Non-Interventional Study Protocol
A0061007

Mycobutin® 150mg Capsules
Drug Use Investigation
- HRD Joint Survey -

Statistical Analysis Plan

Version: 4.0

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[redacted]

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AMENDMENTS FROM THE PREVIOUS VERSION

Version	Date	Author(s)	Summary of Changes/Comments
1.0	25-DEC-2013	PPD	Initial version
2.0	20-Aug-2014	PPD	Revisions reflecting the meeting with CMIC Co., Ltd. on 05-Aug-2014. 4.1. Safety Analysis Set -The target of the HRD survey was changed to patients for whom the case report form was collected. Patients excluded from the safety analysis set were changed to only patients who have received treatment of Mycobutin before marketing. 4.5. Subgroups - "Past history" of "Past history of ophthalmologic conditions/complications" was deleted, because the data of past history are collected in terms of absent or present only, and past history of ophthalmologic conditions/complications cannot be determined. -Virological failure for HIV is defined as an HIV-RNA copy number of <200 before start of treatment. The category of <200 has been included for the analysis by the HRD joint survey since the last year, so this category was added. - Minor erroneous descriptions were corrected. 5.2.2 Therapeutic Treatment -The statement "After each continuous treatment or" was added to the definitions of overall improvement and bacteriological response, considering the possibility of multiple treatments within a year. 7.2.1. Overview of Patients -The description for the "disposition of patients" was changed to start with patients for whom the case report form was collected. 7.2.2. Patient Background and Treatment History of Mycobutin -In the latest version of the EDC for the joint survey, sexual transmission was added to the categories for route of infection; however, sexual transmission is included in "others" in the data collected so far, so the category "others" was changed to "others (including sexual transmission)". -The lowest category for duration of disease was changed to "<1 year", because the data for duration of

Version	Date	Author(s)	Summary of Changes/Comments
			disease are collected in one-year unit. -The analysis of the content of past history was deleted, because it was found that the content of past history is not included in the collected data. - Minor erroneous descriptions were corrected. 7.2.3.1 Adverse Drug Reactions -Tabulation of the number and percentage of patients with serious adverse drug reactions counted for expected and unexpected reactions separately was added. -The analysis of the measures taken for adverse drug reactions was deleted, because those data are collected as comments in the common case report form, and the determination of appropriate category from comment data is infeasible. 7.2.3.2. Adverse Events -To provide basic results, tabulation of the number and percentage of patients with non-serious adverse events was added. 8. LISTINGS -Listings presented in the text of the periodic safety update reports and the application for reexamination were identified and indicated as “for intext”. 9. REFERENCES - “Standard Specifications of the Analysis for the HRD Joint Survey” was added.
3.0	21-DEC-2015	PPD	Status of investigation: Patient registration and investigation ongoing To investigate the drug interaction with SMX/TMP, analysis of safety and effectiveness in terms of the presence or absence of concomitant use of SMX/TMP was added to the following sections: - 4.5 Subgroups -7.2.2. Patient Background and Treatment History of Mycobutin -7.2.3.1. Adverse Drug Reactions -8. LISTINGS Others -In 8. LISTINGS, duplication of “Listing of patients with adverse events” was corrected.
4.0	24-JUN-2016	PPD	Status of investigation: Patient registration and investigation ongoing

Version	Date	Author(s)	Summary of Changes/Comments
			4.3 Bacteriological Response Analysis Set -The definition of the analysis set was changed, taking into account the cases where the causative bacteria is not identified, but Mycobutin is administered for therapeutic purpose by the treating physician based on the patient's past history of treatment, or cases where causative bacteria cannot be identified after all due to negative results of bacteria tests performed pre- and post-treatment. 4.5 Subgroups -Subgroup analysis factors of safety and effectiveness were changed as follows: • The factor “duration of disease” was deleted due to the unavailability of the duration data for the infections investigated in this study. • The categories of 150 mg, 300 mg, and 450 mg were added to the factor “mean daily dose” for clarification. • The categories of 150 mg, 300 mg, and 450 mg were added to the factor “maximum daily dose” for clarification. • The unit of HIV-RNA was corrected. 5.2.2 Therapeutic treatment -Originally, data for survival and growth were planned to be summarized by causative bacteria, but it was found to be infeasible to evaluate the survival and growth from the data of bacteria tests according to the prespecified definition. As a result, the definition of survival and growth by causative bacteria was deleted and data for bacteriological response by reason for use have been determined to be summarized instead. 7.2.2 Patient Background and Treatment History of Mycobutin -The factor “duration of disease” was deleted due to the unavailability of the duration data for the infections investigated in this study. -The unit of HIV-RNA was corrected. -The categories of 150 mg, 300 mg, and 450 mg were added to the factor “mean daily dose” for clarification. -The categories of 150 mg, 300 mg, and 450 mg were

