Delamanid, linezolid, levofloxacin, and pyrazinamide for treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis:
A Phase II/III, Multicenter, Randomized, Open-label, Clinical Trial
(Treatment Shortening of **MDR** TB using **E**xisting and **N**ew **D**rugs, **MDR-END**)

1. Protocol Number: MDR-END
2. Version Number: 14.0, Version Date: 2020.03.20

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Summary of Research Plans

1. Background

Tuberculosis, and especially drug-resistant tuberculosis, is a huge threat to public health not only in Korea, but throughout the world. Treatment of multidrug-resistant tuberculosis (MDR-TB), which exhibits resistance to the two most powerful drugs, must use second-line anti-TB drugs. However, usage of the conventional second-line anti-TB drugs not only has low success rates, but is also accompanied by a range of issues such as side effects due to prolonged use of drugs for about two years for treatment, low compliance, and high costs. Therefore, by developing new treatment regimens for MDR-TB treatment including recently introduced new drugs to improve the treatment efficacy and shortening the therapy period, it will be possible to increase treatment compliance, and consequently raise the treatment success rate.

2. Purpose

This clinical trial is to compare the efficacy of a 'new treatment regimen including delamanid, linezolid, levofloxacin, and pyrazinamide for nine or twelve months (investigational arm)' and 'the standard treatment regimen including injectables for 20 to 24 months (control arm)' for treating fluoroquinolone sensitive multidrug-resistant tuberculosis.

3. Design of the Study

Multicenter, randomized, open-label, two arms, phase II/III clinical trial

① Group 1 (Control arm)

Minimum 20 months treatment according to the 2014 Korean guidelines for the treatment of tuberculosis and 2014 World Health Organization (WHO) guidelines

② Group 2 (Investigational arm)

Treament regimen made up of only oral medication using delamanid, linezolid, levofloxacin, and pyrazinamide, and treatment duration of nine months or twelve months depending on the time to sputum culture conversion to negative.

4. Outcomes

The primary outcome is the treatment success rate at 24 months after the initiation of treatment. The secondary outcomes are the time to sputum culture conversion to negative on liquid and solid media after the initiation of treatment, the proportion of participants with sputum culture conversion at 2 and 6 months of treatment on liquid and solid media, and the occurrence of adverse events grade of 3 and higher, proportion of participants with a treatment success at the end of treatment, proportion of relapse after treatment success, proportion of deaths and time-to-death, comparison of treatment success rates between treatment groups according to pyrazinamide resistance.

5. Expected Effects

If it is proven that the new treatment regimen is not inferior to the existing treatment regimens through this trial, it will be an epochal opportunity for treating MDR-TB in nine months or twelve months, which is a year shorter than the current 20 to 24 months.

Moreover, by reducing the 'time to Mycobacterium tuberculosis (MTB) culture conversion to negative' of the current treatment, it will be possible to reduce the transmission of tuberculosis from patients to others.

1. Background of the Study

1.1. Prevalence of and Threat Posed by MDR-TB

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis that is resistant to at least isoniazid and rifampicin, the two most important anti-TB drugs, and it accounts for 3.5% of newly diagnosed TB patients in the world and 20.5% of patients who have been treated in the past. In 2013, approximately 480,000 people were diagnosed with MDR-TB, and approximately 9% of the cases are extensively drug-resistant tuberculosis (XDR-TB) against the conventional TB drugs.(1)

In 2013, there were 951 patients reported with MDR-TB (2), but considering the drug resistance rate in Korea, it is estimated that there are actually about 2,000 new MDR-TB cases occurring in Korea annually.

1.2. Difficulties with Treatment of MDR-TB

In order to treat MDR-TB, second-line anti-TB drugs including injectables must be used for 18-24 months, but the success rate of treatment has recently been reported as 83.7% in Korea (3). It is only 32.2% to 62.0% in other parts of the world (4,5). The WHO estimates the average treatment success rate of MDR-TB to be approximately 48% (Figure 1).

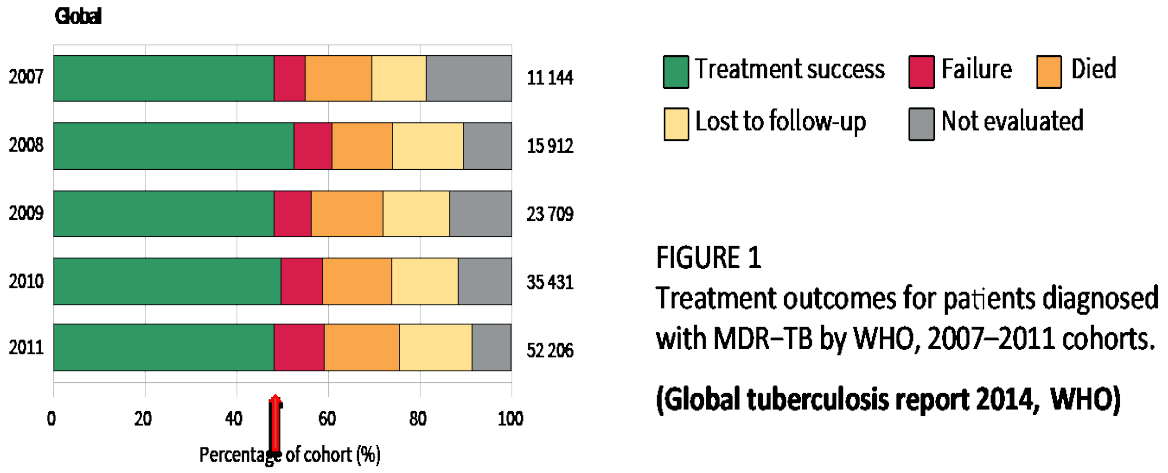

FIGURE 1
Treatment outcomes for patients diagnosed with MDR–TB by WHO, 2007–2011 cohorts.

(Global tuberculosis report 2014, WHO)

Furthermore, there is a report about frequent side effects of using these second-line drugs that commonly have side effects for usage over long periods of time. And 30% of the 818 MDR-TB patients, or 245 patients, had to stop use of drugs because of adverse drug reactions such as nausea/vomiting, diarrhea, joint pains, dizziness, hearing difficulty, headache, and sleep disorders. (6)

A considerable amount of money is used for treating MDR-TB patients. In the case of Korea, it costs 7-22 times more to treat MDR-TB patients than drug-susceptible TB patients. The expenses needed to treat MDR-TB are similar to that for treating malignant diseases, and thus depletes huge amounts of money.(7, Figure 2)

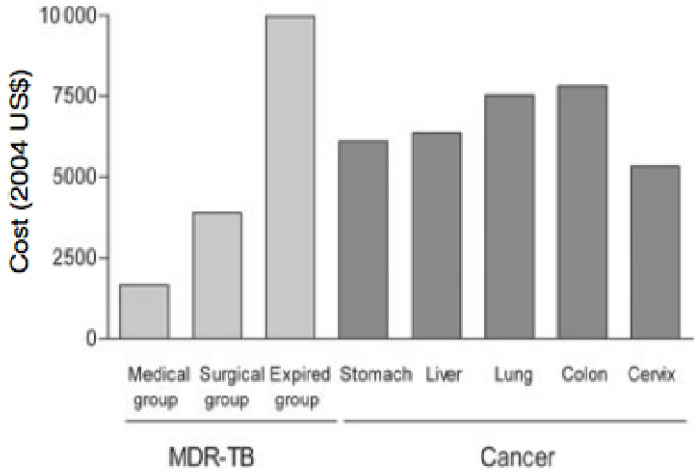

Figure 2 Comparison of the annual cost of multidrug-resistant tuberculosis (MDR-TB) with that of malignant dis- ease in South Korea. All costs demonstrated in this figure are the National Health Insurance Programme-covered annual costs converted to 2004 US dollars.

1.3. Introduction of New Anti-TB Drugs

A few new anti-TB drugs have been clinically introduced recently. These include drugs like moxifloxacin and linezolid which were developed originally to treat ordinary bacterial infections and were found to have strong anti-TB effects, and a few others developed to targeting Mycobacterium tuberculosis (MTB) such as bedaquiline, delamanid and PA-824. Research has been conducted on moxifloxacin to evaluate whether it can reduce the treatment period of drug-susceptible TB patients,(8, 9) and it is also reported that linezolid (10,11), bedaquiline,(12) delamanid (13) can improve the treatment outcomes of MDR-TB patients.

In the case of linezolid, it was administered to extensively drug-resistant TB (XDR-TB) patients who did not report improvement with any drugs. Treatment using linezolid showed powerful anti-TB effects obtaining sputum culture conversion to negative in 87% of these patients after six months of treatment (10). The focus of studies is now on how to use linezolid for MDR-TB patients, instead of administering to only XDR-TB patients.

As strong anti-TB medications, such as delamanid and linezolid, were introduced, Dr. Caminero of the International Union Against Tuberculosis and Lung Disease (IUATLD) suggested a new classification (14). Based on the new classification by Dr. Caminero, the regimen with shorter treatment duration consisted of delamanid, linezolid, levofloxacin, and pyrazinamide.

2. Rationale

2.1. Shortening of Treatment Duration

The main reason for treatment failure in MDR-TB is that patients stop taking their treatment voluntarily for various reasons prematurely. From 1988 to 1996, 342 (39.0%) of 1,175 MDR-TB patients that received treatment at the TB Clinic of Korean National Tuberculosis Association stopped treatment arbitrarily prior to treatment completion (15), and 453 (32.2%) of 1,407 patients who received treatment at eight university hospitals and two national TB hospitals between 2000 and 2002 arbitrarily stopped treatment. (16)

Thus, shortening the treatment duration that currently lasts 24 months is necessary to solve the MDR-TB issue.

There was a recent report that 427 MDR-TB patients in Bangladesh participated in a study and received seven anti-TB drugs including kanamycin and gatifloxacin for 9months. The study reported a cure rate of 82.5%, but 39.8% of participating patients complained of side effects which revealed the difficulties of taking medicine (17).

2.2. Improvement of Treatment Efficacy

Even after treatment failure, MDR-TB patients live for several years and continuously spread MDR-TB bacilli to people they come in contact with. Considering this, it is necessary to raise the treatment success rate that is currently at 48~ 83.7% to solve the issues pertaining to MDR-TB.

It is expected that MDR-TB patient treatment success rate could be improved by using linezolid that was introduced to treat vancomycin resistant bacterial infection or using the newly developed anti-TB drugs like delamanid and bedaquiline. The biggest interest for now is on how to use it together with current anti-TB drugs.

In other words, the most urgent task is to investigate how to combine existing second-line anti-TB drugs such as fluoroquinolone, with the new drugs such as linezolid, delamanid and bedauquiline for treatment use.

2.3. Contribution to International Community through Research on MDR-TB

It is widely known that Korea has excessively high TB incidence for its economic level.

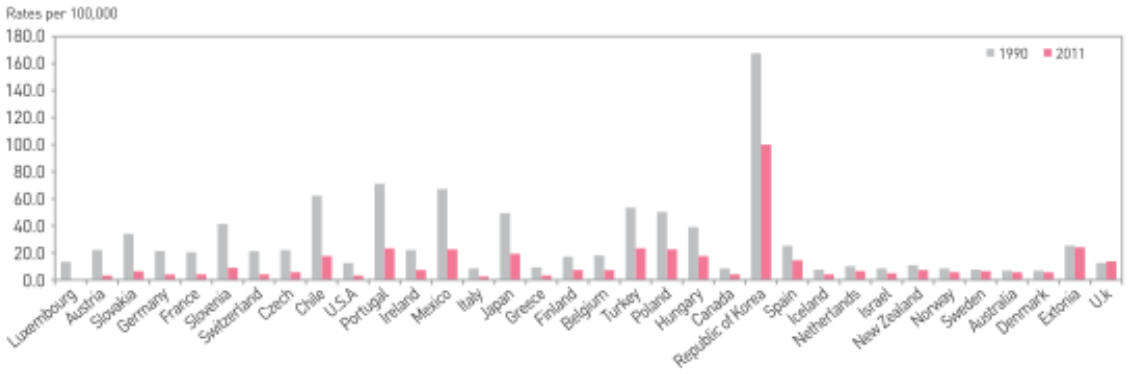

Figure 1. TB Incidence rates by OECD member country, 1990 and 2011
Source : Global Tuberculosis Control WHO Report 2012

The annual TB incidence rate of Korea in 2013 was 97 per 100,000, which is much higher than the rates for Japan (18 per 100,000) and the United States (3.3 per 100,000) (1).

Although the incidence of tuberculosis is shameful, it is also true that a world-class medical environment and excellent researchers provide an appropriate research environment that can lead to innovation in tuberculosis treatment.

It will be a considerable contribution to the international community to solve the burden on public health caused by TB, especially by MDR-TB, as investigators can get meaningful research conclusions through this clinical trial in Korea.

3. Previous Research Results

3.1. Comparison of Levofloxacin versus Moxifloxacin for Multidrug-Resistant Tuberculosis

As a coordinating principal investigator, Yim Jae-Joon is an experienced researcher who oversaw the present clinical trials for comparing the efficacy of levofloxacin versus moxifloxacin for the treatment of MDR-TB patients. The study was conducted in a prospective, multicenter, randomized trial format from February 2010 to July 2012 with cooperation of 19 domestic institutes in total supported by the Korean Academy of Tuberculosis and Respiratory Diseases. (Clinicaltrial.gov Enrollment Number; NCT01055145)

The purpose of this study was to compare the efficacy between levofloxacin and moxifloxacin, two most commonly used fluoroquinolones which should be included in MDR-TB treatment regimen. A total of 182 MDR-TB patients participated in this study, 88.3% of the levofloxacin group and 90.5% of the moxifloxacin group converted culture to negative at three months of treatment, which showed no difference between the two groups. This result was published in the American Journal of Respiratory and Critical Care Medicine. (18)

3.2. Substitution of ethambutol with linezolid during the intensive phase of treatment of pulmonary tuberculosis

The principal investigator is conducting a research, supported by the Korean Health Industry Development Institute, to investigate whether substituting linezolid for ethambutol can accelerate sputum MTB culture conversion to negative for the treatment of drug-susceptible TB patients. This prospective, multicenter, randomized clinical trial is being joined by Seoul National University, Bundang Seoul National University Hospital, Boramae Hospital, and the National Medical Center. (Clinicaltrial.gov Enrollment Number; NCT1994460)

4. Purpose of the Study

This is a multicenter, randomized, open-label, two arms, phase II/III clinical trial to compare the effects of 'new treatment regimen including delamanid, linezolid, levofloxacin, and pyrazinamide for nine or twelve months for fluoroquinolone-sensitive MDR-TB (investigational arm)' and 'standard treatment regimen including injectables for 20 to 24 months (control arm)'. The purpose of this study is to verify that the success rate of the simpler and shorter treatment is not inferior to conventional treatment.

5. Design of the Study

5.1. Study Design

5.1.1. Study Drug

Investigational drugs (delamanid: Otsuka Pharmaceutical, linezolid: Pfizer Pharmaceutical), provided for free from pharmaceutical companies for this study, will be delivered to the sites after labeling at Otsuka and Seoul National University Hospital according to investigational product labeling regulations. The study drugs will be managed by the designated pharmacists at each site, and stock, storage, dispensation, and return will be recorded in research documents.

① Linezolid

• Brand Name: Zyvox Tab (Pfizer Korea)

• Form: White capsule shaped, film coated tablet

• Composition: linezolid 600mg

• Dosage and administration: Take one tablet (600mg) every day

• Storage method: Stored in a sealed container at room temperature (15 - 30°C)

• Expiration date: 36 months from the manufactured date

② Delamanid

• Brand Name: Deltyba Tab (Otsuka Korea), 50mg

• Form: Yellow, round film-coated table (engraving: DLM, 50)

• Composition: Delamanid 50mg

• Dosage and administration: Take 100mg twice a day together with meal

• Storage method: Stored in a sealed container at room temperature (1 - 30°C)

• Expiration date: 60 months from the manufactured date

5.1.2. Multicenter, randomized, open-label, two arms, phase II/III clinical trial

- Once eligibility is confirmed and the subject consents for participation, he/she will be randomly assigned to the following two groups at 1:1.

① Group 1 (Control arm)

Treatment will be according to the 2014 Korean guidelines for the treatment of tuberculosis (19) and 2014 WHO guidelines (20). Treatment principles are summarized as follows.

• Combination of treatment regimen

- Intensive phase regimen comprising four effective second-line anti-TB drugs (including an injectable) and pyrazinamide.
- It is recommended that at least five active drugs be used, selected appropriately based on drug susceptibility testing (DST) results.
- Example of regimen: pyrazinamide, a fluoroquinolone, cycloserine, prothionamide, and an injectable
- Efforts should always be made to use a fluoroquinolone, preferentially use levofloxacin or moxifloxacin.
- Cycloserine should be used preferentially, but when it is not possible para-aminosalicyclic acid (PAS) could be used.
- The medication like linezolid, delamanid, or bedaquiline can be added from the beginning of the treatment if the patient has a resistance to injectables. In addition, linezolid, delamanid, or bedaquiline can be used to fortify the regimen when the adverse drug reactions occur to other anti-TB drugs.
- The usage and dosage follow 2014 Korean guidelines for the treatment of tuberculosis published by the Committee for the Revision of Korean Guidelines for Tuberculosis and the Korea Centers for Disease Control and Prevention (19) but not limited to it.

