Non-Interventional Study Protocol
A6831007

Anaemetro I.V. Infusion 500 mg
Drug Use Investigation

Statistical Analysis Plan

Version: 4.0

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Date: 18-Aug-2017

[redacted]

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version	Date	Author(s)	Summary of Changes/Comments
1.0	28-Nov-2014	PPD	Initial version
2.0	23-Aug-2016	PPD	Study status: Ongoing 5.1. Safety Analysis Set - Changes were made to coordinate with the revision of the "Guidance for Criteria for Inclusion in Analysis Sets and Handling of Data in Drug Use Investigations". 5.4. Subgroups - A statement was added to note that additional subgroups of diagnosis name may be added if some patients have multiple diagnoses. 6.2.1. Clinical Response - Because the clinical response is collected per clinical diagnosis, a clinical response for a certain diagnosis may differ in patients with multiple clinical diagnoses. A statement was added to note that in such case, the patient will be handled as a "inconsistent clinical response" case for overall clinical response evaluation is difficult. 6.2.3. Eradication/Persistence of Each Pathogenic Organism/Strain - This subsection was added to explain the plan of summarizing patients by response to each pathogenic organism/strain. 8.2.2. Patient Background and Treatment History of Anaemetro - A statement was added to note that additional categories of diagnosis may be added if a patient has multiple diagnoses. - A plan of summarizing the patient background by the experience of 4-times-a-day dosing and by the occurrence of a central nervous system disorder was added. - The experience of 4-times-a-day dosing was added to the set of factors by which Anaemetro exposure is to be summarized. 8.2.3.4. Subgroup Analysis - A plan of summarizing the number and proportion of patients with adverse reactions by subgroup using the classification of events by SOC and PT was added. 8.2.3.5. Exploratory Analysis - A plan of summarizing the number and proportion of

Version	Date	Author(s)	Summary of Changes/Comments
			patients with adverse reactions by the experience of 4-times-a-day dosing using the classification of events by SOC and PT was added. 8.2.4.1. Clinical Response - A plan of summarizing the patient by the experience of 4-times-a-day dosing and by the occurrence of a central nervous system disorder was added. - A statement was added to note that if the clinical efficacy analysis set includes patients with inconsistent clinical efficacies, they are handled as patients with "inconsistent clinical efficacies" and the response rate will be calculated by subtracting those patients from the denominator, as in the case where the set includes "indeterminate" patients. 8.2.4.2. Microbiological Response - A plan of summarizing the patients by the experience of 4-times-a-day dosing and by the occurrence of a central nervous system disorder was added. 8.2.4.3 Eradication/Persistence of Each Pathogenic Organism/Strain - This subsection was added to describe how to summarize the results for each pathogenic organism/strain. 8.2.4.5 Exploratory Analysis - Part of this subsection was deleted as a result of the new subsection, Section 8.2.4.3. 9. LISTINGS - Listing of results for clinical response was changed to include results for microbiological response. - Listing of results for clinical evaluations (body temperature, white blood cells, CRP) and listing for Anaemetro exposure were added. Other minor description changes were made for improvement.
3.0	23-Jun-2017	PPD	<u>Study status: Ongoing</u> 5.4. Subgroups - The number of daily doses was added to the set of factors for the subgroup analyses of safety. - The number of daily doses and the status of concomitant medication were added to the set of factors for the subgroup analyses of efficacy. - A statement concerning the patients in whom Anaemetro could be contraindicated per its package insert was added. - The factor of dose escalation/overdose was separated

Version	Date	Author(s)	Summary of Changes/Comments
			into dose escalation and overdose, and a definition of overdose was added. 6.2.3. Eradication/Persistence of Each Pathogenic Organism/Strain - A description for the eradication/persistence was added for the case of pathogenic organism/bacteria being *Eubacterium spp.* or *Entamoeba histolytica*. 8.1.3. Analysis of Binary Data - A plan of calculating risk difference and its 95% confidence interval was added. 8.2.1. Overview of Patients - Added specific categories of discontinuation time for listing of discontinuations and dropouts. - Patients who are to be excluded from the microbiological response analysis set were excluded from the planned listing of excluded patients. 8.2.2. Patient Background and Treatment History of Anaemetro - The plan of summarizing data by the experience of 4-times-a-day dosing was changed to by maximum number of daily doses. - Changes were made for exposure factors (duration of treatment, number of daily doses, and dose per single dose). - Dose escalation and overdose were added to the set of exposure factors. - Considering the existence of patients who were off treatment for a long period, the treatment duration was redefined as an actual treatment duration excluding the period during which Anaemetro is suspended. 8.2.3.1. Adverse Reactions The categories for time to first development were changed. 8.2.3.4. Subgroup Analysis - Clarified that the subgroup analysis will be performed in terms of risk ratio and risk difference. Specified that calculation of the number and proportion of patients with adverse reactions by subgroup based on SOCs and PTs will only be performed for subgroups with risk ratio ≥2 or ≤0.5. - Considering the limited number of patients with AEs, the plan of calculating the risk ratio and risk difference for