Version	Date	Author(s)	Summary of Changes/Comments
			added to the factor “maximum daily dose” for clarification. 7.2.4.3 Bacteriological response -The analysis set was changed to the bacteriological response analysis set. -Calculation of the eradication rate by reason for use was added. 7.2.4.4. Eradication Rates by Causative Bacteria Based on Bacteriological Tests for Nontuberculous Mycobacteriosis (NTM Infections) (including MAC Infection) and Tuberculosis -This section was deleted, reflecting the following change. That is, in the original plan, bacterial data for survival and growth were to be summarized by causative bacteria, but it was found to be infeasible to evaluate the survival and growth from the data of bacteria tests according to the prespecified definition. As a result, data of bacteriological response by reason for use have been determined to be summarized instead. 7.2.4.5 Subgroup Analysis -The analysis of eradication rate by causative bacteria was deleted. 8. LISTENS -Listing of bacteriological tests was added. Other minor clarifications were made.

1. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the drug use investigation of Mycobutin® 150mg Capsules (hereinafter referred to as Mycobutin) conducted as part of the Joint Post-Marketing Survey of HIV-Related Drugs (HRD Joint Survey) using a common case report form. In this plan, sentences cited from the Protocol are shown in *Italics*.

1.1. Study Design

As part of the HRD Joint Survey, this study includes HIV patients for whom Mycobutin is prescribed, including those captured in retrospective surveys. As far as possible, this part of the HRD joint Survey seeks to include all patients who receive Mycobutin at participating medical institutions. The indications and dosage and administration for Mycobutin, the survey periods, and the major investigation items are presented below.

- *Indications*

Susceptible strains: Mycobacteria susceptible to Mycobutin
Indications: Tuberculosis, nontuberculous mycobacteriosis including Mycobacterium avium complex (MAC) infection, and prevention of symptoms of disseminated MAC infection in HIV patients.

- Dosage and Administration

Tuberculosis:
For adults, an oral dose of rifabutin 150 mg to 300 mg is administered once daily.
For adults with multi-drug resistant tuberculosis, an oral dose of rifabutin 300 mg to 450 mg is administered once daily.

Treatment of nontuberculous mycobacteriosis including MAC infection:
For adults, an oral dose of rifabutin 300 mg is administered once daily.

Prevention of symptoms of disseminated MAC infection in HIV patients:
For adults, an oral dose of rifabutin 300 mg is administered once daily.

- Survey Periods

Tuberculosis and nontuberculous mycobacteriosis including MAC infection:
The survey will start on October 7, 2008, and the registration of patients will end at the end of the fiscal year after the 6th year.
Patient registration: October 7, 2008 - March 31, 2015

Prevention of the symptoms of disseminated MAC infection in HIV patients:
The survey will start on October 7, 2008, and the registration of patients will end at the end of the fiscal year after the 8th year.
Patient registration: October 7, 2008 - March 31, 2017

1.2. Study Objectives

The objectives of the study are to grasp the following aspects and to assess whether a specified drug use-results survey or a post-marketing clinical study is needed:

- *Unexpected adverse drug reactions*
- *Incidence of adverse drug reactions under the actual use, and*
- *Factors considered to affect the safety and/or effectiveness, etc.*

In this survey, the incidence of hematologic disorders (including anemia, decreased platelets, decreased white blood cells, and pancytopenia) and uveitis will be assessed as the major investigation items.

2. INTERIM AND FINAL ANALYSES

In this study, interim analyses for periodic safety update report will be performed periodically. At the time of interim analyses, only the analyses of items necessary for periodic safety update report among the statistical analyses specified in this plan will be performed. In addition, the final analysis for the application for reexamination will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

3. HYPOTHESIS AND DECISION RULES

3.1. Statistical Hypothesis

Because this study is not a confirmatory investigation, the tests are considered exploratory and a p-value resulting from a test will be considered as a descriptive statistic with no significance level specified, although a post-hoc threshold value may be introduced for a screening purpose.