Type of Drug	Dose		
	Usual dose	Maximal dose	Usage
Ethambutol	15-20mg/kg	1600mg	Once, before or after

			meal
Kanamycin Amikacin Streptomycin Capreomycin	15mg/kg, < 50 years 10mg/kg, ≥ 50 years	1000mg, < 50years 750mg, ≥50 years	Once
Cycloserine	500mg, < 50 kg 750mg, 50-70 kg 750-1000mg, >70 kg	1000mg	Once or divide in two, before or after meal (best to take on an empty stomach)
Prothionamide	500mg, < 50 kg 750mg, 50-70 kg 750-1000mg, >70 kg	1000mg	Once or divide in two, after meal
PAS	150mg/kg	12g	Divide in two or three after meal

• Treatment duration

- Intensive phase is recommended to be a minimum of 8 months.
- Total treatment duration is recommended to be 20 to 24 months.

② Group 2 (Investigational Group)

Regimen consists of only oral medication using delamanid, linezolid, levofloxacin, and pyrazinamide, for nine or twelve months.

• Treatment duration

- A total of 9 months (40 weeks) when sputum culture conversion to negative occurs within three months of treatment
- A total of 12 months (52 weeks) when sputum culture conversion to negative occurs between 3 and 6 months of treatment

• Combination of treatment regimen

- Delamanid, 200mg/day (100mg bid)
  - Use for the entire treatment period unless it must be stopped for reasons such as adverse events.
- Linezolid
  - 600mg/day during the first two months
  - 300mg/day afterwards until the end of treatment

- If linezolid re-administration is required after temporary discontinuation due to adverse events, the dose reduction to 300mg is allowed even within two months of treatment.

- Levofloxacin
  - ≤ 50kg, 750mg/day
  - >50kg, 1000mg/day
  - Can be reduced or substituted with moxifloxacin due to reasons such as adverse events, and at this time, QT prolongation should be observed closely. Also, this substitution will not be considered as a drug change since both are fluoroquinolones of similar potency.
  - Once a day

- Pyrazinamide
  - <50kg, 1000mg/day
  - 50-70kg, 1500mg/day
  - >70kg, 2000mg/day
  - Can be reduced due to adverse event. Even if pyrazinamide resistance is discovered on the phenotypic drugs susceptibility testing after commencing treatment, it can be continued (20).
  - Once or divide in two or three

Since the definition of treatment outcomes follows the 2014 WHO Guidelines (20), as described in the 'Research Protocol 6. Definition', the change of a drug is allowed according to medical judgments, such as adverse drug reactions. However, the change of two or more drugs is considered 'treatment failed' and the participants will be withdrawn from the study.

5.2. Primary Outcome

• Treatment success rate at 24 months after the initiation of treatment:

- 'Cured' and 'treatment completed' are defined as treatment success, and 'culture' defined below refers to results of liquid culture.

- Treatment failure, death, loss to follow-up, transfer out and relapse were excluded from treatment success.

- Definitions of treatment outcomes refer to 2014 WHO Guidelines (20). However, 'stopping' of drugs during treatment will not be considered as 'drug change' (Please see '6 Definitions' in this protocol below.).

5.3. Secondary Outcomes

- Time to sputum Mycobacterium tuberculosis (MTB) culture conversion to negative (liquid and solid culture media)
- Sputum MTB culture conversion proportion at two months of treatment (liquid and solid culture media)
- Sputum MTB culture conversion proportion at six months of treatment (liquid and solid culture media)
- AE of grade 3 and higher
- Proportion of participants with a treatment success at the end of treatment.
- Proportion of relapse after treatment success (investigational arm)
- Proportion of death and time-to-death
- Comparison of treatment success rates between treatment groups according to pyrazinamide resistance.

5.4. Inclusion Criteria

1) Men and women age ≥19 and ≤85
2) Confirmed pulmonary MDR-TB by phenotypic or genotypic drug susceptibility tests or RR-TB by genotypic tests such as Xpert® MTB/RIF assay regardless of being positive for sputum acid-fast bacilli smear
3) Use of current anti-TB regimen with second-line drugs for ≤ 14 days at the time of enrollment

5.5. Exclusion Criteria

1) Known any fluoroquinolone-resistant MDR-TB patients
2) Known XDR-TB patients
3) Patients who are pregnant or who are unwilling to use proper contraceptives at childbearing age
4) Medical history of galactose intolerance, Lapp lactase deficiency, glucose-galactose

malabsorption

5) The need for ongoing use of prohibited drugs while on study drugs

6) History of optic neuropathy or peripheral neuropathy

7) People with any of the following test results
   i. Absolute neutrophil count < 2000 /㎕
   ii. White blood cell count (WBC) < 3.0 X 10^3/μL
   iii. Hemoglobin < 7.0 g/dL
   iv. Serum creatinine > 2.0 mg/dL
   v. Aspartate aminotransferase (AST or SGOT) >100 IU/L
   vi. Alanine aminotransferase (ALT or SGPT) >100 IU/L
   vii. Total bilirubin > 2.0 mg/dL
   viii. Albumin < 2.8 g/dL
   ix. QTcF > 500 ms

8) History of hypersensitivity reaction to the study drugs

5.6. Precautions for Use and Expected Adverse Events (AE)

5.6.1. Prohibited medications while on the study drugs

- MAOIs (phenelzine, isocarboxazid, selegiline, and moclobemide)
- Strong CYP3A inducer (i.e.; carbamazepine)

5.6.2. Warning and precautions against using simultaneously

① Delamanid

- Drugs listed below that may expand QT intervals
  i. Antiarrhythmic drugs (amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol)
  ii. Neuroleptics (phenothiazine, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, thioridazine), antidepressants
  iii. Antimicrobials: Macrolides (erythromycin, clarithromycin), moxifloxacin, sparfloxacin, Bedaquiline, Triazole antifungal agents, Pentamidine, Saquinavir

iv. Non-sedating antihistamine agents (terfenadine, astemizole, mizolastine)
v. Cisapride, droperidol, domperidone, bepridil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide

- Strong inhibitors of CYP3A: Increases delamanid metabolites in blood (approximately 30%)

- When having medical history related to the following heart abnormality
  i. QTc prolongation (> 450ms for males, and >470ms for females)
  ii. History of symptomatic arrhythmia, or taking anti-arrhythmic agents
  iii. Alleged severe hypertension, left ventricular hypertrophy, or congenital heart disease with decreased ejection fraction of left ventricle

- Breastfeeding patient: It is recommended that women should not breastfeed during treatment

② Linezolid

- When there is possibility of causing serotonin syndrome
  i. Patients with carcinoid syndrome
  ii. Selective Serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, bupropion, or buspirone

- When requiring blood pressure monitoring
  i. Uncontrolled hypertension, pheochromocytoma, thyrotoxicosis
  ii. Administer together with sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine)

- Blood glucose monitoring of diabetic patients: Precaution for possibility of hypoglycemia

5.6.3. Expected Adverse Events (AE)

- The subjects will be monitored for AEs of delamanid and linezolid treatments by the primary medical team at each site. The expected major AEs are as follows.

① Delamanid

System Organ Class	Frequency uncommon	Frequency common	Frequency very common
Infections and infestations	**Herpes zoster Oropharyngeal candidiasis Tinea versicolor***		
Blood and lymphatic system	**Leukopenia Thrombocytopaenia**	**Anemia* Eosinophilia***	**Reticulocytosis**

disorders			
Metabolism and nutrition disorders	**Dehydration** **Hypocalcemia** **Hypercholesterolemia**	**Hypertriglyceridemia**	**Hypokalemia** **Decreased appetite** **Hyperuricemia***
Psychiatric disorders	**Aggression** **Delusional disorder, persecutory type** **Panic disorder** **Adjustment disorder with depressed mood** **Neurosis** **Dysphoria** **Mental disorder** **Sleep disorder** **Libido increased***	**Psychotic disorder** **Agitation** **Anxiety and anxiety disorder** **Depression and depressed mood** **Restlessness**	**Insomnia**
Nervous system disorders	**Lethargy** **Balance disorder** **Radicular pain** **Poor quality sleep**	**Neuropathy peripheral** **Somnolence*** **Hypoesthesia**	**Dizziness*** **Headache** **Paresthesia** **Tremor**
Eye disorders	**Conjunctivitis allergic***	**Dry eye*** **Photophobia**	
Ear and labyrinth disorders		**Ear pain**	**Tinnitus**
Cardiac disorders	**Atrioventricular block first degree** **Ventricular extrasystoles*** **Supraventricular extrasystoles**		**Palpitations**
Vascular disorders		**Hypertension** **Hypotension** **Hematoma*** **Hot flush***	
Respiratory, thoracic and mediastinal disorders		**Dyspnea** **Cough** **Oropharyngeal pain** **Throat irritation** **Dry throat*** **Rhinorrhea***	**Hemoptysis**
Gastrointestinal disorders	**Dysphagia** **Paraesthesia oral** **Abdominal tenderness***	**Gastritis*** **Constipation*** **Abdominal pain** **Abdominal pain (lower)** **Dyspepsia** **Abdominal discomfort**	**Vomiting** **Diarrhoea*** **Nausea** **Abdominal pain (upper)**
Hepatobiliary disorders	**Hepatic function abnormal**		
Skin and subcutaneous tissue disorders	**Alopecia*** **Eosinophilic pustular folliculitis*** **Pruritus generalized*** **Rash erythematous**	**Dermatitis** **Urticaria** **Rash pruritic*** **Pruritus*** **Rash maculo-papular*** **Rash*** **Acne** **Hyperhidrosis**	
Musculoskeletal and connective tissue disorders		**Osteochondrosis** **Muscular weakness** **Musculoskeletal pain*** **Flank pain** **Pain in extremity**	**Arthralgia*** **Myalgia***
Renal and urinary disorders	**Urinary retention** **Dysuria*** **Nocturia**	**Hematuria***	
General	**Feeling hot**	**Pyrexia***	**Asthenia**

disorders and administration site conditions		**Chest pain** **Malaise** **Chest discomfort*** **Oedema peripheral***	
Investigations	**Electrocardiogram ST - segment depression** **Transaminases increased*** **Activated partial thromboplastin time prolonged*** **Gamma-glutamyltransferase increased*** **Blood cortisol decreased** **Blood pressure increased**	**Blood cortisol increased**	**Electrocardiogram QT prolonged**

*** The frequency for these events was lower for the combined Deltyba plus OBR group in comparison to the placebo plus OBR group.**

② Linezolid

The most common adverse events include diarrhea (2.8%-11.0%), headache (0.5%-11.3%), vomiting (3.4%-9.6%), and

- Systemic: headaches, moniliasis, fungal infection, fever
- Mental & Nervous system: dizziness, insomnia
- Special organs: taste alteration
- Digestive system: diarrhea, nausea, vomiting, abdominal pains, abdominal clamping, abdominal distension, constipation, dyspepsia, tongue discoloration and teeth discoloration
- Cardiovascular system: hypertension
- Blood/Lymphatic system: thrombocytopenia, low hemoglobin level, leukopenia, neutropenia
- Urogenital system: vaginal moniliasis
- Skin: rash, pruritus
- Investigation: abnormal blood tests and abnormal liver function tests

6. Definition

6.1. Culture Conversion to Negative

i. Culture is considered to have converted to negative when two consecutive cultures, taken at least 4 weeks apart, are found to be negative.

ii. When a subject cannot produce sputum after the first culture negative sputum, that is also defined as culture conversion.

iii. Encourage to expectorate sputum as much as possible (including induced sputum), but if the subject cannot produce sputum, it will not be deemed as protocol violation.

6.2. Date of Culture Conversion

For both the above i and ii, the date of culture conversion is defined as the date of the initial negative culture.

6.3. Reversion

When Mycobacterium tuberculosis (MTB) is cultured at least two or more times after negative conversion.

6.4. Treatment Outcome Definitions

Definitions of treatment outcomes refer to 2014 WHO Guidelines (20). For investigational group, 6 months will be considered as intensive phase.

<Definitions of treatment outcomes for drug-resistant patients>

TREATMENT OUTCOME	DEFINITION
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: •Lack of conversion[b] by the end of the intensive phase[a]; or •Bacteriological reversion[b] in the continuation phase after conversion[b] to negative; or •Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or •Adverse drug reactions.

Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown).
Treatment success	The sum of Cured and Treatment completed.

[a] For Treatment failed, lack of conversion by the end of the intensive phase[†] implies that the patient does not convert within the maximum duration of the intensive phase[†] applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off eight months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply. ([†]For investigational group, 6 months will be considered as intensive phase.)

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

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days* apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. (*According to intervals of research visits, it will be 4 weeks)

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days* apart, are found to be positive. For the purpose of defining Treatment failure, reversion is considered only when it occurs in the continuation phase. (*According to intervals of research visits, it will be 4 weeks)

7. Study Timeline

7.1. Control arm

	Screening	Baseline Visit[1]	Treatment						End of Treatment [7]	End of Study
Weeks (w)	-2w ~ 0d	0	1w	2w	4w	8w	12w ~ (Every 4w)	52w ~ (Every 2month)	80w ~	24month
Visit window	**n-a**	**n-a**	**±4d**	**±4d**	**±1w**	**±2w**	**±2w**	**±2w**	**±2w**	**±2w**
Consent	O									
Randomization		O								
Medical history	O									
Physical Exam	O		O	O	O	O	O	O	O	O
Neurologic exam	O									
Sputum AFB smear	O[5]	O[5]	O	O	O	O	O	O	O	O
TB culture (solid)	O[5]	O[5]	O	O	O	O	O	O	O	O
TB culture (liquid)	O[5]	O[5]	O	O	O	O	O	O	O	O
Genotypic DST	If available									
Phenotypic DST[2]	With first/reverted cultured M.TB									
Chest X-ray (CXR)	O[5]	O[5]	O[8]	O[8]	O	O	O	O	O	O
Chemistry, Electrolyte	O[5]	O[5]	O	O	O	O	O	O	O	
Complete blood count	O[5]	O[5]	O	O	O	O	O	O	O	
ECG	O[5]									
Urine HCG[3]	O	O								
HIV, HBV[4]		O[5]								
Optic test	O									
Compliance of drug intake			O	O	O	O	O	O	O	
Adverse drug reaction			O	O	O	O	O	O	O	
Other medication[6]	O	O	O	O	O	O	O	O	O	

[1]Administration of anti-TB regimen can begin at baseline visit since drug-resistant TB must be treated immediately.
[2]Drug susceptibility test for isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, amikacin, capreomycin, ofloxacin, levofloxacin, moxifloxacin, prothionamide, cycloserine, and para-aminosalicylic acid (omit for patients with results already provided).
[3]Only for childbearing age (the blood HCG test result can be extracted)
[4]Study drugs can be administered before the obtaining of results since eligibility is not determined by these results.
[5]Could be skipped if previous tests except ECG were done within four weeks. In case of ECG, within 1week.
[6]Check prohibited drugs for exclusion criteria at screening visit, and check immunosuppressants including steroids after enrollment.
[7]End of treatment(EOT) visit will be determined by the standard TB treatment guidelines. If EOT visit and the end of study(EOS) visit are the same, a test corresponding to the EOT visit will be conducted.
[8]Could be skipped if previous CXR test was performed within 2 weeks

7.2. Investigational arm

	Screening	Baseline Visit[1]	Treatment					End of Treatment [7]	Treatment completion to End of Study
Weeks (w)	-2w ~ 0d	0	1w	2w	4w	8w	12w ~ (Every 4w)	40w ~ 52w	~ 24month (Every 2month)
Visit window	**n-a**	**n-a**	**±4d**	**±4d**	**±1w**	**±2w**	**±2w**	**±2w**	**±2w**
Consent	O								
Randomization		O							
Medical history	O								
Physical Exam	O		O	O	O	O	O	O[7]	
Neurologic exam	O		O	O	O	O	O	O[7]	
Sputum AFB smear	O[5]	O[5]	O	O	O	O	O	O	O
TB culture (solid)	O[5]	O[5]	O	O	O	O	O	O	O
TB culture (liquid)	O[5]	O[5]	O	O	O	O	O	O	O
Genotypic DST	If available								
Phenotypic DST[2]	With first/reverted cultured M.TB								
LZD, Delamanid resistance examination	If needed (please see the protocol section 9.0)								
Chest X-ray (CXR)	O[5]	O[5]	O[8]	O[8]	O	O	O	O	O
Chemistry, Electrolyte	O[5]	O[5]	O	O	O	O	O	O[7]	
Complete blood count	O[5]	O[5]	O	O	O	O	O	O[7]	
ECG	O[5]	O[5]	O	O	O	O	O	O[7]	
Urine HCG[3]	O	O	O	O	O	O	O	O[7]	
HIV, HBV[4]		O[5]							
Optic test	O	O	O	O	O	O	O	O[7]	
Compliance of drug intake			O	O	O	O	O	O[7]	
Adverse drug reaction			O	O	O	O	O	O[7]	
Other medication[6]	O	O	O	O	O	O	O	O[7]	

[1]Administration of anti-TB regimen can begin at baseline visit since drug-resistant TB must be treated immediately.
[2]Drug susceptibility test for isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, amikacin, capreomycin, ofloxacin, levofloxacin, moxifloxacin, prothionamide, cycloserine, and para-aminosalicylic acid (omit for patients with results provided already).
[3]Only for childbearing age (the blood HCG test result can be extracted).
[4]Study drugs can be administered before the obtaining of results since eligibility is not determined by these results.
[5]Could be skipped if previous tests except ECG were been done within four weeks. In case of ECG, within 1week.
[6]Check prohibited drugs for exclusion criteria at screening visit, and check immunosupperessants including steroids after enrollment.
[7]End of treatment visit will be determined by the time of culture conversion. Omit test after end of treatment (EOT) visit.
[8]Could be skipped if previous CXR test was performed within 2 weeks

8. Screening and Procedures

8.1. Subject Screening and Enrollment

- When resistance to rifampicin is confirmed, screening can be done after subject signs the consent form.