Version	Date	Author(s)	Summary of Changes/Comments
			serious adverse reactions and serious adverse events was deleted. - An analysis plan for potentially contraindicated patients was added. - The description for the analysis of the incidence of adverse reactions by the experience of 4-times-a-day dosing for each SOC and PT was moved to this subsection of subgroup analyses as an analysis by maximum number of daily doses. - A subgroup analysis for the incidence of serious adverse reactions by maximum number of daily doses was added to the set of subgroup analyses. 8.2.3.5. Exploratory Analysis - Due to the limited number of patients with AEs, the plan for logistic regression was deleted. 8.2.4.1. Clinical Response - A plan of analyzing the response rate for each pathogenic organism/strain by diagnosis was added. - The plan of summarizing data by presence of 4-times-a-day dosing was changed to by maximum number of daily doses. 8.2.4.2. Microbiological Response - The plan of summarizing data by presence of 4-times-a-day dosing was changed to by maximum number of daily doses. 8.2.4.3. Eradication/Persistence of Each Pathogenic Organism/Strain - Considering the fact that the same organism was detected from the same patient multiple times from different test materials as a pathogenic organism, it was determined that all the collected bacterial information should be used and the analysis of pathogenic organism/strain was changed from in terms of the number of patients to in terms of the number of microbes. - The summarization by presence of 4-times-a-day dosing was changed to by maximum number of daily doses. - The analysis plan by diagnosis name and by presence of central nervous system disorder was deleted. 8.2.4.4. Subgroup Analysis - Clarified that each subgroup analysis will be performed in terms of risk ratio and risk difference. 8.2.4.5. Exploratory Analysis

Version	Date	Author(s)	Summary of Changes/Comments
			- Because of the limited number of patients with MIC, the plan of MIC analysis by pathogenic strain was deleted, and MIC results were changed to be presented as a listing. - A plan of summarizing reasons for the determination of clinical response was added. 9. LISTINGS - A plan of listing patients in whom Anaemetro might have been contraindicated per its package insert was added. - A plan of listing the events corresponding to safety specification items was deleted, since it can be substituted by the corresponding listing by SOC and PT. 10.2. Appendix 2: Example of Categorizations for Risk Ratio Analysis - The description was modified to coordinate with the description in Section 5.4 Subgroups. Other minor description changes were made for improvement.
3.0	18-Aug-2017	PPD	<u>Study status: Ongoing (DB release in preparation)</u> 6.1. Safety Endpoints - As a result of a review by Sponsor, the definition of an adverse reaction was changed to adverse events determined to be related to Anaemetro by the physician. - As a result of a review by Pfizer, seriousness was changed to be that assessed by the physician; to incorporate this change, definitions of serious adverse reaction and serious adverse event were added. - The description of the safety specification items was coordinated with the items in the latest version of RMP (January 2017). It was noted that the analysis will be performed in accordance with the latest version of RMP. 6.2.2. Microbiological Response - Since *Eubacterium spp.* is an anaerobic bacterium, and not an amebic protozoon, the description for this strain was deleted from the part added in the previous version. 8.2.3 Safety Analysis - It was noted that safety analysis will be primarily based on the data collected during the observation period (i.e., from the start of Anaemetro administration to the end of administration). 8.2.3.1. Adverse Reactions - The description of the safety specification items was

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Version	Date	Author(s)	Summary of Changes/Comments
			coordinated with the items in the latest version of RMP (January 2017). - A plan of summarizing the incidence of adverse reactions by whether each reaction developed within or outside the observation period, with reaction names classified by SOCs and PTs, was added. 8.2.3.4. Subgroup Analysis - It was noted that if adverse reactions developed in less than a total of 10 patients, risk ratio and risk difference will not be calculated. 8.2.4.3. Eradication/Persistence of Each Pathogenic Organism/Strain - It was noted that results will also be summarized by diagnosis. 10.2. Appendix 2: Example of Categorizations for Risk Ratio Analysis - In the table, the item “Dose escalation” was added.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the drug use investigation of Anaemetro I.V. Infusion 500 mg (hereinafter referred to as Anaemetro). In this plan, sentences cited from the Protocol are shown in *Italics*.