3.2. Statistical Decision Rules

Not applicable.

4. ANALYSIS SETS

4.1. Safety Analysis Set

The safety analysis set consists of the patients who meet the inclusion criteria for this study and are confirmed to have received at least one dose of Mycobutin. However patients who have received treatment with Mycobutin before marketing (those who discontinued or completed their treatment with Mycobutin before the marketing of Mycobutin® 150mg Capsules) will be excluded from the safety analysis set.

4.2. (Preventive) Effectiveness Analysis Set

Among the patients in the safety analysis set, those who received Mycobutin for the prevention of MAC infection and underwent an effectiveness evaluation (determination of whether an onset of MAC infection is observed or not) comprise the (preventive) effectiveness analysis set.

4.3. (Therapeutic) Effectiveness Analysis Set

Among the patients in the safety analysis set, those who underwent at least one post-treatment effectiveness evaluation (determination of bacteriological response or clinical efficacy at the end of the observation period) comprise the (therapeutic) effectiveness analysis set.

4.4. Bacteriological Response Analysis Set

Among the patients in the (therapeutic) effectiveness analysis set, those who underwent at least one bacteriological response determination comprise the bacteriological response analysis set. However, the patients with a bacteriological response determination for whom the result is considered inappropriate based on the results of the bacteriological tests will be excluded from the bacteriological response analysis set.

4.5. Subgroups

Subgroup analyses of safety will be performed for the following patient background factors:

- Sex [male, female]
- Pregnancy (in females) [absent, present]
- Age group 1 [<15 years, ≥15 years to <65 years, ≥65 years]
- Age group 2 [<20 years, ≥20 years to <30 years, ≥30 years to <40 years, ≥40 years to <50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years to <80 years, ≥80 years]
- Primary disease [HIV infection, others]
- Race [Japanese, others]
- Hepatic dysfunction [absent, present]
- Hepatitis [absent, present]
- Renal dysfunction [absent, present]
- Past history [absent, present]
- Complications [absent, present]
- Ophthalmologic complications [absent, present]
- Baseline HIV-RNA copy number (copies/mL) [<200, ≥200 to <400, ≥400 to <10,000, ≥10,000 to <100,000, ≥100,000]
- Baseline CD4 count (cells/mm^3) [≥0 to <100, ≥100 to <200, ≥200 to <350, ≥350 to <500, ≥500]
- Centers for Disease Control and Prevention (CDC) classification [A, B, C, P-0, P-1, P-2]

Subgroup analyses of safety will also be performed for the following other factors:

- Maximum daily dose [<150 mg, 150 mg, 300 mg, 450 mg, >450 mg]
- Mean daily dose [<150 mg, 150 mg, >150 mg to <300 mg, 300 mg, >300 mg to <450 mg, 450 mg, >450 mg]
- Duration of treatment [≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤8 weeks, >8 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, >24 weeks to ≤36 weeks, >36 weeks to ≤1 year, >1 year to ≤3 years, >3 years to ≤6 years, >6 years to ≤8 years, >8 years]
- Concomitant medications (anti-HIV drugs) [absent, present]
- Concomitant medications (anti-MAC drugs) [absent, present]

- Concomitant use of the combination of sulfamethoxazole and trimethoprim (SMX/TMP) [absent, present]

Subgroup analyses of effectiveness will be performed for the following patient background factors:

- Sex [male, female]
- Pregnancy (in females) [absent, present]
- Age group 1 [<15 years, ≥15 years to <65 years, ≥65 years]
- Age group 2 [<20 years, ≥20 years to <30 years, ≥30 years to <40 years, ≥40 years to <50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years to <80 years, ≥80 years]
- Primary disease [HIV infection, others]
- Race [Japanese, others]
- Hepatic dysfunction [absent, present]
- Renal dysfunction [absent, present]
- Past history [absent, present]
- Complications [absent, present]
- Baseline HIV-RNA copy number (copies/mL) [<200, ≥200 to <400, ≥400 to <10,000, ≥10,000 to <100,000, ≥100,000]
- Baseline CD4 count (cells/mm^3) [≥0 to <100, ≥100 to <200, ≥200 to <350, ≥350 to <500, ≥500]
- Centers for Disease Control and Prevention (CDC) classification [A, B, C, P-0, P-1, P-2]

Subgroup analyses of effectiveness will also be performed for the following other factors:

