Non-Interventional Study Protocol

B1811187

Tygacil® Injection

Drug Use Investigation

Statistical Analysis Plan

Version: 4.0

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version	Date	Author(s)	Summary of Changes/Comments
1.0	30-Sep-2013	PPD	Initial version
2.0	20-Nov-2014	PPD	5.2 Effectiveness Analysis Sets - The names of the two analysis sets were changed. 5.3. Subgroups - The presence or absence of hepatic dysfunction, the presence or absence of renal dysfunction, and age were added to the subgroup analyses of effectiveness. 6.4. Covariates - Descriptions were changed. 8.1.3. Analysis of Binary Data - The analysis method was changed from statistical test to risk ratio and its 95% confidence interval. 8.2.2. Patient background and treatment history of Tygacil - An analysis in pregnant and parturient women (pregnancy confirmed) was added. 8.2.3.1. Adverse Drug Reactions - The analysis of adverse drug reactions (by System Organ Class [SOC] and Preferred Term [PT]) by duration of infusion was added for provision of information. - Categories for time to onset were changed. - The analysis by “during the observation period”/“during the follow-up period” was deleted. - It was changed to identify major investigation items using Standardized MedDRA Queries (SMQs). 8.2.3.2. Adverse Events - The analysis of non-serious adverse events necessary in Basic Results was added. 8.2.3.3. Other Endpoints - The calculation of the summary statistics of laboratory test values by timing was deleted, and it was specified to prepare plots of the changes only. - The targets of the plots were changed from “patients with specific adverse drug reactions” and “overall” to “patients with specific adverse drug reactions” and “patients without specific adverse drug reactions.” - Bacteriologic culture for *Clostridium difficile* and antigen test were added in this section.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.5. Exploratory Analysis - The analysis by duration of infusion and analysis by time to onset were moved to Section 8.2.3.1 and deleted from this section. 8.2.4.1. Clinical Response at the End of the Observation Period - Clinical response rate by susceptibility by pathogenic strain was moved to Section 8.2.4.6 and deleted from this section. 8.2.4.6. Exploratory Aanalysis - Effectiveness rate and cure rate by susceptibility by pathogenic strain were added. 9. LISTINGS - The listing of patients with adverse drug reactions was added for provision of information. - The listing of deaths was deleted. - For listings to be included in the text of the report, [Intext] was added after the name of the table. CCI [redacted] CCI [redacted].
3.0	31-Mar-2017	PPD [redacted]	<u>Status of investigation: Ongoing</u> 5.1. Safety Analysis Set - The definition was modified based on "Guidance for Criteria for Inclusion in Analysis Sets and Handling of Data in Drug Use Investigations" Version 2.0. 5.3. Subgroups - Categories to be used as the reference for risk ratio and risk difference were underlined. In addition, it was specified that categories not underlined will not be used for the calculation of risk ratio and risk difference. - "Patients with indications, patients without indications" and "patients with susceptible strains, patients without susceptible strains" were added to subgroups. - The detailed categories of age and the presence or absence of concurrent illness and past medical history other than hepatic and renal dysfunction were deleted. - The categories of duration of treatment were changed to meet the proper use guide. 8.1.3. Analysis of Binary Data - The calculation of risk difference and 95%

Version	Date	Author(s)	Summary of Changes/Comments
			confidence interval was added. 8.2.2. Patient background and treatment history of Tygacil - The tabulation of details of other in diagnostic names was added. - It was specified to count patients with superinfection multiple times. - An analysis to be performed in patients with indications and patients without indications separately was added. - An analysis to be performed in patients with susceptible strains and patients without susceptible strains separately was added. - The categories of duration of treatment were changed to meet the proper use guide. - The tabulation of information on administration of Tygacil by children/adults was added. - Tabulation of reasons for administering Tygacil was added. 8.2.3.1. Adverse Drug Reactions - The categories of time to onset were changed to meet the proper use guide. 8.2.3.3. Other Endpoints - “Major investigation items” and “adverse drug reactions” were additionally specified so that items to be evaluated are clarified. 8.2.3.4. Subgroup Analysis - The analysis method was specified. 8.2.3.5. Exploratory Analysis - Description adjustments were made so that the details of analysis are clarified. 8.2.4.1. Clinical Response at the end of the observation period - A tabulations by patients with indications/patients without indications was added. 8.2.4.2. Clinical Response at the Assessment of Cure -Tabulations by diagnostic name and by patients with indications/patients without indications were added. 8.2.4.5. Subgroup Analysis - Analysis sets, definitions, analysis methods, etc. were clarified. 9. LISTINGS

