TBTC Study 30: A phase I/II pilot study for evaluation of low dose, once daily, linezolid plus optimized background therapy (OBT) versus placebo plus OBT for the treatment of multi-drug resistant tuberculosis

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AFB</td>
<td>Acid fast bacilli</td>
</tr>
<tr>
<td>AI</td>
<td>Associate investigator</td>
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<tr>
<td>AUC</td>
<td>Area under the concentration-time curve</td>
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<tr>
<td>BID</td>
<td>Twice a day</td>
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<tr>
<td>BPNS</td>
<td>Brief Peripheral Neuropathy Screen</td>
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<tr>
<td>BREC</td>
<td>Biomedical Research Ethics Committee</td>
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<tr>
<td>CAPRISA</td>
<td>Centre for the AIDS Program of Research in South Africa</td>
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<tr>
<td>CBC</td>
<td>Complete blood count</td>
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<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>CL</td>
<td>Systemic Clearance</td>
</tr>
<tr>
<td>Cmax</td>
<td>Peak plasma concentration</td>
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<tr>
<td>Cmin</td>
<td>Minimum plasma concentration</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P-450</td>
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<tr>
<td>DOT</td>
<td>Directly observed therapy</td>
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<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>DST</td>
<td>Drug susceptibility testing</td>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>HCL</td>
<td>Hydrochlorate</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<tr>
<td>HRPO</td>
<td>Human Research Protection Office</td>
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<tr>
<td>INH</td>
<td>Isoniazid</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ITRC</td>
<td>International Training and Research Centre for MDR TB</td>
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<td>KGVH</td>
<td>King George V Hospital</td>
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<td>KZN</td>
<td>KwaZulu-Natal</td>
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<td>LZD</td>
<td>Linezolid</td>
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<tr>
<td>MCC</td>
<td>South African Medicine Control Council</td>
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<tr>
<td>MDR</td>
<td>Multi-drug resistant</td>
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<tr>
<td>MG</td>
<td>Milligrams</td>
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<tr>
<td>MGIT</td>
<td>Mycobacterial growth indicator tube</td>
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<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
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<tr>
<td>M. tuberculosis</td>
<td>Mycobacterium tuberculosis</td>
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<tr>
<td>OBT</td>
<td>Optimized background therapy</td>
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<tr>
<td>PAS</td>
<td>Para-amino salicylic acid</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>P.O.</td>
<td>By mouth</td>
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<tr>
<td>PZA</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>QD</td>
<td>Every day</td>
</tr>
<tr>
<td>RIF</td>
<td>Rifampin</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RSA</td>
<td>Republic of South Africa</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SSRI</td>
<td>Serotonin reuptake inhibitor</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<td>TBTC</td>
<td>Tuberculosis Trials Consortium</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>$T \frac{1}{2}$</td>
<td>Elimination half-life</td>
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<tr>
<td>$T_{max}$</td>
<td>Time to reach the peak concentration</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR</td>
<td>Extensively-drug resistant</td>
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1 Protocol Synopsis

1.1 Background
World-wide, there is an increasing incidence of multi-drug resistant tuberculosis (MDR TB) and extensively drug-resistant TB (XDR TB). For patients diagnosed with either of these diseases, effective drug treatment options are sub-optimal or non-existent. In the Republic of South Africa where HIV rates are high among TB patients, there are a growing number of patients with XDR TB who have little hope for survival without new drugs for its treatment. Unlike the treatment of drug susceptible TB, the treatment of MDR TB is presently based upon expert opinion, case studies and anecdotal experience, not randomized, clinical controlled trials. Treatment regimens are long, require multiple medications, and their efficacy is uncertain in many cases. Thus, there is a need to rigorously evaluate the drugs used to treat MDR TB and XDR TB to assess efficacy endpoints and treatment duration, particularly as new anti-tuberculosis agents are developed.

Linezolid (LZD), an oxazolidinone class antimicrobial approved for Gram-positive bacterial infections, is increasingly being used off-label for drug resistant TB disease. This has occurred despite lack of clinical trial evidence of efficacy. MDR TB case series have reported relatively high rates of treatment success and of adverse effects associated with or attributed to prolonged LZD administration. With the limited number of options available for treating XDR TB, clinicians are increasingly using LZD in treatment regimens. Therefore, it is critical to examine the benefits versus risks of LZD for treatment of MDR and XDR TB in a clinical trial. As the only new potential agent on the market active against MDR TB, study of the impact of LZD on treatment of MDR TB is warranted. This study will provide overall information that will be helpful in the conduct of future MDR TB trials. The proposed phase I/II pilot study will provide information regarding the efficacy, safety and tolerability of low dose, limited duration LZD in the treatment of MDR TB and XDR TB. The findings will inform decisions regarding whether the development of a larger study should proceed. The MDR TB treatment program supervised by King George V Hospital (KGVH) in Durban, Republic of South Africa (RSA) provides us with an opportunity to conduct a pilot study addressing the safety and tolerability of LZD in patients who have MDR or XDR TB.

It is anticipated that after completing 112 doses of study therapy, some patients enrolled in TBTC Study 30 may merit consideration for the administration of unblinded, compassionate use LZD therapy. Approval for compassionate use LZD will be the purview of the KGVH MDR TB Treatment Committee. Patients for whom the benefits of compassionate use LZD may outweigh the risks could include: (a) patients with confirmed XDR TB and (b) patients with substantial drug intolerance that produces an XDR TB equivalent situation.

1.2 Treatment of MDR/XDR TB in Durban, RSA and at KGVH
South Africa has experienced accelerated growth in new TB cases, with incidence rising from less than 100 per 100,000 persons in 1990 to 558 per 100,000 in 2003. With more than 200,000 new TB patients per year, the majority of which are infected with HIV, health resources are strained. In KwaZulu-Natal (KZN) Province, 1,146 TB cases were registered
in 2001-2002, and in Durban 776 cases of tuberculosis were registered. About 1.7% of new TB cases are MDR TB while approximately 7.7% of previously treated cases have MDR TB in KwaZulu-Natal Province (National survey of tuberculosis drug resistance in KwaZulu-Natal, 2001 – 2002).

KGVH was established in the 1950’s as a TB hospital. It is a centralized treatment and referral site in Durban for KwaZulu-Natal Province, RSA. Currently there are 160 beds, 32 of which are pediatric. Its inpatient population is now almost exclusively (97%) MDR and XDR TB patients. Approximately one quarter to one third of the inpatients have XDR and about 60% of these have HIV. Among the MDR TB inpatients the prevalence of HIV infection is about 40%. MDR TB has thus steadily been increasing since 1995 with total cases increasing from 205 in 2000 to 686 cases in 2006.

Currently, patients with MDR or XDR TB are typically admitted to KGVH for 4 months for intensive phase treatment. They may be reluctant to be admitted and isolated due to disruption of their social life, pressing family commitments, dependents at home, loss of income, fear for their job/school or home, and fear of treatment/injections. There have often been delays in admitting patients due to bed shortages. Transportation to this centralized facility from remote locations is often difficult. On admission, patients are counseled regarding treatment policies and objectives and sign a consent form for treatment of MDR TB. Baseline testing is obtained, including chest x-ray, audiometry, complete blood count, liver enzymes, electrolytes including calcium, phosphate and magnesium, HIV testing, and CD4 count, when appropriate. A social worker is consulted for each case. Contacts of the case are identified for subsequent control efforts; however the latter are often limited due to lack of sufficient resources.

An MDR TB Committee reviews all cases and helps determine the regimen to be used, although this is usually a standardized regimen in accordance with national guidelines. Following the 4 months of intensive phase treatment, injectable agents (e.g., aminoglycosides) have often been stopped. Patients are discharged irrespective of status of acid fast bacillus smear results. Care for HIV infection (including anti-retroviral agents and prophylaxis for opportunistic infections) is provided to patients according to provincial and national guidelines.

In March 2008, treatment of MDR TB in KZN is scheduled to be enhanced to allow increased access to treatment through outpatient treatment and prolongation of treatment with injectable agents to six months. Patients referred to KGVH for MDR TB treatment will be assessed and receive directly observed therapy either as an inpatient or at special MDR TB clinics or from Mobile MDR TB Units. The site of treatment will be based upon standard program criteria including level of drug resistance, co-morbid medical conditions, access to outpatient MDR TB clinics, and social circumstances.

Outpatient MDR TB patients attend monthly outpatient follow-up clinic at KGVH, which meets twice weekly. Approximately 150 patients are seen per clinic session or about 1000/month. To date, patients attended from throughout KZN & Eastern Cape Province. Many face great difficulty obtaining transport to the clinic. The outpatient MDR TB treatment program is hoped to address this and enhance access to MDR TB treatment. Patients are treated until 18 months of treatment is completed or until acid fast bacilli (AFB) cultures are negative for one year with at least 5 consecutive negative cultures.
1.3 Objectives

1.2.1 Primary Objectives

The major aims of this pilot, randomized, double-blind Phase I/II clinical trial are to assess the safety (significant adverse events) and tolerability (treatment discontinuation) of low dose, limited duration, LZD (600 mg p.o. QD for 16 weeks or 112 doses) added to Optimized Background Therapy (OBT) for MDR TB or XDR TB. OBT is defined as treatment with ≥ 4 drugs with activity against tuberculosis to which the patient’s isolate is believed to be sensitive by history or drug susceptibility testing. Specifically, the primary objectives will be:

1) To evaluate tolerability by examining the proportion of patients in each arm who take at least 80% of the 112 directly observed doses of study drug (i.e. at least 90 doses) within 18 weeks of study treatment initiation.

2) To evaluate safety by examining the cumulative rate of serious adverse events (SAEs, measured as the number of SAEs per person days) during the period of study drug therapy and the four weeks of post-study drug therapy follow-up.

1.2.2 Secondary Objectives

Secondary objectives of this pilot study will be:

1) To compare microbiologic outcomes, including the proportion of culture-conversions at two week intervals, time-to-conversion of cultures, and Mycobacterial Growth Indicator Tube (MGIT) “time to detection,” during the first 16 weeks in the two study arms,

2) To compare microbiologic outcomes and survival rates in those treated with LZD and OBT vs. those of patients treated with OBT at 16 weeks and 5 months of therapy

3) Determine the ability to identify and recruit eligible patients with MDR TB and XDR TB treatment trial, and to retain and follow them for up to 5 months.

In summary, the time points for evaluating the primary and secondary outcomes are as follows:

1) Tolerability will be assessed at 18 weeks
2) Safety will be assessed for the period when patients are on study therapy and the first four weeks post study therapy (to assess for delayed adverse affects)
3) Microbiologic outcomes will be assessed every two weeks during the first 16 weeks of therapy.
4) Survival will be assessed at 16 weeks of study therapy and at 5 months after enrollment.

1.2.3 Pilot Study Objectives.

Assessment of these primary and secondary outcomes will determine if there is reasonable cause to proceed to phase 2 and 3 clinical trials of LZD in MDR TB.
treatment. While the primary objectives of this pilot study is to evaluate the safety and tolerability of LZD, our ultimate objective is to see if LZD containing regimens could allow a shorter treatment course or have improved efficacy compared to the currently recommended 18-24 month treatment of MDR TB. In addition to providing information regarding safety and tolerability of LZD, this pilot study would inform the design of such a larger study and assess the feasibility of long term follow-up in this patient population.

1.4 Eligibility Criteria

1.4.1 Inclusion Criteria

1) Pulmonary tuberculosis with or without extrapulmonary TB with a M. tuberculosis isolate that is confirmed to be resistant to at least rifampin and isoniazid (without regard to prior treatment for TB).

2) A documented positive sputum culture result for M. tuberculosis from a sputum obtained in the four months prior to enrollment.

3) Willingness to have HIV testing performed, if HIV serostatus is not known or if the last documented negative HIV test was more than 6 months prior to enrollment.

4) Age ≥ 18 years.

5) Karnofsky score of > 40 (see section 18.1)

6) Willingness by the patient to attend scheduled follow-up visits and undergo study assessments.

7) Women with child-bearing potential must agree to practice an adequate method of birth control or to abstain from heterosexual intercourse during study therapy. (Standard birth control measures are provided free of charge by public health institutions)

8) Laboratory parameters done within 14 days prior to screening:
   a. Serum creatinine level < 2 times upper limit of normal
   b. Hemoglobin level ≥ 9.0 g/dL
   c. Platelet count of ≥ 80,000/mm³
   d. Absolute neutrophil count (ANC) > 1000/ mm³
   e. Negative pregnancy test (for women of childbearing potential)

9) Able to provide informed consent or legally authorized representative able to do so if decisionally impaired.

1.4.2 Exclusion Criteria

1) Currently breast-feeding or pregnant.

2) Known allergy or intolerance to LZD.

3) Planned therapy during the intensive phase of tuberculosis treatment using drugs having unacceptable interactions with LZD, including dopamine, selective serotonin uptake inhibitors (citalopram, fluoxetine, fluvoxamine,
paroxetine, and sertraline), amitriptyline, bupropion, mirtazepine, levodopa, carbidopa, sinemet, or herbal medications.

4) Significant peripheral neuropathy as evidenced by \( \leq 5 \) seconds of vibratory sense to a 128 Hz tuning fork on either big toe when tested bilaterally.

5) Pain, aching or burning of the feet that interfere with walking or sleep.

6) In the judgment of the physician the patient is not expected to survive for more than 4 weeks.

7) Anticipated surgical intervention for the treatment of pulmonary tuberculosis.

8) Visual acuity of 20/200 (6/60 meters) best corrected vision or less.

9) Poor color vision as evidenced by incorrect answers on \( \geq 4 \) of 12 screening Ishihara plates.

10) Participation in another drug trial.

11) The patient has received second line TB drugs for \( > 14 \) days immediately prior to enrollment (note: use of first line drugs such as INH, Rifampin, PZA, or ethambutol for \( > 7 \) days immediately prior to enrollment is allowed).

### 1.5 Methods

#### 1.5.1 Study Type

This is a phase I/II randomized, double-blind, placebo-controlled, two arm pilot study.

#### 1.5.2 Study Population

The study population will be drawn from patients being referred to the King George V Hospital (KGVH) in Durban, KZN, Republic of South Africa for treatment of MDR or XDR TB without regard to previous TB treatment. Patients presenting to KGVH for treatment of MDR TB who fulfill the inclusion/exclusion criteria will be eligible for this study.

#### 1.5.3 Treatment Regimen and Treatment Period(s)

All participants will be treated with OBT together with either daily (seven days per week) LZD or placebo. OBT is defined as treatment with \( \geq 4 \) drugs with evidence of activity against the patient’s tuberculosis isolate, each given 3 to 7 times per week according to the judgment of the treating physician. For a fuller discussion of OBT please see section 15.10. Evidence of activity may be historical or derived from drug susceptibility testing (DST). All participants will have evidence of resistance to at least isoniazid (INH) and rifampin (RIF). DST for second line drugs, while usually available, may not always be available at the time of presentation to KGVH and study enrollment. Patients for whom second line DST is not available will receive a standard empiric regimen of second line drugs approved by the RSA government (see section 7.2).
Participants will be randomly assigned to either the daily LZD or placebo arm in a double-blinded fashion (also see 2.1.2 Study Schema). The initial, 16-week phase of treatment includes 112 daily (7 days/week) oral doses of study drug (600 mg LZD or placebo) together with OBT. Participants will remain on assigned drug treatment for 112 doses of study drug unless they cannot tolerate therapy (see Section 6.2).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Initial phase (112 daily doses)</th>
<th>Post 112 daily doses†</th>
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<tbody>
<tr>
<td>OBT</td>
<td>OBT (+ placebo daily*)</td>
<td>OBT + LZD**</td>
</tr>
<tr>
<td>OBT + LZD</td>
<td>OBT + LZD daily*</td>
<td></td>
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</tbody>
</table>

*Daily therapy will be directly observed a minimum of 5 days per week
† for a total of 18-24 months of treatment depending on regimen, response to therapy, development of adverse effects and treating physician
** LZD may be added at the end of study treatment (112 daily doses of LZD or placebo) to the regimen of patients who have received the approval of the KGVH MDR TB Committee (see Section 16)

2 Introduction and Design

2.1 Design

This is a phase I/II, randomized, double-blind, placebo-controlled, two arm study of LZD for the treatment of MDR and XDR TB patients during the first 16 weeks of therapy (given for 112 doses of 600 mg p.o. QD 7 days per week). Study patients will have a sputum culture isolate that is known to be resistant to at least isoniazid and rifampin. Patients with confirmed MDR TB (including patients with XDR TB) will be randomly assigned in a double-blind manner to receive OBT, a regimen of ≥ 4 drugs chosen by the patient and their care provider on the basis of prior drug experience or documented drug resistance with placebo, or OBT with LZD for the first 16 weeks (112 daily doses) of therapy. Randomization is expected to provide similar distributions of OBT in both arms, even though OBT will be heterogeneous. Most commonly a regimen of pyrazinamide; amikacin or kanamycin; ethionamide; ofloxacin or ciprofloxacin; ethambutol; and terizidone or cycloserine is employed. This study will provide a preliminary evaluation of the safety, tolerability and efficacy of LZD in the treatment of MDR and XDR TB patients. We will investigate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of LZD in blood as well as its drug-drug interactions with other co-administered antituberculosis chemotherapies in a sub-study with a separate protocol. The main analysis will be performed no sooner than 20 weeks after the last patient enrolled starts study therapy.