- Maximum daily dose [<150 mg, 150 mg, 300 mg, 450 mg, >450 mg]
- Mean daily dose [<150 mg, 150 mg, >150 mg to <300 mg, 300 mg, >300 mg to <450 mg, 450 mg, >450 mg]
- Duration of one prophylactic or therapeutic treatment [≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤8 weeks, >8 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, >24 weeks to ≤36 weeks, >36 weeks to ≤1 year, >1 year]
- Concomitant medications (anti-MAC drugs) [absent, present]
- Concomitant use of SMX/TMP [absent, present]

5. ENDPOINTS AND COVARIATES

5.1. Safety Endpoints

- Adverse drug reactions: adverse events (AEs) determined to be related to Mycobutin by the physician or Sponsor

- Adverse events: All-causality adverse events

- Major investigation items: The events of major investigation items will be identified according to a separate list that provides the event names corresponding to each specified AE.

5.2. Effectiveness Endpoints

5.2.1. Prophylactic Treatment

- Occurrence of MAC symptoms in patients treated with Mycobutin for the prophylaxis of MAC infection will be determined as

  Absent, or
  Present.

5.2.2. Therapeutic Treatment

- Clinical efficacy (overall improvement): After each continuous treatment or at the final fiscal year of registration (the end of observation), clinical efficacy (overall improvement) will be determined using the following categories:

  1. Markedly improved
  2. Improved
  3. Slightly improved
  4. Unchanged
  5. Aggravated
  9. Indeterminable

- Bacteriological response: After each continuous treatment or at the final fiscal year of registration (the end of observation), bacteriological response will be determined according to the following categories:

  1. Eradicated
  2. Decreased
  3. Unchanged
  4. Increased
  9. Unknown

5.3. Other Endpoints

Not applicable.

5.4. Covariates

In the analysis of safety, the presence or absence of contraindicated for coadministration (e.g., some azoles and macrolides) noted in PRECAUTIONS of the package insert as the drugs that require precautions for coadministration will be used as a covariate.

6. HANDLING OF MISSING DATA

Any missing value for a laboratory parameter or effectiveness endpoint will be handled as a missing value and no imputation will be carried out.

If the seriousness, measures taken, or outcome for an AE is missing, they are counted as "unknown".

If a date such as the onset date of an AE is missing, handling of those data will be defined in separate statistical analysis specifications prepared for the drug use investigation of Mycobutin® 150mg capsules.

7. STATISTICAL METHODS AND STATISTICAL ANALYSIS

7.1. Statistical Methods

7.1.1. Analysis of Continuous Data

Summary statistics (number of patients, mean, standard deviation, median, minimum and maximum) will be calculated.

7.1.2. Analysis of Categorical Data

Categorical variables will be calculated by frequency and percentage.

7.1.3. Analysis of Binary Data

Binary variables will be calculated by frequency and percentage. Confidence intervals (CIs) for the percentages may also be calculated; in this case, the 95% CIs (two-sided) will be calculated using an exact method. Statistical tests may also be performed when appropriate; an association with a nominal variable will be tested by Fisher's exact test, and an association with an ordinal variable by the exact Cochran-Armitage test.

7.2. Statistical Analysis

7.2.1. Overview of Patients

- **Number of sites by establisher and number of patients**

In patients for whom the case report form was collected, the number and percentage of sites by establisher shown below and the number and percentage of patients will be calculated:

- University hospitals
- National hospitals established by the Ministry of Health, Labour and Welfare
- Prefectural and municipal hospitals
- Public organizations
- Hospitals established by corporations and individuals other than the above four
- General practitioners/clinics

In addition, the mean, minimum, and maximum of the number of patients per site will be calculated.

- **Disposition of patients**

In the patients for whom the case report form was collected, the number of those for whom the case report form was collected and those included in the safety analysis set will be tabulated. The patients excluded from the safety analysis set will also be counted in total and by reason for exclusion. In addition, Among the safety analysis set, the patients who are eligible for the effectiveness analysis will be counted for each of preventive and therapeutic treatments. The patients excluded from the effectiveness analysis set will also be counted in total and by reason for exclusion for each of preventive and therapeutic treatments. Total number of treated patients will be counted in a treatment-based manner for each of preventive and therapeutic treatments, because in this investigation, cases of multiple treatments in a single patient are expected to occur.

- **Listing of excluded patients**

Patients excluded from the safety analysis set and those excluded from the effectiveness analysis set will be tabulated with their reason for exclusion.