- Recording of medical history, physical examinations and neurological examinations will be performed. Sputum AFB smear microscopy, MTB culture on both liquid and solid media will be performed.

- Genotypic DST (MTBDRsl and etc.) could be performed, if available.

- Phenotypic DST will be performed for the first positive culture and reversion specimen if available.

- Chest X-ray (CXR), Electrocardiogram (ECG), complete blood count, electrolytes, chemistry (glucose, albumin, total bilirubin, AST, ALT, Creatinine) will be performed. The results of the test performed according to the standard TB treatment guidelines (calcium, phosphorus, uric acid, cholesterol, protein, alkaline phosphatase, BUN, etc.) can be further reviewed.

* Tests could be skipped in case of having available results or tests were performed recently within four weeks (In case of ECG, within a week). It is possible to extract chest CT results instead of chest X-ray(CXR) test.
- For subject of childbearing potential, urine HCG will be performed (the blood HCG test result can be extracted).

8.2. Randomization

- Once a subject has signed informed consent form and found eligible, subject will be randomly assigned to investigational or control arm at a rate of 1:1 on week 0.

- The study will use block randomization method, using block sizes of 4 or 6 chosen randomly, stratified by ①presence/absence of cavitation on baseline chest radiographs, ②presence/absence of baseline diabetes mellitus. Randomization table will be prepared by using SAS 9.3.

- Randomization table and web-based randomization is operated by the person in charge of this clinical trial at the Medical Research Collaborating Center (MRCC) in Seoul National University Hospital Biomedical Research Institute. The access and management of randomization information will be carried out independently from the clinical investigator or clinical trial sponsor.

- Diabetes mellitus will be diagnosed for one of the following three. ① fasting blood glucose ≥ 126mg/dL ② random blood glucose ≥ 200mg/dL ③ currently taking hypoglycemics.

8.3. Baseline Visit and Beginning of Treatment

- AFB smear microscopy, and MTB culture on liquid and solid media of sputum or bronchoscopic specimen will be performed.

- CXR, ECG, complete blood count, electrolytes, chemistry (albumin, total bilirubin, alkaline phosphatase, AST, ALT, Creatinine), anti-HIV antibody and HBsAg will be performed.

- Ishihara Test for Color-blindness will be performed to check baseline abnormalities of color blindness.

* Tests could be skipped in case of having available results or tests were performed recently within four weeks (In case of ECG, within a week).

* Study drugs can be administered before the obtaining of anti-HIV Ab, HBsAg, and alkaline phosphatase results since eligibility is not determined by these results.

* Administration of anti-TB regimen can begin at baseline visit since drug-resistant TB must be treated immediately.

8.4. Study Visits

- Subjects will visit for study at 1 week, 2 weeks and 4 weeks after enrollment, and then every four weeks until 12 months(52 weeks), afterwards every 2 months until the end of treatment (EOT). The time of EOT is 40 or 52 weeks for the Investigational arm and will be determined individually for control arm according to the standard of care treatment.

- Subjects in the investigational arm will visit every 2 months after EOT even if it is before 12 months(52weeks).

8.4.1. Study tests of visits while on anti-TB medication

① Control arm

- Physical examination
- Sputum AFB smear microscopy and MTB culture on liquid and solid media
- CXR
- Complete blood count, chemistry (total bilirubin, alkaline phosphatase, AST, ALT, creatinine)

- Check taking systemic steroid and immunosuppressive agents.

② Investigational arm

- Physical examination, neurological examination
- Sputum AFB smear microscopy and MTB culture on liquid and solid media
- CXR, ECG
- Complete blood count, electrolyte, chemistry (total bilirubin, albumin alkaline phosphatase, AST, ALT, creatinine)
- Ishihara Test for Color-blindness to detect occurrence of color vision abnormalites.
- Check all other concomitant medications including systemic steroid and immunosuppressive agents.
- For subject of childbearing potential, urine HCG will be performed (the blood HCG test result can be extracted).

8.4.2. Follow-up visits after EOT (Investigational arm only)

- Sputum AFB smear microscopy and MTB culture on liquid and solid media
- CXR

8.5. Details of Study Procedures

Standard-of-care testing for the treatment and differentiation of multi-drug resistant TB will be performed after obtaining informed consent form of the study. The following test results may be used for research purposes.

1) Medical history

Medical history, especially for TB treatment history, diabetes mellitus and abnormal color vision

2) Physical examination

Routine physical examination

3) Neurological examination

Neurological examination, especially for abnormal sensation on legs and feet.
Any neurologic AE is developed, information including location, severity, and the relationship to the

study drug will be documented. Additional neurologic tests could be done, if necessary.

4) Sputum acid-fast bacilli (AFB) smear and culture

Approximately 4mL or more of sputum will be collected and mixed with the same amount of 4% sodium hydroxide and then centrifuged for 20 minutes at 3,000xg to get pellet for AFB smear microscopy and MTB culture. AFB smear will be performed with Auramine-Rhodamine fluorescent staining at first and then with Ziehl-Neelsen staining for positive samples. For MTB culture, tubes with samples in the solid media (Ogawa culture medium) and liquid media (BACTEC MGIT™ or other) are continuously incubated at 5~10% CO_2 incubator for 6 weeks.

5) Drug Susceptibility Test (DST)

Phenotypic DST will be performed at outside laboratories other than the treatment sites. Resistance to each drug tested is defined as ≥1% bacterial growth in Löwenstein- Jensen medium using the absolute concentration method observed with the following critical concentrations of anti-tuberculosis drugs: isoniazid 0.2 μg/ml; streptomycin 10.0 μg/ml; ethambutol 2.0 μg/ml; rifampicin 40.0 μg/ml; para-aminosalicylic acid 1.0 μg/ml; prothionamide 40.0 μg/ml; cycloserine 30.0 μg/ml; kanamycin 40.0 μg/ml; capreomycin 40.0 μg/ml; ofloxacin 2.0 μg/ml; levofloxacin 2.0 μg/ml; and moxifloxacin 2.0 μg/ml;. Pyrazinamide susceptibility is determined using the pyrazinamidase test.

Genotypic DST (MTBDRsl and etc.) could be performed, if available.

6) CXR

Plain chest PA is performed per routine diagnostic method at each site. If possible, below conditions will be followed: 120kV, tube current (in milliamperes) with automatic exposure control, and a 12:1 antiscatter grid with a 180-cm focus-detector distance.

7) HIV, HBV Test

Peripheral blood 5mL is collected in plain tube and ELISA performed to detect anti-HIV antibody, HBs Ag.

8) Complete Blood Count

Peripheral blood 3mL is collected in EDTA tube to test red blood cell count (RBC), mean corpuscular volume (MCV), white blood cell count (WBC) with differential count, hemoglobin, hematocrit, and platelet count.

9) Chemistry

Peripheral blood 3mL is collected in SST tube to test total bilirubin, albumin, alkaline phosphatase, AST, ALT, Creatinine, and electrolytes examination.

10) Urine HCG Test

Urine 10-50mLis collected to test pregnancy by human chorionic gonadotropin (β-hCG) determination kit.

11) Color vision test

Identify number of plates accurately read using the Ishihara Test for Color Blindness (24 plates).

12) Electrocardiography

Measure QT interval.

8.6. Study Drug Adherence

- DOT (Directly Observed Therapy) is not performed per Korean guidelines for the treatment of tuberculosis.

- The study nurse checks the study drug adherence by comparing the drug packaging with residual pill count at each visit. In the event that a scheduled visit is changed, the administration status of the study drugs and other drugs during that period will be checked as well.

Drug adherence = (actually taken dosage/prescribed dosage) * 100

8.7. Withdrawal

1) When the investigator judges that participating in this clinical trial would not be in the best interests of the subject

2) When the subject withdraws consent

3) Treatment failure

4) When the subject becomes pregnant while on anti-TB medication.

5) When investigators get additional test results of resistance like below,
   a) fluoroquinolone resistance (phenotypic or molecular method)
   b) rifampicin monoresistance is confirmed
   c) rifampicin susceptible

* Subjects who withdrawn from the study will receive the same treatment with other TB patients by standard of care treatment.

9. Checking for Developing Resistance Against Study Drug

9.1. Subjects

When culture conversion fails 6 months into treatment among subjects assigned to the investigational group, identify whether resistance to linezolid and delamanid manifested in MTB isolate cultured in sputum or bronchoscopic specimens at the time of participating in the study and at 6 months after treatment.

9.2. Method

1) Linezolid resistance examination: Same as method in ① or ②.

① MGIT960: Judge resistance using 1.0 μg/ml critical concentration.

② Broth microdilution method: Inoculate bacteria in Middlebrook 7H9 containing a suitable concentration of linezolid in culture media and determine minimal concentration for suppressing bacterial growth, and judge as having resistance when the minimal suppression concentration considerably increases than the strain when first participating in the research.

③ May check mutation of genes related to already known linezolid resistance.

2) Delamanid resistance test

① Agar proportion method using Middlebrook 7H11 culture media, and judged as having resistance when, for over 1% of control group, growth of strain is not included in drug at Delamanid 0.2 μg/ml.

② May check mutation of genes related to already known delamanid resistance.

10. Sample size justification and Statistical Analysis Method

10.1. Sample size justification

The hypothesis of this study is that the treatment success rate at 24 months after the initiation of treatment for MDR TB using the new regimen including new anti-TB drugs will not be inferior to conventional treatment regimens. (Non-inferiority test)

Presumptions when calculating sample size are as follows.

1) Level of significance, $\alpha = 0.025$ (one-sided test)
2) Type 2 error (β) set at 0.20 to maintain 80% for power of the test
3) Subject no. ratio (control arm : investigational arm) = 1 : 1
4) Primary outcome: treatment success rate at 24 months after the initiation of treatment
5) The hypothesis of the study is as follows.
   ① Null hypothesis: Four drug regimen treatment success rates at 24 month are inferior to conventional treatment outcomes. ($H_0 : P_T - P_C \leq \delta$)
   ② Alternative hypothesis: Four drug regimen treatment success rates at 24 month are not inferior to conventional treatment outcomes. ($H_1 : P_T - P_C > \delta$)

Based on the study result of Kwak et al, 'Changes in treatment outcomes of multidrug-resistant tuberculosis, Int J Tuberc Lung Dis 19(5):525-530'(3), presuming 24 month treatment success rate of control arm as 80% and 24 month treatment success rate of investigational arm as 90%, the non-inferiority margin (δ) is -0.10 which is regarded as non-inferior when the difference is less than 10% between the two arms. The number of study subjects is 48 per arm.

In addition, reflecting 1) proportion of fluoroquinolone-susceptible MDR-TB among participants with positive Xpert MTB/RIF assay of 50%, and 2) anticipating 5% lost to follow-up, the final number of participants is calculated as N/(0.50*0.95) resulting in 102 persons per arm, 204 in total.

If a participant withdrew for any reasons within two weeks after enrollment, the participant will be replaced. Considering the number of replaced participants, the enrollment accrual ceiling is 220 persons maximum.

10.2. Statistical Analysis Method

1) Analysis Group Definition

Data obtained from subjects through clinical trials will be analyzed by mITT (Modified Intention-To-Treatment) analysis and PP (Per-Protocol) analysis. Efficacy evaluation will be based on a mITT (Modified Intention-To-Treatment) and additional analysis on PP (Per-Protocol) group. Safety analysis will be performed on the safety group.

- The mITT (Modified Intention-To-Treatment) group includes participants who are randomized after satisfying eligibility criteria and receive study drugs at least one time.

- The PP (Per-Protocol) group includes participants that satisfy the following among mITT group.

  1) When completing over 80% of the planned treatment (in other words, for control arm, 64 weeks or longer treatment; For investigational arm, 32 weeks or longer treatment in the 9-month treatment group and 42 weeks or longer treatment in the 12-month treatment group)

  2) Participants who completed the study per protocol during the clinical trial period.

- The Safety analysis group includes participants who receive study drugs at least one time.

2) Handling of Missing Data

When categorized as 'loss to follow-up', 'withdrawal', or 'withdrawal of consent', it is deemed as following.

① 'Treatment failure' in the case of dropping out due to 'loss to follow-up', 'investigator's decision', 'withdrawal of consent', 'treatment failure', or 'death' during the treatment
② 'Not accessible' in the case of dropping out due to pregnancy during the treatment
③ 'Treatment failure' in the case of dropping out due to 'relapse' after the treatment completion
④ 'Not accessible' when there is no evidence of treatment failure, such as bacteria reversion in the case of withdrawal due to 'loss to follow-up', 'investigator's decision', 'withdrawal of consent', 'pregnancy', or 'death' after the treatment completion

3) Basic Characteristics Analysis of Subjects Prior to Administration of Study Drugs

In order to check if there is any significant difference in demographic or clinical characteristics among the two arms prior to administration of study drugs, the serial data is summarized as mean, standard deviation, median and minimum and maximum, and the two arms are compared by independent t-test or Wilcoxon rank sum test. For categorical variables, the frequency and proportion per group is found and the two arms are compared by Chi-square test and Fisher's exact test. This analysis is carried out on the ITT analysis group.

4) Efficacy Evaluation

All statistical analysis of the two arms is carried out at significance level of 5% for both sides unless stated otherwise. For additional analysis, stratified analysis will be performed for primary and secondary outcome evaluation by stratification into sputum smear positive patient groups and sputum smear negative patient groups based on the sputum smear microscopy results.

① **Primary Efficacy Evaluation**

The primary outcome of this clinical trial is treatment success rate at 24 months after the initiation of treatment.

Describe the treatment success rate of the control arm and the investigational arm with a two-sided 95% confidence interval. Then, in order to test for non-inferiority of the investigational arm, when the lower limit of one-sided 97.5% confidence interval of the difference (P_T - P_C) between control and investigational arm is larger than the non-inferiority margin of -10%, it is concluded that the treatment success rate of the investigational arm is non-inferior to the treatment success rate of the control arm. The subjects whose treatment result is assessed 'Not accessible' are excluded from the primary outcome evaluation.

② **Secondary Efficacy Evaluation**

The secondary outcomes are analyzed as following and describe at exploratory levels.

- **Time to sputum culture conversion after the initiation of treatment (liquid and solid culture media)**

- In order to test whether the time to sputum culture conversion after the initiation of treatment of the control arm and investigational arm (liquid and solid culture media) are different statistically, the median time is estimated in each group using the Kaplan-Meier method, and the difference of the distribution of time to culture conversion of the two arms is compared using the Log-rank test.

- **Sputum culture conversion proportion at two months of treatment (liquid and solid culture media)**

- In order to test whether there is a statistical difference in sputum culture conversion proportion at two months of treatment between the control arm and the investigational arm (liquid and solid culture media), each arm is summarized by conversion frequency and proportion, and the sputum culture conversion proportions at two months between the two arms are compared using the Chi-square test and Fisher's exact test.

- **Sputum culture conversion proportion at six months of treatment (liquid and solid culture media)**

- In order to test whether there is a statistical difference in sputum culture conversion proportion at six months of treatment between the control arm and the investigational arm (liquid and solid culture media), each arm is summarized by conversion frequency and proportion, and the sputum culture conversion proportions at six months between the two arms are compared using the Chi-square test and Fisher's exact test.

- **Proportion of treatment success at the end of treatment**

  -Summarize the frequency and proportion of treatment success at the end of treatment in the investigational arm.

- **Proportion of relapse after treatment success**

  -Summarize the frequency and proportion of relapse after treatment success in the investigational arm.

- **Proportion of deaths and time-to-death**

  -Summarize the frequency and proportion of death in the investigational arm, and estimate median survival time using the Kaplan-Meier method.

- **Primary outcome evaluation between treatment groups according to pyrazinamide resistance**

  -Presentation of treatment success rate in the control arm and the investigational arm in small groups according to the presence or absence of pyrazinamide resistance, and verification of non-inferiority of treatment success rate difference between the treatment groups

5) Safety Evaluation

Safety evaluation is performed using adverse events that occur during the clinical trial period. Summarize all adverse events and serious adverse events, adverse event frequency and percentage, and 95% confidence interval on it. Also, summarize and evaluate the occurrence rate of adverse events in relationship to the study drug and severity. The incidence of adverse events (CTCAE Grade 3 and above toxicity) between the two arms are compared using the Chi-square test or Fisher's exact test.

11. Safety Assessment

11.1. Definition

1) Adverse Events (AEs)

Adverse events are undesirable medical occurrence in subjects administered a pharmaceutical product in clinical trials, and which does not necessarily have a causal relationship with the drugs. An adverse event(AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptoms or diseases temporarily associated with the use of medicinal (investigational) product, whether or not related to the medicinal(investigational) product.

Adverse events may include not only those newly occurring after the participation in the research, but also worsened severity or frequencies compared to the initial evaluation, as well as abnormal diagnostic test results including abnormal laboratory findings.

2) Serious Adverse Events (SAEs)

In this study, SAE is defined as any untoward medical occurrence that:

① Results in death during the study
② Is life-threatening
③ Results in a persistent or significant disability/incapacity
④ Results in congenital anomaly/birth defect
⑤ Results in inpatient hospitalization or prolongation of existing hospitalization

In addition to the situations stated above, medical and scientific judgments will be made to determine whether the prompt reports are suitable. For example, an AE that may place the subject in danger, or that needs treatment to prevent worsening from the situations stated above, or that is regarded as having significant clinical influence by the investigator's decision, will be regarded as a SAE although it is not life-threatening or does not result in death or hospitalization.

3) Unlisted (Unexpected) Adverse Event

Unexpected Adverse Events refer to AEs in which the nature or severity is different compared to the information of approved package insert.

4) Relationship to the Study Drug

The definition of relationship is as follows.