2.2 Randomization and Blinding

The study will use unrestricted randomization. The statistician will prepare the randomization procedure and provide it to the research pharmacist. The pharmacist will execute the randomization procedure when a patient is enrolled and will assign the study ID and provide blinded medication to study personnel. All other clinical, programmatic and study personnel and patients will be blinded to patient assignment. Drugs provided during the initial phase of therapy will be mechanically packaged by the study pharmacist and
labeled similarly with patient name and ward number by the site pharmacy using a label printer. Patients will take study drug while being directly observed by study personnel.

### 2.3 Treatment Arms

There will be two treatment arms with 32 patients in each arm; one will receive OBT plus LZD (600 mg po daily/7 days per week) while the other receives OBT plus placebo for 16 weeks of therapy. Study medications will be over-encapsulated prior to delivery to study site to ensure blinding.

### 2.4 Study Objectives

#### 2.4.1 Primary Objectives

1) To evaluate tolerability by examining the proportion of patients in each arm who complete at least 80% of supervised doses (at least 90 doses) in the proposed regimen within 18 weeks of treatment initiation.

2) To evaluate safety by examining the cumulative rate of serious adverse events (SAEs, measured as the number of SAEs per person days) during the period of study drug therapy and the four weeks of post-study drug therapy follow-up.

#### 2.4.2 Secondary Objectives

Secondary objectives of this pilot study will be:

1) To compare microbiologic outcomes, including the proportion of culture-conversions at two week intervals, time-to-conversion of cultures, and MGIT “time to detection,” during the first 16 weeks in the two study arms,

2) To compare microbiologic outcomes and survival rates in those treated with LZD and OBT vs. those of patients treated with placebo and OBT at 16 weeks and 5 months of therapy

3) Determine the ability to identify and recruit eligible patients with MDR TB and XDR TB in a treatment trial, and to retain and follow them for up to 5 months.

### 2.5 Background

Resistance of *Mycobacterium tuberculosis* (MTB) to antimicrobials has been recognized since the advent of streptomycin in the 1940’s. In cavitary pulmonary TB there are sufficient replicating bacilli for the selection of mutants resistant to an antimicrobial given as monotherapy. However, treatment with multiple anti-tuberculous agents simultaneously, when taken properly for susceptible infections, can help prevent further acquired drug resistance. In the late 1980’s and early 1990’s there were documented outbreaks of MTB tuberculosis resistant to both isoniazid (INH) and rifampin (RIF) (defined as multi-drug resistant TB or MDR TB) as well as to other first and second line agents. The mortality was high, especially among HIV co-infected patients (72-92%), but even without HIV co-infection MDR TB was associated with a devastating 43% mortality. During these outbreaks, out of 159 exposed healthcare workers, 17 health care workers developed active TB, four died, and an additional 43 had evidence of recently acquired latent TB infection.
These outbreaks and transmissions occurred in 8 hospitals and one prison, impacting patients, prisoners and healthcare workers [1, 2].

Factors leading to the outbreaks of MDR TB described above were thought to be multiple and, included host factors (e.g., HIV infection), intermittent or incomplete therapy, delayed recognition of the resistant infection, and poor infection control leading to the development and transmission of drug resistant organisms. Although the current treatment of MDR TB has improved with better second-line agents, public health efforts, including directly observed therapy (DOT), and infection control measures, there are still large hurdles to overcome.

Treatment for MDR TB is somewhat standardized in South Africa and second line drug susceptibility data is generally available, but may not always be available initially. Care is typically centralized for the initial phases of care, but patients are generally released to complete treatment as outpatients. Increasing use of second-line anti-tuberculosis agents has had the predictable consequence of inducing further drug resistance with the emergence of extensively drug resistant tuberculosis (XDR TB).

XDR TB is defined as MDR TB plus resistance to any fluoroquinolone and a second line injectable agent (kanamycin, amikacin or capreomycin) [3]. XDR TB is difficult to treat as most patients may be susceptible only to few, if any, of the available second-line agents. In a recent analysis of data between 2000 and 2004, researchers reviewed DST results from 13 WHO reference labs around the world. Thirty nine (39) percent of the studied isolates were MDR TB and of these, 7% were XDR. As one would expect there is significant morbidity and mortality associated with XDR TB [4]. In a recent alarming example from rural South Africa, of 53 patients with XDR TB and HIV co-infection, 52 died during the study period with a mean survival of only 16 days from time of sputum collection [5].

Improved understanding and treatment of XDR TB is imperative. Very few new drugs have been added for TB therapy in past two decades (e.g., quinolones); however LZD (Zyvox, Pfizer, Inc.), a drug with known in vitro and in vivo activity against M. tuberculosis, has been shown to have promising activity in drug resistant TB patients [6]. LZD may have an important role in the treatment of MDR TB and in salvage therapy for patients suffering from XDR TB.

Off-label use of LZD for MDR TB may result in M. tuberculosis developing resistance to LZD, according to one report. In 4 out of 240 isolates (at least three with prior exposure to LZD) three had MICs of 8 µg/ml and one of 4 µg/ml (resistance defined as MIC>1.0 µg/ml). Interestingly, when the genetic makeup of these resistant strains was compared with drug sensitive and MDR TB strains no specific mutation was identified [7].

The good clinical response of chronic patients with resistant TB to LZD is puzzling. LZD is a largely static drug with modest MIC in vitro and has no known effect on non-replicating, stationary-phase organisms [8]. According to current criteria for TB drug development [9] a pre-clinical candidate with these characteristics would not be advanced to clinical evaluation. Understanding what properties of this agent contribute to its apparent clinical activity (see Section 2.5) would provide valuable information for early pre-clinical development programs. PK/PD is a critical property of many anti-infectives and recent reports suggest that LZD may be present in the epithelial lining fluid at concentrations much higher than the serum, a finding that may also contribute to the observed clinical efficacy of LZD [10].
LZD has not been extensively explored for TB treatment primarily because of concerns regarding toxicity associated with long-term administration of this drug. This toxicity is thought to be mechanism-related. LZD is a protein synthesis inhibitor and may affect both bacterial and human mitochondrial protein synthesis [11, 12]. This toxicity is known to be duration-related but no examination of the differential sensitivity of mitochondrial and bacterial effects has been done. A recent study correlated LZD related hyperlactatemia with reduced mitochondrial protein synthesis and mass and with reduced cytochrome C oxidase activity, effects which were reversible upon LZD discontinuation [11]. It may be possible to preserve mitochondrial function by decreasing the dose of LZD being administered and circumvent more severe side-effects.

2.6 Rationale for Evaluating Linezolid for MDR TB

Use of LZD has been limited by toxicity when used in doses of 600 mg BID. Based on MIC’s exceeding those needed to inhibit the growth of TB and the slow doubling time of M. tuberculosis, there is a rational basis in terms of potential efficacy for proceeding with a dose of 600 mg po QD. LZD given at this dose over a longer duration than LZD is presently licensed (28 days) for needs evaluation for safety and tolerability, pharmacokinetics/pharmacodynamics, efficacy, survival/treatment failure, and microbiologic endpoints.

Toxicity associated with the use of LZD for TB treatment has been largely gastrointestinal (diarrhea), neurologic (optic and peripheral neuropathy), lactic acidosis, and hematologic (anemia, thrombocytopenia, and leucopenia). The hematologic side effects are reversible and appear to be dose related with less anemia associated with LZD given at 600 mg QD than with BID dosing. While the optic neuropathy associated with LZD is generally reversible with drug discontinuation, the peripheral neuropathy is not. In published case series, peripheral neuropathy occurring among patients receiving LZD generally occurred after 16 weeks of once daily therapy suggesting that peripheral neuropathy may be related to the cumulative dose of LZD received. For this reason we have elected to limit LZD administration to 112 doses of 600 mg QD (the equivalent of 16 weeks of once daily therapy).

Neuropathy in patients treated for TB in this study may result from a multitude of factors, including drug toxicity. Other anti-tuberculosis medications used for MDR- and XDR TB may cause peripheral neuropathy (e.g., ethionamide) and optic neuropathy (e.g., ethambutol). Nutritional deficiencies, HIV infection, excessive alcohol abuse, and other medications may also play a role in the development of neuropathy.

LZD is a weak monoamine oxidase inhibitor. In post-marketing experience 29 cases of serotonin syndrome have been reported in patients being treated for non-mycobacterial infections with LZD concomitantly with other serotoninergic medications. No cases of serotonin syndrome were reported in the series of patients treated for MDR TB with LZD. The majority of the patients with serotonin syndrome had manifestations within 1 week (range, 1–21 days) of initiation of treatment. Eleven of 29 reported post-marketing cases of serotonin syndrome were associated with use of LZD with selective serotonin uptake inhibitors (SSRIs), and the majority of the remaining cases were associated with LZD and anti-Parkinsonian medications (carbidopa/levodopa and sinemet), amitriptyline, or the use of
multiple potentially serotonergic medications. Time to resolution of symptoms was within 48 h (range, 24 h–9 days) for 7 of 11 patients (14).

In this double-blinded pilot study, tolerability will be evaluated by comparing the proportion of patients completing at least 80% of study drug between the two study arms during the first 18 weeks of therapy. Safety will be evaluated by comparing the proportion of patients experiencing significant adverse effects between the two arms during the first 20 weeks of therapy.

Culture conversion rates are a commonly utilized surrogate marker for the sterilizing activity of anti-tuberculosis drugs. However, these rates may be problematic in this patient population. Therefore, this pilot study will assess three measures of antimycobacterial activity: the frequency of culture conversion by the end of the initial phase of therapy, the time to culture conversion, and the time to detect mycobacteria in a liquid assay. Once the initial tolerability, safety and antimicrobial activity of LZD, as well as study feasibility at the site, have been assessed in this pilot study and determined to be worthwhile to proceed, studies to evaluate the therapeutic efficacy, potential to reduce treatment time, and its long-term safety will be needed.

The treatment of MDR TB and XDR TB is protracted, toxic, resource-intensive, fraught with compliance issues, and has poorer outcomes. Current treatment of MDR TB requires a minimum of 18 months of drug therapy, a treatment duration that is challenging for patients and tuberculosis control programs. Therefore, a high priority in tuberculosis research is the identification of agents that can shorten treatment and enhance outcomes. Several case series of patients with MDR TB have suggested that LZD may be a potent addition to the best available regimen [14-17].

A treatment study of MDR/XDR TB constitutes a significant challenge. There have been no randomized studies completed in this population, although several are planned or underway. Patients with MDR or XDR TB often have co-morbidities such as HIV infection and its complications. They may take multiple medications, may be nutritionally compromised, may live in extreme poverty or geographic isolation and may have substance abuse problems. The ability to provide treatment, sustain follow-up, and measure study outcomes within such medical and social contexts needs to be evaluated. Therefore, the current study will be a pilot study to assess the feasibility of conducting such a study with measured outcomes at KGVH. If the pilot study determines that it is feasible to conduct such a study with these outcomes, we will proceed with a larger study.

Finally, worldwide there is little experience regarding the conduct of clinical trials to evaluate the treatment of MDR and XDR TB. This pilot study will provide valuable information regarding the difficult tasks of enrollment and assessment of patients with highly resistant tuberculosis in a programmatic setting.

### 2.7 Animal Studies

LZD was found to have “considerable activity” against *M. tuberculosis* ATCC 35801 (Erdman strain), a strain that is sensitive to isoniazide and rifampin, in a murine model of infection [13]. No published animal studies are available on the activity of LZD against resistant strains of *M. tuberculosis*. 
2.8 Clinical Studies

Several clinical series of off-label use of LZD for TB have been described (see Table 2). The first case series used LZD at a dose of 600 mg twice daily (bid) along with second line agents to treat 5 patients with refractory MDR TB complex (3 M. tuberculosis and 2 M. bovis). All patients converted their sputum acid fast bacillus (AFB) smears to negative at an average of 82 days of treatment. The most common adverse event was anemia, although neuropathy was also seen [14].

In Norway, 10 consecutive patients with MDR TB were treated with LZD 600 mg BID along with second line agents. Nine patients converted their sputum to AFB smear negative between 10 and 37 days. The single non-responder was HIV-infected and had disseminated disease. Seven patients developed peripheral neuropathy and 5 developed anemia. The onset and duration of peripheral neuropathy in these patients was different than in the other case series with earlier onset (4 – 20 weeks) and improvement or resolution of neuropathic symptoms with time. [15].

In a series of 8 patients with intractable MDR TB in South Korea, patients were given LZD 600mg daily (6 of the patients received LZD twice daily for the first 2 weeks) along with other second line agents. The duration of LZD treatment was 3 to 18 months (therapy was discontinued when side effects became too severe to continue). All of the patients’ sputa became AFB smear negative at an average of 82 days (range 25-147 days). The most common adverse events were peripheral neuropathy (4 patients, occurring at an average 28 weeks), optic neuropathy (2 patients) and anemia (1 patient). The reduced dose was effective in clearing the sputum adequately. However, it did not appear to decrease neurologic toxicity, but anemia appeared to be less common (12.5%) than in other series [16].

In summary, there are four published case series of MDR TB treated with LZD (14-17). In three of these, patients were given LZD 600 mg BID (14,15,17). Significant adverse side effects associated with this dose included cytopenias (primarily anemia), lactic acidosis, and peripheral and optic neuropathies, related to mitochondrial toxicity. The anemia appeared to be dose related and resolved with discontinuation or dose reduction of LZD (14, 15). The peripheral and optic neuropathies attributed to LZD tended to occur after four months of therapy. Peripheral neuropathy did not resolve with discontinuation of LZD (14-17). These observations suggest that the cumulative dose of LZD may be a factor associated with these neuropathies. In assessing LZD-induced neuropathy in the MDR TB patient population, a randomized controlled trial is needed to assess for other potential causes for contributors to neurologic toxicity, such as nutritional factors, medications other than LZD, and co-morbidities such as HIV and diabetes.

In the published cases series, patients treated with LZD for MDR TB had relatively high rates of culture conversion at two months (70%, 19/27) and cure/treatment completion (71%, 15/21 with six patients remaining on treatment at the time of publication). Patient data from three case studies found that while taking 600 mg LZD 1-2 times per day along with their standard second line agents, 22/23 individuals had converted by 16 weeks. For these individuals, 9 had converted by 1 month, 5 had converted between the first and second months, and 8 had converted between the second and fourth months. However, there are no randomized studies evaluating LZD for the treatment of MDR TB and the published case series may represent publication bias towards promising results.
Table 2: Published Case Series of Pulmonary MDR TB Patients Treated with Linezolid

<table>
<thead>
<tr>
<th>Series</th>
<th>ID</th>
<th>Age</th>
<th>Outcome</th>
<th>Weeks on LZD</th>
<th>Dosage</th>
<th>Days to Culture Conversion</th>
<th>Peripheral Neuropathy</th>
<th>Optic Neuropathy</th>
<th>Anemia</th>
<th>Thrombocytopenia</th>
<th>Cavitary</th>
<th>Trans-fusion</th>
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<td>Norway</td>
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<td>23</td>
<td>Death</td>
<td>12</td>
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<td>10 to 37</td>
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<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>1</td>
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<td>2</td>
<td>24</td>
<td>Lost</td>
<td>11</td>
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<td>no</td>
<td>no</td>
<td>no</td>
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<td></td>
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<tr>
<td></td>
<td>3</td>
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<td>Cure</td>
<td>17</td>
<td>600 BID</td>
<td>10 to 37</td>
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<td>no</td>
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<tr>
<td></td>
<td>4</td>
<td>23</td>
<td>Cure</td>
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<td>no</td>
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<td>no</td>
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<tr>
<td></td>
<td>9</td>
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<td>Lost</td>
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<td>no</td>
<td>no</td>
<td>no</td>
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<tr>
<td></td>
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<td>no</td>
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<tr>
<td>Korea</td>
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<td>on Rx</td>
<td>32</td>
<td>600 BID/QD*</td>
<td>38</td>
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<td>yes</td>
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<td>Spain</td>
<td>1</td>
<td>33</td>
<td>Rx comp</td>
<td>96</td>
<td>600 BID</td>
<td>60*</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>?</td>
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<td>2</td>
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<td>on Rx</td>
<td>20</td>
<td>600 BID</td>
<td>30*</td>
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<td>no</td>
<td>yes</td>
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<td>Lost</td>
<td>16</td>
<td>600 BID</td>
<td>30*</td>
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<td>no</td>
<td>no</td>
<td>yes</td>
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<tr>
<td></td>
<td>4</td>
<td>29</td>
<td>Rx comp</td>
<td>56</td>
<td>600 BID/QD**</td>
<td>30*</td>
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<td>yes</td>
<td>yes</td>
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<td>5</td>
<td>21</td>
<td>Rx comp</td>
<td>44</td>
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<td>30*</td>
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<td>no</td>
<td>yes</td>
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<tr>
<td>Galicia, Spain</td>
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<td>34</td>
<td>Cure</td>
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<td>600 BID/QD**</td>
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<td>yes</td>
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<td>Cure</td>
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<td>600 BID/QD**</td>
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<td>600 QD</td>
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<td>no</td>
<td>pre</td>
<td>no</td>
<td>no</td>
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<td>600 QD</td>
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<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
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</tbody>
</table>

* linezolid 600 mg BID for 14 days and then 600 mg QD thereafter as part of standard treatment
** linezolid 600 mg BID given as standard therapy, but the dosage was reduced to 600 mg QD in response to adverse events
2.9 Pharmacokinetic and Pharmacodynamic Studies

LZD is rapidly and extensively absorbed after oral dosing [18]. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. When high fat food is given with LZD, the peak concentration ($C_{\text{max}}$) is decreased by about 17%, and the time to reach peak concentration ($T_{\text{max}}$) is delayed from 1.5 hours to 2.2 hours. However, the total exposure measured as $\text{AUC}_{0-\infty}$ values is similar under both conditions.