2.1. Study Design

This investigation is a prospective study with a central registration system in patients who have not used metronidazole (injection) in the past and have been administered this drug for treatment of anaerobic infection, infectious enterocolitis, or amebic dysentery. The observation period shall start on the day the treatment with this drug begins and end on the day the treatment is completed; however, it shall be cut off at Week 8 after the initiation of treatment (Day 56 counting from Day 1 as the day the treatment begins) if the treatment is prolonged. A sample size of 100 patients was selected based on the following consideration.

<Rationale for the Sample Size Determination>

The target sample size was set to be 100 patients, which should enable to detect, at 95% probability, an adverse reaction of which the true incidence rate is 3% in reference to adverse reaction of the least incidence in a clinical study of this drug (Study A6831005). This sample size should enable to confirm whether the types and incidence of adverse reaction related to this drug used for diseases other than intra-abdominal infection, and pelvic

inflammatory disease and other related diseases that were targeted in the clinical study would be similar to those occurred in Study A6831005.

2.2. Study Objectives

This Study will be conducted to investigate the safety and effectiveness of Anaemetro I.V. Infusion 500 mg in daily clinical practice. Additionally, it is intended to assess the following:

- *Adverse reactions unexpected from precautions, and*
- *Occurrence of adverse reactions under actual clinical settings*

3. INTERIM AND FINAL ANALYSIS

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.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Because this Study is not a confirmatory investigation, the tests are considered as exploratory tests.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is the full analysis set that is as close as possible to all Anaemetro-treated patients. Specifically, the safety analysis set includes all registered or reported patients excluding any patients who meet any of the following criteria:

a. The case report form could not be collected at all (description in the report, “case report form not collected”)

b. There was a violation or deficiency in the contract (description in the report, “contract violation/deficiency”)

c. There was a violation of registration (description in the report, “registration violation”)

d. Administration of the drug under investigation is not reported at all (description in the report, “no administration information”)

e. Information on adverse events is not reported at all - no visits after the first prescription day (description in the report “no adverse event information - no visits”)

f. Information on adverse events is not reported at all - there is a visit after the first prescription day but no description of safety information (description in the report, “no adverse event information - no description”)

Details for each criterion should follow the “Guidance for Criteria for Inclusion in Analysis Sets and Handling of Data in Drug Use Investigations”.

5.2. Effectiveness Analysis Sets

There are two effectiveness analysis sets, the clinical response analysis set and the microbiological response analysis set.

5.2.1. Clinical Response Analysis Set

The clinical response analysis set consists of the patients in the safety analysis set excluding any patients who meet any of the following criteria:

g. No information of clinical response (description in the report, “no clinical response information”)

h. Non-target disease of the study (description in the report, “Non-target disease of the study”)
That is, “others” is checked with no other information in the CRF item that asks the disease (diagnosis) that required the use of Anaemetro.

5.2.2. Microbiological Response Analysis Set

The microbiological response analysis set is defined as the patients in the safety analysis set excluding any patients who meet any of the following criteria:

i. No information of microbiological response (description in the report, “no microbiological response information”)

j. Non-target disease of the study (description in the report, “Non-target disease of the study”)
That is, “others” is checked with no other information in the CRF item that asks the disease (diagnosis) that required the use of Anaemetro.

5.3. Other Analysis Sets

Not applicable.

5.4. Subgroups

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

- Presence or absence of hepatic dysfunction
- Presence or absence of renal dysfunction
- Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)
- Diagnosis* (anaerobic infection, infectious enterocolitis [incl. pseudomembranous colitis], amebic dysentery)

* The same patient may have multiple diagnoses. In such case, additional subgroups may be added (e.g., anaerobic infection plus infectious enterocolitis).

Subgroup analyses of safety will also be performed according to the following factors:

- Pregnant and parturient women (pregnancy confirmed)
- Prior treatment (medication for infection) [absent, present]
- Concomitant medications (medication for infection) [absent, present]
- Maximum number of daily doses (1, 2, 3, 4, or >4 times)
- Dose escalation [absent, present]
- Overdose ** [absent, present]

** Patients who have had a daily dose of >500 mg or had >4 doses a day are defined as having experienced overdose.

Patients in whom Anaemetro might have been contraindicated per the package insert (hereinafter referred to as contraindicated patients) will be sampled from the registry according to separately-specified criteria and be analyzed for the safety of Anaemetro as a subgroup analysis.

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

- Presence or absence of hepatic dysfunction
- Presence or absence of renal dysfunction
- Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)
- Diagnosis* (anaerobic infection, infectious enterocolitis [incl. pseudomembranous colitis], amebic dysentery)

* The same patient may have multiple diagnoses. In such case, additional categories may be added (e.g., anaerobic infection plus infectious enterocolitis).