① Not related: Adverse Event having no relationship with use of study drug
② Unlikely (Doubtful): Adverse events whose relationship to study drug makes a temporary causal relationship or improbable and in which other concomitant medications or underlying disease provides plausible explanations

③ Possible: Adverse events may be due to the use of the study drug. Other explanations, such as other concomitant medications or underlying diseases, are not conclusive. As the temporal relationship is reasonable, the causal relationship cannot be excluded.

④ Probable: Adverse events may be due to the use of the study drug. The temporal relationship is reasonable (e.g., confirmed by drug discontinuation) and does not appear to be due to concomitant medications or underlying diseases.

⑤ Definite: Adverse event is described as a possible adverse reaction and cannot be explained as a concomitant drug or a underlying disease. The temporal relationship is very plausible (e.g., confirmed by stopping and re-administering the study drug).

The Adverse Event will be judged to be related to the use of the study drug when the contribution of the drug to adverse event is Possible, Probable or Definite according to the above definition.

5) Grading for Severity

The severity of AE will be determined using CTCAE Version 4.0.

11.2. Adverse Event Collection and Reporting

1) All Adverse Events(AEs)

All AEs found in subjects who received the study drugs from baseline visit or after the randomization will be collected. Any AEs that falls within the definition of a serious adverse event(SAE) will be reported as SAE regardless of specific evaluation items in the protocol.

All AEs regardless of the severity, seriousness, or relationship to the study drug, will be documented on source document (SD) and case report form (CRF) using English medical terms. When possible, if the signs and symptoms are due to common diseases (e.g., cough, runny nose, sneezing, laryngopharyngitis, stuffy head, will be reported as “upper respiratory infection”), it will be recorded using its diagnostic name in principle. The investigator will record his/her opinion of the relationship of AE to the study drugs on both SD and CRF, and record all evaluations necessary for management of AE on SD and report according to the regulations.

2) Serious Adverse Events (SAEs)

The investigator will report all SAEs that occur during the study in a timely manner according to the regulations of their respective IRB.

All SAEs that are not recovered by the end of the study or not resolved due to withdrawal from the study will be followed-up until the following instances.

① Recovery of AE

② Stabilization of AE

③ When there are baseline evaluations, until restoration to the baseline status
④ When judged to be due to drugs other than the study drug or factors other than the study intervention
⑤ When there is a high possibility of not being able to receive additional information (when the subject or health manager denies giving additional information or when follow-up is not possible despite attempts)

Deaths of subjects during clinical trials will be judged as a SAE regardless of relationship to the study drug or whether or not being expected.

Requiring hospitalization (or prolongation of hospitalization) during the study will also be reported as a SAE, except for hospitalization in the following cases:

① Hospitalization scheduled for the study
② Hospitalization for social reasons without having AE
③ Elective operations or procedures scheduled prior to participation in the study (must be recorded in the case report form (CRF))

3) Pregnancy

Pregnancy of subjects while on medication of the study drugs must be reported within 24 hours of awareness by the investigator. The investigator must complete a pregnancy notification form and submit it to the relevant person. Subjects who become pregnant while on medication of the study drugs must be withdrawn from the study immediately. Additional follow-up evaluation information is requested for side effects on newborns after giving birth as well as during pregnancy.

11.3. Suspected Unexpected Serious Adverse Reaction (SUSAR) Report

In the event a Suspected Unexpected Serious Adverse Reaction (SUSAR) occurs during the clinical trial, the principal investigator (PI) will report to the Institutional Review Board (IRB) to determine whether to continue or stop the study, and the main PI will report to the Minister of Food and Drug Safety (MFDS) within a period described below.

1) Unexpected Adverse Drug Reaction causing death or life threatening conditions will be reported immediately. The coordinating principal investigator will report it to MFDS within 7 days of awareness by phone calls, Fax, or report forms. Full documentation will be reported within 15 days of awareness.

2) Other unexpected and serious adverse drug reactions will be reported within 15 days of awareness.by the coordinating principal investigator.

3) The coordinating principal investigator will report follow-up report with additional safety information until the AE is resolved (or until lost to follow-up). At this time, the investigator will actively cooperate in providing data and information on the report.

12. Monitoring

12.1. Installation of Data and Safety Monitoring Board (DSMB)

- A DSMB composed of two respiratory specialists (including one who has MDR-TB experience, if available) and one statistician from other institutes having no conflict of interests will be formed.

- The DSMB may review data on side effects in the middle of the study, and may provide recommendations such as change, continuation or stopping of protocols to the investigators based on the results.

12.2. Monitoring Plans

- The coordinating principal investigator will be responsible for monitoring. Doctors and nurses, not participating in this study and having abundant clinical trial experience, designated by the main principal investigator will check GCP compliance, protection of study subjects, and accuracy of data by source document verification (SDV) of the study per each 50 subjects (i.e., when 50, 100).

- AE, unexpected problems and noncompliance of protocols discovered through DSMB will be reported by the coordinating principal investigator to Institutional Review Board(IRB) according to the regulations and the SOPs of the Human Research Protection Program (HRPP) of Seoul National University Hospital and each site.

- The respective investigator should take corrective action to resolve issues identified during the monitoring process, and cooperate with the monitoring personnel to implement countermeasures to prevent the recurrence of the issue. In the event that compliance is not achieved, the respective investigator's participation in the study will be discontinued.

13. Ethical Considerations of the Study

13.1. Compliance of Study Ethical Regulations

1) Duties of the Investigator

Investigators will be responsible for guaranteeing that the clinical study is conducted according to the protocols, the most recent International Conference on Harmonization of Technical Requirements for Enrollment of Pharmaceuticals for Human Use (ICH), the tenets of Good Clinical Practice (GCP) and relevant regulations.

GCP is a set of internationally-recognized ethical and scientific quality requirements that must be followed when designing, conducting, recording and reporting clinical trials that involve people. GCP compliance from the Helsinki Declaration provides public assurance that the rights, safety and well-being of human subjects involved in research are protected, and that it is officially guaranteed that the clinical trial data are reliable.

2) Institutional Review Board(IRB)

Prior to beginning trials, investigators will submit all of the most recent documents listed below to the IRB.

① Final protocol and if applicable, amended protocol
② Subject informed consent form (and all other documents provided to subjects)
③ Investigator's brochure (or equivalent information) and revised versions
④ Tools for recruiting subjects
⑤ Information on compensation for damages related to the study and, if applicable, information on financial compensation for participants of the study
⑥ Resume or equivalent information of the investigator
⑦ Study funding, sponsor name, related institutes and information on other potential conflict of interest elements and those related to compensation of subjects
⑧ All other documents required by the IRB to fulfill its responsibilities

This trial will begin after receiving full approval by the IRB for the final protocol, amended protocol (if applicable), subject informed consent form, applicable recruitment tools and subject compensation programs.

When necessary, investigators will submit the following documents during clinical trials to the IRB for review and approval.

① Amended version of the protocol
② Revised version of subject informed consent form and written tools provided to the subjects
③ If applicable, all new or revised subject recruitment tools
④ Compensation for damages related to the clinical trial and, if applicable, revisions on financial

compensation for participants of the studies

⑤ Revisions or the latest version of clinical trial data book

⑥ Summary of the clinical trial situations (at least once a year or when otherwise specified by the IRB)

⑦ Report of serious and unlisted adverse events related to the test drugs

⑧ New information that can have an adverse effect on the safety of subjects or clinical execution

⑨ Change and modification of the protocol to remove immediate threat elements to subjects

⑩ Report of death of subjects under the administration of the investigator

⑪ Notification in the case that a new clinical investigator from the trial institute becomes the principal investigator

- All other requirements of the IRB

In the case of changes to protocol that may increase threats to subjects, the changes and the corresponding revised version of the subject informed consent form will be submitted to the IRB for review and approval to apply the changes.

Once the trials are complete, the investigators will notify the IRB of the time that the trial has ended.

13.2. Obtaining written informed consent from Subjects

- Each subject will fill out the consent form according to relevant regulations after sufficiently listening to explanations on this clinical trial, and the consent forms must be signed prior to beginning any activities related to the trial. The consent form will be used after being approved by the IRB. Investigators are to draft the subject informed consent form in accordance with the Helsinki Declaration, current ICH and GCP guidelines, and relevant regulations.

- Prior to commencing trials, the principal investigator and co-investigators will explain to potential subjects the purpose and method of the clinical trial, reasonably expected benefits of the trial and potential risks and all associated discomforts. Subjects will be notified that participation is voluntary and that they may retract their consent at any time, and that even if the subject does not participate in the clinical trials, it will not affect treatment of their current diseases. Subjects will also be notified that there may be other treatment regimens available even if they deny participation, and that denying participation will not affect their treatment in the future. Lastly, subjects will also be notified that the investigator will hold the subject's personal information for long-term follow-ups, and that there will be no infringement on the subject's privacy within the allowable range of the corresponding laws and regulations, and that the institute and relevant investigators reserve the right to peruse the information. The subject's signature on the informed consent form is deemed to allow such provision of information by the subject or their legal representative.

- Subjects and/or their legal representative will be given sufficient time and opportunity to look over and ask questions about the informed consent form, and after listening to the explanation and prior to participating in clinical trials, the subject and their legal representative will be instructed to properly record their signature and date on the consent form. After receiving the consent form, the principal investigator and co-investigator will issue a copy of the consent form to the subjects.

13.3. Protection of Personal Records

- Collection and operation of personal information of the subjects who participate in this study will be limited to only information necessary for the efficacy, safety and tolerability evaluation of the study drugs. Such data will be collected and operated taking precautions for compliance to laws on privacy protection and to guarantee confidentiality.

- The investigator will guarantee the following contents for personal information.

① Be operated fairly and legally
② Collected for a clear and fair purpose, and will not be operated in methods inappropriate for such purpose
③ Will be collected appropriately and relatively, and will not exceed the mentioned purpose
④ Possess accurate, and if necessary, the latest information

- The investigators must receive clear consent for use of personal information from participating subjects prior to collection of data. Such consent will mention that it may be passed on to other institutes or countries.

- Subjects have the right to request their personal information from the investigator and reserve the right to request revision of inaccurate or incomplete information. For such a request, reasonable procedures must be completed considering the essence of the request, trial situation, and relevant laws and regulations.

- Appropriate technical and structural methods must be established to protect personal information from unauthorized viewing, disclosure, accidental or illegal destruction, or coincidental loss or change. Personnel requiring access to personal information will agree to confidentiality on the identities of the subjects.

- Information collected for the study will be stored as a password-protected file in a lab with a locking device. Access to the research files will be limited to authorized investigators.

13.4. Compensation and Indemnities Provided to Subjects

No monetary compensation will be given for participating in this clinical trial. However, transportation costs used for visiting the trial institute by subjects will be compensated for at 100,000 KRW each at the time of completing the intensive phase and when completing treatment. In the case of AE caused by the investigational productor to correct and handle adverse events that may have occurred, the principal investigator will appropriately treat damages caused directly by the clinical trial drug and provide compensation to trial subjects according to the ‘Rules on Victim Compensation’.

14. Administrative Requirements

14.1. Change of Study Protocols

- Investigators are not allowed to change the protocols without official amendment procedure. All amended versions of study protocols must be issued by the investigator and be signed and dated. If the IRB or the relevant authorities may find basis for disapproval of the amendment, the amended protocol must not be applied unless there is need to immediately remove risks against subjects (in this case, the amended version must be submitted to the IRB and competent authorities immediately). When changes are on the managerial or administrative procedures of the trial, it can be notified only to the IRB.

14.2. Subject identification log and screening/enrollment log

- During or after trials, investigators will record subject identification log to easily identify each subject.

- The subject identification log will be dealt with confidentially, and investigators will store them in the trial institute files. No copies will be maintained for the sake of the confidentiality of subjects. All reports and exchange of information regarding the trials will mark subjects by only their initials or assigned numbers.

- Investigators will record a subject screening/enrollment log. This is a document for all subjects to determine eligibility of this trial.

14.3. Completing Case Report Forms (CRF)

- All data related to the study will be entered in the case report forms (CRF). Excluding results for tests conducted outside of the investigator's office, CRF will be completed upon the subject's visit, and the latest observations will be reflected for subjects who participated in the trials.

- All subjective evaluations recorded in CRF will, whenever possible, be continuously performed by the person who made the initial evaluation. Investigators will confirm that all information recorded in the CRF is consistent with the corresponding source document (SD).

- All inputs, edits and changes of CRF will be carried out by the investigator or delegated personnel.

- Data entry will be made directly in the e-CRF (www.phactax.org) constructed at the request of the Medical Research Collaborating Center(MRCC) and management of data will be performed by the MRCC.

14.4. Quality Assurance of Data

The process to guarantee the accuracy and reliability of data will include selection of qualified investigators and study institutes, as well as review of protocol procedures by all investigators, and delegated persons.

14.5. Storage of Records

- The investigators/institutes will store essential documents in accordance to ICH/GCP E6 part 8, KGCP part 9 and relevant laws and regulations. The investigator/institute will take necessary measures to prevent loss or discarding due to accidents.

- Study documents, including essential documents, must be stored for at least three years from the date of study completion. These documents may be stored for a longer period at the request of the administrative authority.

- In the event that the investigator responsible for archiving retires, is repositioned, or cannot fulfill the responsibility for storing the study documents due to any other reason, the duty of archiving will be handed over to another person qualified to fulfill the said duties.

- The coordinating principal investigator determines the retention period of research documents of each institution and disposal after the expiration, and the detailed procedure follows the internal disposal regulation of each institution.

14.6. Completion and Stopping the Study

- Completion of Study

The study is defined as being completed when the final visit of the last subject participating in this study has been completed.

- Stopping of the Study

The investigator may close the trial site at any time when there is a feasible reason, and it must be notified sufficiently prior to termination. Reasons for closing the trial site or termination of the study are defined as follows.

① When the investigator does not comply with protocols or GCP guidelines
② Safety issues
③ Sufficient data to prove the lack of efficacy
④ Inappropriate recruitment by investigator

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Statistical Analysis Plan

Delamanid, linezolid, levofloxacin, and pyrazinamide for treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis: A Phase 2/3, Multicenter, Randomized, Open-label, Clinical Trial (Treatment Shortening of MDR TB using Existing and New Drugs, MDR-END)

Version	v 2.2
Collaborating Institutions	Seoul National University Hospital, National Medical Center, Dankook University Hospital, Pusan National University Hospital, Korea University Ansan Hospital, Samsung Medical Center, Asan Medical Center, SMG-SNU Boramae Medical Center, Pusan National University Yangsan Hospital, Severance Hospital, Ulsan University Hospital, The Catholic University of Korea Incheon St. Mary's Hospital, International Tuberculosis Research Center, and The Korean Institute of Tuberculosis
Principal Investigator	Professor Yim Jae-Jun, Department of Pulmonary and Critical Care Medicine, Seoul National University Hospital
Data management and analysis	Medical Research Collaborating Center, Biomedical Research Institute, Seoul National University Hospital

Contents

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1. Objective

The purpose of this statistical analysis plan is to describe the statistical analysis method to be performed in this clinical trial to state the analyzed items clearly and prevent unplanned analysis in the future.

2. Objective and Design of Clinical Trial

2.1 Objective

The purpose of this clinical trial is to compare the efficacy of a new treatment regimen including Delamanid, Linezolid, Levofloxacin, and Pyrazinamide for 9 or 12 months (investigational arm) and the standard treatment regimen including injectables for 20 to 24 months (control arm) for treating fluoroquinolone-sensitive multidrug-resistant tuberculosis (TB) patients through a phase 2/3, multicenter, randomized, open-label, clinical trial.

2.2 Design

Multicenter, randomized, open-label, two arms, phase II clinical trial.

2.3 Sample Size Justification

2.3.1 Sample Size

The hypothesis of this study is that the treatment success rate at 24 months of treatment for multidrug-resistant TB using the new regimen including new anti-TB drugs will not be inferior to conventional treatment regimen (Non-inferiority test). Presumptions when calculating sample size are as follows.

1) The level of significance, $\alpha=0.025$ (one-sided test)

2) The type II error (β) set at 0.20 to maintain 80% for the power of the test

3) The ratio of the number of subjects (control arm investigational arm) = 1 : 1

4) Primary outcome: treatment success rate at 24 months after the initiation of treatment

5) The hypothesis of the study is as follows.

① Null hypothesis: Treatment success rates of the four-drug regimen at 24 month are inferior to those of the conventional treatment. (H_0: $P_T - P_C \leq \delta$).

② Alternative hypothesis: Treatment success rates of the four-drug regimen at 24 month are not inferior to those of the conventional treatment. (H_1: $P_T - P_C > \delta$).

Based on the study result of Kwak et al, ‘Changes in treatment outcomes of multidrug-resistant tuberculosis, Int J Tuberc Lung Dis 19(5):525-530’(3), presuming 24 month treatment success rate of control arm as 80% and 24 month treatment success rate of investigational arm as 90%, the

noninferiority margin (δ) is -0.10 which is regarded as non-inferior when the difference is less than 10% between the two arms. The number of study subjects is 48 per arm.

Additionally, reflecting 1) proportion of fluoroquinolone-susceptible MDR-TB among participants with positive Xpert MTB/RIF assay of 50%, and 2) anticipating 5% lost to follow-up, the final number of participants is calculated as N/(0.50*0.95), resulting in 102 persons per arm, 204 in total.

If a participant withdrew for any reasons within two weeks after enrollment, the participant will be replaced. Considering the number of replaced participants, the enrollment accrual ceiling is 220 persons maximum.

3. Statistical Analysis Plan

3.1 General Principle of Result Analysis

Data obtained from subjects through clinical trial will be analyzed by mITT (modified Intention-To-Treatment) analysis and PP (Per-Protocol) analysis. Efficacy evaluation will be based on a mITT (modified Intention-To-Treatment) and additional analysis on PP (Per-Protocol) group. Safety analysis will be performed on mITT, PP and the safety group (study drug administration group).