Animal and human pharmacokinetic studies have demonstrated that LZD readily distributes to well-perfused tissues. The plasma protein binding of LZD is approximately 31% and is concentration-independent. The volume of distribution of LZD at steady-state averaged 40 to 50 liters in healthy adult volunteers.

The mean pharmacokinetic parameters of LZD in adults after single and multiple oral doses are summarized in Table 3 below.

<table>
<thead>
<tr>
<th>Dose of Linezolid</th>
<th>Cmax $\mu$g/ml</th>
<th>Cmin $\mu$g/ml</th>
<th>Tmax hrs</th>
<th>AUC* $\mu$g·h/ml</th>
<th>t½ hrs</th>
<th>CL mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 mg tablets</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>single dose</td>
<td>12.70</td>
<td>-</td>
<td>1.28</td>
<td>91.40</td>
<td>4.26</td>
<td>127 (48)</td>
</tr>
<tr>
<td>(3.96)</td>
<td>(0.66)</td>
<td>(39.30)</td>
<td>(1.65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>every 12 hours</td>
<td>21.20</td>
<td>6.15</td>
<td>1.03</td>
<td>138.00</td>
<td>5.40</td>
<td>80 (29)</td>
</tr>
<tr>
<td>(5.78)</td>
<td>(2.94)</td>
<td>(42.10)</td>
<td>(2.06)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*AUC for single dose = $\text{AUC}_{0-\infty}$; for multiple-dose = $\text{AUC}_{0-T}$

Cmax = Maximum plasma concentration; Cmin = Minimal plasma concentration; Tmax = Time to Cmax; AUC = Area under concentration-time curve; t½ = Elimination half-life; CL = Systemic clearance

The primary metabolic pathway for LZD is by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminooethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). LZD is not an inducer of cytochrome P450 (CYP) in rats, and it has been demonstrated from in vitro studies that LZD is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4).

Non-renal clearance accounts for approximately 65% of the total clearance of LZD. Under steady-state conditions, approximately 30% of the dose appears in the urine as LZD, 40% as metabolite B, and 10% as metabolite A. The renal clearance of LZD is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no LZD appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.
The pharmacodynamic parameters associated with efficacy of Gram-positive bacterial pathogens are AUC/MIC and time over MIC. The MIC of LZD for streptococci and enterococci are 1-2 µg/ml and for staphylococci is 2-4 µg/ml. The preferred pharmacodynamic parameter of AUC/MIC for Gram-positives is 50-100 per day. Therefore the daily LZD AUC target is up to 200 and 400 µg*h/ml for respectively, streptococci and staphylococci.

However compared to Gram-positive bacteria, the LZD MIC for M. tuberculosis is lower at 1 µg/ml. If it is posited that the desired AUC/MIC is the same for M. tuberculosis as for Gram positive pathogens (50-100), then a desired daily AUC for MTB would be 50-100 µg*h/ml, and a cumulatively weekly AUC may be 350-700 (7 days) (Pharmacodynamics of LZD table below). Charles Peloquin, PharmD estimated in a one compartment model the LZD AUC$_{0-24}$ of 600 mg dose at 138 µg*h/ml (see Estimated AUC table below). Thus 7 doses of LZD per week would give cumulative doses of AUC/MIC of 999 per week above the posited desired range of 350-700 for 7 days per week.

A minimum effective dose for tuberculosis has not been established. One early bactericidal activity study comparing 600 mg q day vs. 600 mg bid has been conducted and is in analysis.

| Table 4: Pharmacodynamics of LZD to gram-positive bacterial pathogens and MTB |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| MIC | | strepto+entero | Staph | MTB |
| Desired daily AUC/MIC | 1-2 | 2-4 | 1 |
| Desired daily AUC | 100-200 | 200-400 | ?50-100 |
| Weekly AUC | 700-1400 | 1400-2800 | ?350-700 |
| 7 days | 7 days | 7 days |

| Table 5. Estimated AUC for different dosages and frequencies per week of LZD |
|-------------------|-------------------|-------------------|-------------------|-------------------|
| 600 mg TIW x 3 | 300 mg QD x 5 | 300 mg BID x 5 | 600 mg QD x 5 | 600 mg BID x 5 |
| AUC 0-12 | 114 | 57 | 57 | 114 | 114 |
| AUC 0-24 | 138 | 69 | 126 | 138 | 252 |
| AUC 0-48 | 143 | 141 | 269 | 281 | 538 |
| AUC 0-72 | 281 | 212 | 412 | 425 | 825 |
| AUC 0-96 | 287 | 284 | 556 | 568 | 1112 |
| AUC 0-120 | 425 | 356 | 669 | 712 | 1399 |
| AUC 0-144 | 430 | 359 | 717 | 717 | 1434 |
| AUC 0-168 | 431 | 359 | 718 | 718 | 1435 |
2.10 Qualifications of Investigators
This study is being conducted by a multidisciplinary team including individuals with expertise in the areas of clinical infectious diseases, pulmonary medicine, biostatistics, epidemiology, clinical trial design and implementation, patient advocacy and the conduct of good clinical research, microbiology (with a focus on M. tuberculosis), as well as the protection of human subjects. Copies of curricula vitae (CVs) to demonstrate the experience and qualifications of all of the investigators (Principal Investigator [PI] and Associate Investigators [AIs]) will be kept in the protocol file (essential documents file).

2.11 Conflict of Interest
The investigators conducting this clinical trial are aware of the potential conflicts of interest according to their institutional guidelines; specifically, these relate to assets, income, liabilities, outside positions, agreements, arrangements, gifts and travel reimbursements of the investigators, their spouses and their minor children. No reportable conflicts of interest have been identified by any of the investigators conducting this trial.

3 Study Agent and Tests

3.1 Study Agent
LZD is an oxazolidinone whose antimicrobial effects are thought to be related to inhibition of protein synthesis by preventing the formation of the 70S ribosomal subunit. LZD interacts with domain V of the 23S rRNA of the ribosomal subunit. This domain is also the binding site for chloramphenicol, macrolides, and lincosamides, but the lack of cross-resistance between oxazolidinones and other antibiotics supports evidence for a novel mechanism of action. It has the advantage of having excellent bioavailability when given orally and is commonly used in clinical practice to treat infections caused by gram positive organisms such as Staphylococcus aureus (including methicillin resistant strains), coagulase negative Staphylococcus, and Enterococcal infections. The recommended dose for these infections is 600 mg twice daily.

LZD exhibits activity both in vitro and in vivo, against Mycobacterium tuberculosis (MTB), including resistant strains with minimum inhibitory concentrations (MICs) ranging from 0.125-1 [19]. The mutant prevention concentration of 90% of MTB strains tested (MPC90) was 1.2 mg/L for LZD in a study of isolates from southern Spain [20]. Simulated pharmacodynamic/kinetic profiles of LZD at both 300 mg once daily (qd) and 600 mg qd indicate that LZD concentrations remain above the MIC and MCP 90 of MTB for almost 24 hours (unpublished).

The chemical structure of Linezolid is as pictured here.

Linezolid’s chemical name is N-[[3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl]methyl]acetamide

Linezolid
3.2 Other Agents
While on study drug, patients will also receive second-line agents determined by drug susceptibility testing results and prior drug exposure. The possible drugs used include but are not limited to prothionamide, para-amino salicylic acid (PAS), pyrazinamide, ofloxacin, levofloxacin, cycloserine, capreomycin, amikacin, and kanamycin. There are no known interactions between these drugs and LZD.

Patients will also receive vitamin B6 (50 mg) with their anti-TB regimen as this is thought to mitigate the peripheral neuropathy associated with long term LZD [21, 22] and other agents.

The treating physician and study staff should weigh the risks and potential benefits of initiating or continuing medications known to increase central nervous system serotonin or to be associated with serotonin syndrome and of entry into or remaining in this study. Appended to this protocol are medications that can at least theoretically increase central nervous system serotonin. Monitoring for serotonin syndrome should be done utilizing the appended Hunter Serotonin Syndrome criteria (See Appendix 18.6). Management of serotonin syndrome should be by withdrawal of study drug, but rapid discontinuation of an SSRI is associated with potentially severe withdrawal symptoms [23]. Cyproheptadine has been used as an effective antidote for serotonin toxicity.

4 Endpoints and Statistical Methods

4.1 Primary Objectives
The primary goals of this pilot, phase I/II study are to determine whether LZD is safe, tolerable, and feasible enough to support further research as a treatment for MDR TB. Therefore, the sample size is designed to characterize the relative safety and tolerability but not to establish significant superiority.

We target enrollment of 64 participants over a 12-month period with the expectation that there will be a 20% loss to follow-up for reasons unrelated to tolerability, leaving 50 participants who will remain in the pilot study throughout the initial phase of therapy. To assess tolerability, if we use a one-sided comparison with type 1 error rate of 10%, we will have 56% power to detect a difference between 90% treatment completion of initial-phase therapy in the placebo group and 65% treatment completion in the LZD group. To assess safety, if we use a one-sided comparison with type 1 error rate of 10%, we will have 75% power to detect a difference between 20% cumulative incidence of serious adverse events in the placebo group and 50% cumulative incidence in the LZD group. If the cumulative incidence is not different between groups, time to event methods will be used to evaluate whether SAEs tend to accumulate earlier in those on LZD. These calculations are based upon tests comparing proportions which supply conservative estimates.

4.2 Secondary Objectives
To comply with the conventions of the Consolidated Standards of Reporting Trials (CONSORT) [24], we will determine the number of MDR/XDR TB patients during the study period referred for treatment to King George V Hospital who were eligible for the study during the study period, the number approached for study participation, offered entry
into the pilot study, actually entered the study, and received at least one dose of study drug (LZD or placebo).

The secondary endpoints are listed in section 8.3.2. Thus, we intend also to compare:
1) Adverse events, treatment failure, and culture conversion rates at 16 weeks and 5 months among HIV-infected patients vs. HIV-uninfected patients.
2) Baseline weight/body mass index and weight/body mass index change from baseline by treatment arm and relation of these two parameters to outcomes (survival, culture conversion rates)
3) Rates of acquired drug resistance of tuberculosis isolates, which includes resistance to linezolid.
4) Number of supervised doses per patient received within 16 weeks of treatment initiation in each treatment arm.
5) Completion of 100% of the proposed treatment regimen (112 doses) within 20 weeks of initiation of therapy in the treatment arms.
6) Completion of 100% of the proposed treatment regimen (112 doses) without regard to treatment duration.
7) Determine the proportion of eligible patients that were enrolled, retained for the first 16 weeks, and followed for up to 5 months.

Statistical tests will be one sided and $P$-values less than 0.1 will be considered important when evaluating differences between groups in this pilot study. The magnitude of the difference between groups and the strength of association will additionally be considered when evaluating this pilot study’s data to determine whether a larger study of LZD is warranted.

To estimate the statistical power of this study to evaluate the efficacy of LZD + OBT compared to placebo + OBT, we used culture conversion rates from the medical literature [8] and expert opinion. Thus, with a two-sided comparison with type 1 error rate of 10%, we would have 58% power to detect a difference between a 30% conversion rate in the placebo group and a 50% conversion rate in the LZD group.

Secondary endpoints include the comparison of the frequency of sputum culture conversion between the LZD and placebo groups during the initial phase of therapy and the comparison of time to culture conversion. The time to conversion will be evaluated at two-week intervals during the first 16 weeks from initiation of study therapy. Under the hypothesis that 600 mg of LZD is beneficial, one would expect the conversion times to be shorter for those in the LZD arm.

For interpretive purposes, the result of the usual generalized Wilcoxon test for time to sputum conversion censored at 16 weeks, treating deaths the same as all other forms of censoring, will be calculated and compared to the test of the primary endpoint described above. Since death is unlikely to be independent of factors associated with completing study treatment, however, conventional statistical procedures for censored data must be supplemented by more appropriate methods. A generalized Wilcoxon test statistic for interval-censored data will be used to summarize the between-group difference in a severity score based on the time from randomization to sputum-conversion, with an accommodation for death as follows. This severity score will be equal to the time to conversion for
individuals observed to sputum convert before 16 weeks. For individuals who die before conversion, they will be assigned a severity score that is worse than all patients observed to convert by 16 weeks. Mathematically, this can be achieved by setting their severity score to $2T - t$, where $T$ is the maximum allowable observed time to conversion (i.e., 16 weeks) and $t$ is the time from treatment assignment to the individual’s death. This also ranks individuals who die sooner without conversion worse than those who die later without conversion. Patients lost to follow-up without a known conversion are interval-censored with their severity score ranked worse than anyone who converted before the time of their last known sputum-positive status and better than anyone who had died without known conversion before that time. In other words, someone lost to follow-up at time $t$ would have a severity score censored in the interval $(t, 2T - t)$.

5 Patient Enrollment

5.1 Accrual
Patients referred to King George V Hospital in Durban South Africa for treatment of MDR or XDR TB will be potentially eligible for enrollment into this study. Patients meeting the study eligibility criteria will be offered the opportunity to participate in the study (See Appendix 18.2). After obtaining written informed consent patients will be randomly assigned to the study's two arms in a double-blinded fashion. Sixty four patients will be enrolled over a 12 month period with the expectation that there will be a 20% loss to follow-up leaving 50 patients who will complete the protocol, taking 112 doses of study drug.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria
1) Pulmonary tuberculosis with or without extrapulmonary TB with a *M. tuberculosis* isolate that is confirmed to be resistant to at least rifampin and isoniazid (without regard to prior treatment for TB)
2) A documented positive sputum culture result for *M. tuberculosis* from a sputum obtained in the four months prior to enrollment.
3) Willingness to have HIV testing performed, if HIV serostatus is not known or if the last documented negative HIV test was more than 6 months prior to enrollment.
4) Age $\geq$ 18 years.
5) Karnofsky score of $> 40$ (see section 18.1).
6) Willingness to attend scheduled follow-up visits and undergo study assessments.
7) Willingness of women with child-bearing potential to practice an adequate method of birth control or to abstain from heterosexual intercourse during study therapy. (Standard birth control measures are provided free of charge by public health institutions)
8) Laboratory parameters done within 14 days prior to screening:
   a. Serum creatinine level less than 2 times upper limit of normal
   b. Hemoglobin level of $\geq$ 9.0 g/dL
   c. Platelet count $\geq$ 80,000/mm$^3$
   d. Absolute neutrophil count (ANC) $> 1000/\text{mm}^3$
   e. Negative pregnancy test (for women of childbearing potential)
9) Able to provide informed consent or legally authorized representative able to do so if decisionally impaired.

5.2.2 Exclusion Criteria

1) Currently breast-feeding or pregnant.
2) Known allergy or intolerance to linezolid.
3) Planned therapy during the intensive phase of tuberculosis treatment using drugs having unacceptable interactions with linezolid, including dopamine, selective serotonin uptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), amitriptyline, bupropion, mirtazapine, levodopa, carbidopa, sinemet, or herbal medications.
4) Significant peripheral neuropathy as evidenced by < 5 seconds of vibratory sense to a 128 Hz tuning fork on either big toe when tested bilaterally.
5) Pain, aching or burning of the feet that interfere with walking or sleep.
6) In the judgment of the physician the patient is not expected to survive for more than 4 weeks.
7) Anticipated surgical intervention for the treatment of pulmonary tuberculosis.
8) Visual acuity of 20/200 (6/60 meters) best corrected vision or less.
9) Poor color vision as evidenced by incorrect answers on > four of 12 screening Ishihara plates.
10) Participation in another drug trial
11) The patient has taken second line TB drugs for > 14 days immediately prior to enrollment (note: use of first line drugs such as INH, Rifampin, PZA, or ethambutol for > 7 days immediately prior to enrollment is allowed)

5.3 Screening Process

Physicians with primary responsibility for caring for the patient will invite potentially eligible patients to meet with study staff to discuss the study and their potential participation. Study staff will not approach patients without the consent of treating physician. Referring physicians will not receive remuneration for referring patients to study staff. Pre-enrollment screening procedures will be performed, after written informed consent is obtained, unless the results of these tests performed within 14 days prior to enrollment are available. Routinely collected medical information and tests will be used to screen patients including medical and medication histories, clinical examination, chest x-ray, and mycobacterial culture, and an HIV serum rapid test (see appendix 18.2). For women of childbearing potential, a urine pregnancy test will be performed prior to study entry. A log will be kept of patients identified, screened, deemed ineligible (with reason why), approached and consented.