Subgroup analyses of effectiveness will also be performed according to the following factors:

- Prior treatment (medication for infection) [absent, present]
- Concomitant medications (medication for infection) [absent, present]
- Maximum number of daily doses (1, 2, 3, 4, or >4 times)

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

Safety endpoints include:

- Adverse reactions: Adverse events determined to be related to Anaemetro by the physician
- Adverse events: All-causality adverse events
- Serious adverse reactions or events: Adverse reactions or adverse events in which the seriousness was determined to be serious by the physician
- Safety specification items: The following events will be handled as safety specification items:
  - Central nervous system (CNS) disorder: Events that were considered as a central nervous system disorder by the physician and had a check mark on "yes/unknown" in the corresponding AE item of the CRF
  - Peripheral nerve disorders
  - Aseptic meningitis
  - Toxic epidermal necrolysis, oculomucocutaneous syndrome
  - Acute pancreatitis
  - Leukopenia, neutropenia
  - Carcinogenicity

All safety specification items except central nervous system disorder and all events included in safety specifications will be defined according to MedDRA SMQ, System Organ Classes (SOCs), or Preferred Terms (PTs), or classified according to a classification table prepared using observed AEs based on the risk management plan (RMP). Safety specification items are in accordance with the RMP of Anaemetro submitted in January 2017.

6.2. Effectiveness Endpoints

6.2.1. Clinical Response

At the end of observation period or at the time of discontinuation, clinical response will be assessed by the physician from a comprehensive perspective according to the criteria below. If this drug is administered continuously for more than 8 weeks, the clinical response should be evaluated comprehensively at Week 8. The definitions are as follows.

- Reason for the use: anaerobic infection:
  - Effective: Clinical symptoms accompanying the infection observed at the initiation of treatment with this drug has improved at the time of assessment, and treatment

with other antibacterial drugs after the time of assessment is determined not necessary.
- Not effective: "Effective" criteria are not met.
- Indeterminate: Clinical response is difficult to evaluate.

- Reason for the use: infectious enterocolitis (incl. pseudomembranous colitis):

  - Effective: Clinical symptoms accompanying the infection observed at the initiation of treatment with this drug has improved at the time of assessment, and treatment with other antibacterial drugs after the time of assessment is determined not necessary.
  - Not effective: "Effective" criteria are not met.
  - Indeterminate: Clinical response is difficult to evaluate.

- Reason for the use: amebic dysentery:

  - Effective: Clinical symptoms accompanying the infection observed at the initiation of treatment with this drug has improved at the time of assessment, and treatment with other antibacterial drugs other than antiamebic agents (paromomycin, etc.) after the time of assessment is determined not necessary.
  - Not effective: "Effective" criteria are not met.
  - Indeterminate: Clinical response is difficult to evaluate.

In this Study, clinical response may be evaluated for each diagnosis. If the same patient have multiple diagnoses under investigation with different clinical response, the patient will be handled as a “inconsistent clinical response” case for overall clinical response evaluation is difficult.

6.2.2. Microbiological Response

At the end of observation period or at the time of discontinuation, microbiological response will be assessed by the physician according to the criteria below. If this drug is administered continuously for more than 8 weeks, the clinical response should be evaluated comprehensively at Week 8.

- Eradication: Pathogen is not detected in the specimen appropriately collected following administration of this drug.
- Presumed eradication: Pathogen is presumed eradicated if the treatment improves or resolves the clinical symptoms, and a specimen suitable for the test is no longer available in the original infection focus.
- Partial eradication: Pathogen is partially detected in the specimen appropriately collected following administration of this drug.
- Persistence: No improvement of clinical symptoms is confirmed, and the pathogen is detected in the infection focus.

- Indeterminate: A microbiological test was conducted, but no pathogen could be isolated or estimated. Or a microbiological test was not conducted due to various reasons.

6.2.3. Eradication/Persistence of Each Pathogenic Organism/Strain

Eradication/persistence of each pathogenic organism/strain may be determined based on the pathogenic organism/strain detected before Anaemetro treatment in microbiological testing. The survival of pathogenic organism/strain is defined as follows.

- Eradication: The pathogenic organism/strain detected at the commencement of treatment was not detected after treatment (the bacterial load is "-") or no specimens could be collected. When the pathogenic organism is *Entamoeba histolytica*, it is considered eradicated if amebic protozoa test had been positive before treatment and changed to negative after treatment.
- Persistence: The pathogenic organism/strain detected at the commencement of treatment was detected from a specimen after treatment. When the pathogenic organism is *Entamoeba histolytica*, it is considered persistent if amebic protozoa test had been positive before treatment and remained positive after treatment.
- Indeterminate: Microbiological test after treatment was not performed at all for various reasons.