7.2.2. Patient Background and Treatment History of Mycobutin

- **Patient background**

For the safety analysis set, (preventive) effectiveness analysis set, and (therapeutic) effectiveness analysis set, the following patient background factors will be tabulated in accordance with Section 7.1:

- Sex [male, female]
- Pregnancy (only in females) [absent, present]
- Age (continuous)
- Age group 1 [<15 years, ≥15 years to <65 years, ≥65 years]
- Age group 2 [<20 years, ≥20 years to <30 years, ≥30 years to <40 years, ≥40 years to <50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years to <80 years, ≥80 years]
- Body weight (continuous)
- Body weight group [<40 kg, ≥40 kg to <50 kg, ≥50 kg to <60 kg, ≥60 kg to <70 kg, ≥70 kg, unknown]
- Inpatient/outpatient [inpatient, outpatient, mixture of inpatient and outpatient]
- Route of infection [blood preparation, vertical transmission, medical accident, others (including sexual transmission), unknown]
- Primary disease [HIV infection, others]
- Race [Japanese, others]
- Allergy [absent, present, unknown]

- Complications [absent, present]
- Hemophilia (A/B) as a complication [absent, present]
- Renal dysfunction as a complication: [absent, present]
- Hepatitis A as a complication [absent, present]
- Hepatitis B as a complication [absent, present]
- Hepatitis C as a complication [absent, present]
- Other hepatic dysfunction as a complication [absent, present]
- Syphilis as a complication [absent, present]
- Other condition as a complication: [absent, present]
- Ophthalmologic complications [absent, present]
- Concomitant use of SMX/TMP [absent, present]
- Concomitant therapy [absent, present]
- Use of medications other than Mycobutin [absent, present]
- Baseline HIV-RNA copy number (copies/mL) [<200, ≥200 to <400, ≥400 to <10,000, ≥10,000 to <100,000, ≥100,000, unknown]
- Baseline CD4 count (cells/mm^3) [≥0 to <100, ≥100 to <200, ≥200 to <350, ≥350 to <500, ≥500, unknown]
- Centers for Disease Control and Prevention (CDC) classification [A, B, C, P-0, P-1, P-2, unknown]

In the safety analysis set, the number and percentage of relevant patients will be tabulated for the following characteristic by system organ class (SOC) and preferred term (PT):

- Complications

In the safety analysis set and effectiveness analysis sets, the number and percentage of relevant patients will be tabulated for the following characteristics:

- Concomitant medications other than anti-HIV drugs
- Non-drug concomitant therapies

- **Status of treatment of Mycobutin**

In the safety analysis set, the exposure of patients to Mycobutin will be tabulated with respect to the following status of treatment:

- Duration of treatment * [≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤8 weeks, >8 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, >24 weeks to ≤36 weeks, >36 weeks to ≤1 year, >1 year to ≤3 years, >3 years to ≤6 years, >6 years to ≤8 years, >8 years]
- Duration of one prophylactic or therapeutic treatment [≤1 week, >1 week to ≤2 weeks, >2 weeks to ≤4 weeks, >4 weeks to ≤8 weeks, >8 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, >24 weeks to ≤36 weeks, >36 weeks to ≤1 year, >1 year]
- Maximum daily dose [<150 mg, 150 mg, 300 mg, 450 mg, >450 mg]

- Mean daily dose [<150 mg, 150 mg, >150 mg to <300 mg, 300 mg, >300 mg to <450 mg, 450 mg, >450 mg]
- Continued or discontinued
- Reason of the use of Mycobutin [MAC (therapeutic), MAC (prophylactic), tuberculosis, Nontuberculous Mycobacteriosis (NTM Infections) other than MAC]

The duration of treatment is defined as the period from the first to the last confirmed dose of Mycobutin during this survey, and does not include the period during which Mycobutin is suspended.

7.2.3. Safety Analysis

7.2.3.1. Adverse Drug Reactions

- **Adverse drug reactions**

The number and percentage of patients with adverse drug reactions will be tabulated by SOC and PT.

- **Serious adverse drug reactions**

The number and percentage of patients with serious adverse drug reactions will be tabulated by SOC and PT.

The number and percentage of patients with serious adverse drug reactions will also be tabulated separately for expected and unexpected reactions by SOC and PT.