5.4 Informed Consent Process

Written informed consent will be obtained prior to any study related procedure. The study will be discussed in detail, especially risks and potential benefits of the study, with the patient if the patient and treating provider agree. The patient will have the opportunity to ask questions, review the informed consent form with family, friends, and providers caring for the patient, including primary care physician. The patient will have the opportunity to have any questions answered. The patient will be informed in all instances that participation is voluntary and withdrawal from the study is possible at any time without any penalty or loss of
services or compromise of medical care. During the conduct of the study the patient will have the opportunity to have any additional concerns answered.

As the majority of the patient populations from which the study patients are drawn are likely to be literate, written consent will be obtained. Since greater than 90% of the study patients are likely to be primarily Zulu speakers, the consent form will be translated by an RSA government certified translator into Zulu and back-translated to assure correctness of the translation. The patient will be asked to sign the form or thumb-print the form if unable to sign. For illiterate patients, an impartial third party will witness the consent process and will also sign the consent form. A copy of the consent form will be given to the patient. An investigator will sign the consent form at a later date to verify that consent has been received for each patient enrolled. Consent forms will be stored in accordance to good practice guidelines.

Patients who are decisionally-impaired and who have not previously designated a health care proxy, legally authorized representative for research or other decision-maker who would represent patients’ wishes would not be eligible.

6 Study Implementation

6.1 Pre-Enrollment Screening

1) Medical history--including prior history of TB and its treatment (previous or current) and a review of systems.
2) HIV testing, if documented results of testing within six months prior to enrollment are not available.
3) Medication history including a complete history of any prescription or non-prescription medications taken, including actual or estimated start and stop dates; and any medication allergies
4) Targeted physical examination, including body temperature, pulse, blood pressure, respiratory rate, weight, height, signs and symptoms of tuberculosis
5) Sputum sample collected within three days for smear microscopy and TB culture and DST including for LZD
6) Urine pregnancy test for female patients who are of child-bearing potential.
7) Baseline blood specimens will be obtained for evaluation and will consist of a CBC, reticulocyte count, serum potassium, ALT, AST, albumin, bilirubin, blood sugar and creatinine unless results of these tests done within the previous 14 days are available.
8) Postero anterior and lateral chest x-ray if not available within 14 days of enrollment.
9) Vision testing [best corrected Snellen or Jaeger] with or without correction to allow evaluation of visual acuity and testing with Ishihara color plates to evaluate color vision
10) Neurologic history, examination, and testing for peripheral neuropathy to include administration of a standardized set of questions characterizing and quantifying foot pain and paresthesias, 128 Hz tuning fork tests for vibratory perception on both great toes and Queen’s square reflex hammer test of bilateral ankle reflexes. The modified method from the Brief Peripheral Neuropathy Screen (BPNS) will be used [25] (see Appendix 17.7)
### 6.2 Study Timeline for patients enrolled prior to March 15, 2010 (for study visits up to September 30, 2010)

<table>
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<th>Evaluation</th>
<th>Screen</th>
<th>Entry</th>
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<td>Concomitant meds</td>
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<td>Pregnancy test</td>
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### Notes:
- **a** Evaluation tests must be performed within 3 days of scheduled bi-weekly exams and within 14 days of scheduled monthly exams.
- **b** Screening and entry exams may be accomplished on the same visit.
- **c** Additional vision evaluations when participant returns from holiday or leave.
- **d** Unless test HIV+ at last testing.
- **e** Fasting blood sugar will be tested only once during the screening visit or the week 2 or week 4 study visit.
- **f** Serum sodium, potassium, chloride, bicarbonate, creatinine, BUN, ALT, AST, Bilirubin.
- **g** Monthly sputum smears and cultures until their cultures are negative for two consecutive months or patients have completed 12 months of therapy as per usual clinical practice.
- **h** Kanamycin, ciprofloxacin, ethambutol, pyrazinamide, cycloserine/terizidone and linezolid sensitivities will be done on all isolates of M. tuberculosis.
- **i** CD4 count in HIV-infected individuals at screening, enrollment, or at first draw after the patient is known to be HIV positive, and also at months 6 and 12.
### Study Timeline for patients enrolled on or after March 15, 2010

#### Evaluation a

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- **a** Evaluation tests must be performed within 3 days of scheduled bi-weekly exams and within 14 days of scheduled monthly exams
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- **i** CD4 count in HIV-infected individuals at screening, enrollment, or at first draw after the patient is known to be HIV positive, and also at month 5
6.3 Interventions

6.3.1 Study Intervention
Check any item(s) that characterize the proposed study:
- Drug Administration
- FDA-labeled for use
- Gene Transfer
- Radiation Treatment
- Surgery
- Diagnostic Studies
- Mechanistic Studies
- Concurrent Therapies
- Cell Therapy
- Treatment Modifications
- Pharmacokinetic Studies
- Questionnaire
- Natural History
- Other Study

6.3.2 Drug Administration
Study drug ingestion will be directly observed a minimum of five days a week with the option for self-administered study medication instead of DOT during weekends and holidays. During the study treatment the patient may receive daily study drug as an inpatient at KGVH or as an outpatient at specified clinic or through daily delivery by an MDR TB Mobile Unit.

6.3.3 Dosing
LZD will be administered at 600 mg orally once daily (7 days per week). For participants assigned to placebo during the initial phase, placebo will be administered orally once daily in a form that appears identical to LZD.

6.3.4 Diagnostic Radiation
All subjects will have baseline and serial radiographic assessments with plain PA and lateral chest X-rays according to routine KZN protocol for MDR TB patients at 8 weeks and 6 months after treatment initiation.

6.3.5 Study Visits – Clinical Assessments
Enrolled patients will have directly observed therapy (DOT) a minimum of 5 days a week, with the option for self-administered study therapy instead of DOT on weekends and holidays and study visits every other week (which will include a history, targeted physical exam, and laboratories) during the first 16 weeks or 112 doses of therapy. Patients enrolled prior to March 15, 2010 will receive follow-up as previously specified through September 30, 2010 (see study timeline for patients enrolled prior to March 15, 2010). There will be a month 5 follow-up visit for patients enrolled on or after March 15, 2010. Patient monitoring for patients newly
enrolled in the study will be accomplished as summarized in the Study Timeline for patients enrolled on or after March 15, 2010. No study visits will occur past September 30, 2010. At each study visit, a focused clinical assessment will be conducted and evidence of any toxicities obtained by interview and examination. Study visits during the first 16 weeks and at months 5, 6, and 12 will also include obtaining a complete blood count, specified blood chemistries, a directed physical examination (using BPNS tools to assess for peripheral neuropathy: ankle jerk reflexes, vibration sense, and pain/numbness scale), visual acuity screening with Snellen chart (or Jaeger handheld chart if needed, e.g., glasses forgotten), and Ishihara plate testing for color blindness. An expectorated (or induced) sputum will be obtained at each scheduled study visit through week 16 and thereafter if programmatically appropriate. Patient height should be documented at baseline and patient weight will be assessed at baseline and at all study visits. Standardized questions will be posed to each patient at study visits and recorded in source documentation and on the Follow-up Visit Form.

6.3.6 Diagnostic/Laboratory Procedures

TB diagnostic procedures
Five to thirty mL of expectorated sputum will be collected in a sterile container for AFB smear and culture (7H11, MGIT), and in vitro drug susceptibility testing, according to the schedule in the Study Timeline. If the patient cannot produce sputum spontaneously, a sterile saline solution will be used for induction of sputum. Smear and culture will be obtained every two weeks; drug susceptibility testing, including for LZD, will be done on all M. tuberculosis isolates. Subjects entering MDR TB therapy provide two consecutive morning sputa prior to the start of treatment (entry samples). Sputa will undergo AFB smear assessment and bacilli culture (7H11 and MGIT). Patients who remain culture positive at week 16 of therapy will continue to have monthly sputum smears and cultures during scheduled follow-up visits until their cultures are negative for two consecutive months as per usual clinical practice.

AFB smears will be scored by the World Health Organization (WHO) standard scale (0 – 3+). Drug susceptibility testing will be conducted by the clinical laboratory and results collected on case report forms (CRFs). Method of drug susceptibility testing for LZD will be the proportional method. Determination of “days to culture positivity” on liquid media (MGIT) will be used for this protocol. Volumes of sputum received in the lab, used in the procedure, and days to positivity will be recorded.

Isolate specimens at baseline and 16 weeks will be stored.

Routine Blood Tests
Laboratory monitoring will be obtained at baseline, 2, 4, 6, 8, 10, 12, 14, 16 weeks, and at months 5, 6, 7, 8, 9, 10, 11, 12, and 18. Five mL of blood will be collected in a no-additive tube (serum separator/red top) for serum collection. It will be used for performance of HIV rapid test, liver enzymes [total bilirubin, AST (SGOT), ALT (SGPT)], and serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen and creatinine) following the schedule in the Study Timelines.
Five mL of blood will be collected in an EDTA tube for hematology--red blood cell count (RBC), mean corpuscular volume (MCV), white blood cell count (WBC), differential and platelets at each scheduled blood draw following the schedule in the Study Timeline.

A blood sample for CD4 count in HIV infected individuals will be obtained at baseline (at screening, enrollment or first draw after the patient is known to be HIV positive), months 6 and 12.

**Pharmacokinetic/Pharmacodynamic (PK/PD) analysis of LZD**
A separate detailed protocol will be available for PK/PD sub-study.

**Pregnancy Testing**
Ten to 50 mL of urine will be collected for pregnancy testing at entry by commercial human chorionic gonadotropin (β-hCG) determination kit from women who can get pregnant.

**HIV Testing**
HIV testing is routinely offered before study enrollment as per standard of care. Positive rapid HIV tests are repeated. Two rapid HIV tests are considered confirmatory per South African protocols. Discrepant rapid test results undergo HIV ELISA testing per South African protocols. All study subjects will have appropriate pre- and post-test counseling. Participants will have HIV testing done at study entry if results are not available from a test performed within the previous 6 months.

**Peripheral Neuropathy Testing**
Screening for peripheral neuropathy will use a minor modification of the Brief Peripheral Neuropathy Screen (BPNS) [25] (Please see Appendix 17.7). All subjects will undergo peripheral neuropathy testing at entry which will include a modified BPNS for pain and numbness that will grade peripheral neuropathy, ankle reflex testing and vibratory perception testing of the both great toes by the study team [25]. The history and exam will be repeated at two week intervals by the study team during the first 16 weeks, then monthly through month 12. If symptoms or signs of peripheral neuropathy of grade 3 or above develop during the first 6 months of the study the patient will be referred to a neurologist for further assessment and management.

**Optic Neuropathy Testing**
At baseline, every two weeks during the first 16 weeks and monthly through month 12 subjects will undergo baseline vision testing including, including visual acuity testing (Snellen or Jaeger, with or without correction) and color blindness testing (Ishihara plates). If there is a worsening of more than 5 lines of visual acuity during subsequent study visits utilizing the same type of chart or poor color vision as evidenced by incorrect answers on ≥ four of 12 screening Ishihara plates, study medication will be held and further evaluation by an ophthalmologist will be sought. If signs or symptoms of optic neuropathy develop the subject will follow up with an ophthalmologist for further evaluation.

The Ishihara plates are designed to be appreciated correctly in a room which is lit adequately by daylight. The introduction of direct sunlight or the use of electric
light may produce some discrepancy in the results because of an alteration in the appearance of shades of color. When it is convenient only to use electric light, it should be adjusted as far as possible to resemble the effect of natural daylight. The plates are held 75 cm. from the subject and tilted so that the plane of the paper is at right angles to the line of vision.

6.3.7 Concurrent Therapies
Concomitant medications, including start dates, stop dates, and dose changes, will be recorded in the medical chart and CRF at each study visit. Study adherence will also be monitored and recorded in both places. Study personnel will not be providing direct care for HIV infection in study patients. HIV care will be provided to patient by their primary care clinicians according to provincial and national guidelines. In recognition that HIV care can profoundly influence outcomes for persons infected with both HIV and TB, HIV infected patients will additionally be questioned at each study visit regarding their use of anti-retroviral agents and medicines to treat and prevent opportunistic infections.

6.4 Dose Modifications

6.4.1 Dosing Delays/Dose Modifications
Subject-initiated, provider-initiated and protocol-mandated interruptions include both inadvertent and deliberate interruptions of study drug dose. For the study’s primary endpoint, 18 consecutive weeks are allowed for completion of at least 90 doses of study medication.

6.4.2 Dose Limiting Toxicity
Any Grade 3 or above myelosuppression, neuropathy or hepatitis that is likely to be attributed to LZD will result in a recommendation for the termination of study drug to that subject (See Section 9.6).

6.5 Unblinding
Generalized unblinding of treatment allocation for all patients will not occur until all enrolled have finished study therapy (maximum 112 doses) plus four weeks of post-last dose of study therapy follow-up. There are two potential situations that may lead to earlier unblinding of treatment on a patient by patient basis:
1. The assessment of an adverse event and its management will benefit from knowing the drug allocation. This situation is anticipated to be rarely needed and it requires the review and endorsement by the study protocol team. All unscheduled early unblinding episodes will be reported to the DSMB at the same time as the reporting of the related adverse event.
2. Unblinding of the KGVH MDR TB Treatment Committee for patients under review for administration of compassionate use LZD. (See section 16) All unscheduled unblinding episodes for compassionate use LZD will be reported to the DSMB (see section 11 for information regarding the DSMB).
6.6 Assessment of Enrollment and Follow-up

All patients will have follow-up through September 30, 2010 to determine feasibility of follow-up of this particular patient population and to inform future research in MDR and XDR TB. If patients do not return for their monthly follow-up visits, study staff will either call or visit the patients. This will be done for two reasons – to determine reasons for non-attendance (other illness, death, etc) and to persuade the patient to return for regular follow-up. If patients are ‘recovered’ this way, on their next missed visit, the same intervention would be repeated, until patient is: (i) not found; (ii) withdraws consent for further follow-up (reason why will be asked and recorded); or (iii) has died. This will serve to assess feasibility of long-term follow-up at this site. Outcomes of the feasibility study would include proportion of patients followed successfully the number of months followed and the months of treatment through September 30, 2010. Additional outcomes, useful for planning future studies would include obtaining estimates of time and other costs spent tracking patients and collecting data on reasons for patient drop-out during therapy.

6.7 Follow-up After Premature Study Drug Discontinuation and Study Withdrawal

6.7.1 Premature Discontinuation

Patients who permanently discontinue study treatment prior to completion of the study, if possible, will be followed until study completion (on September 30, 2010). Patients may be taken off study drug but continue to receive follow-up in the following circumstances:

1) Drug-related toxicity (see sections 9.6 Adverse Event Stopping Rules and 9.9 Potential Hazards)
2) Requirement for prohibited concomitant medications
3) Any reason deemed necessary by the investigator or treating physician
4) If the patients requests to stop study treatment, but does not withdraw consent for follow-up

6.7.2 Study Withdrawal

Patients who withdraw consent for further participation, including follow-up, prior to completion of the study will not undergo any further study procedures or data collection. Data collected prior to withdrawal will be analyzed with complete data sets as is appropriate (e.g., time to sputum negativity for a patient who withdraws after becoming AFB negative).

7 Concomitant Care

7.1 Concomitant TB Medications

Concomitant medications include four or more of the standard drugs used for antituberculous chemotherapy for documented drug-resistant tuberculosis, including ofloxacin, moxifloxacin, amikacin, kanamycin, capreomycin, ethionamide, cycloserine, terizidone, ofloxacin, para-amino salicylic acid (PAS),
pyrazinamide (PZA), ethambutol and streptomycin. Subjects will also receive pyridoxine (Vitamin B6) with their regimen.