6.3. Other Endpoints

Not applicable.

6.4. Covariates

As for the safety and effectiveness of Anaemetro, there are no covariates identified from clinical study data thus far obtained or potential covariates.

7. HANDLING OF MISSING DATA

When the seriousness/outcome of adverse events and action taken with Anaemetro for the adverse events are missing, these data are handled as "unknown" for counting.

8. STATISTICAL METHODS AND STATISTICAL ANALYSIS

8.1. Statistical Methods

8.1.1. Analysis of Continuous Data

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

8.1.2. Analysis of Categorical Data

The number of patients and proportion of each category will be calculated.

8.1.3. Analysis of Binary Data

The number of patients and proportion will be calculated. If the confidence interval of proportion is calculated, two-sided 95% confidence interval (exact method) will be calculated.

If the proportion is compared between subgroups, risk ratio and its 95% confidence interval, and risk difference and its 95% confidence interval will be calculated. In addition, risk ratio and its 95% confidence interval will be graphically presented (see Appendix 1).

8.2. Statistical Analysis

8.2.1. Overview of Patients

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

In completed patients, the number and proportion of sites by establisher shown below and the number and proportion 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 other than the above four established by corporations and individuals
- General practitioners/clinics

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

- **Dispositions of patients**

In patients who registered to the Study, the number of registered patients, the number of completed patients, the number of patients included in the analysis of safety, the number of patients included in the analysis of clinical response, and the number of patients included in the analysis of microbiological response will be tabulated. In addition, the number of no-CRF-collected patients, the number of patients excluded from the analysis of safety, clinical response, and microbiological response and the number of patients by reason for exclusion will be tabulated.

- **Listing of discontinuations and dropouts**

In the safety analysis set, clinical response analysis set, and microbiological response analysis set, the number and proportion of discontinued patients per discontinuation time [<3

days, ≥4 to ≤7 days, ≥8 to ≤14 days, ≥15 to ≤21 days, ≥22 days] will be tabulated. In addition, the number and proportion of patients by reason for discontinuation will be tabulated.

- **Listing of excluded patients**

The listing of reasons for exclusion in patients excluded from the analysis of safety and clinical response will be prepared.

8.2.2. Patient Background and Treatment History of Anaemetro

- **Patient background**

In the safety analysis set, clinical response analysis set, and microbiological response analysis set, the following patient background factors will be tabulated in accordance with Section 8.1.

- Sex [male, female]
- Age (continuous)
- Age group [<15 years, ≥15 to <65 years, ≥65 years]
- Age group [≥10 to <20 years, ≥20 to <40 years, ≥40 to <65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 years]
- Inpatient/outpatient status at the first prescription [inpatient, outpatient]
- Body weight (continuous)
- Body Mass Index (continuous)
- Diagnostic name* (anaerobic infection, infectious enterocolitis, amebic dysentery, others)
- Detailed diagnosis name of anaerobic infection
- Severity [mild, moderate, severe, unknown]
- Hepatic dysfunction [absent, present]
- Renal dysfunction [absent, present]
- Past medical history other than hepatic/renal dysfunction [absent, present]
- Concurrent illness other than hepatic/renal dysfunction [absent, present]
- Prior treatment (medication for infection) [absent, present]
- Concomitant medication (medication for infection) [absent, present]

* The same patient may have multiple diagnoses. In such case, additional categories may be added (e.g., anaerobic infection plus infectious enterocolitis).

In addition, patient background will also be tabulated by maximum number of daily doses and by the presence or absence of a central nervous system disorder.

In the safety analysis set, the number and proportion of the following patients will be tabulated by SOCs and PTs of MedDRA.

- Past medical history other than hepatic/renal dysfunction

- Concurrent illness other than hepatic/renal dysfunction.

In the safety analysis set and clinical response analysis set, the number and proportion of the following patients will be tabulated.

- Presence or absence of pregnancy
- Concomitant medication (medication for infection)
- Prior treatment (medication for infection)

- **Status of treatment of Anaemetro**

In the safety analysis set, the following status of treatment of Anaemetro will be tabulated:

- Duration of treatment (continuous)
- Duration of treatment (1) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, ≥22 days]
- Duration of treatment (2) [≤3 day, ≥4 to ≤7 days, ≥8 to ≤14 days, ≥15 to ≤21 days, ≥22 days]
- Duration of treatment (3) [≤3 days, ≥4 to ≤10 days, >10 days]
- Maximum dose per single dose [<500 mg, 500 mg, >500 mg]
- Mean dose per single dose [<500 mg, 500 mg, >500 mg]
- Mean dose per single dose (continuous)
- Maximum number of daily doses [1, 2, 3, 4, >4 times]
- Mean number of daily doses [<1 time, 1 time, >1 to <2 times, 2 times, >2 to <3 times, 3 times, >3 to <4 times, 4 times, >4 times]
- Mean number of daily doses (continuous)
- Dose escalation [absent, present]
- Overdose [absent, present].