- **Other details of adverse drug reactions**

The number and percentage of patients with adverse drug reactions will be tabulated for the following aspects by SOC and PT:

- Seriousness [serious, non-serious]
- Expected/unexpected [expected, unexpected]
- Time to onset [≤1 week, >1 week to ≤2 weeks, >2 weeks≤ to 4 weeks, >4 weeks to ≤8 weeks, >8 weeks to ≤12 weeks, >12 weeks to ≤24 weeks, >24 weeks to ≤36 weeks, >36 weeks to ≤1 year, >1 year]
- Outcome [death, sequela, not recovered, recovering, recovered, unknown]

If the same AE (the same PT) occurs more than once in the same patient, it will be handled as follows in the tabulation of the number of patients with events:

- Seriousness: If at least one event is reported as serious, they are counted as a serious event.
- Expected/unexpected: If at least one event is reported as unexpected, they are counted as an unexpected event.
- Time to onset: The time to the first onset will be used.

- Outcome: The outcome for the last event will be used. For multiple-time occurrence in the same fiscal year, the outcome for the severest event should preferably be used.

- **Major investigation items**

For the following major investigation items, the number and percentage of patient who experienced each event will be tabulated:

- Hematologic disorders (including anemia, decreased platelets, decreased white blood cells, and pancytopenia)
- Uveitis

The number and percentage of patients who experienced the events of major investigation items will also be tabulated for different outcomes by SOC and PT.

In addition, the number and percentage of patients who experienced the events of major investigation items will be tabulated with respect to whether they concomitantly used the drugs contraindicated for coadministration, those for which precautions should be taken for coadministration (e.g., some of azoles and macrolides), or SMX/TMP and with respect to the concomitant drug's dose by SOC and PT.

- **Adverse drug reactions by patients of included in/excluded from the safety analysis set**

In patients for whom the case report form was collected, the listing of adverse drug reactions in patients excluded from the safety analysis set will be prepared. The number of patients with adverse drug reactions will also be tabulated by SOC and PT.

7.2.3.2. Adverse Events

- **Adverse events**

The number and percentage of patients with Adverse events will be tabulated by SOC and PT.

- Serious adverse events (SAE)

The number and percentage of patients with SAEs will be tabulated by SOC and PT.

- Non-serious adverse events

The number and percentage of patients with non-serious adverse events will be tabulated by SOC and PT.

7.2.3.3. Other endpoints

None

7.2.3.4. Subgroup Analysis

The number and percentage of patients who experienced at least one adverse drug reaction will be tabulated for each factor specified in Section 4.5. The statistical tests stated in Section 7.1 will be performed to evaluate the association between the patient background factors and development of adverse drug reactions.

The number and percentage of patients who experienced adverse drug reactions will be tabulated by SOC and PT for each of the subgroups defined by the following factor:

- Reason for the use of Mycobutin [MAC (therapeutic), MAC (prophylactic), tuberculosis, NTM other than MAC]

Similar analysis will also be performed for serious adverse drug reactions and SAEs.

7.2.3.5. Exploratory Analysis

Additional analyses may be performed as necessary. The results of an exploratory analysis will be reported only when they result in an important interpretation.

7.2.4. Effectiveness Analysis

7.2.4.1. Success Rate of MAC Prevention in Patients Treated for the Prevention of MAC Infection

Using the (preventive) effectiveness analysis set, the numbers of patients with and without occurrence of MAC infection will be counted, and the number and percentage of patients without MAC infection will be calculated as the success rate of MAC prevention. If a single patient received multiple prophylactic treatments, the patient is counted as many times as the number of the prophylactic treatments the patient received. The percentage will be calculated using the total number of preventive treatments in the analysis set as the denominator, and the 95% CI of the percentage will also be calculated. If there is a case of multiple prophylactic treatments in a single patient, the number of patients who never experienced MAC infection will be counted, and the percentage and its 95% CI will be calculated as the patient-based success rate of MAC prevention.