### 7.2 Standard of Care for MDR TB in KZN

Treatment for drug-resistant TB is determined on an individual basis, according to each patient’s isolates’ DST results according to KZN’s standard operating procedures for MDR TB treatment. Medications that comprise potential second-line drug regimens at KGVH include ethionamide, para-amino salicylic acid (PAS), ofloxacin, cycloserine, amikacin, kanamycin, capreomycin, ethambutol, amoxicillin-clavulanic acid, clarithromycin, and pyrazinamide. Patients commencing treatment of MDR TB in KZN generally have had DST to first-line TB drugs, but all patients may not have DST to second-line TB drugs. Based upon WHO guidelines the RSA standard initial treatment regimen for MDR TB is ethionamide, kanamycin, pyrazinamide (PZA), ethambutol or cycloserine/terizidone, and ofloxacin. The duration of therapy is 18 months following conversion to sputum culture negative (typically within 6 months following initiation) for a total of 24 months of therapy. Patients with chronic disease that are persistently culture positive and fail to respond to standard second-line therapy typically experience several regimen changes based upon their organisms’ DST result. Patients with documented resistance to typical second-line agents are given alternative agents that are often used indefinitely in their care such as: amoxicillin/clavulanic acid (Augmentin), cycloserine, PAS, ethionamide, and clarithromycin. The standard empiric XDR TB regimen for RSA consists of capreomycin, PAS, ethambutol and/or cycloserine, PZA. Potential side effects include the following:

1) Ethionamide: gastrointestinal disturbances, hepatitis, drowsiness, dizziness, headache, restlessness, and depression;
2) PAS: gastrointestinal intolerance, hypersensitivity reactions, and hepatitis;
3) Augmentin: diarrhea, vaginal mycosis, nausea
4) Cycloserine or terizidone: neurotoxicity including behavioral disturbances, hallucinations, and seizures
5) Clarithromycin: diarrhea, nausea, abnormal taste, dyspepsia, abdominal pain, headache.
6) Kanamycin or amikacin: nephrotoxicity, hearing loss, dizziness, tinnitus, peripheral neuropathy
7) Capreomycin: nephrotoxicity, urticaria, maculopapular rash, ototoxicity (vestibular > auditory)
8) Fluoroquinolones (including ciprofloxacin, ofloxacin, and moxifloxacin): diarrhea; headache, rare tendon rupture, rare QT interval prolongation
9) Ethambutol: gout, optic neuropathy

MDR TB patients seen at KGVH and affiliated MDR TB clinics will be monitored by staff physicians for potential adverse drug effects with a blood count, serum liver enzymes, blood urea nitrogen measurements, and serum creatinine determinations at the start of treatment and as needed according to clinical signs.
and symptoms during follow-up. Patients with elevated serum liver enzymes are not generally prescribed a regimen including ethionamide or PAS. Patients showing evidence of significant drug toxicities are evaluated and the regimen changed to a regimen with agents that avoid these side effects. Patients under standard care at KGVH and affiliated MDR TB clinics undergo chest radiography at the beginning of MDR TB therapy, at one month and again at two months of therapy. Monthly sputum smear and culture is performed until patients have a negative culture for two consecutive months, thereafter cultures are obtained every other month for the duration of MDR TB treatment.

While in the hospital, all MDR TB inpatients obtain their medication from the ward nurse daily. Patients with MDR TB being treated with study drug as outpatients will daily receive their medications either from the local clinic or from the Mobile MDR TB Unit nurse. Patients will be observed while they take their TB medications as part of directly observed therapy (DOT). Nursing records and physician’s progress notes will be used as source documentation of any drug adverse effect.

8 Data Collection and Sample Storage

8.1 Data Collection, Management, Storage and Publication

8.1.1 Data Collection

Local sputum, blood, and urine testing will be conducted at the Nelson R. Mandela Department of Investigative Microbiology Laboratory.

Case report forms (CRFs) will be filled out by the study staff. Information for the CRFs will be obtained from the patient interview upon consent, medical records, and data accrued in the trial, and will include a medical history, lab results and specimen data, and radiographic results obtained in the trial. Information collected on the CRFs will be entered into the database.

8.1.2 Data Management

Data entered onto the CRF will be entered into the study electronic database, which will be managed and monitored by the KZN-CDC study team. CRFs will be maintained in a locked cabinet in a locked office. Access to the database is password controlled and will be limited to those with data entry and management responsibilities. Records are protected by ownership control and a complete log of all activities within the system is recorded. All study related data will be maintained on servers located at CDC.

8.1.3 Data Storage

All essential documentation for all study subjects including history and physical findings, laboratory data, and results of consultations are to be maintained by the investigators in a secure storage facility for a minimum of three years. These records are to be maintained in compliance with IRB/EC (Institutional Review Board/Ethics Committee), local and government requirements, whichever is longest. All records are to be kept confidential to the extent provided by law.
8.1.1.4 Publication of Research Findings

Collaborating protocol team members will own the research data generated by or resulting from this project, and they may arrange for publication of this original research (with permission of all study investigators) in a primary scientific journal, and for copyright by the journal unless the journal's copyright policy would preclude individuals from making or having made a single copy of any such article for their own use.

8.2 Sample Storage

For patients who consent to sample collection and storage of specimens for future testing (see section 18.3) sputum and serum specimens (5 ml) will be collected at study entry and at 4, 8, 12, and 16 weeks; transported to; processed and stored study site specimen bank at BARC laboratories (serum) and Medical Microbiology (sputum), Durban, KZN, RSA. All specimens will be labeled, indexed and stored by study ID so that review of the actual specimens is possible by all investigators on the protocol. Non-infectious specimens will be stored in the specimen bank freezer room in -80 degrees C freezers. Infectious specimens will be stored inside the ITRC BSL-3 laboratory. Both sets of specimens will be stored in locked rooms; access to the specimens will be controlled and use will be recorded in study specific log books.

Each patient will be asked to specify whether they elect to 1) allow storage and future testing of their specimens for the purpose of improving the understanding of tuberculosis pathogenesis and care of TB patients without additional contact/consent or 2) would not allow further testing of their specimens.

No one on the study team will benefit monetarily from the collection, storage, or future testing of patient specimens. A 20% loss of or destruction of samples will constitute a compromise of the scientific integrity of the data collected and will be reported to both IRBs. At the termination of the TBTC study, any remaining samples will be retained or disposed of as determined by the Durban study site and the RSA IRB according to South African laws.

8.3 Outcome Measures

8.3.1 Primary Endpoints

Proportion of patients in each arm who are directly observed to take at least 80% of the 112 doses of study drug (90 doses) within 18 weeks of study treatment initiation.

Cumulative rate of SAEs (measured as the number of SAEs per person days) during the period of study therapy and the four weeks of post-study therapy follow-up.

8.3.2 Secondary Endpoints

1) The number of days required to convert to culture negative status in sputum of those in each treatment arm on solid and liquid media, respectively.

2) The proportion of culture-negative patients during the first 16 weeks of therapy (at two week intervals) of linezolid with OBT vs. that of OBT with placebo on solid and liquid media, respectively.
3) Time to detection of *M. tuberculosis* on MGIT for each positive culture for sputum specimens collected every 2 weeks during the first 16 weeks of therapy.

4) The occurrence of treatment failure following initiation of study therapy.

5) DST for patient isolates up to 16 weeks to determine drug sensitivity, including linezolid sensitivity, and assess for the development of resistance.

6) Changes from baseline in assessments for peripheral neuropathy.

7) Changes from baselines in Snellen or Jaeger visual acuity test and Ishihara color plate test results to assess for optic neuropathy.

8) Occurrence of anemia or thrombocytopenia that require transfusion of blood products or lead to permanent discontinuation of study drug.

9) Plan for Monitoring Patients and Criteria for Withdrawal of Patients from the Study.

9.1 Definition of an Adverse Event

*Adverse Events* (AEs) include any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. Stable chronic conditions which are present prior to clinical trial entry and do not worsen are not considered adverse events and will be accounted for in the patient’s medical history.

*Serious Adverse Events* (SAEs) are any untoward medical occurrences that: (1) result in death, (2) are life-threatening, (3) require (or prolong) hospitalization, (4) cause persistent or significant disability/incapacity, (5) result in congenital anomalies or birth defects.

*Expected Adverse Events* are adverse events that are listed as possibly related to the study agent/intervention in the protocol, informed consent document, or the package insert.

9.2 Grading Adverse Events for Severity

The severity of each adverse event will be determined using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published August 9, 2006 which can be found at http://ctep.cancer.gov/forms/CTCAEv3.pdf. Any events that are not listed in this toxicity table will be graded by the local PI as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mild</th>
<th>Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Moderate</td>
<td>Moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe</td>
<td>Marked limitation in activity; some assistance usually required; medical intervention/therapy required,</td>
</tr>
<tr>
<td>GRADE 4</td>
<td>Life-threatening</td>
<td>Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>

Grade 5  
Death

For peripheral neuropathy the grading of severity would be as follows

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory alteration (including paresthesia and painful neuropathy)</td>
<td>Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing inability to perform usual social &amp; functional activities</td>
<td>Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Neuromuscular weakness (including myopathy &amp; neuropathy)</td>
<td>Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social &amp; functional activities</td>
<td>Muscle weakness causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Muscle weakness causing inability to perform usual social &amp; functional activities</td>
<td>Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation</td>
</tr>
</tbody>
</table>

For hematologic adverse events the grading of severity would be as follows

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (Hgb)</td>
<td>8.5 – 10.0 g/dL</td>
<td>7.5 – 8.4 g/dL</td>
<td>6.50 – 7.4 g/dL</td>
<td>&lt; 6.5 g/dL</td>
</tr>
<tr>
<td>Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)</td>
<td>1.32 – 1.55 mmol/L</td>
<td>1.16 – 1.37 mmol/L</td>
<td>1.01 – 1.15 mmol/L</td>
<td>&lt; 1.01 mmol/L</td>
</tr>
<tr>
<td>Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)</td>
<td>10.0 – 10.9 g/dL</td>
<td>9.0 – 9.9 g/dL</td>
<td>7.0 – 8.9 g/dL</td>
<td>&lt; 7.0 g/dL</td>
</tr>
<tr>
<td>1.55 – 1.69 mmol/L</td>
<td>1.40 – 1.54 mmol/L</td>
<td>1.09 – 1.39 mmol/L</td>
<td>OR Any decrease</td>
<td>&lt; 1.09 mmol/L</td>
</tr>
<tr>
<td>OR Any decrease</td>
<td>Any decrease</td>
<td>2.5 – 3.4 g/dL</td>
<td>3.5 – 4.4 g/dL</td>
<td>4.5 g/dL</td>
</tr>
<tr>
<td>0.39 – 0.53 mmol/L</td>
<td>0.54 – 0.68 mmol/L</td>
<td>≥ 0.69 mmol/L</td>
<td>≥ 0.69 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Platelets, decreased</td>
<td>100,000 – 124,999/mm³</td>
<td>50,000 – 99,999/mm³</td>
<td>25,000 – 49,999/mm³</td>
<td>&lt; 25,000/mm³</td>
</tr>
<tr>
<td>100,000 x 10⁹/L – 124,999 x 10⁹/L</td>
<td>50,000 x 10⁹/L – 99,999 x 10⁹/L</td>
<td>25,000 x 10⁹/L – 49,999 x 10⁹/L</td>
<td>&lt; 25,000 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>1.000 – 1.300/mm³</td>
<td>750 – 999/mm³</td>
<td>500 – 749/mm³</td>
<td>&lt; 500/mm³</td>
</tr>
<tr>
<td>Adult and Pediatric, &gt; 7 days</td>
<td>1.000 x 10⁹/L – 1.300 x 10⁹/L</td>
<td>750 x 10⁹/L – 999 x 10⁹/L</td>
<td>500 x 10⁹/L – 749 x 10⁹/L</td>
<td>&lt; 500 x 10⁹/L</td>
</tr>
<tr>
<td>1.000 x 10⁹/L – 1.300 x 10⁹/L</td>
<td>750 x 10⁹/L – 999 x 10⁹/L</td>
<td>500 x 10⁹/L – 749 x 10⁹/L</td>
<td>&lt; 500 x 10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>

* In the table above the term “Pediatric > 57 days” refers to the age of children for whom the grading of severity criteria encompasses. Children are not eligible for this study; however, these criteria also include grading of severity for the adults enrolled in this study.

9.3 Monitoring for Adverse Events

Patients will be monitored prospectively for the development of adverse events during study visits as well as through communication with the primary team caring for the patient.
If the primary care team suspects an adverse event between study visits, this will trigger an unscheduled study visit to assess the potential adverse event.

9.4 Assessing Adverse Events for Relationship to Study Drug
Any AE that occurs in a patient will be assessed for relationship to the study drug. A causal relationship means that the drug caused (or is reasonably likely to have caused) the AE. This usually implies a relationship in time between the drug/study agent and the AE— for example, the AE occurred shortly after the patient received the drug/study agent. Whether to re-challenge the patient with study drug or not will be left to the discretion of study staff in combination with the primary providers for the patient in conjunction with the patient. Re-challenges will be documented by recording when patient resumed study drug and any subsequent AE’s. Experience from re-challenge may be used for design of a re-challenge protocol for a subsequent larger study, if it is warranted based on the results of this pilot study.

For all AEs, the principal investigator or his/her designee who examines and evaluates the patient will determine the adverse event’s causality based upon the temporal relationship to administration of the study agent(s), the pharmacology of the study agent(s), and his/her clinical judgment.

The following scale will be used to reflect the PI’s or his/her designee’s judgment as to the relationship between the study agent/intervention and the AE:

**Definitely Related:** The AE is clearly related to the study agent – follows a reasonable temporal sequence from administration of the study agent, follows a known or expected response pattern to the study agent that is confirmed by improvement on stopping or worsening/reappearance of the event in repeated exposure and that could not be reasonably explained by the known characteristics of the patient’s clinical state.

**Probably Related:** The adverse event and administration of study agent are reasonably related in time or follows a known pattern of response, and the adverse event is more likely explained by study agent than other causes.

**Possibly Related:** AE follows a reasonable temporal sequence from administration of the study drug/intervention, follows a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.

**Probably not Related:** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent (e.g., could readily have been produced by the patient’s clinical state or could have been due to environmental or other interventions)

**Not Related:** AE is clearly not related to the study agent – another cause of the event is most plausible or a clinically plausible, temporal sequence is consistent with the onset of the event and the study medication administration or event is biologically implausible.

9.5 Adverse Event Documentation
Any AE, grade 3 or above, whether or not considered related to the study drug, or whether considered non-serious or unexpected, that occurs between the times a patient signs the informed consent form and the time s/he departs the study (for any reason) must be fully and completely documented on the Adverse Event Case Report Form (CRF) and in the patient/study participant’s clinical chart. The start date, the stop date, the severity of each reportable event, and the principal investigator’s or his/her designee’s judgment of the AEs relationship to the study agent/intervention will also be recorded on the Adverse Event CRF.

### 9.6 Adverse Event Stopping Rules

It will be strongly recommended that study medication (or unblinded compassionate use LZD—see section 16) be stopped if patients develop:

- Hypersensitivity or allergic reaction
- Neutropenia with an absolute neutrophil count count below 750
- Thrombocytopenia below 50,000
- Anemia requiring more than two transfusions of ≥ 2 units of packed red blood cells
- Peripheral neuropathy with pain in the feet described as being 5 or more on the visual analogue scale associated with a change of two numbers in increasing severity,
- Pain in the feet that regularly interferes with walking or sleep
- Decrease in vibratory sense to ≤5 seconds.
- Optic neuropathy with a drop in visual acuity to 20/200 (6/60 meters) best corrected vision or a drop in visual acuity of five lines on Snellen or Jaeger charts, whichever is less severe.
- Detection of loss of color vision by Ishihara plates defined as ≥ 4 errors on the 12 plate screening test.
- Development of lactic acidosis
- Development of serotonin syndrome

Patients meeting any of these criteria would be told by study personnel that it is recommended that the patient stop the study drug (or unblinded compassionate use LZD—see section 16) to limit progression of the patient's adverse effects. However, if based upon discussions with the treating physician and the clinical circumstances they find themselves (e.g., high extent of drug resistance of their TB) the patient may decide to continue study drug if the treating and study physicians (or the KGVH MDR TB Treatment Committee in the case of patients receiving compassionate use unblinded LZD) are in agreement. Every two weeks thereafter while on study medicines the patient will receive further examinations and must readdress the issue of recommended discontinuation of study medicines.

### 9.7 Management of Adverse Events

Once an AE is recognized, staff at the study site should ensure that the patient receives prompt and appropriate care. Should a patient call a study clinician to report an adverse event, it will be determined at that time if an extra visit(s) will be scheduled, and appropriate medical advice will be provided. All actions taken by the investigator after observing an AE should be documented, including increased monitoring of the patient/study participant, suspension of the treatment, etc. Additionally, all calls will be documented in the patient/study participant’s study chart, and discussed with the principal investigator.
All serious and non-serious AEs reported in this study will be followed until resolution or until the investigator and the treating physician are in agreement that the AE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

In the event that the patient’s study medication is stopped due to an AE, it must be recorded on the CRF as such. The patient should be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized. It is up to the clinician to determine that the AE is either resolved, or that it has reached a stable state, after which no further follow-up is necessary. There should be documentation to support that determination.