The duration of treatment is from the initial day of administration in this Study to the last confirmed day of administration, and is the actual dosing days that excludes the period during which Anaemetro is suspended.

8.2.3. Safety Analysis

Safety analysis will be primarily based on the data collected during the observation period that is from the start of Anaemetro administration to the end of Anaemetro administration.

8.2.3.1. Adverse Reactions

- **Adverse reactions**

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

- **Serious adverse reactions**

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

- **Details of adverse reactions**

The number and proportion of patients with adverse reactions will be tabulated by SOC and PT for each of the following items.

- Seriousness [serious, non-serious]
- Expected/unexpected [Expected, unexpected]
- Intervention [discontinuation, temporarily discontinued or dose reduced]
- Outcome [not recovered, recovered with sequela, recovering, resolved/recovered, unknown]

In addition, the number and proportion of patients with adverse reaction that meets all of the following items will be tabulated by SOC and PT:

- The seriousness was considered “non-serious”;
- The intervention was “discontinuation”, “temporarily discontinued”, or “dose reduced”
- The outcome was “not recovered” or “recovered with sequela”.

If the same adverse reaction (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 both serious and non-serious events are reported, “serious” will be adopted.
- Expected/unexpected: If both expected and unexpected events are reported, “expected” will be adopted.
- Number of days to onset: The number of days to the first event will be adopted
- Intervention: If multiple types of action are reported, one of discontinuation, temporarily discontinued or dose reduced, or other (none, dose increased), in descending order of precedence, will be adopted.
- Outcome: The outcome of the last occurring event will be used.

- **Safety specification items**

The number and proportion of patients with the following safety specification items will be tabulated.

- Central nervous system disorder
- Peripheral nerve disorders
- Aseptic meningitis
- Toxic epidermal necrolysis, oculomucocutaneous syndrome
- Acute pancreatitis

- Leukopenia, neutropenia
- Carcinogenicity

In addition, the number and proportion of patients who experienced each safety specification item will be tabulated by intervention and outcome, by SOC and PT.

In order to explore factors common to those who experienced the safety specification items, listings of patient background and concomitant medications for patients who experienced the most frequent safety specification items will be tabulated.

- **Time to adverse reaction**

The number of patients who experienced an adverse reaction will be tabulated by time to first development (≤3 days, ≥4 to ≤10 days, >10 days), by SOC and PT.

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

In completed patients, the listing of adverse reactions in patients excluded from the safety analysis set will be prepared. In addition, the number of patients with events will be tabulated by SOC and PT.

- **Adverse reactions that developed within and outside the observation period**

Using the safety analysis set, the number of patients with adverse reactions will be tabulated by whether each reaction developed within or outside the observation period, by SOC and PT.

8.2.3.2. Adverse Events

- **Adverse events**

The number and proportion of patients with adverse events will be tabulated by SOC and PT.

- **Adverse events by serious/non-serious**

The number and proportion of patients with serious adverse events will be tabulated by SOC and PT. The same tabulation will be performed for non-serious adverse events.

8.2.3.3. Other Endpoints

Not applicable.

8.2.3.4. Subgroup Analysis

The number and proportion of patients who experienced at least one adverse reaction will be tabulated for each factor specified in Section 5.4. To evaluate the relationship between patient background factors and the development of adverse reactions, the analysis based on risk ratio and risk difference specified in Section 8.1.3 will be performed. For subgroups with

risk ratio ≥2 or ≤0.5, the number and proportion of patients who experienced adverse reaction will be summarized for each factors, using SOCs and PTs. It should be noted that if adverse reactions developed in less than a total of 10 patients, the risk ratio and risk difference will not be calculated, although the proportion will be presented for each factors.

The number and proportion of patients who experienced adverse reaction will be summarized by maximum number of daily doses, based on SOCs and PTs. Similarly, the number and proportion of patients who experienced serious adverse reaction will be summarized by maximum number of daily doses.

Listing of adverse reactions that developed in contraindicated patients will be tabulated. In addition, the number and proportion of those contraindicated patients who experienced adverse reactions will be tabulated by SOC and PT, as necessary.

8.2.3.5. Exploratory Analysis

Additional exploratory analysis may be performed, as necessary. Among those exploratory analysis, only those that resulted in important interpretations will be reported.