Subject Group	Definition
mITT	- The mITT group includes participants who are randomized after satisfying eligibility criteria and receive study drugs at least one time. The subjects are not confirmed to be additionally resistant to fluoroquinolone, mono-resistant to rifampicin, or susceptible to rifampicin.
PP	The PP (Per-Protocol) group includes participants that satisfy the following among the mITT group. When completing over 80% of the planned treatment : For control arm, 64 weeks or longer treatment; For investigational arm, 32 weeks or longer treatment in the 9-month treatment group and 42 weeks or longer treatment in the 12-month treatment group Participants who completed the study per protocol during the clinical trial period : More than 80% of the planned period before treatment is completed, the following cases are considered protocol violation and excluded from the analysis group ① withdrawal or death. ② The sputum test before culture conversion was not conducted ③ Administration of study drug in the control arm
Safety	The Safety analysis group includes participants who have taken study drugs at least one time. : Evaluation based on the administration of study drug (delamanid or linezolid)

3.2 Handling of Missing Data

When categorized as ‘loss to follow-up’, ‘withdrawal’, or ‘withdrawal of consent’ will be considered as below.

①‘Treatment failure’ in the case of dropping out due to ‘loss to follow-up’, ‘investigator’s decision’, ‘withdrawal of consent', ‘treatment failure’, or ‘death’ during the treatment

② ‘Not accessible’ in the case of dropping out due to ‘pregnancy’ during the treatment

③ ‘Treatment failure’ in the case of dropping out due to ‘relapse’ after the treatment completion. However, reinfection by other strain is ‘not assessable’.

④ ‘Not accessible’ when there is no evidence of treatment failure, such as bacteria reversion in the case of withdrawal due to ‘loss to follow-up’, ‘investigator’s decision’, ‘withdrawal of consent’, ‘pregnancy’, or ‘death’ after the treatment completion

3.3 Clinical Trial Participation Status of Subjects and Protocol Violation

The table of clinical trial participation status of subjects (mITT, PP, and safety analysis groups), reasons for early withdrawal, and the distribution of the clinical trial protocol violations will be presented.

3.4 Demographic Characteristics and Characteristics Prior to Administration of Study Drug

As a way to check significant differences in demographic and clinical characteristics between the two arms prior to administration of study drugs, the serial data is summarized into mean, standard deviation, median, minimum, and maximum values, and the two arm are compared by an independent t-test or the Wilcoxon rank sum test. For categorical variables, the frequency and proportion per group is found and the two arms are compared by Chi-square test or Fisher's exact test. This analysis is performed for the ITT analysis group.

The following items will be evaluated for the subjects’ characteristics prior to administration of the study drug and presented for each randomized arm.

Type	Endpoints
Enrollment of each site and randomization stratification factor	- To summarize the frequency and proportion of randomization per each site, stratification factor (presence/absence of cavitation on baseline chest radiographs, presence/absence of baseline diabetes mellitus)
Demographic characteristics and vitality signs	- Age, gender, height, weight, blood pressure, and pulse
Past history	- Past history of tuberculosis and the number of treatments - Diabetes mellitus, optic neuropathy, or peripheral neuropathy

	- Galactose intolerance, Lapp lactase deficiency, and glucose-galactose malabsorption - Other diseases
Medication history	- Other medication except for TB medication or use of prohibited medication while on study drug
Physical/neurological examination	- Physical examination result and neurological examination result
Drug susceptibility test	- Screening visit: Xpert MTB/RIF assay (MTB and RIF resistance), MTBDRsl (fluoroquinolone resistance and XDR-TB), resistance, and resistant drug - Baseline visit: Resistance and resistant drug
Sputum AFB smear and CXR (Chest CT)	- Sputum AFB panel (AFB smear, solid culture, liquid culture) - CXR (range of lesions and presence or absence of cavity), Chest CT (range of lesions and presence or absence of cavity)
HIV/HBV test	- HIV test and HBV test result
Chemistry/Electrolyte/Complete blood count	Chemistry - T-bilirubin, alkaline phosphatase, BUN, AST, ALT, creatinine, calcium, phosphorus, uric acid, glucose, cholesterol, protein, and albumin Electrolyte - Sodium, potassium, and chloride Complete blood count - WBC, ANC, hemoglobin, and PLT
Urine HCG/ECG/Optic Test (Ishihara Color Plate)	Urine HCG - Performance and result ECG - Performance and result, Rhythm, QTcF Optic test (Ishihara Color Plate) - Performance and the number of correct answers of 24 Ishihara color plates

3.5 Adherence Assessment

- The study coordinator checks the study drug adherence by comparing the drug package with residual pill count at each visit.

In the event that a scheduled visit is changed, the study coordinator checks administration status of the study drug and other medication during that period as well.

- Drug Adherence by each drug = (actual dosing day/ prescribed dosing day) * 100

- Final Adherence = Average value of medication adherence by each drug

In this case, the prescribed dosing day is defined as the sum of the prescribed dosing days for the entire period and the actual dosing day is defined as the total of the actual dosing days for the entire period, and the Final Adherence is defined as the average value of the Drug Adherence by each drug.

The Adherence to study drug and throughout the total treatment period of both arms is summarized with the final adherence and by each drug taken, with the mean, standard deviation, median and minimum and maximum value, and the final adherence will be compared between the two arms by conducting an independent t-test or Wilcoxon rank sum test.

3.6 Efficacy Evaluation

All statistical analysis of the two arms is carried out at a significance level of 5% for both sides unless stated otherwise. For additional analysis, a stratified analysis is performed for primary and secondary outcomes evaluation by stratification into sputum smear positive patient groups and sputum smear negative patient groups based on the sputum smear microscopy results.

3.6.1 Primary Efficacy Evaluation

The primary outcome of this clinical trial is the treatment success rate at 24 months after the initiation of treatment **(based on the results of liquid culture)**. It describes the treatment success rate of the control arm and the investigational arm with a two-sided 95% confidence interval. Then, in order to tests for non-inferiority of the investigational arm, when the lower limit of one-sided 97.5% confidence interval of the difference (P_T - P_C) between control and investigational arm is larger than the non-inferiority margin of -10%, it is concluded that the treatment success rate of the investigational arm is non-inferior to the treatment success rate of the control arm. The subjects whose treatment result is assessed as ‘Not accessible’ are excluded from the primary outcome evaluation.

3.6.2 Secondary Efficacy Evaluation

① Time to sputum culture conversion[1] after the initiation of treatment (liquid and solid culture media)
② Sputum culture conversion proportion at two months of treatment (liquid and solid culture media)
③ Sputum culture conversion proportion at six months of treatment (liquid and solid culture media)

[1] The definition of ‘culture conversion to negative’ is per the protocol section '6. Definition’. Contamination after the first negative culture also corresponds to the 'culture conversion' because Mycobacterium tuberculosis was not cultured based on the section 6.1 ① in the protocol.

④ Proportion of treatment success at the end of treatment
⑤ Proportion of relapse after treatment success
⑥ Proportion of death and time-to-death
⑦ Primary outcome evaluation between treatment groups according to pyrazinamide resistance

The secondary outcomes are analyzed as following and describe at exploratory levels.

1) Time To Sputum Culture Conversion After the initiation of treatment (Liquid and Solid Culture Media)

- In order to test whether the time to sputum culture conversion after initiation of treatment of the control arm and investigational arm (liquid and solid culture media) are different statistically, the median time is estimated in each group using the Kaplan-Meier method, and the difference of the distribution of time to culture conversion of the two arms is compared using the log-rank test.

2) Sputum Culture Conversion Proportion at Two Months of Treatment (Liquid and Solid Culture Media)

- In order to test whether there is a statistical difference in sputum culture conversion proportions at two months of the treatment between the control arm and the investigational arm (liquid and solid culture media), each arm is summarized by conversion frequency and proportion, and the proportion of sputum culture conversion at two months between the two arms are compared using the Chi-square test and Fisher's exact test.

3) Sputum Culture Conversion Proportion at Six Months of Treatment (Liquid and Solid Culture Media)

- In order to test whether there is a statistical difference in sputum culture conversion proportions at six months of the treatment between the control arm and the investigational arm (liquid and solid culture media), each arm is summarized by conversion frequency and proportion, and the sputum culture conversion proportion at six months between the two arms are compared using the Chi-square test and Fisher's exact test.

4) Proportion of Treatment Success at the End of Treatment

- Summarize the frequency and proportion of treatment success at the end of Treatment in the investigational arm.

5) Proportion of Relapse after Treatment Success

- Summarize the frequency and proportion of relapse after the treatment success in the investigational arm.

Relapse is defined as mycobacterium tuberculosis (MTB) is cultured again at least two or more consecutive times, taken at least 4 weeks apart, after treatment success (excluding re-infection confirmed by other strains).

6) Proportion of deaths and Time-to-Death

- Summarize the frequency and proportion of death in the investigational arm and estimates the median survival time using the Kaplan-Meier method.

7) Primary Outcome Evaluation Between Treatment Groups According to the Pyrazinamide Resistance

- Presentation of treatment success rate in the control arm and the investigational arm in small groups according to the presence or absence of Pyrazinamide resistance, and verification of non-inferiority of treatment success rate difference between the treatment groups.

3.7 Safety Analysis

The safety analysis evaluates subjects enrolled in this clinical trial and administered the study drug at least one time.

1) Adverse Events

- The analysis obtains the 95% confidence interval of the proportion of the subjects who have experienced one or more adverse event within each arm and performs the Chi-Square Test or Fisher's Exact Test to compare the treatment groups.

- It compares the occurrence rate of adverse drug reactions of the two arms using the Chi-square test or Fisher’s exact test.

- It summarizes the number of adverse events of each arm.

- It summaries the number of expressions of five items (seriousness, severity, relation, action taken, and outcome) for each arm.

- The classification of adverse events by body system is organized according to the SOC (System Organ Class) and PT (Preferred Term) of MedDRA system.

- It describes the details such as demographic information, event date, end date, severity, relation, action taken, and outcome for the subjects who reveal serious adverse events.

2) Physical/Neurological Examination Result

- For the results of the physical/neurological examination, the analysis presents the proportion of subjects who were normal in screening visit (Visit1) and changed to abnormal at the final visit.

3) Chemistry/Electrolyte/Complete Blood Count Result

- The analysis presents the proportion of subjects who showed the chemistry/electrolyte/complete blood count result of “Normal” or “Abnormal NCS” at the baseline visit (Visit2) and changed to “Abnormal CS” at the final visit.

4) Concomitant Medication

- The analysis classifies the concomitant medication using the ATC (Anatomical Therapeutic Chemical)

Code presents it for each arm.

4. Subjects

4.1 Subject Participation Status in Clinical Trial

The subject distribution can be summarized as follows as the result of the clinical trial (Figure 1 and Table 1).

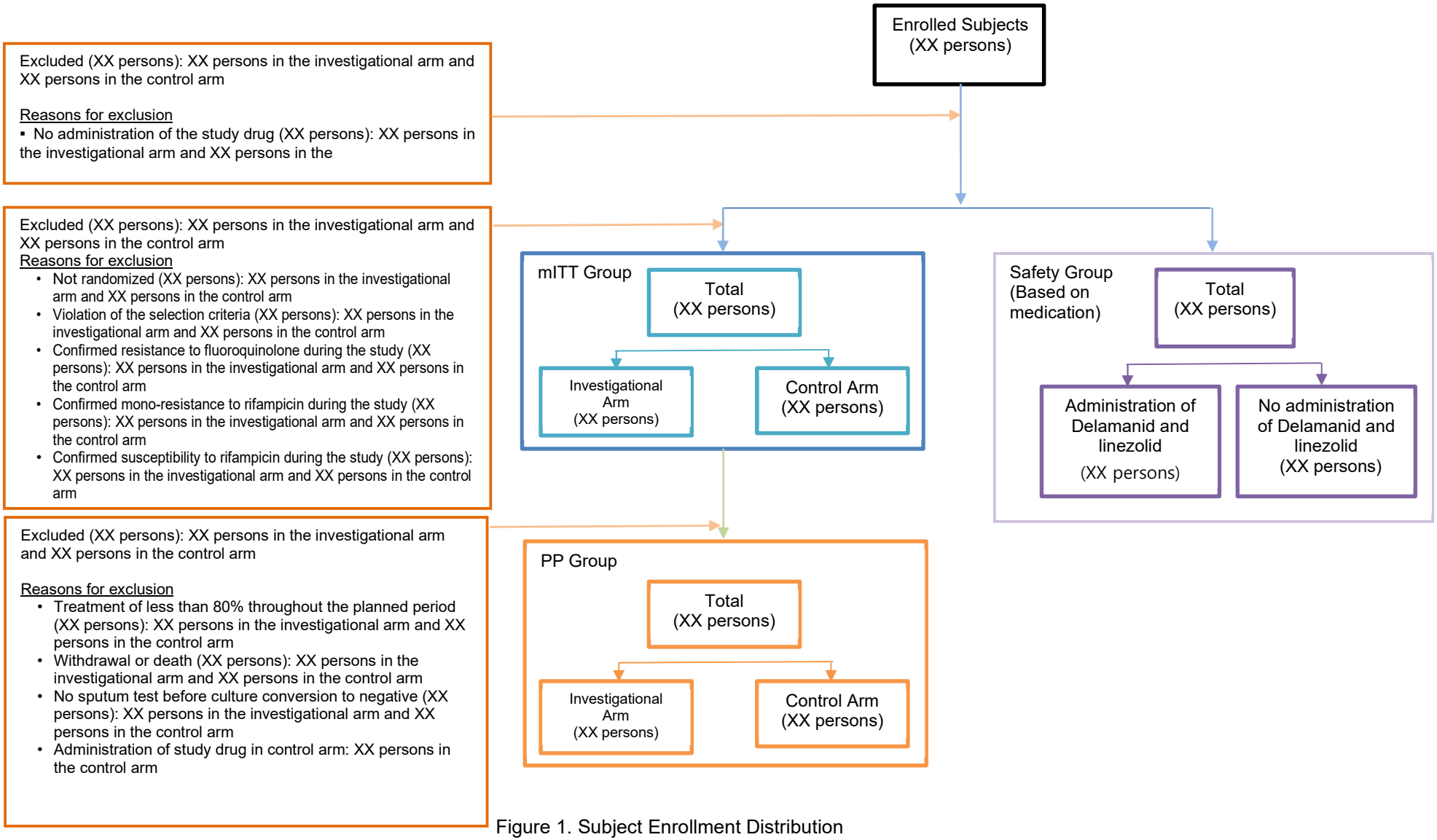


Figure 1. Subject Enrollment Distribution

Table 1. Clinical Trial Results

	Investigational Arm	Control Arm
Enrollment, n	xx	xx
Non administration of study drug	xx	xx
No randomization due to screening failure	xx	xx
Violation of inclusion/exclusion criteria	xx	xx
Violation of the inclusion criterion 1	xx	xx
Violation of the inclusion criterion 2	xx	xx
Violation of the inclusion criterion 3	xx	xx
Violation of the exclusion criterion 1	xx	xx
Violation of the exclusion criterion 2	xx	xx
Violation of the exclusion criterion 3	xx	xx
Violation of the exclusion criterion 4	xx	xx
Violation of the exclusion criterion 5	xx	xx
Violation of the exclusion criterion 6	xx	xx
Violation of the exclusion criterion 7	xx	xx
Violation of the exclusion criterion 8	xx	xx
Fluoroquinolone resistance confirmed during the study	xx	xx
Rifampicin mono-resistance confirmed during the study	xx	xx
Rifampicin susceptibility confirmed during the study	xx	xx
mITT analysis group, n	xx	xx
Treatment of less than 80% throughout the planned period	xx	xx
Withdrawal or death before treatment completion (less than 80% of the planned period)	xx	xx
Investigator’s judgment that participating in the study is not beneficial to the subject	xx	xx

Withdrawal of consent	xx	xx
Treatment failure	xx	xx
Pregnancy	xx	xx
Death	xx	xx
Non-execution of sputum testing before culture conversion to negative	xx	xx
Administration of study drug in the control arm	xx	xx
PP analysis group, n	xx	xx

※ Safety analysis (per the administration of study drugs)

	Investigational Arm	Control Arm	Total
Number of enrollments, n	xx	xx	xx
Non-administration of study drug	xx	xx	xx
Safety analysis (per the administration of study drugs), n	xx	xx	xx
Administration of Delamanid or linezolid	xx	xx	xx
No administration of Delamanid or linezolid	xx	xx	xx

4.2 Enrollment Status for Each Site/Randomization Stratification

The analysis presents enrollment status by each site and randomization stratification factor (presence or absence of cavity in CXR or chest CT/diabetes mellitus) (Table 2).

Table 2. Enrollment Status for Each Site/Randomization Stratification Factor

	Investigational arm (N=xx)	Control arm (N=xx)
Site, n (%)		
Seoul National University Hospital	xx (xx.xx)	xx (xx.xx)
National Medical Center	xx (xx.xx)	xx (xx.xx)
Dankook University Hospital	xx (xx.xx)	xx (xx.xx)
Pusan National University Hospital	xx (xx.xx)	xx (xx.xx)
Korea University Ansan Hospital	xx (xx.xx)	xx (xx.xx)
Samsung Medical Center	xx (xx.xx)	xx (xx.xx)
Asan Medical Center	xx (xx.xx)	xx (xx.xx)
SMG-SNU Boramae Medical Center	xx (xx.xx)	xx (xx.xx)
Pusan National University Yangsan Hospital	xx (xx.xx)	xx (xx.xx)
Severance Hospital	xx (xx.xx)	xx (xx.xx)
Ulsan National University Hospital	xx (xx.xx)	xx (xx.xx)
The Catholic University of Korea Incheon St. Mary's Hospital	xx (xx.xx)	xx (xx.xx)
Presence of cavity in CXR or chest CT, n (%)		
Yes	xx (xx.xx)	xx (xx.xx)
No	xx (xx.xx)	xx (xx.xx)
Diabetes mellitus, n (%)		
Yes	xx (xx.xx)	xx (xx.xx)

No	xx (xx.xx)	xx (xx.xx)

4.3 Subjects' Demographic Characteristics and Characteristics Before Treatment

The analysis investigates the subjects' demographic characteristics and the characteristics before treatment.