In the rare instance when a clinicians caring for patients believe that unblinding of study drug allocation would help in management of an adverse event the clinician can petition the local principal investigator follow steps for potential unblinding—see section 6.5

9.8 External Review of Adverse Events
The DSMB will review all serious adverse events individually and in aggregate according to the analysis plan.

9.9 Potential Hazards
All study participants will be monitored by study staff and their primary care team for potential adverse effects of LZD treatment including myelosuppression, peripheral neuropathy (i.e., numbness or paresthesias), optic neuropathy, persistent nausea or vomiting, serotonin syndrome, and pseudomembranous colitis. Study staff and the primary care team will communicate changes in patient status to each other. It will be recommended by the investigators that study medication be discontinued if the following moderate-to-severe Grade 3 expected adverse events develop: hepatitis, peripheral or optic neuropathy, seizures or hematological disorders (i.e. thrombocytopenia, anemia or leucopenia). A patient may be re-challenged with study medication at a later date; however if the patient has had a lapse of treatment for 10 or more consecutive day she/she will not be permitted to reinitiate study treatment.

10 Adverse Event Reporting Plan

10.1 Internal Reporting Requirements
All deaths and life-threatening SAEs which occur during the course of this investigation, whether or not considered to be related to the study agent or considered to be an expected event associated with the study agent, will be reported to the CDC Project Officer within 2 business days, and all other SAEs will be reported within 3 business days. This reporting time has been determined to account for the time it may take the treating doctors working with the patients to report to the local study staff who in turn will report to CDC. All SAEs will be reported by telephone, fax or e-mail to the following:

<table>
<thead>
<tr>
<th>Name</th>
<th>Phone</th>
<th>Fax</th>
<th>e-mail</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>William R. MacKenzie, MD</td>
<td>404-639-8456</td>
<td>404-639-1566</td>
<td><a href="mailto:wrm0@cdc.gov">wrm0@cdc.gov</a></td>
<td>1600 Clifton Road, NE, MS E-10, Atlanta, GA 30333</td>
</tr>
</tbody>
</table>
10.2 External Reporting Requirements

The CDC IRB requires prompt reporting of adverse events that are serious, unexpected, and at least possibly related to the research. For such events, the procedure follows:

1) The CDC project officer sends an e-mail message to HRPO within 2 working days of CDC awareness of a reportable incident.

2) Within 2 weeks, the CDC project officer submits form 0.1254 and any additional documentation to HRPO. Forms must be submitted even if information is not yet complete.

A summary of all adverse events with severity of grade 3 or greater (relative to patient history at entry as specified above) will be reported to the CDC IRB by the CDC project officer with submission of a request for continuing review. This summary will also be submitted to the Biomedical Research Ethics Committee (BREC) of the Nelson R. Mandela School of Medicine with the continuing review.

Adverse event reporting requirements to the BREC and the RSA Medicine Control Council (MCC) for this protocol are as follows:

1) KZN Investigators must provide a preliminary report to BREC and MCC within 3 working days after becoming aware of a patient death or a potentially life-threatening serious adverse event. This preliminary report must be followed by a progress report within 8 days.

2) KZN Investigators must provide a final report to the BREC and MCC within 15 days after becoming aware of an inpatient hospitalization (other than elective), a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

11 Data and Safety Monitoring Plan

A three person Data and Safety Monitoring Board (DSMB) will be constituted to review the safety data for this study. The DSMB will review cumulative study data twice per year to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB will also assess the performance of overall study operations and any other relevant issues, as necessary. The first DSMB review will occur after 33% of patients projected to complete the initial study phase (17 patients) have completed study therapy and four weeks of post-study therapy follow-up or after the occurrence of three optic neuropathy treatment endpoints (decrease in visual acuity to 20/200 (6/60 meters) best corrected vision or decrease by 5 lines on Jaeger or Snellen chart or development of color vision deficiency by Ishihara plates [defined as ≥ 4 incorrect responses on the 12 plate screening test]), whichever occurs first. In the case of two SAEs potentially attributed to LZD the DSMB and the protocol team will have the opportunity to review and discuss the events.

Items reviewed by the DSMB include:

1) Primary/cumulative data for evidence of study-related adverse events
2) Data quality, completeness, and timeliness
3) Demographic information on study participants
4) Site monitoring reports related to adherence to the protocol and applicable regulations
5) Factors that might affect the study outcome or compromise the confidentiality of the trial data (protocol violations, unmasking, etc.)

6) Factors external to the study, such as scientific or therapeutic developments, that may impact participant safety or the ethics of the study

12 Data Management Plan

Westat, a contract research organization that specializes in clinical trials management (see http://www.westat.com/), will monitor this trial for source document verification and regulatory compliance. The Westat monitoring team will discuss a detailed monitoring plan with the principal investigator.

Study data will be collected on standardized paper CRFs prepared by the TBTC study team in conjunction with Westat. The local study team will use only TBTC-approved CRFs. The Principal Investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. The CRFs will be collected and placed into a patient-specific binder. Source documentation (the point of initial recording of a piece of data) should support the data collected on the case report form, and be signed and dated by the person recording or reviewing the data. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Source documents include, but are not limited to, the patient medical records, electronic chart records, laboratory reports, electrocardiogram (EKG) tracings, x-rays, radiologist reports, biopsy reports, ultrasound photographs, patient progress notes, pharmacy records and any other similar reports or records of procedures performed during the patient’s participation in the protocol. Data for CRFs will be collected during patient visits by health care providers and abstracted from the medical record. Once the data is collected, it will be reviewed by the Westat monitoring team or their contractors. Once reviewed, a copy of each CRF will remain at the site while the original will be retained by the monitoring team and a copy sent to the CDC investigators. Any data that is compiled for statistic or other manipulation will be handled in an Access database. The scientific results from this study will require various formats, depending on the data type. Locked copies of these files containing the results will be compiled by the research supervisor and made available to monitoring and regulatory agencies as necessary.

13 Protocol Monitoring Plan

The study will be conducted in compliance with this protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP) and all applicable regulatory requirements. Westat monitors under contract to the TBTC/CDC will visit designated clinical research sites to monitor all aspects of the study in accordance with the appropriate regulations. The objectives of a monitoring visit will be:

1) To verify the prompt reporting of all data points, (for example, verification of expedited reporting of adverse events)

2) To compare individual patients’ records (case report forms, data pulls) to the source documents (supporting data, laboratory specimen records, medical records to include physician progress notes, nurses notes, patients’ hospital charts)

3) To ensure protection of study patients, compliance with the protocol, and accuracy and completeness of records
The monitors will also inspect the clinical site’s regulatory files to ensure that applicable regulatory requirements are being followed. During the monitoring visits the Investigator, or designee, and other study personnel will be available to discuss the study. The Investigator (or designee) will make study documents (e.g., consent forms, CRFs) and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the CDC staff for confirmation of the study data.

Any changes or additions to the protocol will be submitted to BREC and the Columbia University and CDC IRBs and relevant regulatory agencies for review. The written IRB approvals will be filed in the local investigator’s study binder, and a copy of the approvals will be forwarded to the monitoring team. Furthermore, essential documents will be collected in the study binders and will include:

1) IRB/EC approvals for the study protocol and all amendments
2) All source documents and laboratory records
3) CRF copies
4) Informed consent forms

14 Patient Protection

This protocol must receive the approval of the CDC, Columbia University Institutional Review Boards and BREC prior to implementation. The study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and any applicable regulatory requirement(s), as well as in accordance with the CDC policies. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Principal Investigator will promptly report to the IRB and to CDC any proposed changes in research activity and will promptly report to the IRB all unanticipated problems involving risk to human subjects or others.

14.1 Rationale for Patient Selection

The population referred to and treated by the KGVH was selected for study for several reasons: (1) South Africa has a high rate of tuberculosis infection, with 700 – 1000 cases of active tuberculosis per 10,000 population; (2) South Africa has a high rate of infection with drug-resistant strains of \textit{M. tuberculosis} (2% and 7% prevalence of multi-drug resistance among new and previously-treated cases of tuberculosis, respectively), as well as patients resistant to almost all known TB therapies; (3) existence of a specialized hospital and outpatient staff for the treatment of drug resistant TB and (4) with the presence of trained study staff familiar with conducting clinical trials for TB.

14.2 Participation of Children and Other Vulnerable Patients

This study will enroll only persons age 18 years and older. Patients who are not competent may be enrolled in the study if their guardian provides and informed consent and treating physician agrees with enrollment. The same stipulations regarding voluntary participation
and withdrawal without penalty apply with guardian making such decisions for the patient. Guidance is provided for patients who are decisionally impaired in obtaining informed consent in the Appendix. Patients who are decisionally impaired and who have not previously designated a health care proxy, legally authorized representative for research or other decision-maker who would represent patients’ wishes would not be eligible.

14.3 Harm-Benefit Analysis including Considerations of Alternatives to Participation

14.3.1 Potential Benefits to Study Patients

1) There may be no benefit to patients for participating in this study. However, it is possible that their drug-resistant disease may be more effectively treated because of the study drug, LZD.

2) Because of the increase in the number of diagnostic radiology procedures, sputum cultures, and testing of TB isolates for drug resistance, the patients may have disease-progression and drug resistance diagnosed earlier than if they were not in the study. In addition, because of the follow-up visit they may receive treatment for failing to improve with drug-resistant disease more quickly than patients who are not enrolled in this protocol.

14.3.2 Risks to Study Patients

Possible side-effects of LZD include myelosuppression and neuropathies (optic and peripheral), gastrointestinal (nausea, vomiting), lactic acidosis, serotonin syndrome with use of serotonergic agents (e.g., SSRI antidepressants), and pseudomembranous colitis. LZD is classified as a Category C drug when taken in pregnancy; treatment is generally not recommended during the first trimester of pregnancy. Additional risks or harms to the patients include venipuncture with bleeding, anemia, infection, and pain.

There is a potential risk that using LZD at 600 mg daily could induce resistance to LZD which may make LZD less useful in the treatment of the patient at a later date. However, to date, there is no evidence for significant induction of LZD resistance in the literature when used at this dose.

14.3.3 Harm-Benefit Analysis (Main Study)

Patients with drug resistant TB (MDR/XDR TB) face a substantial risk of morbidity and early mortality, which increase with increased drug resistance. The treatment of MDR TB and especially XDR TB requires difficult, lengthy, and intensive interventions, and without these interventions, their lethality rates are large—essentially 100% in the presence of HIV infection.

While we expect to see side-effects from LZD in the group of patients receiving this agent these are not expected to be life-threatening. Neuropathic complications have been reported to increase in incidence after four months of treatment, when most patients would be coming off study medications. Patients that elect not to participate in the protocol will receive the same second-line drugs that patients not on the protocol will receive (initially with empiric regimens according to RSA
guidelines for the treatment of MDR and XDR TB and then according to individualized DST results), thus there is no penalty for not participating. Patients receiving LZD may have an improved likelihood of resolving their super-resistant disease, but may also have an increased risk of adverse side effects. The information gained from this study will help medical knowledge. Overall the potential benefits to MDR and XDR TB patients of participating in the study outweigh the risks of the interventions that will be performed.

14.4 Privacy and Confidentiality
All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain patient confidentiality. All paper study records will be kept locked in an office within a locked file drawer. Access to these files is limited to four study personnel. Electronic study records will be entered and stored on a single, password protected computer that can only be accessed by these same four study personnel. All computer entry and networking programs will be done with coded numbers only. Transmission of electronic records to CDC will occur using a secure CDC File Transfer Protocol (FTP). The only identifier on the electronic study records received by CDC will be the study identification number. No direct identifier will be transferred to CDC. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB, CDC, or regulatory agencies.

14.5 Remuneration
Patients will receive remuneration for their time and effort involved in participation in the study as stipulated by the Republic of South Africa Medicines Control Committee (MCC). Patients will receive R150.00 ($20) per study visit for loss of income, inconvenience, transport as stipulated by the MCC. Study medication and study related diagnostic exams will be provided free of charge, for the duration of planned study follow-up. Patients qualifying for compassionate use of unblinded LZD treatment following completion of 112 doses of study medication will receive LZD and additional follow-up visits free of charge.

Physicians referring patients for enrollment into this study will not receive remuneration for their referral.

15 Pharmaceutical, Biologic, and Device Info

15.1 Source of LZD
LZD will be donated by Pfizer Pharmaceuticals.

15.2 Toxicity of LZD
The following are known side-effects of LZD, with frequency percentages shown (where known) reference: diarrhea (4%), nausea (3.3%), headache (1.9%) vomiting, rash, erythema, increased serum creatinine, myelosuppression, lactic acidosis, peripheral neuropathy (with prolonged therapy > 30 days), optic neuropathy, and rare serotonin syndrome.
15.3 Source and Toxicity of Pyridoxine HCl
Pyridoxine HCl will be procured locally and dispensed from a study pharmacist at KGVH. Pyridoxine is available in 50 mg tablets. Photoallergic reaction, headache, drowsiness and nausea may be seen at normal 50 mg doses of pyridoxine HCl. Side effects that may been seen at high doses (typically greater than 2 grams/day) and after prolonged therapy are sensory neuropathic syndromes; unstable gait; numb feet; awkwardness of hands; perioral numbness; decreased sensation to touch, temperature, and vibration; paresthesia; and ataxia.

15.4 Formulation and Preparation of LZD
LZD tablets contain 600 mg of active LZD and the following inactive ingredients: corn starch, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide and carnauba wax. LZD tablets will be overencapsulated by Bilcare Pharmaceutical Services using size 000 white opaque gelatin capsules from Capsugel.

15.5 Formulation and Preparation of Placebo
Placebo will be made by Bilcare Pharmaceutical Services. The composition of placebo tablet will include microcrystalline cellulose (Avicel PH102) as the diluent/ductile binder, sodium starch glycolate (Explotab) as the disintegrant, and vegetable-derived magnesium stearate as the lubricant. The components will be blended and compressed using a rotary tablet press into caplets of appropriate weight and thickness to match that of overencapsulated LZD caplets. Placebo tablets will then be overencapsulated by using size 000 Swedish red gelatin capsules from Capsugel.

15.6 Formulation and Preparation of Pyridoxine HCl
Pyridoxine will be procured locally and will have the following formulation: pyridoxine (50 mg), corn starch (31 mg), lactose (46 mg), gelatin (2 mg), and stearic acid magnesium (1 mg).

15.7 Stability and Storage of LZD and Placebo
The manufacturer’s instructions are to store LZD at 77°F (25°C) and protect the drug from light. Bottles must be kept tightly closed to protect them from moisture. These instructions will be followed for both LZD and placebo.

15.8 Stability and Storage of Pyridoxine HCl
The manufacturer’s instructions are to store pyridoxine below 77°F (25°C) and protect from light. Pyridoxine should be stored alone without other medications in same bottle. These instructions will be followed.

15.9 Incompatibilities of LZD
Drugs having unacceptable interactions with LZD are prohibited, including dopamine, selective seroton uptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), amitriptyline, bupropion, mirtazepine, levodopa, carbidopa, or sinemet. Herbal or traditional medicines will be prohibited during the time that study medications are administered (including treatment beyond the first 18 weeks).
15.10 Incompatibilities of Pyridoxine HCL
1. Hypersensitivity to pyridoxine
2. *Prohibited Medications:* Levodopa
3. A physician should be consulted prior to using INH, penicillamine and estrogen containing oral contraceptives along with pyridoxine.

15.11 Optimized Background Therapy of MDR TB treatment
This trial will utilize a clinical trial design developed to evaluate new medications used for the treatment of resistant HIV-infection. Patients are treated with the best available combination of medications individualized according to drug susceptibility test results, tolerability and previous treatment as background therapy. These patients are randomized to additionally receive the new drug to be tested or placebo. This design depends on randomization to equally distribute between study arms factors that could significantly skew study results. This allows the study population to be heterogeneous with respect to such characteristics as disease severity, prior drug treatment, drug susceptibilities, or demographics. This type of clinical trial design has recently been used to successfully evaluate the efficacy of four antiretroviral drugs, viz. enfuvirtide, tipranavir, darunavir, and maraviroc(26-30) This approach has recently been advocated for trials of agents for MDR TB (31).

Drugs used in this study for OBT for MDR TB will be provided by the government of the Republic of South Africa to KGVH for the treatment of study patients.

15.12 Administration Procedures
The study pharmacist will be required to maintain complete records of the study drug that is purchased or dispensed. All unused study product must be returned to the study pharmacist after the study is completed or terminated.