8.2.4. Effectiveness Analysis

8.2.4.1. Clinical Response

In the clinical response analysis set, the number and proportion of patients with each clinical response will be calculated. In addition, the number and proportion (response rate) of responders and the 95% CI of response rate will be calculated in the clinical efficacy analysis set excluding patients with indeterminate response. Similar calculations will be tabulated by diagnosis (including by detailed diagnostic name of anaerobic infection), by maximum number of daily doses, and by the occurrence of central nervous system disorder. The response rate can be calculated by the following formula:

Clinical response rate (%) = (Number of patients with “effective”/ Number of clinically-evaluable patients excluding “indeterminate”) × 100.

If the clinical efficacy analysis set includes patients with inconsistent clinical efficacies, the response rate will be calculated by subtracting those patients from the denominator, as in the case where the set includes “indeterminate” patients.

In addition, the number and proportion (clinical response rate) of responders and the 95% CI of response rate for each pathogenic organism/strain will also be tabulated by diagnosis.

8.2.4.2. Microbiological Response

In the microbiological response analysis set, the number and proportion of patients with each microbiological response will be calculated. In addition, the number and proportion (eradication rate) of patients who fall in “eradication” or “presumed eradication” categories

and the 95% CI of eradication rate will be calculated in the microbiological response analysis set excluding patients with indeterminate response. Similar calculations will be tabulated by diagnosis (including by detailed diagnostic name of anaerobic infection), by maximum number of daily doses, and by the occurrence of central nervous system disorder. The eradication rate can be calculated by the following formula:

Eradication rate (%) = (Number of patients with "eradication" plus "presumed eradication"/ Number of patients in the microbiological analysis set excluding "indeterminate") × 100.

In addition, the number and proportion (eradication rate) of patients who fall in "eradication" or "presumed eradication" categories and the 95% CI of eradication rate for each pathogenic organism/strain will also be tabulated by diagnosis.

8.2.4.3. Eradication/Persistence of Each Pathogenic Organism/Strain

In the microbiological response analysis set, the number and proportion of microbes that were considered eradicated will be calculated by pathogenic organism/strain detected by the pretreatment microorganism test. The 95% CI of eradication rate will also be calculated, using indeterminate cases subtracted from the denominator. Similar calculations will be tabulated by diagnosis and by maximum number of daily doses. The eradication rate for a specific pathogenic organism/strain can be calculated by the following formula:

Eradication rate for a specific pathogenic organism/strain (%) = (number of pathogenic organism/strain/number of pathogenic organism/strain detected pretreatment except "indeterminate") × 100.

8.2.4.4. Subgroup Analysis

For each factor specified in Section 5.4, subgroup analysis on clinical response and microbiological response will be performed based on risk ratio and risk difference. Similar calculations will be tabulated by disease category (anaerobic infection, infectious enterocolitis, amebic dysentery).

8.2.4.5. Exploratory Analysis

For rationales for the assessment of clinical response, the number and proportion of patients will be calculated by diagnosis, clinical response (effective/not effective) and for each rationale.

Furthermore, an additional analysis may be performed as necessary. The exploratory analysis will be reported only when results providing an important interpretation are obtained.

9. LISTINGS

The following listings will be prepared.

- Listing of patients

- Listing of patients with adverse events
- Listing of patients with adverse reactions
- Listing of patients with adverse reactions among patients excluded from the safety analysis set
- Listing of patients with adverse reactions among contraindicated patients
- Listing of patients with serious adverse reactions
- Listing of patients with serious adverse events
- Listing of patients with adverse reactions among patients with hepatic dysfunction
- Listing of patients with adverse reactions among patients with renal dysfunction
- Listing of elderly patients with adverse reactions
- Listing of patients with adverse reactions in the safety specification items
- Listing of patients with central nervous system disorder
- Listing of clinical response and microbiological response
- Listing of microbiological test results
- Listing of results for clinical evaluations (body temperature, white blood cells, CRP)
- Listing for Anaemetro exposure
- Listing of patients who received Anaemetro four times a day at least for one day.