4.3.1 Demographic Characteristics and Vital Signs

Table 3 below presents the comparison of the demographic characteristics and vital signs of the two arms.

Table 3. Demographic Characteristics and Vital Signs

				Investigational arm (N=xx)		Control arm (N=xx)	p-value
Age (Years)	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Gender		Male, n (%)		xx (xx.xx)		xx (xx.xx)	0.xxxx †† or **
		Female, n (%)		xx (xx.xx)		xx (xx.xx)	
Height (cm)	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Weight (kg)	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
SBP (mmHg)	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
DBP (mmHg)	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *

		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Pulse	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	

† p-value by the t-test * p-value by the Wilcoxon rank sum test

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.2 Past History

Table 4 below presents the past history distribution of the two arms before treatment.

Table 4. Past History

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
Past history of TB				
Yes or No	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Number of times	1 time, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	2 times, n (%)	xx (xx.xx)	xx (xx.xx)	
	3 times, n (%)	xx (xx.xx)	xx (xx.xx)	
	4 times, n (%)	xx (xx.xx)	xx (xx.xx)	
	5 times, n (%)	xx (xx.xx)	xx (xx.xx)	
	6 times, n (%)	xx (xx.xx)	xx (xx.xx)	
	Unknown	xx (xx.xx)	xx (xx.xx)	
Diabetes mellitus				
	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Optic neuropathy				

	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Peripheral neuropathy				
	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption				
	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Other diseases				
	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.3 Medication History

Table 5 below presents medication history other than the TB medication before treatment of study drug of the two arms.

Table 5. Medication History

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
Medication other than TB medication				
	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Prohibited medications/cautious medication				
Antidepressant, n (%)		xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Meperidine, n (%)		xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Dopaminergic drug, n (%)		xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

Buspirone, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Strong CYP3A inducer like carbamazepine, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Others, specify, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.4 Physical/Neurological Examination

Table 6 below presents the distribution of physical/neurological examination results of the two arms before treatment of study drug.

Table 6. Physical/Neurological Examination

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
Physical Examination	Normal, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Abnormal, n (%)	xx (xx.xx)	xx (xx.xx)	
Neurological examination	Normal, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Abnormal, n (%)	xx (xx.xx)	xx (xx.xx)	

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.5 Drug Susceptibility Test

Table 7 below presents drug susceptibility test before treatment of study drug to the two arms.

Table 7. Drug Susceptibility Test

	Investigational arm (N=xx)	Control arm (N=xx)	p-value
Screening			

Xpert MTB/RIF assay				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
MTB	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
RIF resistance	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
MTBDRsl				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Fluoroquinolone resistance	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
XDR TB	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Drug Susceptibility Test				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Resistance	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Resistant drug				
Isoniazid, n (%)		xx (xx.xx)	xx (xx.xx)	
Rifampicin, n (%)		xx (xx.xx)	xx (xx.xx)	
Ethambutol, n (%)		xx (xx.xx)	xx (xx.xx)	
Pyrazinamide, n (%)		xx (xx.xx)	xx (xx.xx)	
Streptomycin, n (%)		xx (xx.xx)	xx (xx.xx)	
Kanamycin, n (%)		xx (xx.xx)	xx (xx.xx)	
Amikacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Capreomycin, n (%)		xx (xx.xx)	xx (xx.xx)	
Ofloxacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Levofloxacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Moxifloxacin, n (%)		xx (xx.xx)	xx (xx.xx)	

Prothionamide, n (%)		xx (xx.xx)	xx (xx.xx)	
Cycloserine, n (%)		xx (xx.xx)	xx (xx.xx)	
Para-aminosalicyllc acid, n (%)		xx (xx.xx)	xx (xx.xx)	
Baseline visit				
Drug susceptibility test				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Resistance	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Resistant drug				
Isoniazid, n (%)		xx (xx.xx)	xx (xx.xx)	
Rifampicin, n (%)		xx (xx.xx)	xx (xx.xx)	
Ethambutol, n (%)		xx (xx.xx)	xx (xx.xx)	
Pyrazinamide, n (%)		xx (xx.xx)	xx (xx.xx)	
Streptomycin, n (%)		xx (xx.xx)	xx (xx.xx)	
Kanamycin, n (%)		xx (xx.xx)	xx (xx.xx)	
Amikacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Capreomycin, n (%)		xx (xx.xx)	xx (xx.xx)	
Ofloxacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Levofloxacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Moxifloxacin, n (%)		xx (xx.xx)	xx (xx.xx)	
Prothionamide, n (%)		xx (xx.xx)	xx (xx.xx)	
Cycloserine, n (%)		xx (xx.xx)	xx (xx.xx)	
Para-aminosalicyllc acid, n (%)		xx (xx.xx)	xx (xx.xx)	

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.6 Sputum AFB Smear and CXR

Table 8 below presents the distribution of sputum AFB smear and CXR results of the two arms before treatment of study drug.

Table 8. Sputum AFB Smear and CXR

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
Screening				
Sputum AFB panel				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
AFB smear	-, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	scanty, n (%)	xx (xx.xx)	xx (xx.xx)	
	1+, n (%)	xx (xx.xx)	xx (xx.xx)	
	2+, n (%)	xx (xx.xx)	xx (xx.xx)	
	3+, n (%)	xx (xx.xx)	xx (xx.xx)	
	4+, n (%)	xx (xx.xx)	xx (xx.xx)	
Solid culture	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	
	NTM suspected			
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
	No, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
	Contaminated, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
Liquid culture	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	
	PCR results			
	MTB, n (%)	xx (xx.xx)	xx (xx.xx)	
	NTM, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
	Contaminated, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
CXR/Chest CT				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	

Examination type	CXR, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Chest CT, n (%)	xx (xx.xx)	xx (xx.xx)	
Lesion range	One lung, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Both lungs, n (%)	xx (xx.xx)	xx (xx.xx)	
Cavity presence	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	No, n (%)	xx (xx.xx)	xx (xx.xx)	
Baseline visit				
Sputum AFB panel				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
AFB smear	-, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Scanty, n (%)	xx (xx.xx)	xx (xx.xx)	
	1+, n (%)	xx (xx.xx)	xx (xx.xx)	
	2+, n (%)	xx (xx.xx)	xx (xx.xx)	
	3+, n (%)	xx (xx.xx)	xx (xx.xx)	
	4+, n (%)	xx (xx.xx)	xx (xx.xx)	
Solid culture	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	
	NTM suspected			
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
	No, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
	Contaminated, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
Liquid culture	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	
	PCR results			
	MTB, n (%)	xx (xx.xx)	xx (xx.xx)	
	NTM, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
	Contaminated, n (%)	xx (xx.xx)	xx (xx.xx)	

	Not done, n (%)	xx (xx.xx)	xx (xx.xx)	
CXR/Chest CT				
Execution	No, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	
Examination type	CXR, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Chest CT, n (%)	xx (xx.xx)	xx (xx.xx)	
Lesion range	One lung, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Both lungs, n (%)	xx (xx.xx)	xx (xx.xx)	
Cavity presence	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	No, n (%)	xx (xx.xx)	xx (xx.xx)	

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.7 HIV/HBV test

Table 9 below presents the distribution of the HIV/HBV test results of the two arms before treatment of study drug.

Table 9. HIV/HBV test

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
HIV				
Result	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	
HBV				
results	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.8 Chemistry/Electrolyte/Complete Blood Count

Table 10 below presents the distribution of the chemistry/electrolyte/complete blood count results of the two arms before treatment of study drug.

Table 10. Chemistry/Electrolyte/Complete Blood Count

				Investigational arm (N=xx)		Control arm (N=xx)	p-value
Screening							
Chemistry							
T-bilirubin	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Alkaline phosphatase	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
AST	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
ALT	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Creatinine	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Electrolyte							
Sodium	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Potassium	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Chloride	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *

		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Complete blood count							
WBC	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
ANC	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Hemoglobin	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
PLT	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Baseline visit							
Chemistry							
T-bilirubin	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Alkaline phosphatase	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
AST	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
ALT	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Creatinine	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Electrolyte							
Sodium	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	

Potassium	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Chloride	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Complete blood count							
WBC	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
ANC	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Hemoglobin	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
PLT	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	

† p-value by t-test * p-value by Wilcoxon rank sum test

4.3.9 Urine HCG

Table 11 below presents the distribution of the urine HCG examination results of the two arms before treatment of study drug.

Table 11. Urine HCG

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
Screening				
Urine HCG				
Execution	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

	No, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not applicable, n (%)	xx (xx.xx)	xx (xx.xx)	
Result	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	
Baseline visit				
Urine HCG				
Execution	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	No, n (%)	xx (xx.xx)	xx (xx.xx)	
	Not applicable, n (%)	xx (xx.xx)	xx (xx.xx)	
Result	Negative, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	Positive, n (%)	xx (xx.xx)	xx (xx.xx)	

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.10 ECG

Table 12 below presents the distribution of the ECG examination results of the two arms before treatment of study drug.

Table 12. ECG Examination

		Investigational arm(N=xx)	Control arm(N=xx)	p-value
Screening				
ECG				
Execution	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
	No, n (%)	xx (xx.xx)	xx (xx.xx)	
Rhythm	Sinus rhythm, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

		Other, n (%)		xx (xx.xx)		xx (xx.xx)	
QTcF	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Baseline visit							
ECG							
Execution		Yes, n (%)		xx (xx.xx)		xx (xx.xx)	
		No, n (%)		xx (xx.xx)		xx (xx.xx)	
		Not applicable, n (%)		xx (xx.xx)		xx (xx.xx)	
Rhythm		Sinus rhythm, n (%)		xx (xx.xx)		-	
		Others, n (%)		xx (xx.xx)		-	
QTcF	n	mean±sd	xx	xx.xx±xx.xx		-	
		median [min, max]		xx.xx[xx.xx,xx.xx]		-	

† p-value by t-test * p-value by Wilcoxon rank sum test

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.3.11 Optic test (Ishihara Color Plate)

Table 13 below presents the distribution of the optic test results of the two arms before treatment of study drug.

Table 13. Optic Test (Ishihara Color Plate)

		Investigational arm (N=xx)	Control arm (N=xx)	p-value
Screening				
Execution				
	Yes, n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

		No, n (%)		xx (xx.xx)		xx (xx.xx)	
- Performance and the number of correct answers of 24 Ishihara color plates	n	mean±sd	x x	xx.xx±xx.xx	x x	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Baseline visit							
Execution							
		Yes, n (%)		xx (xx.xx)		xx (xx.xx)	-
		No, n (%)		xx (xx.xx)		xx (xx.xx)	
- Performance and the number of correct answers of 24 Ishihara color plates	n	mean±sd	x x	xx.xx±xx.xx	x x	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	

† p-value by t-test * p-value by Wilcoxon rank sum test

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

4.4 Adherence Assessment

Table 14 below presents the distribution of adherence to study drug of both arms at each visit and throughout the entire treatment period.

In this case, for the final adherence of each subject, the total adherence to each drug is calculated separately, and the average value is defined as the final adherence. An independent t-test or Wilcoxon rank sum test is performed only for final adherence and comparisons are made between groups.

Table 14.Adherence Assessment

				Investigational arm (N=xx)		Control arm (N=xx)	p-value
Final Adherence	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
Delamanid		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Linezolid	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *

		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Levofloxacin	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Pyrazinamide	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Other drug 1	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
Other drug 2	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	
	n	mean±sd	xx	xx.xx±xx.xx	xx	xx.xx±xx.xx	0.xxxx † or *
		median [min, max]		xx.xx[xx.xx,xx.xx]		xx.xx[xx.xx,xx.xx]	

† p-value by t-test * p-value by Wilcoxon rank sum test

5. Efficacy Evaluation Results

The efficacy evaluation uses the mITT group as the main analysis group and the PP group as the auxiliary analysis group. The mITT analysis includes randomized subjects after satisfying eligibility criteria and receive study drugs at least one time. The subjects are not confirmed to be additionally resistant to fluoroquinolone, mono-resistant to rifampicin, or susceptible to rifampicin.

The PP analysis includes subjects included in the mITT group and have completed 80% or more administration through the planned treatment period has completed the clinical trial according to the study protocol during the clinical trial period.

The mITT analysis of the primary efficacy evaluation excludes the subjects judged to be “Not assessable”. The subgroups according to the presence or absence of pyrazinamide resistance are additionally analyzed of the primary outcome.

Stratification analysis is performed for primary and secondary outcome evaluation by dividing subjects into sputum smear positive and sputum smear negative patient groups based on the sputum smear results.

5.1 Primary Efficacy Evaluation Results

5.1.1 Treatment Success Rate at 24 Months after the initiation of treatment

- The analysis presents the frequency and proportion of treatment success rate after 24 months of each arm to check if the treatment success rate of the investigational arm 24 months after the initiation of treatment is inferior to the control arm. It presents the 95% confidence interval of the treatment success rate difference (investigational arm's treatment success rate - control arm's treatment success rate) 24 months after the initiation of treatment. The one-sided test is performed at the significant level of 2.5% using the lower limit of the 95% confidence interval about the difference of the treatment success rate between the two arms. If the lower limit of the confidence interval is larger than 0.1, it proves that the treatment success rate of the investigational arm is inferior to the control arm. If it is equal to or less than 0.1, it cannot prove that the investigational arm is not inferior to the control arm (Table 15).

Table 15. Treatment Success Rate at 24 Months after the initiation of treatment

	Investigational Arm	Control Arm	All
mITT analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx, ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PP analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx, ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)

Sub-group analysis	xx	xx	xx
1-1. Sputum smear positive[3)]	xx	xx	xx
mITT analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx, ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PP analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx, ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
1-2. Sputum smear negative[4)]	xx	xx	xx
mITT analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx, ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PP analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx, ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)

[1)] If the lower limit of the confidence interval is larger than -10%, it proves that the efficacy of the study drug is inferior to the control drug.
[2)] The subjects judged to be “Not assessable are excluded from the primary assessment.

[3)] Sputum smear positive at screening visit (visit1)
[4)] Sputum smear negative at screening visit (visit1)

5.2 Secondary Efficacy Evaluation Results

The secondary outcomes of this clinical trial include the time to sputum Mycobacterium TB (MTB) culture conversion to negative (liquid and solid culture media), the proportion of sputum MTB culture conversion to negative at two months of treatment (liquid and solid culture media), the proportion of sputum MTB culture conversion to negative at six months of treatment (liquid and solid culture media), the proportion of treatment success at the end of treatment, the proportion of relapse after treatment success (investigational arm), and the proportion of death and time-to-death. Additionally, the primary outcome between treatment groups according to resistance to pyrazinamide is performed.

5.2.1 Time to sputum culture conversion after the initiation of treatment (Liquid and Solid Culture Media)

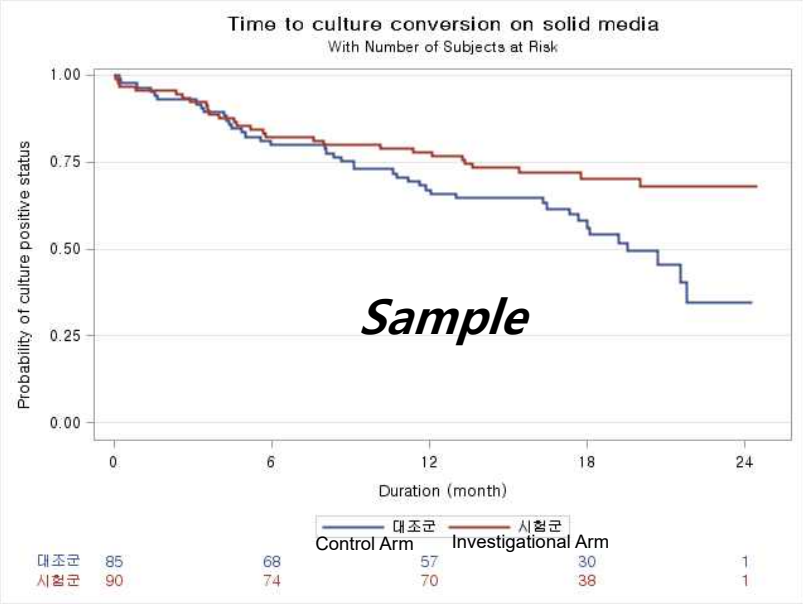
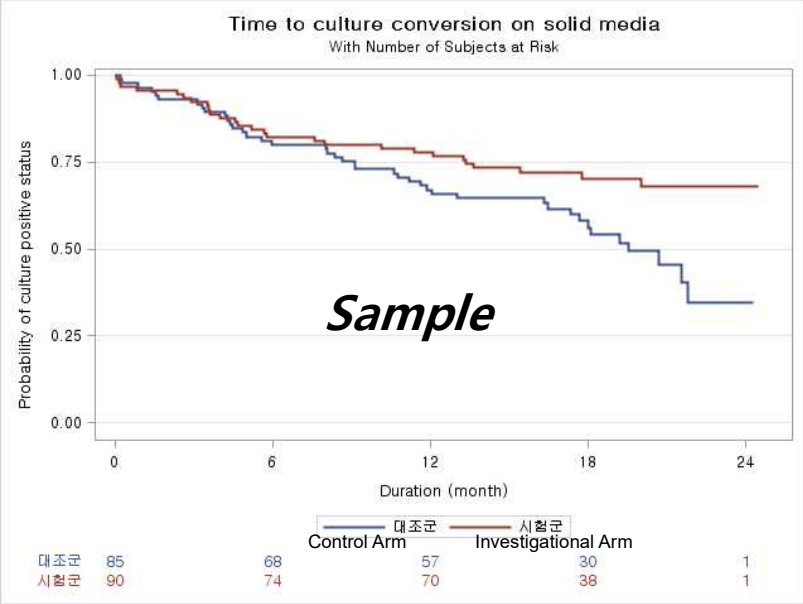
To test whether the time to sputum culture conversion after the initiation of treatment of the control arm and investigational arm (liquid and solid culture media) are different statistically, the median time is estimated in each group using the Kaplan-Meier method, and the difference of the distribution of time to culture conversion of the two arms is compared using the Log-rank test (Table 16).