7.2.4.2. Clinical efficacy (overall improvement)

Using the (therapeutic) effectiveness analysis set, the number of patients falling into each category of clinical efficacy (overall improvement) will be counted, and the clinical response rate (improvement rate) defined in the formula below and its 95% CI will be calculated. Because a single patient can be infected and treated multiple times during the survey period, patients are counted in a treatment-based manner, i.e., they are counted as many times as the number of the treatments they received. If there is a case of multiple therapeutic treatments in a single patient, the clinical response rate (improvement rate) at the final observation point defined in the formula below, and its 95% CI will also be calculated.

$$\text{Clinical response rate (improvement rate) based on total number of cases (\%)} = \frac{\text{(Total number of markedly improved cases + Total number of improved cases)}}{\text{(Total number of cases eligible for the therapeutic effectiveness analysis except indeterminable cases)}} \times 100$$

$$\text{Clinical response rate (improvement rate) at the final observation point (\%)} = \frac{\text{(Numbers of markedly improved patients at the final observation point + Numbers of improved patients at the final observation point)}}{\text{(Number of patients eligible for the therapeutic effectiveness analysis except indeterminable patients at the final time point)}} \times 100$$

7.2.4.3. Bacteriological response

Using the bacteriological response analysis set, the number of patients for each of the categories of bacteriological response will be counted, and the eradication rate defined in the formula below and its 95% CI will be calculated. Because a single patient can be infected and treated multiple times during the survey period, patients are counted in a treatment-based manner, i.e., they are counted as many times as the number of the treatments they received. If there is a case of multiple therapeutic treatments in a single patient, the eradication rate at the final observation point defined in the formula below, and its 95% CI will also be calculated. A similar analysis will be performed by reason of Mycobutin use.

$$\text{Eradication rate based on total number of cases (\%)} = \frac{\text{(Total number of eradicated cases)}}{\text{(Total number of cases evaluated for bacteriological response except unknown)}} \times 100$$

$$\text{Eradication rate at the final observation point (\%)} = \frac{\text{(Number of eradicated patients at the final observation point)}}{\text{(Number of patients evaluated for bacteriological response except unknown at the final observation point)}} \times 100$$

7.2.4.4. Subgroup Analysis

Subgroup analyses of the success rates of MAC prevention, clinical response rates (improvement rate), and eradication rates will be performed for each of the factors listed in Section 4.5.

7.2.4.5. Exploratory Analysis

Additional analyses may be performed as necessary. The results of an exploratory analysis will be reported only when they result in an important interpretation.

8. LISTINGS

The following listings will be prepared (Tabulated summaries that are intended to be included in the study report are indicated as “for intext”):

- Listing for registered patients and patients for whom the case report form was collected
- Listing for the decision of eligibility
- Listing of patients of all registered patients
- Listing of patients in the safety analysis set
- Listing of patients in the (preventive) effectiveness analysis set
- Listing of patients in the (therapeutic) effectiveness analysis set
- Listing of patients in the bacteriological response analysis set
- Listing of patients with adverse events
- Listing of patients with adverse drug reactions
- Listing of patients with adverse drug reactions among patients excluded from the safety analysis set
- Listing of patients with serious adverse drug reactions (for intext)
- Listing of patients with SAEs
- Listing of patients with adverse drug reactions among patients with hepatic dysfunction (for intext)
- Listing of patients with adverse drug reactions among patients with renal dysfunction (for intext)
- Listing of patients with adverse drug reactions among elderly patients
- Listing of patients with adverse drug reactions after long-term (>1 year) treatment
- Listing of patients with adverse drug reactions due to overdose
- Listing of events falling under major investigation items
- Listing of patients with adverse drug reactions falling under major investigation items (for intext)
- Listing of the status of administration of Mycobutin
- Listing of concomitant medications used
- Listing of bacteriological tests
- Listing of patients who concomitantly used SMX/TMP
- Listing of concomitant medications used for NTM infections (including MAC infection) and tuberculosis
- Listing of the changes in HIV-RNA copy number, CD4 count, and body weight for individual patients

In addition, the following tables that correspond to the Appendix Forms required for the periodic safety update report will be prepared:

- Appendix Form 3 (Listing of overview of patients)
- Appendix Form 2 (Listing of occurrence of adverse drug reaction and infections)
- Appendix Form 10 (Appendix Form 2-2) (Listing of occurrence of SAEs)

9. REFERENCES

Standard Specifications of the Analysis for the HRD Joint Survey, Ver. 6.0

10. APPENDIX

10.1. Appendix 1: Details of Data Collection

A1.1 Definition of visits

Visit	Endpoints	Definition [Allowance]
At start of treatment	HIV-RNA, CD4, CDC category, body weight, bacteriological tests	Data obtained before and on the day of the first dose (treatment start) of this survey. If there are multiple data, select data on the day closest to the first dose day of this survey.
At end of observation	Effectiveness endpoints	Data obtained on the day of the last dose of this survey or before and after the day. If there are multiple data, select data on the day closest to the last dose day of this survey.