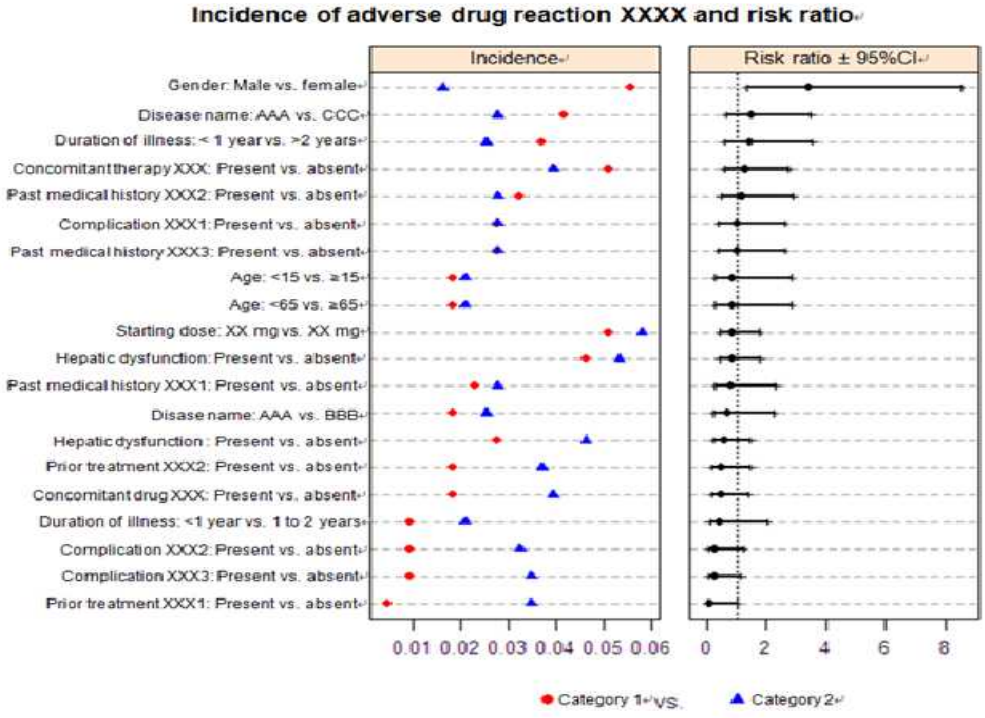
Furthermore, the following tables to be used as documents for periodic safety report (PSUR) will be prepared:

- Attachment Form 3 (Listing of overview of patients)
- Attachment Form 2 (Listing of occurrence of ADR and infections)
- Attachment Form 10 (Attachment Form 2-2) (Listing of occurrence of serious adverse events)

10. APPENDIX

10.1. Appendix 1: Example of Table and Figure of Risk Ratio of Incidence of Adverse Reactions by Subgroups

Event name: XXX increased	Category 1		Category 2		Risk ratio (RR)	
	Number of patients/N	(%)	Number of patients/N	(%)	RR	95 %CI
Gender (male vs. female)	18/2220	(0.8)	3/1099	(0.3)	2.97	(0.88-10.06)
≥65 years vs. <65 years	19/2788	(0.7)	2/531	(0.4)	1.81	(0.42-7.74)
Diagnosis (Disease A vs. Disease B)	3/221	(1.4)	18/3098	(0.6)	2.34	(0.69-7.87)
Duration of illness (<1 year vs. ≥1 year)	9/771	(1.2)	7/866	(0.8)	1.44	(0.54-3.86)
Drug A Concomitant use (present vs. absent)	9/798	(1.1)	12/2521	(0.5)	2.37	(1.00-5.60)
Drug A Prior treatment (present vs. absent)	1/148	(0.7)	20/3171	(0.6)	1.07	(0.14-7.93)
Disease B Complications (present vs. absent)	16/1614	(1.0)	5/1703	(0.3)	3.38	(1.24-9.20)
Disease B Past medical history (present vs. absent)	7/674	(1.0)	14/2643	(0.5)	1.96	(0.79-4.84)
Hepatic dysfunction (present vs. absent)	0/80		18/2056	(0.9)		
Renal dysfunction (present vs. absent)	1/140	(0.7)	17/2004	(0.8)	0.84	(0.11-6.28)



10.2. Appendix 2: Example of Categorizations for Risk Ratio Analysis

Exploratory categorization factors might be added to the set below. If an additional factor is one that categorized by absent or present, "absent" will be chosen as the reference.

Categorization item	Categories	Reference
Age	[<65 years, ≥65 years]	<65 years
Diagnostic name 1	[anaerobic infection, infectious enterocolitis]	anaerobic infection
Diagnostic name 2	[anaerobic infection, amebic dysentery]	anaerobic infection
Diagnostic name 3	[anaerobic infection, anaerobic infection plus infectious enterocolitis]	anaerobic infection
Hepatic dysfunction	[absent, present]	absent
Renal dysfunction	[absent, present]	absent
Prior treatment (medication for infection)	[absent, present]	absent
Concomitant medications (medication for infection)	[absent, present]	absent
Number of daily Anaemetro doses (1)	[1 time, 3 times]	3 times
Number of daily Anaemetro doses (2)	[2 times, 3 times]	3 times
Number of daily Anaemetro doses (3)	[3 times, 4 times]	3 times
Number of daily Anaemetro doses (4)	[3 times, >4 times]	3 times
Dose escalation	[absent, present]	absent