Table 16. Time to sputum culture conversion after the initiation of treatment (Liquid and Solid Culture Media)

		Investigational Arm	Control Arm	p-value [1)]
mITT analysis group, n		xx	xx	
Solid media	median time [95% CI]	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	0.xxxx
Liquid media	median time [95% CI]	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	
PP analysis group, n				
Solid media	median time (95% CI)	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	0.xxxx

Liquid media	median time (95% CI)	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	
Sub-group analysis		xx	xx	
1-1. Sputum smear positive[2)]		xx	xx	
mITT analysis group, n		xx	xx	
Solid media	median time [95% CI]	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	0.xxxx
Liquid media	median time [95% CI]	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	
PP analysis group, n				
Solid media	median time (95% CI)	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	0.xxxx
Liquid media	median time (95% CI)	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	
1-2. Sputum smear negative[3)]		xx	xx	
mITT analysis group, n		xx	xx	
Solid media	median time [95% CI]	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	0.xxxx
Liquid media	median time [95% CI]	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	
PP analysis group, n				
Solid media	median time (95% CI)	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	0.xxxx
Liquid media	median time (95% CI)	xx[xx.xx-xx.xx]	xx[xx.xx-xx.xx]	

[1)] P-value for the comparison test of the time to negative between Investigational arm and Control arm. The test assumes that the negative distribution difference between Investigational and Control arm is the same at all time points.
[2)] Sputum smear positive at screening visit (visit1)
[3)] Sputum smear negative at screening visit (visit1)

	mITT analysis group	PP analysis group
Solid media		

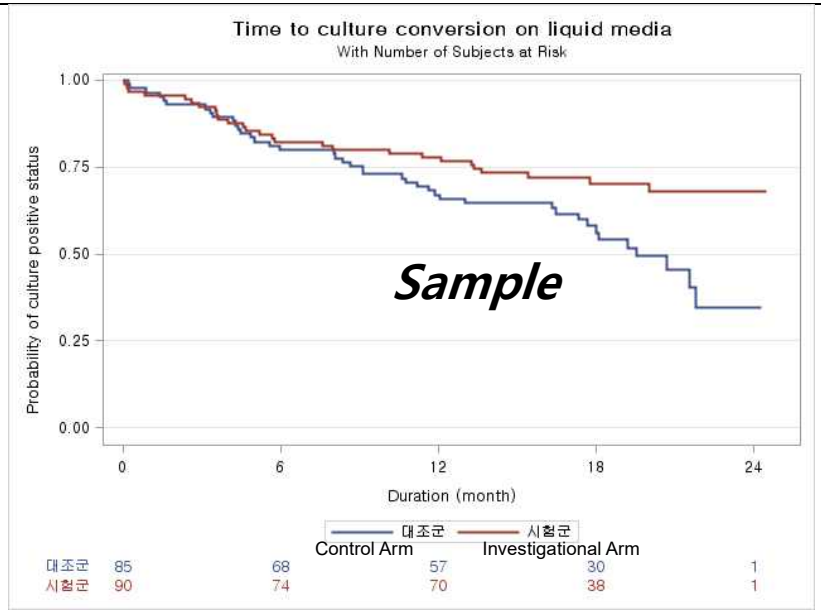
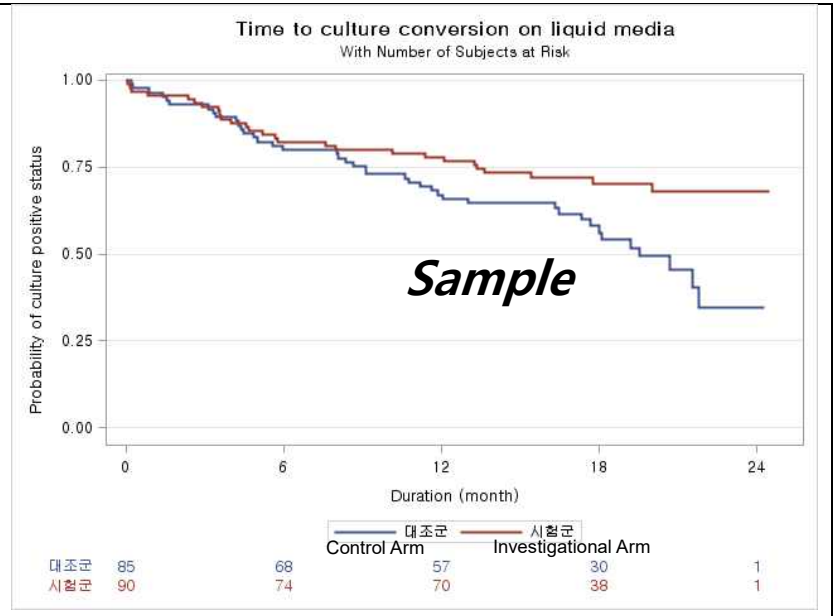
Liquid media		

Figure 2. Time to Sputum Culture Conversion after Initiation of treatment (Liquid and Solid Culture media)

5.2.2 Sputum culture conversion proportion at two months of treatment (Liquid and Solid Culture Media)

- To compare the proportion of sputum MTB culture conversion to negative between the investigational arm and control arm at two months of treatment, the frequency and proportion of each arm are summarized, and the Chi-square test or Fisher's exact test is performed (Table 17).

Table 17. Sputum culture conversion proportions at two months of treatment

		Investigational Arm	Control Arm	p-value [1)]
mITT analysis group, xx persons (Investigational arm: xx persons, Control arm: xx persons)				
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
PP analysis group, xx persons (Investigational arm: xx persons, Control arm: xx persons)				
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Sub-group analysis				
1-1. Sputum smear positive[2)]				
mITT analysis group, xx persons (Investigational arm: xx persons, Control arm: xx persons)				
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
PP analysis group, xx persons (Investigational arm: xx persons, Control arm: xx persons)				
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
1-2. Sputum smear negative[3)]				
mITT analysis group, xx persons (Investigational arm: xx persons, Control arm: xx persons)				
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
PP analysis group, xx persons (Investigational arm: xx persons, Control arm: xx persons)				
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

1) p-value of the comparison test of the negative conversion rate between the Investigational arm and Control arm
2) Sputum smear positive at screening visit (visit1)
3) Sputum smear negative at screening visit (visit1)

5.2.3 Sputum culture conversion proportion at six months of treatment (Liquid and Solid Culture Media)

To compare the proportion of sputum MTB culture conversion to negative between the investigational arm and control arm at six months of treatment, the frequency and proportion of each arm are summarized, and the chi-square test or Fisher's exact test is performed (Table 18).

Table 18. Sputum culture conversion proportion at six months of treatment

		Investigational arm	Control arm	p-value 1)
mITT analysis group		xx	xx	
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
PP analysis group		xx	xx	
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Sub-group analysis		xx	xx	
1-1. Sputum smear positive2)		xx	xx	
mITT analysis group		xx	xx	
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
PP analysis group		xx	xx	
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

1-2. Sputum smear negative[3)]		xx	xx	
mITT analysis group		xx	xx	
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
PP analysis group		xx	xx	
Solid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **
Liquid media	n (%)	xx (xx.xx)	xx (xx.xx)	0.xxxx †† or **

†† p-value by the Chi-square test ** p-value by the Fisher's exact test

1) p-value of the comparison test of the negative rate between the Investigational and Control arms
2) Sputum smear positive at screening visit (visit1)
3) Sputum smear negative at screening visit (visit1)

5.2.4 Proportion of Treatment Success at the End of Treatment

- The analysis presents the frequency and proportion of treatment success and failure in the investigational arm (Table 19).

Table 19. Proportion of Treatment Success at the End of Treatment

	Investigational arm
mITT analysis group	xx
Proportion of treatment success at the end of treatment, n (%)	xx (xx.xx)
Treatment failure, n (%)	xx (xx.xx)
PP analysis group	xx
Proportion of treatment success at the end of treatment, n (%)	xx (xx.xx)
Treatment failure, n (%)	xx (xx.xx)
Sub-group analysis	xx

1-1. Sputum smear positive[1)]	xx
mITT analysis group	xx
Proportion of treatment success at the end of treatment, n (%)	xx (xx.xx)
Treatment failure, n (%)	xx (xx.xx)
PP analysis group	xx
Proportion of treatment success at the end of treatment, n (%)	xx (xx.xx)
Treatment failure, n (%)	xx (xx.xx)
1-2. Sputum smear negative[2)]	xx
mITT analysis group	xx
Proportion of treatment success at the end of treatment, n (%)	xx (xx.xx)
Treatment failure, n (%)	xx (xx.xx)
PP analysis group	xx
Proportion of treatment success at the end of treatment, n (%)	xx (xx.xx)
Treatment failure, n (%)	xx (xx.xx)

[1)] Sputum smear positive at screening visit (visit1)
[2)] Sputum smear negative at screening visit (visit1)

5.2.5 Proportion of Relapse after Treatment Success

The analysis presents the frequency and proportion of relapse after treatment success in the investigational arm.

Table 20. Proportion of Relapse after Treatment Success

	Investigational Arm
mITT analysis group	xx

Treatment success	xx
Proportion of relapse after treatment success, n (%)	xx (xx.xx)
PP analysis group	xx
Treatment success	xx
Proportion of relapse after treatment success, n (%)	xx (xx.xx)
Sub-group analysis	xx
1-1. Sputum smear positive[1)]	xx
mITT analysis group	xx
Treatment success	xx
Proportion of relapse after treatment success, n (%)	xx (xx.xx)
PP analysis group	xx
Treatment success	xx
Proportion of relapse after treatment success, n (%)	xx (xx.xx)
1-2. Sputum smear negative[2)]	xx
mITT analysis group	xx
Treatment success	xx
Proportion of relapse after treatment success, n (%)	xx (xx.xx)
PP analysis group	xx
Treatment success	xx
Proportion of relapse after treatment success, n (%)	xx (xx.xx)

[1)] Sputum smear positive at screening visit (visit1)
[2)] Sputum smear negative at screening visit (visit1)

5.2.6 Proportion of Death and Time-to-Death

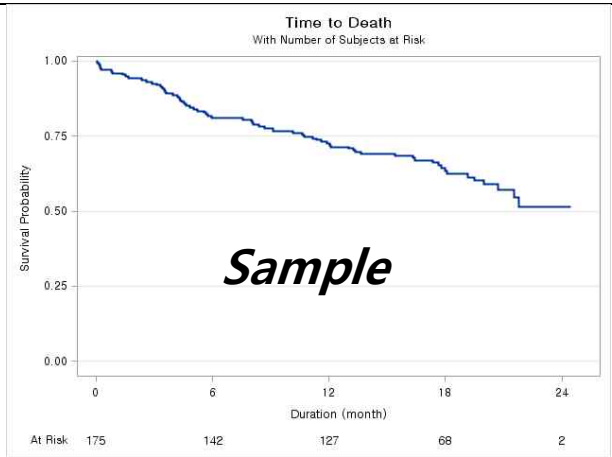
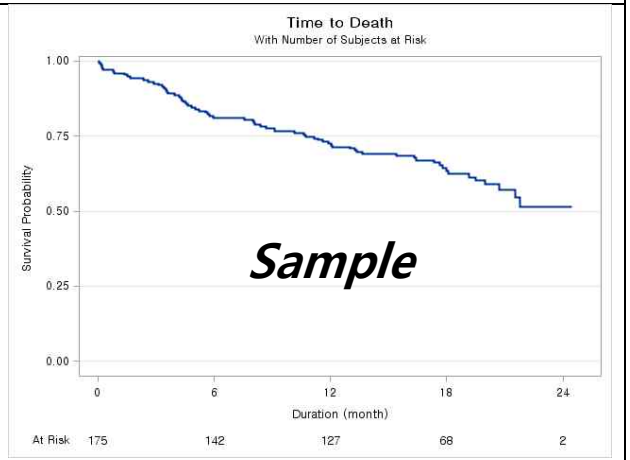
The analysis presents the frequency and proportion of death in the investigational arm and estimates the median survival time using Kaplan-Meier method (Table 21).

Table 21. Proportion of death and Time-to-Death

	Investigational Arm
mITT analysis group	xx
Death, n (%)	xx (xx.xx)
median survival time [95% CI]	xx[xx.xx-xx.xx]
PP analysis group	xx
Death, n (%)	xx (xx.xx)
median survival time [95% CI]	xx[xx.xx-xx.xx]
Sub-group analysis	
1-1. Sputum smear positive[1)]	
mITT analysis group	xx
Death, n (%)	xx (xx.xx)
median survival time [95% CI]	xx[xx.xx-xx.xx]
PP analysis group	xx
Death, n (%)	xx (xx.xx)
median survival time [95% CI]	xx[xx.xx-xx.xx]
1-2. Sputum smear negative[2)]	
mITT analysis group	xx
Death, n (%)	xx (xx.xx)
median survival time [95% CI]	xx[xx.xx-xx.xx]
PP analysis group	xx

Death, n (%)	xx (xx.xx)
median survival time [95% CI]	xx[xx.xx-xx.xx]

[1] Sputum smear positive at screening visit (visit1)
[2] Sputum smear negative at screening visit (visit1)

	mITT analysis group	PP analysis group
Total Investigational Arm		

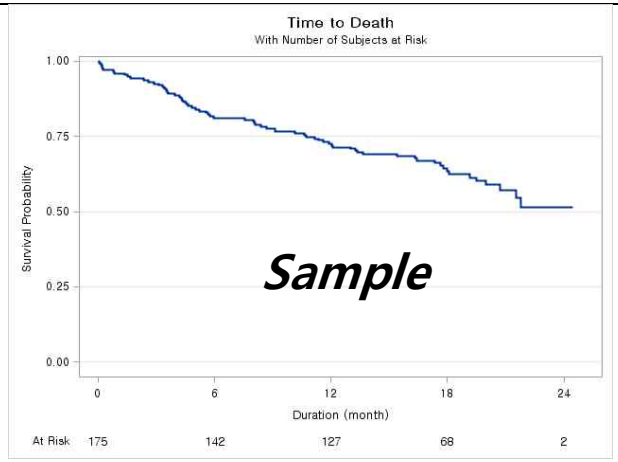
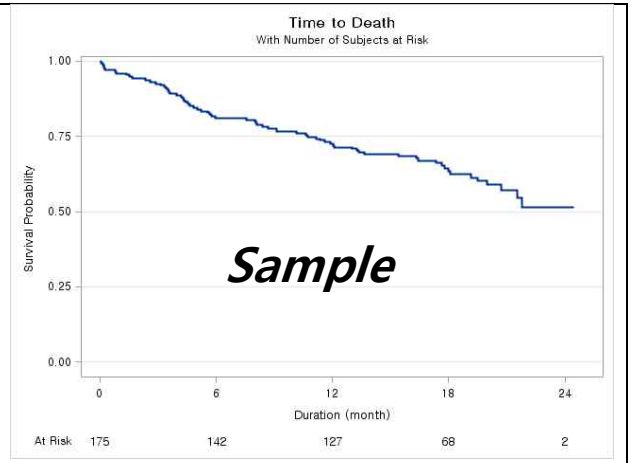
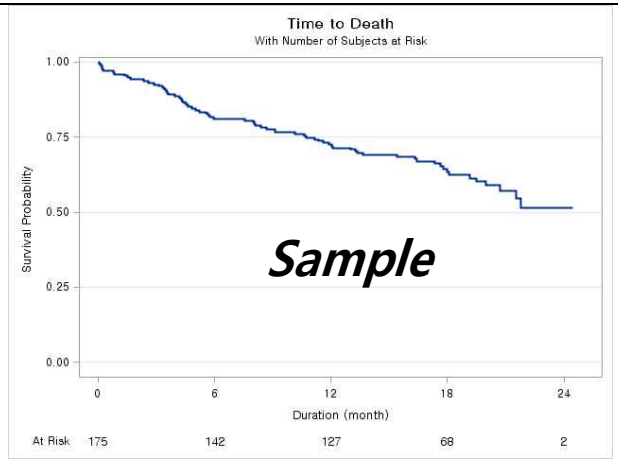
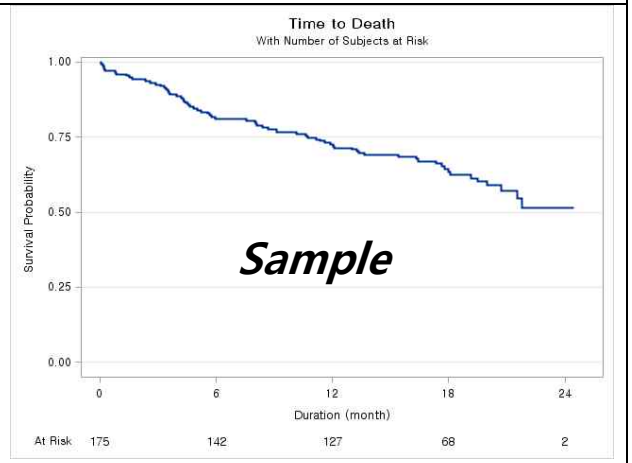
Sputum smear positive		
Sputum smear negative		

Figure 3. Time to Death

5.2.7 Treatment Success Rate at 24 Months after the initiation of treatment According to Pyrazinamide Resistance

In order to test whether the treatment success rate after 24 months of the investigational arm is non-inferior to the control arm in the subgroup according to the presence or absence of pyrazinamide resistance, 95% confidence interval of the treatment success rate after 24 months in each arm is presented in terms of frequency. It presents the 95% confidence interval of the treatment success rate difference (investigational arm's treatment success rate - control arm's treatment success rate) 24 months after initiation of treatment. The one-sided test is performed at the significant level of 2.5% using the lower limit of the 95% confidence interval of the treatment success rate difference between the two arms. If the lower limit of the confidence interval is larger than 0.1, it proves that the success rate of the investigational arm is inferior to the control arm. If it is equal to or less than 0.1, it cannot prove that the investigational arm is not inferior to the control arm (Table 22).