16 Unblinded, Post 112 Dose, Compassionate Use Linezolid Administration

16.1 Approval Mechanism for Compassionate Use Linezolid Administration
It is anticipated that after completing 112 doses of study therapy, a yet unknown number of patients enrolled in TBTC Study 30 may merit consideration for the administration of unblinded, compassionate use LZD therapy. Approval for compassionate use LZD will be the purview of the KGVH MDR TB Treatment Committee. The request for consideration for post 112 dose compassionate use LZD may be submitted any time after the patient has received 90 doses of study drug. To allow adequate time for the MDR TB Treatment Committee review and decision and minimize breaks in therapy, treating physicians should consider submitting requests for unblinded administration of LZD by the time the patient has received no more than 105 doses of protocol-prescribed study drug.
The TBTC Study 30 protocol team recommends the following suggested guidelines be considered by the KGVH MDR TB Treatment Committee when reviewing individual requests:

1. The weight of the evidence favors the benefit of LZD over its potential risks. Patients for whom the benefits may outweigh the risks could include: (a) patients with confirmed XDR TB (i.e. patients infected with strains of *M. tuberculosis* resistant to both fluoroquinolones and at least one injectable antituberculosis agent), (b) patients with substantial drug intolerance that produces an XDR TB equivalent situation, (c) patients presenting with circumstances yet unforeseen that suggest an added benefit of treatment with LZD.

2. For patients in the placebo arm, there should be evidence that there is at least one drug (preferably two) to which the patient’s TB isolate is likely susceptible based on prior TB therapy history or susceptibility testing results that can be used in conjunction with LZD.

3. Upon review of the patient’s personal circumstances it is believed to be likely that monthly follow-up examinations for peripheral and optic neuropathy and anemia can be conducted to evaluate for LZD toxicity. This follow-up will be provided as part of routine study follow-up by study personnel through month 12 of the study.

### 16.2 Unblinding of Study Treatment Allocation for Evaluation for Compassionate Use Linezolid

Unblinding of protocol prescribed LZD therapy will be done upon request of this committee, directly to the committee for purposes of post 112 dose of study therapy compassionate use treatment decisions only, and at all times trying to maintain the integrity of the protocol blinded nature. For patients receiving approval for receipt of compassionate use LZD they and their treating physicians will be unblinded to treatment allocation when the patient has completed 112 dose of study therapy.

### 16.3 Informed Consent for Patients Approved to Receive Unblinded, Compassionate Use Linezolid

All patients receiving approval for receipt of unblinded, compassionate use LZD after completing study therapy will need to provide informed consent to receive unblinded LZD (see consent form in Section 18.9). This is done to assure the patient understands the potential risks associated with prolonged LZD use, the need to receive follow-up examinations to receive LZD and his right to not take LZD. This consent is essentially a medical consent to receive LZD, not a consent to participate in research. Patients will already have consented to participate in the study and receive regular evaluation for adverse effects. Patients who retract consent for their participation in the research study may still receive LZD, but for their safety they must receive regular follow-up for adverse effects (see Section 16.4). For patients retract consent for participation in the research study no data from the follow-up examinations would be recorded for study purposes, but this information would be available to the patient, his treating physician and the KGVH MDR TB Treatment Committee for patient management.
16.4 Follow-up of Patients Receiving Unblinded, Compassionate Use, Linezolid

Patients who are approved by the KGVH MDR TB Committee for unblinded post study LZD administration patients should be seen monthly to evaluate for LZD toxicity. These study visits conducted by TBTC Study 30 personnel will include a CBC and peripheral and optic neuropathy testing as outlined in section 6.3.6. The adverse event stopping rules that apply to study patients during the protocol prescribed therapy phase (see Section 9.6) will be recommended to the KGVH MDR TB Treatment Committee for recommending discontinuation of LZD for patients receiving unblinded, compassionate use LZD. After September 30, 2010 patients who are approved for compassionate use LZD will be medically followed for side effects by their provincial TB program.

17 References

3. WHO. Laboratory XDR-TB definitions. . 2006


18 Appendices

18.1: Karnofsky Performance Scale

18.2 Enrollment Form

18.3 Informed Consent Form for patients enrolled on or after March 15, 2010

18.4 Consent Form for the Storage and Future Use of Blood and Sputum Samples

18.5 Drugs that Increase CNS Serotonin Concentrations.

18.6: Original and Modified Hunter Serotonin Toxicity Criteria (HSTC).

18.7: The Brief Peripheral Neuropathy Screen

18.8 Pain / Faces Scale

18.9 Informed Consent Form for Receipt of Unblinded, Compassionate Use Linezolid
### 18.1 Karnofsky Performance Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance but is able to care for most of his/her needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly</td>
</tr>
<tr>
<td>30</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>20</td>
<td>Severely disabled; hospitalization is indicated although death is not imminent</td>
</tr>
<tr>
<td>10</td>
<td>Very sick; hospitalization necessary; active supportive treatment is necessary</td>
</tr>
<tr>
<td>0</td>
<td>Moribund; fatal process progressing rapidly</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
</tr>
</tbody>
</table>
Form 1: Enrollment
Evaluation of Linezolid for the Treatment of MDR TB

TBTC STUDY 30  Study site: 32  Enrollment Date: [MM-DD-YYYY]
Local ID: [ ] Instructions: Complete this form BEFORE enrolling the patient
Screening Date: [MM-DD-YYYY]

A. Patient Information

Patient’s Gender: [ ] Male  [ ] Female
Date of Birth: [MM-DD-YYYY]
Is the patient ≥ 18 years of age? [ ] Yes  [ ] No
(if no, ineligible)
Check this box if the date of birth is estimated [ ]
Will the patient be able to receive 5 months of follow-up? [ ] Yes  [ ] No
(if no, ineligible)

B. Inclusion Criteria (Note: If "No" or doesn’t meet criteria, patient is ineligible)

1a. Does patient have culture-confirmed pulmonary tuberculosis that is resistant to both isoniazid and rifampin? [ ] Yes  [ ] No
1b. Does patient have a culture positive sputum for M. tuberculosis collected within the previous four months? [ ] Yes  [ ] No
1c. If the patient has both clinical pulmonary and extrapulmonary tuberculosis specify anatomic code for extrapulmonary sites only
(Refer to last page for extrapulmonary site codes)
[ ] NA (Skip to B2) OR [ ] extrapul site 1  [ ] extrapul site 2  [ ] extrapul site 3
(For patient with > 3 extrapul sites, the last entry should be “O3” for “multiple sites”)
If code “O2” for “other sites specify” is selected, please list site(s):

2. Has patient been tested for HIV or agrees to be tested for HIV? [ ] Yes  [ ] No
(Repeat HIV testing needed if prior HIV test result documentation is not available or the test date of a negative HIV test is more than 6 months before enrollment)

3. Is the patient willing to attend scheduled follow-up visits for up to 18 months? [ ] Yes  [ ] No

4. Karnofsky score at enrollment (must be > 40)

5. Has patient signed study consent or legally authorized representative able to do so if decisionally impaired? [ ] Yes  [ ] No

6. Date of Chemistry: [MM-DD-YYYY] (must be at, or < 14 days prior to, screening)

Patient Value  Upper Limit

7. Creatinine  [ ] mg/dL  OR  [ ] µmol/L  (must be < 2x UNL)

8. Date of CBC: [MM-DD-YYYY] (must be at, or < 14 days prior to, screening)

Patient Value

8a. Hemoglobin  [ ] g/dL  OR  [ ] g/L  (must be at least 9.0 g/dL OR 90 g/L)
8b. Platelets x 10⁹/L  (must be at least 80,000/mm³)
8c. WBC x 10⁹/L
8d. Absolute neutrophil count (ANC) cells/mm³ (must be at least 1000/mm³)
C. For women with childbearing potential only (If not applicable, check box □ and skip to section D)

1. Date of negative pregnancy test: [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] (must be ≤ 14 days prior to, screening)

2. Is patient breast feeding?  □ Y Yes □ N No (if “yes”, ineligible)

3. Does patient agree to practice an adequate method of birth control or abstain from heterosexual intercourse while taking study medication?  □ Y Yes □ N No (if “no”, ineligible)

D. Exclusion Criteria (Note: If “yes”, patient is ineligible)

1. Does the patient have known intolerance or allergy to linezolid?  □ Y Yes □ N No

2. Has the patient taken linezolid in the last four months?  □ Y Yes □ N No

3. Does the patient have current or planned therapy during the intensive phase of tuberculosis treatment using drugs having unacceptable interactions with linezolid, including herbal medications, dopamine, selective serotonin uptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), amitriptyline, bupropion, mirtazapine, levodopa, carbidopa, or sinemet?  □ Y Yes □ N No

4. Does the patient have ≤ 5 seconds of vibratory sense to a 128 Hz tuning fork on either big toe?  □ Y Yes □ N No

5. Does the patient have pain, aching or burning in his feet that interfere with walking or sleeping?  □ Y Yes □ N No

6. Is it the judgment of the physician that the patient is not expected to survive for more than 4 weeks?  □ Y Yes □ N No

7. Is surgical intervention anticipated for the treatment of this patient’s pulmonary tuberculosis?  □ Y Yes □ N No

8. Is the patient’s best corrected visual acuity as measured using a Snellen or Jaeger chart worse than 20/200 (6/60 meters)?  □ Y Yes □ N No

9. Did the patient have ≥ 4 incorrect answers when tested using the first 12 Ishihara plates?  □ Y Yes □ N No

10. Is the patient participating in another drug trial?  □ Y Yes □ N No

11. Has the patient taken second line TB drugs for > 14 days immediately prior to today?  □ Y Yes □ N No

E. Enrollment

Patient Identification: 30-32- [ ] [ ] [ ] [ ] [ ] [ ] Kit number [ ] [ ]

Treatment Start Date [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

F. Comments

______________________________________________________________
______________________________________________________________
______________________________________________________________

G. Signature

Signature of person completing form: _______________________________________________________________

PRINT name of person completing form: __________________________________________________________

Date Form Completed: [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

30-32- [ ] [ ] [ ] [ ] Local ID [ ] [ ] [ ] [ ] [ ] [ ]
18.3 Informed Consent Form

A phase I/II pilot study for evaluation of low dose, once daily, linezolid plus optimized background therapy (OBT) versus placebo plus OBT for the treatment of multi-drug resistant tuberculosis

Principal Investigator: Nesri Padayatchi, MD [Nelson R. Mandela School of Medicine]
Phone: (031) 260 4555
Sponsor: Harlem Hospital Center/Columbia University and CDC, USA

Consent for Research

INTRODUCTION.
You are being asked to be in this research study because you have tuberculosis (TB) resistant to the usual TB drugs. This is called multi-drug resistant TB or MDR TB and requires at least 4 drugs to treat it. New treatments are needed for patients with MDR-TB. The Nelson Mandela School of Medicine and the US Centers for Disease Control and Prevention (CDC) are working together to test a medicine against MDR-TB. Linezolid is a medicine that works against tuberculosis but needs careful study in patients with TB. Linezolid is used for treatment of other bacterial infections usually for a couple of weeks. Linezolid has not been tested for treatment lasting longer than 2 to 3 weeks and is not a part of usual TB treatment.

WHY IS THIS STUDY BEING DONE?
We are doing this study to see how well patients are able to take linezolid for the first 16 weeks of treatment along with the usual medicines given for MDR TB. The study will also help find out what side effects are caused by linezolid. We will also look at whether linezolid improves the killing of TB during the first 16 weeks of treatment when given with other drugs commonly used to treat MDR TB.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 60 people will be in this study. It will take about one year to have 60 people join.

HOW LONG WILL I BE IN THE STUDY?
- For 16 weeks you will receive study medicine along with your usual MDR TB medicines.
  - We would keep in touch with you and review your records for up to 5 months.
- We will take you out of the study if:
  - your first sputum cultures for TB are negative (do not grow TB) or
  - your TB is can be treated with two of the usual TB medicines, called isoniazid and rifampin.
- We will recommend you stop study drug if you have a bad reaction (called an “adverse event”) after taking the medicine. However, you can decide to continue to take the study drug if you and your physician decide that taking the study drug may be in your interest.

WHAT IS INVOLVED IN THE STUDY?
Everyone in this study will receive the usual MDR TB treatment with 4 to 5 medicines that his or her doctor thinks will be good in treating MDR TB.
If you agree to be in this study, it will change your TB care in the following ways:
- You may be part of a group that also gets a medicine called linezolid or you may part of a
group that is given a placebo “sugar pill.” You have a 50:50 chance of being in the group that gets the medicine. No one will know which group you are in. You will not know if you are being given linezolid or the sugar pill and your doctor will not know either.

- You will have a test for HIV (human immunodeficiency virus, the virus that causes AIDS), using about 1 teaspoon (5 cc) of blood drawn from a vein. This is recommended for everyone with TB and is required for this study. If you have had a negative HIV test within 6 months or less (and we can get the written result), you will not need another test. If you are HIV positive, we need a copy of your HIV-positive test results for this study. We will keep the test results private as much as the law allows. It does not matter if you are HIV positive or HIV negative – both HIV positive and HIV negative people can be a part of this study.

- Women will need to have a pregnancy test If you are found to be pregnant, you may not participate in this study. Also, you must use contraception to prevent pregnancy during the time of this study (see INFORMATION FOR WOMEN below).

- You will have blood tests (using about 2 teaspoons (10 cc) of blood drawn from a vein) to check your liver, kidneys, and blood count. You will have the tests before starting the study, unless we can get the results from tests done within 14 days or less. You will also have the tests every 2 weeks during the first 16 weeks of the study, and at month 5.

- You will have a blood test (using about 1 teaspoon (5 cc) of blood drawn from a vein) to check your blood count during study visits at months 7 – 11.

- You will be asked questions about your health, such as whether you have had past treatment for TB, and what medicines you are taking. We will ask about any other illnesses and if you drink alcohol or take drugs. We will ask about how you might have caught TB. Some of these questions are personal and you do not have to answer them if you do not want to.

- Your weight, temperature, heart rate, breathing rate and blood pressure will be checked at the beginning of the study and at month 5 of the study.

- You will have your eyesight tested at the beginning of the study, every two weeks during the first 16 weeks of treatment and at month 5.

- You will be asked some questions and have physical examinations to check the health of the nerves in your legs at the beginning of the study and every two weeks during the first 16 weeks and at month 5

- You will have sputum tests before starting the study and every 2 weeks during the first 16 weeks of the study. Sputum is material coughed up from the lungs and windpipe. Sputum tests are important in this study, because they tell us if the medicines are working to treat your TB. If you are not able to cough up anything, we will have you breathe in a mist of moist air with sterile salt water in it. This may help loosen any sputum in your lungs so you can cough it up. This is not painful. It takes about 15 minutes.

- An X-ray of your lungs will be done at the beginning of the study unless we have the results of one done within the past 14 days and will also be done at month 2 and 5.

- In this study, you cannot take certain medicines including traditional and herbal medication while you take study medicine.

**Study Treatment.**

You will be placed in one of two study treatment groups. Neither you nor the research team will choose which group you are in. The treatment group for you will be chosen by chance like flipping a coin. The study treatment groups to which you might be assigned are:

- **16 weeks of daily linezolid and commonly used MDR TB medicines** chosen by your doctor.

  **OR**

- **16 weeks of daily placebo (a sugar pill that does not work against TB) and commonly**
used MDR TB medicines chosen by your doctor. This is more like the treatment you would receive if you were not taking part in this study.

If you miss some doses of study drug you will be allowed up to two extra weeks to finish the expected number of doses.

Everyone in the study will get vitamin B₆ with each dose of TB medicines.

A health care worker or treatment supervisor will give you a dose of the study treatment medicine for at least 5 days of the week. You will need to take your study medicine on the weekend days and holidays. During the 16 weeks you are taking the study treatment, you will meet with a study doctor or nurse at 2, 4, 6, 8, 10, 12, 14, and 16 weeks after you start the study. These study visits will take about 30 minutes. During these visits you will:

- Have blood tests to check your liver, kidneys, and blood count. We will draw about 2 teaspoons (10 cc) of blood from a vein for these tests.
- Have your sputum tested for TB.
- Be asked if you have taken any other medicines or had any illnesses since we last met.
- Have your vision tested.
- Have simple testing of your nervous system to look at your ankle reflexes and ability to feel vibration in your feet.
- Be asked questions about pain and numbness in your feet and whether pain in your feet affects your ability to walk or sleep.
- If you are HIV positive, you will have about 3 teaspoons (15 cc) of blood drawn for a CD4 (T-cell) count. This will be done at the week 2 study visit (or at the first study visit after we receive positive HIV test results). We will only do this test if we cannot get a copy of one that you might have had in the 6 months before you started the study medicines. We will give you the result at the first study visit that we have it.

Follow-up.
This part of the study starts when you finish the first 16 to 18 weeks of taking the study medicines. Your usual TB treatment with 4 or more medications recommended by your doctor will continue until you have had a total of 18 to 24 months of treatment. Your doctor or health department will decide your TB treatment in the follow-up part of the study which may include linezolid.

