilities is expected to be implemented in July 2015. Staff who receive training are those people directly involved in the treatment of patients with BDQ-containing regimens at the facility (including treatment doctors, pharmacists, nurses and staff assigned to be in charge of eTB Manager software).

2) After the above-mentioned training, the supervision/technical support team (1 staff from National DI & ADR Center and 1 staff from the NTP) will directly visit each research participating facilities to set up operations, ensure necessary conditions at the facility to conduct research, and guide staff to complete forms and collect patient information if necessary.

3) In the process of data collection, electronic data will be sent and retrieved directly. At the National DI & ADR Center, to ensure data quality and

support for the facility during the process of collecting data, there are 2 staff from National DI & ADR Center and 1 staff from the NTP will be assigned to be in charge of information management in research. This Information Management Group will directly control/inspect data sent from the facilities and contact staff at the facilities when any problems arise. The research team regularly meets monthly to discuss the problems encountered in the process of conducting research and planning to pay supervisory visits to the facilities.

4) Depending on the plans of the research team, a working group (1 staff from National DI & ADR Center and 1 staff from the NTP) will be sent for monitoring, providing technical support to facilities. The above supervision mission will conduct the field supervision at each facility 6 times through the course of conducting research. The purpose of the trip is to examine the situation of managing patient admission at the facility, the work of collecting information into the forms and eTB software, detect and resolve problems occurring in the facility for data collection.

5) The monthly adverse events reports will be transferred to the committee of Experts on adverse events evaluation/examination within the framework of the study to evaluate the association between medication and occurrence of adverse events. Each adverse events report will be evaluated by two experts using WHO's rating scale (Appendix 2). For serious adverse events and some important adverse events (especially cardiovascular events), the reports will be transferred immediately to members of the Committee to evaluate and faster respond results to report sending facilities.

6) Finally, the database will be accessed/retrieved and processed on SPSS or R software. There are 2 staffs for data entry from forms for collection of patient information (Forms 1, 2) to minimize the risk of errors. Data analysts will check the entire database (both paper-based and electronic ones). The suspected errors with the entered data will be checked immediately by the initial data collected forms.

Data processing

Descriptive statistical analysis: The continuous variables with normal/standard distribution are expressed as mean ± SD (standard deviation). The nominal and categorical/ordering variables are expressed as percentages.

Linear Regression Analysis: For dependent variable which are continuous ones, univariate and multivariate linear regression analysis are applied to determine the influencing factors.

Logistic Regression Analysis: The dependent variables which are nominal and categorical/ordering variables will be converted into binary variables and applying univariate and multivariate logistic regression analysis to find factors influencing the odds ratio (OR).

Cox regression analysis: With prospective data over time, survival analysis is applied. Kaplan - Meier estimator/chart will be used to describe the adverse events that occur over time. Cox multivariate regression analysis will be made to identify influencing factors on hazard risk and estimates of relative risks.

Ethics in Research

- The approved research proposal for pilot use of BDQ in patients developed by the NTP will be adopted by the IRB of the National Lung hospital, the IRBs of the 3 research sites and IRB of the Ministry of Health
- The research monitoring adverse events occurring on this BDQ-containing regimen is an observational/descriptive study (in parallel with the general proposal clinical research conducted by the NTP), will conduct interventions (if severity of BDQ-related adverse event occurrence is recorded and evaluated) by advising the National clinical council so that it will evaluate and make decisions on changing treatment regimens.

5. Plan of implementation

Seq.	Activity	Timeline	Funding
1	Field visits to research sites	Completed September, October -	Prior to 6/2016: GFATM (estimated

		2014	58,818 USD)
2	Developing research proposals, data collection tools and guidelines on managements of adverse events	10/4/2015 – 22/5/2015	
3	Consultation with experts on research proposals and toolkit for data collection	15/05/2015 – 31/05/2015	
4	Defence of research proposals and data collection toolkit	During June, 2015	
5	Training on research roll-out for 3 sites	During July, 2015	
6	Screening, admission of patients	From August, 2015 till end of 30/4/2016	
8	Supervision and support of research sites	2 rounds (August, 2015 and May, 2016)	
7	Monitoring/following up patients (within 20 months)	From August, 2015 till end of 31/12/2017	After 6/2016: The NTP coordinating other funding sources (estimated 90,052 USD).
9	Supervision and support of research sites	4 rounds (September, 2016, November, 2016, June, 2017 and December, 2017)	
9	Raw data inspection and cleaning; data entry and	Monthly during the period from 01/08/2015	

	processing	until 31/12/2017	
10	Research review	During Quarter 1/2018	

6. Expected outcomes/products of the research

Seq	Expected products/deliverables	Product quality requirements	Quantity
1	Research finding reports (periodic reports and a final report)	Analytical reports and data sheets on assessments of adverse events of BDQ	02
2	Dissemination (*papers on specialized journals, conference reports, workshops* ...)		01

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