Table 22. Treatment Success Rate at 24 Months after the initiation of treatment According to Pyrazinamide Resistance

	Investigational Arm	Control Arm	All
Pyrazinamide resistant			
mITT analysis group	xx	xx	xx
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx,∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PP analysis group			
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx,∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
No pyrazinamide resistant	xx	xx	xx
mITT analysis group			

Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PP analysis group			
Not assessable[2)]	xx	xx	xx
Treatment success rate at 24 months after the initiation of treatment, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Difference [95% CI]	xx.xx[xx.xx ∞][1)]		
Treatment failure, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)

[1)] If the lower limit of the confidence interval is larger than -10%, it proves that the efficacy of the study drug is inferior to the control drug.
[2)] The subjects judged to be “Not assessable are excluded from the assessment.

6. Safety Assessment Results

The safety analysis will be conducted for the mITT analysis group and the PP analysis group. Additionally, the safety analysis regarding the safety analysis group, that divides groups according to whether study drug delamanid or linezolid is administered, will be carried out for the subjects enrolled in this clinical trial and administered the study drug at least one time. The results of the safety evaluation will be summarized, focusing on adverse reactions and physical examinations, neurological examinations, chemistry, electrolyte, and complete blood count evaluated during this clinical trial period. The severity of adverse event will be evaluated based on CTCAE Version 4.0.

6.1 Adverse Events

The analysis presents the summary of the total number of adverse events, the number of subjects experiencing adverse events, and the serious adverse events, adverse event with grade 3-5 in this clinical trial (Table 23).

Table 23. Summary of Adverse Event Reported during Study Period

	Investigational Arm	Control Arm	Total
mITT	N=xx	N=xx	N=xx
Number of subjects showing adverse events, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
95% confidence interval of adverse event rate	xx.xx±xx.xx	xx.xx±xx.xx	xx.xx±xx.xx
p-value[1)]	0.xxxx †† or **		
Number of adverse events, n	xx	xx	xx
Adverse drug reaction[2)]			
Number of subjects showing adverse drug reaction, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[3)]	0.xxxx †† or **		
Number of adverse drug reaction, n	xx	xx	xx
Serious adverse events			

Number of subjects showing serious adverse events, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[4)]	0.xxxx †† or **		
Number of adverse events, n	xx	xx	xx
Adverse event of grade 3-5			
Number of subjects showing over grade 3 of adverse event, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[5)]	0.xxxx †† or **		
Number of grade 3 of adverse event, n	xx	xx	xx
Death			
Death, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[6)]	0.xxxx †† or **		
Seriousness			
Not serious, n	xx	xx	xx
Serious, n	xx	xx	xx
Severity			
Mild, n	xx	xx	xx
Moderate, n	xx	xx	xx
Severe, n	xx	xx	xx
life threatening or disabling, n	xx	xx	xx
Death, n	xx	xx	xx
Relation			
not related, n	xx	xx	xx
doubtful, n	xx	xx	xx
possible, n	xx	xx	xx
probable, n	xx	xx	xx

definite, n	xx	xx	xx
Action taken			
No action taken, n	xx	xx	xx
Dosage Adjustment of study drug, n	xx	xx	xx
Suspension of study drug, n	xx	xx	xx
Permanent termination of study drug, n	xx	xx	xx
Unknown, n	xx	xx	xx
Not applicable, n	xx	xx	xx
Dosage adjustment of TB medication other than the study drug, n	xx	xx	xx
Suspension of TB medication other than the study drug, n	xx	xx	xx
Permanent termination of TB medication other than the study drug, n	xx	xx	xx
Outcome			
Resolved, n	xx	xx	xx
Resolved with residual effect, n	xx	xx	xx
Ongoing, n	xx	xx	xx
Death, n	xx	xx	xx
Unknown, n	xx	xx	xx
PP	N=xx	N=xx	N=xx
Number of subjects showing adverse event, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
95% confidence interval of adverse event rate	[xx.xx, xx.xx]	[xx.xx, xx.xx]	[xx.xx, xx.xx]
p-value[1)]	0.xxxx †† or **		xx
Number of adverse events, n	xx	xx	xx
Adverse drug reaction[2)]			

Number of subjects showing adverse drug reaction, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[3)]	0.xxxx †† or **		xx
Number of adverse drug reaction, n	xx	xx	xx
Serious adverse event			
Number of subjects showing serious adverse events, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[4)]	0.xxxx †† or **		xx
Number of adverse events, n	xx	xx	xx
Adverse event of Grade 3-5			
Number of subjects showing over grade 3 of adverse event, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[5)]	0.xxxx †† or **		
Number of grade 3 of adverse event, n	xx	xx	xx
Death			
Death, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[6)]	0.xxxx †† or **		xx
Seriousness			
Not serious, n	xx	xx	xx
Serious, n	xx	xx	xx
Severity			
Mild, n	xx	xx	xx
Moderate, n	xx	xx	xx
Severe, n	xx	xx	xx
life threatening or disabling, n	xx	xx	xx
Death, n	xx	xx	xx
Relation			

not related, n	xx	xx	xx
doubtful, n	xx	xx	xx
possible, n	xx	xx	xx
probable, n	xx	xx	xx
definite, n	xx	xx	xx
Action taken			
No action taken, n	xx	xx	xx
Dosage Adjustment of study drug, n	xx	xx	xx
Suspension of study drug, n	xx	xx	xx
Permanent termination of study drug, n	xx	xx	xx
Unknown, n	xx	xx	xx
Not applicable, n	xx	xx	xx
Dosage adjustment of TB medication other than the study drug, n	xx	xx	xx
Suspension of TB medication other than the study drug, n	xx	xx	xx
Permanent termination of TB medication other than the study drug, n	xx	xx	xx
Outcome			
Resolved, n	xx	xx	xx
Resolved with residual effect, n	xx	xx	xx
Ongoing, n	xx	xx	xx
Death, n	xx	xx	xx
Unknown, n	xx	xx	xx
Safety	N=xx	N=xx	N=xx
Number of subjects showing adverse events, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
95% confidence interval of adverse event rate	[xx.xx, xx.xx]	[xx.xx, xx.xx]	[xx.xx, xx.xx]

p-value[1)]	0.xxxx †† or **		
Number of adverse events, n	xx	xx	xx
Adverse drug reaction[2)]			
Number of subjects showing adverse drug reaction, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[3)]	0.xxxx †† or **		
Number of adverse drug reaction, n	xx	xx	xx
Serious adverse events			
Number of subjects showing serious adverse events, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[4)]	0.xxxx †† or **		
Number of adverse events, n	xx	xx	xx
Adverse event of grade 3-5			
Number of subjects showing over grade 3 of adverse event, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[5)]	0.xxxx †† or **		
Number of grade 3 of adverse event, n	xx	xx	xx
Death			
Death, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
p-value[6)]	0.xxxx †† or **		
Seriousness			
Not serious, n	xx	xx	xx
Serious, n	xx	xx	xx
Severity			
Mild, n	xx	xx	xx
Moderate, n	xx	xx	xx
Severe, n	xx	xx	xx

life threatening or disabling, n	xx	xx	xx
Death, n	xx	xx	xx
Relation			
not related, n	xx	xx	xx
doubtful, n	xx	xx	xx
possible, n	xx	xx	xx
probable, n	xx	xx	xx
definite, n	xx	xx	xx
Action taken			
No action taken, n	xx	xx	xx
Dosage Adjustment of study drug, n	xx	xx	xx
Suspension of study drug, n	xx	xx	xx
Permanent termination of study drug, n	xx	xx	xx
Unknown, n	xx	xx	xx
Not applicable, n	xx	xx	xx
Dosage adjustment of TB medication other than the study drug, n	xx	xx	xx
Suspension of TB medication other than the study drug, n	xx	xx	xx
Permanent termination of TB medication other than the study drug, n	xx	xx	xx
Outcome			
Resolved, n	xx	xx	xx
Resolved with residual effect, n	xx	xx	xx
Ongoing, n	xx	xx	xx
Death, n	xx	xx	xx
Unknown, n	xx	xx	xx

†† p-value by the Chi-square test ** p-value by the Fisher's exact test
1) p-value for comparison test of adverse reaction incidence rate between groups
2) In the case of an adverse reaction related to the drug used, the contribution of the drug is Possible, Probable, or Definite
3) p-value for comparison test of the incidence of adverse drug reactions between groups
4) p-value for comparison test of incidence of serious adverse events between groups
5) p-value for the comparison test for the incidence of grade 3 adverse events between groups
6) p-value for intergroup mortality comparison test

The analysis presents the adverse events occurring for each body system during the clinical trial period. The body system is classified according to SOC (System Organ Class) and PT (Preferred Term) of the MedDRA system. The adverse events are summarized for each severity of the body system, relation, and body system (Tables 24, 25, and 26).

Table 24. Adverse Events for Each Body System

		Investigational Arm (N=xx)		Control Arm (N=xx)		Total (N=xx)	
mITT							
System Organ Class	Preferred Term						
SOC1		x		x		x	
	xxx		*x*		*x*		*x*
	xxx		*x*		*x*		*x*
SOC2		x		x		x	
	xxx		*x*		*x*		*x*
	xxx		*x*		*x*		*x*
PP							
System Organ Class	Preferred Term						

SOC1		x		x		x	
	xxx		*x*		*x*		*x*
	xxx		*x*		*x*		*x*
SOC2		x		x		x	
	xxx		*x*		*x*		*x*
	xxx		*x*		*x*		*x*
Safety							
System Organ Class	Preferred Term						
SOC1		x		x		x	
	xxx		*x*		*x*		*x*
	xxx		*x*		*x*		*x*
SOC2		x		x		x	
	xxx		*x*		*x*		*x*
	xxx		*x*		*x*		*x*

Table 25. Adverse Events for Each Severity of Body System

		Investigational Arm (N=xx)						Control Arm (N=xx)					
		Severity						Severity					
		1	2	3	4	5	>=3	1	2	3	4	5	>=3
mITT													
System Organ Class	Preferred Term												
SOC1		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x

	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SOC2		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
PP													
System Organ Class	Preferred Term												
SOC1		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SOC2		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Safety													
System Organ Class	Preferred Term												
SOC1		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SOC2		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Table 26. Adverse Events for Each Relation of Body System

		Investigational Arm (N=xx)						Control Arm (N=xx)					
		Relation						Relation					
		1	2	3	4	5	>=3	1	2	3	4	5	>=3
mITT													
System Organ Class	Preferred Term												
SOC1		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*
SOC2		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*
PP													
System Organ Class	Preferred Term												
SOC1		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SOC2		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Safety													
System Organ Class	Preferred Term												
SOC1		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

SOC2		x	x	x	x	x	x	x	x	x	x	x	x
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
	xxx	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

The analysis summarizes in detail the serious adverse events reported during this clinical trial period (Table 27).

Table 27. Serious Adverse Event Evaluation Results

Subject No	Gender	Age	Adverse event name	Adverse event Onset date	Adverse event End date	Severity	Relation	Action taken	Outcome	Remarks
mITT										
Investigational Arm										
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Control Group										
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
PP										
Investigational Arm										
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Control Group										
	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx

xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Safety									
Investigational arm									
xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Control arm									
xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xx	xx	xx	xx	xx	xx	xx	xx	xx	xx

6.2 Physical/Neurological Examination Result

For the results of the physical/neurological examination, the analysis presents the proportion of subjects who were normal at Screening visit (Visit1) and changed to abnormal at End of Study (Table 28).

Table 28. Physical/Neurological Examination Result

	Investigational arm (N=xx)		Control arm (N=xx)	
	n (%)	Normal → Abnormal, n (%)	n (%)	Normal → Abnormal, n (%)
mITT				
Physical examination	xx	xx (xx.xx)	xx	xx (xx.xx)
Neurological examination	xx	xx (xx.xx)	xx	xx (xx.xx)
PP				
Physical examination	xx	xx (xx.xx)	xx	xx (xx.xx)

Neurological examination	xx	xx (xx.xx)	xx	xx (xx.xx)
Safety				
Physical examination	xx	xx (xx.xx)	xx	xx (xx.xx)
Neurological examination	xx	xx (xx.xx)	xx	xx (xx.xx)

6.3 Chemistry/Electrolyte/Complete Blood Count

The analysis presents the proportion of subjects who showed the chemistry/electrolyte/complete blood count result of “Normal” or “Abnormal NCS” at Baseline visit (Visit2) and changed to “Abnormal CS” at End of Study (Table 29).

Table 29. Chemistry/Electrolyte/Complete Blood Count

	Investigational arm (N=xx)		Control arm (N=xx)	
	n	Normal or Abnormal NCS → Abnormal CS, n (%)	n	Normal or Abnormal NCS →Abnormal CS, n (%)
mITT				
Chemistry				
T-bilirubin	xx	xx (xx.xx)	xx	xx (xx.xx)
Alkaline phosphatase	xx	xx (xx.xx)	xx	xx (xx.xx)
AST	xx	xx (xx.xx)	xx	xx (xx.xx)
ALT	xx	xx (xx.xx)	xx	xx (xx.xx)
Creatinine	xx	xx (xx.xx)	xx	xx (xx.xx)
Albumin	xx	xx (xx.xx)	xx	xx (xx.xx)

Electrolyte				
Sodium	xx	xx (xx.xx)	xx	xx (xx.xx)
Potassium	xx	xx (xx.xx)	xx	xx (xx.xx)
Chloride	xx	xx (xx.xx)	xx	xx (xx.xx)
Complete blood count				
WBC	xx	xx (xx.xx)	xx	xx (xx.xx)
ANC	xx	xx (xx.xx)	xx	xx (xx.xx)
Hemoglobin	xx	xx (xx.xx)	xx	xx (xx.xx)
PLT	xx	xx (xx.xx)	xx	xx (xx.xx)
PP				
Chemistry				
T-bilirubin	xx	xx (xx.xx)	xx	xx (xx.xx)
Alkaline phosphatase	xx	xx (xx.xx)	xx	xx (xx.xx)
AST	xx	xx (xx.xx)	xx	xx (xx.xx)
ALT	xx	xx (xx.xx)	xx	xx (xx.xx)
Creatinine	xx	xx (xx.xx)	xx	xx (xx.xx)
Albumin	xx	xx (xx.xx)	xx	xx (xx.xx)
Electrolyte				
Sodium	xx	xx (xx.xx)	xx	xx (xx.xx)
Potassium	xx	xx (xx.xx)	xx	xx (xx.xx)
Chloride	xx	xx (xx.xx)	xx	xx (xx.xx)
Complete blood count				
WBC	xx	xx (xx.xx)	xx	xx (xx.xx)
ANC	xx	xx (xx.xx)	xx	xx (xx.xx)
Hemoglobin	xx	xx (xx.xx)	xx	xx (xx.xx)

PLT	xx	xx (xx.xx)	xx	xx (xx.xx)
Safety				
Chemistry				
T-bilirubin	xx	xx (xx.xx)	xx	xx (xx.xx)
Alkaline phosphatase	xx	xx (xx.xx)	xx	xx (xx.xx)
AST	xx	xx (xx.xx)	xx	xx (xx.xx)
ALT	xx	xx (xx.xx)	xx	xx (xx.xx)
Creatinine	xx	xx (xx.xx)	xx	xx (xx.xx)
Albumin	xx	xx (xx.xx)	xx	xx (xx.xx)
Electrolyte				
Sodium	xx	xx (xx.xx)	xx	xx (xx.xx)
Potassium	xx	xx (xx.xx)	xx	xx (xx.xx)
Chloride	xx	xx (xx.xx)	xx	xx (xx.xx)
Complete blood count				
WBC	xx	xx (xx.xx)	xx	xx (xx.xx)
ANC	xx	xx (xx.xx)	xx	xx (xx.xx)
Hemoglobin	xx	xx (xx.xx)	xx	xx (xx.xx)
PLT	xx	xx (xx.xx)	xx	xx (xx.xx)

6.4 Concomitant Medication

Concomitant medication during the study period will be classified using the ATC (Anatomical Therapeutic Chemical) Code and presented and presented for each arm (Table 30).

Table 30. Concomitant Medication (Unit: Persons)

ATC code	Investigational arm (N=xx)	Control arm (N=xx)	Total (N=xx)
mITT			
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PP			
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
Safety			
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
XXX, n (%)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)

7. Conclusion

7.1 Efficacy

The analysis describes the statistical analysis results.

7.2 Safety

The analysis describes the statistical analysis results.