During the follow-up part of the study through September 30, 2010, study staff will schedule a follow-up study visits with you at 5 months. This study visit will take about 20 minutes. At the follow-up visit at months 5 you will:

- Have blood tests.. We will draw about 2 teaspoons (10 cc) of blood from a vein for these tests to check your liver, kidneys, and blood count.
- Have a test of your sputum to see if the TB is responding to treatment (if appropriate).
- Have your eyesight and nerves in your arms and legs tested by physical examination and by answering some questions.
- Be asked if you had taken any new medicines or had any illnesses since the last study visit.
- Have your weight, temperature, heart rate, breathing rate, and blood pressure checked

If you move away while you are in the study, we will still continue to follow you. If we cannot see you in person, we will contact your new doctor or clinic, or the health department in your area, for help in carrying out study visits. The study visits will be the same as described in this
consent form. Dr. Nesri Padayatchi will continue to be in charge of the study work as much as the authorities will allow.

**WHAT ARE THE RISKS OF THE STUDY?**
All medicines have possible side-effects. Most people who take the study medicines do not get these problems. Some medicines should not be taken with TB medicines. You should tell the study nurse or doctor about all the medicine you are taking. You should talk with them before you start any new medicine during your TB treatment. This includes even over-the-counter medicine such as antacids, Panado, or any other over-the-counter medicines.

*Possible side effects from the study medicine, linezolid.*
Most of the information available about linezolid’s side effects comes from people who have taken linezolid for 14 to 21 days.

*Common side effects (1-7%)*
- Upset stomach, nausea, vomiting, diarrhea,
- Low blood count (anemia) or tiredness with prolonged use of linezolid that goes away when the linezolid is stopped
- Numbness and tingling and pain of the feet and hands when linezolid is taken for several months. These problems may not go away when linezolid is stopped.

*Rare, but serious side effects (less than 1%)*
- Allergic reaction – rash and fever
- Decrease or loss of vision or loss of color vision that usually gets better with stopping linezolid
- Low platelet or white cell count that goes away with stopping linezolid

There are reports of side effects in people being treated with several medicines for MDR TB, including linezolid given in higher amounts than in this study. Although these patients were on several medicines and may have had other medical problems that caused these problems, it is possible that linezolid was responsible for these side effects. That is one of the reasons this study is being done. It will help us learn if the side effects are related to linezolid and how often linezolid causes side effects when used at lower amount.

If you have side effects or you have new symptoms, you must tell your study doctor or nurse right away. If that happens you will be evaluated and told what to do. For serious side effects you might have some extra blood tests. You may be taken off the study medicine. Your TB doctor will then decide what treatment is best for you.

**RISKS FROM DRAWING BLOOD**
There are a few small risks from having blood drawn. These include brief pain from the needle stick, bruising, bleeding, lightheadedness, and rarely, infection where the needle enters the vein. We will try to have blood drawn for this study when you are scheduled to have blood drawn for your usual medical care. The least amount of blood that is needed to get the lab test will be used.

**RISKS FROM AN HIV TEST**
HIV testing includes counseling before and after the test. You will be told the test result. You will be told the meaning of the test result, whether it is positive or negative. Some people who have an HIV test might feel anxious. If you feel this way, you can talk about it with Dr. Nesri Padayatchi by calling (031) 260 4555. Positive HIV results are reported to (institution; insert other site
specific information about reporting HIV results.) We will keep HIV test results private as much as the law allows, but there is a small risk of loss of confidentiality about HIV test results.

**INFORMATION FOR WOMEN.**
We do not know enough about the safety of linezolid for pregnant women or women who are breastfeeding their child. Therefore, you will not be allowed to take part in this study if you:
- are now pregnant,
- plan to become pregnant during TB treatment, or
- are breastfeeding.
If you can get pregnant, you will get a pregnancy test before starting this study. The test must be negative before you can start this study.

While you are in the study, you must use some kind of effective method of birth control such as a birth control pills, hormone injections, implants, diaphragm or cervical cap (each used with spermicidal foam or jelly), condom, birth control sponge, or intrauterine device. These standard birth control measures are accessible free of charge at public, health institutions. Not having sex is also a way to avoid pregnancy while in the study.

If you become pregnant during the study, you must tell the study doctor or nurse right away. The study treatment with linezolid or placebo will then be stopped. Your doctor will decide what TB treatment is best for you. No X-rays for the study will be done during pregnancy.

**BENEFITS.** There may be no direct benefits for you for taking part in this study. Your taking part in this research will help us find out if linezolid can improve MDR TB treatment.

**CONFIDENTIALITY.** We will check your medical records to get information for the study. We will not use your name in any speech or paper about the study. We will not send your name to the study’s data center (CDC). The FDA and study monitors from CDC may also check your records. We will keep all information from your medical records private as much as the law allows.

**COSTS AND PAYMENT FOR BEING IN THE STUDY.** There is no cost to you for being in the study. You will not have to pay for any medicine or tests that are part of this study. You will be compensated R150.00 per visit for your travel, food, and inconvenience at each study visit.

**IN CASE OF INJURY.** If you are hurt because you are taking part in this study, the King George V Hospital will treat you at no cost to you if you need immediate attention. If additional treatment for injuries is required, you will be informed where to obtain such assistance. Usually, neither King George V Hospital nor the sponsors of this study (CDC/ Columbia University) pay for additional treatment of injuries someone might suffer during a clinical trial. Thus you or your medical aid would have to pay for such treatment of an injury suffered during the trial. By signing this consent form and agreeing to be in this study, you are not giving up any of your rights. If you believe that you have been harmed, please contact the Nelson R Mandela Biomedical Research Ethics Committee (NRMBREC) by calling (031) 260-4495 for information on your rights and advice on how to proceed.

**RIGHT TO REFUSE AND REASONS FOR WITHDRAWAL.** Taking part in this study is voluntary. If you choose not to take part, it will not change your regular medical care. If you choose to be in the study, you may quit at any time without changing your regular medical care. If you quit the study, you will still be treated for TB. If important new information is found that might change your decision to be in the study, we will tell you.
We may stop your study medicine if:
- you have bad side effects,
- the study doctor or investigators decides it is best for you to stop the medicine,
- the study medicine is not working against your TB,
- you do not take the medicines like you should, or
- the study ends.

Even if the study medicines are stopped, we will still follow you in the study for a total time of 5 months.

**ALTERNATIVE TREATMENT.** If you do not take part in this study, you will be treated for MDR TB with the standard medicines.

**COMPASSIONATE USE OF LINEZOLID AFTER FINISHING STUDY TREATMENT.** For patients with limited treatment options your treating physician may request that you receive linezolid after you have completed 112 doses of the study drug. The King George V Hospital MDR TB Treatment Committee will review such requests and decide who should benefit from and receive compassionate use linezolid.

**PERSONS TO CONTACT.** If you:
- Have questions about this research study, contact Dr. Nesri Padayatchi by calling (031) 260-4555.
- Have questions about your rights as a research subject, contact NRMBREC on (031) 260-4495.

**CONSENT STATEMENT.** “My signature below indicates that I agree to be in this study. I was given a chance to ask questions. I feel that my questions have been answered. I know that being in this study is my choice. I know that after choosing to be in this study, I may withdraw at any time. I have been told that I will receive a signed copy of this consent.”

Printed patient name: ________________________________________

Printed guardian name (if applicable): ________________________________________

Signature of patient or guardian: __________________________ Date: __________

Signature of witness: __________________________ Date: __________

(when prospective participant is unable to read)

Signature of interpreter: __________________________ Date: __________

Printed name of person obtaining consent: __________________________

Signature of person obtaining consent: __________________________ Date: __________

Signature of principal investigator: __________________________ Date: __________
18.4 Consent Form for the Storage and Future Use of Blood and Sputum Samples

The study investigators would like to know your wishes regarding the use of your blood and sputum samples when the present study is completed.

What am I being asked permission to do?
With your consent the investigators would save and use your blood and sputum for future studies to improve our understanding of tuberculosis and how to best treat TB patients. Approximately one teaspoon more of blood would be obtained at the same time as routine study blood draws. You will NOT have an additional needle stick to obtain this blood.

What would happen to my samples?
Your samples will not be sold or used in products that make money for the researchers. Your samples will be stored at laboratories that are specially designed to keep stored samples safely. The people who work at these laboratories will have access to your samples when they store them and keep track of them, but they will not know who you are as your samples will be stored by number. There is no time limit on how long your samples may be stored.

Will I benefit from having my samples stored and tested in the future?
These specimens will be tested long after the sample was obtained. The results of these tests will not be useful for your care. You will not be contacted with the results. You will receive no direct benefit from having your samples stored for future testing. It is hoped that future TB patient will benefit from what we learn through such testing.

What if I decide not to have my samples stored for future testing?
It is your choice. Either choice will not affect your medical care. If you do decide to allow your samples to be stored, you can change your mind at any time. You must contact the study doctor or nurse and let them know that you do not want your samples to be stored any more. If you decide to do this, any samples that have been stored and can be linked to you will be destroyed.

Please specify below your wishes regarding the storage and future use of your blood and sputum samples (please check only one of the following):

☐ I permit storage and use of my blood and sputum for future TB studies without contacting me.

OR

☐ I do not permit storage and use of my blood and sputum samples for future TB studies.

Printed patient name: ________________________________________

Printed guardian name (if applicable): ________________________________________

Signature of patient or guardian: __________________________ Date: __________

Signature of witness: __________________________ Date: __________
(when prospective participant is unable to read)

Signature of interpreter: __________________________ Date: __________
Printed name of person obtaining consent: ________________________________

Signature of person obtaining consent: ______________________   Date: __________

Signature of principal investigator: ________________________   Date: __________
18.5 Drugs that Increase CNS Serotonin Concentrations.
Source: K. R. Lawrence, M. Adra, and P. K. Gillman Clinical Infectious Diseases 2006;42:1578-1583

Analgesics
- Codeine
- Dextropropoxyphene
- Fentanyl
- Meperidine
- Pentazocine
- Tramadol

Anti-Parkinsonians
- Amantadine
- Bromocriptine
- Levodopa
- Selegiline

Migraine therapy
- Dihydroergotamine
- 5-HT1 agonists
  - Naratriptan
  - Rizatriptan
  - Sumatriptan
  - Zolmitriptan

Antidepressants
  *Monoamine oxidase inhibitors*
  - Isocarboxazide
  - Moclobemide
  - Phenelzine
  - Tranylcypromine
  *Selective serotonin reuptake inhibitors*
  - Citalopram
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine
  - Sertraline
  *Tricyclic antidepressants*
  - Amitriptyline
  - Clomipramine
  - Desipramine
  - Doxepine
  - Imipramine
  - Nortriptyline
  *Others*
  - Bupropion
  - Mirtazapine
  - Nefazodone
  - Trazodone
  - Venlafaxine

Amphetamine and derivatives
Dextramphetamine
Metamphetamine
Fenfluramine
Dexfenfluramine
Phentermine

**Atypical antipsychotics**
- Clozapine
- Olanzapine
- Risperidone
- Zispradone

**Antiemetics**
- 5-HT3 antagonists
  - Dolasetron
  - Granisetron
  - Ondansetron
- Droperidol
- Metoclopramide

**Illicit drugs**
- Cocaine
- Lysergic acid diethylamide (LSD)
- 3,4-methylenedioxymethamphetamine (MDMA)
- Mescaline

**Miscellaneous**
- Bromopheniramine
- Buspirone
- Carbamazepine
- Dextromethorphan
- Diphenhydramine

**L-tryptophan**
- Linezolid
- Lithium
- Moclobemide
- Reserpine
- Sibutramine
- St. John's wort
- Tetrabenazine
18.6 Original and Modified Hunter Serotonin Toxicity Criteria (HSTC).

Source: K. R. Lawrence, M. Adra, and P. K. Gillman Clinical Infectious Diseases 2006;42:1578-1583

**Original HSTC**
- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia, a temperature of >38°C, and ocular clonus or inducible clonus

**Modified HSTC**
- Clonus
- Seizure
- Myoclonus
- Ataxia
- Incoordination
- Jaw-trismus
- Rigidity
- Shivering
- Rigors
- Nystagmus.
- Tremor or twitching and hyperreflexia

**NOTE.** Serotonin toxicity is defined as meeting 1 of the criteria.
18.7 The Brief Peripheral Neuropathy Screen
(Source: JH McArthur) found in online supplements to Cherry CL et al, Neurology 2005, 65:1778

In the last two weeks have the pain, aching or burning in your feet interfered with your walking or sleeping?

\[ \text{Y} \text{ Yes} \quad \text{N} \text{ No} \]

If yes, ask the patient to rate the severity of the interference of his pain, ache, or burning on his walking/sleeping

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In the last two weeks have the pain, aching or burning in your feet interfered with your walking or sleeping?  \[ \text{Y} \text{ Yes} \quad \text{N} \text{ No} \]

If yes, ask the patient to rate the severity of the interference of his pain, ache, or burning on his walking/sleeping

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BRIEF PERIPHERAL NEUROPATHY SCREENING

INSTRUCTIONS FOR EVALUATING PERCEPTION OF VIBRATION:

Strike the end of a 128 Hz tuning fork hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject’s wrist to be sure that they can recognize the vibration or “buzzing” quality of the tuning fork. Again strike the ends of the tuning fork hard enough so that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the “buzzing” stops. Repeat for the other great toe.

4. Was an evaluation of perception of vibration completed? (1-Yes, 2-No)
   - If No, go to question 5.
   - If Yes, complete ‘a.’

   Vibration Perception
   0-Vibration felt for > 10 seconds (normal)
   1-Vibration felt for 6-10 seconds (mild loss)
   2-Vibration felt for 5 seconds or less (moderate loss)
   3-No feeling of vibration (severe loss)
   4-Unable to evaluate or did not assess

   a. Great toe distal interphalangeal (DIP) joint: ____________________________ Right Left

INSTRUCTIONS FOR EVALUATING DEEP TENDON REFLEXES:

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject’s ankle to 90 degrees. Using a reflex hammer (preferable long-handled), the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner’s hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck.

5. Was an evaluation of deep tendon reflexes completed? (1-Yes, 2-No)
   - If No, STOP.
   - If Yes, complete ‘a.’

   Ankle Reflexes
   0-Absent
   1-Hypoactive
   2-Normal deep tendon reflexes
   3-Hyperactive deep tendon reflexes, e.g. with prominent spread
   4-Clonus
   5-Unable to evaluate or did not assess

   a. Ankle Reflexes: ______________________________________________________ Right Left

Date Form Keyed (DO NOT KEY): ______ / ______ / ______

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18.8 Pain / Faces Scale

0  Very Happy  2  Hurts just a little bit.  4  Hurts a little More.  6  Hurts even More  8  Hurts a whole lot  10  Worst pain

No hurt
18.9 Informed Consent for Receipt of Unblinded, Compassionate Use Linezolid

The King George V Hospital (KGVH) Committee overseeing the treatment of patients with Multi-Drug Resistant Tuberculosis (MDR TB) has approved for you to receive compassionate use of the drug linezolid after completing 112 doses of study drug. This approval was given because of the limited drug options available to treat your tuberculosis.

Linezolid is the active study drug that was being evaluated in the study in which you have been participating. In that study half the people received linezolid while the other half received a similar looking pill that had no effect. At present it is not clear that linezolid is effective in treating MDR TB.

When linezolid is taken for a long period of time there is an increased chance that some patients will develop side effects. The side effects that can occur with prolonged linezolid use include anemia; numbness, pain, and tingling of the feet; and a decrease in vision. The anemia and decrease in vision tend to go away when linezolid is discontinued. The numbness, pain, and tingling of the feet tend to continue even if the linezolid is stopped.

For your safety to receive linezolid we recommend you have regular medical follow-up to look for these side effects which could include a blood test and examinations of your nerve function and vision. We recommend you undergo testing for these side effects every month while on linezolid. If you begin to have side effects that could be due to taking linezolid we recommend you consider stopping linezolid. However, the decision to stop linezolid is one for which you should seek the advice of your physician and the KGVH MDR Treatment Committee.

You are in no way required to take linezolid. Once you have started linezolid you can stop taking it at any time.

**INFORMATION FOR WOMEN.**
We do not know enough about the safety of linezolid for pregnant women. Therefore, while you are taking linezolid you must use some kind of effective method of birth control. Birth control measures are available to you for free from public clinics. Not having sex is also a way to avoid pregnancy.

**CONSENT STATEMENT.** “My signature below indicates that I desire to take compassion use linezolid to treat my tuberculosis. I was given a chance to ask questions. I feel that my questions have been answered. I know that taking linezolid is my choice. I know that I may stop taking linezolid at any time. I have been told that I will receive a signed copy of this consent.”

Printed patient name: ________________________________

Printed guardian name (if applicable): ________________________________

Signature of patient or guardian: ________________________________ Date: __________

Signature of witness: ________________________________ Date: __________
(when prospective participant is unable to read)

Signature of interpreter: __________________________ Date: ________

Printed name of person obtaining consent: __________________________

Signature of person obtaining consent: __________________________ Date: ________

Signature of principal investigator: __________________________ Date: ________