Version	Date	Author(s)	Summary of Changes/Comments
			- The listing of patients in the clinical response analysis set and the listing of serious adverse events were deleted. - The listing of deaths and the listing of the status of administration of Tygacil for children were added. Other description adjustments were made.
4.0	29-Aug-2017	PPD	Status of investigation: Completed 8.2.3.1. Adverse Drug Reactions - The tabulation of serious adverse drug reactions (by SOC and PT) by duration of infusion was added. 8.2.4.6. Exploratory Analysis - The tabulation of rationales for the assessment of clinical response was added. The list of rationales for other assessments was added. Other description adjustments were made.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the drug use investigation of Tygacil Injection (hereinafter referred to as Tygacil). In this plan, sentences cited from the Protocol are shown in *Italics*.

2.1. Study Design

This study is conducted with all patients surveillance system, and performed retrospectively. The indications of patients to be included in the Study (susceptible strains, indications, and precautions related to indications), dosage and administration, and target sample size are shown below. The observation period will be from the commencement of Tygacil treatment (Day 1) to Day 14 at maximum, and the follow-up period will be 28 days from the end of the observation period.

INDICATIONS: *(Susceptible strains)*

Tigecycline-susceptible Escherichia coli, Citrobacter spp., Klebsiella spp., Enterobacter spp., Acinetobacter spp.

It should be limited to the strain being resistant to other antibacterial drug.

(Indications)

Deep skin infections, chronic pyoderma, secondary infections associated with trauma, thermal burns, surgical wounds, etc., secondary infection of erosion or ulcer, peritonitis, intra-abdominal abscess, cholecystitis

[Precautions related to INDICATIONS]

1. *Tigecycline should be only use the strain showing resistant to two or more antimicrobial agent in beta–lactams, fluoroquinolones and aminoglycosides, and when other antibiotic drug showing antibacterial activity cannot be used.*
2. *Tigecycline does not have an antibacterial activity against Pseudomonas aeruginosa. Therefore, if superinfection with Pseudomonas aeruginosa is evident, tigecycline should be used in combination with an antibacterial drug with an anti-Pseudomonas aeruginosa action.*

DOSAGE AND ADMINISTRATION: For adults, 100 mg of tigecycline is initially administered via intravenous infusion over 30 minutes followed by 50 mg every 12 hours over 30 to 60 minutes.

Target sample size: 100 subjects

[Rationale]

The data collected from 100 subjects to whom Tygacil is administered should enable to detect and verify, with a probability of 95% or higher, at least 1 subject in whom each adverse event with an incidence of 3% or higher occurs, and thus enable to verify the post-marketing occurrences of major adverse events that occurred in domestic and overseas clinical studies (nausea, vomiting, diarrhea, abdominal pain, headache, hypoproteinaemia, ALT increased, and AST increased). Also, the target sample size of 100 subjects should enable to assess the actual use status of Tygacil in clinical setting including patient characteristics and responder rate, in addition to safety evaluation.

Tygacil use is restricted to strains showing resistant to two or more antimicrobial agent in beta–lactams, fluoroquinolones and aminoglycosides, and when other antibacterial drug showing antibacterial activity cannot be used. The number of patients in whom multi-drug resistant Acinetobacter was reported in JANIS in 2011 was only 115, regardless of the presence of infection, and thus, it is estimated that Tygacil use will be limited in actual clinical settings. Therefore, it is not easy to collect information from 100 patients who received Tygacil in this Study.

2.2. Study Objectives

The drug use investigation of Tygacil Injection is intended to assess the following information concerning Tygacil in daily medical practice.

- *Adverse drug reactions which cannot be predicted from the post-marketing precautions of this drug*
- *Incidence of adverse drug reactions under the actual use, and*

- *Factors considered to affect the safety and effectiveness, etc.*

Additionally, as the major investigation items, the incidence of the following adverse events will be confirmed.

- *Thrombocytopenia*
- *Hepatobiliary disorder*
- *Pancreatitis*
- *Diarrhea and pseudomembranous colitis*

3. 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.

4. HYPOTHESIS AND DECISION RULES

4.1. Statistical Hypothesis

Because this Study is not a confirmatory investigation, the tests are considered as exploratory tests. The P value of test results will be used to examine the uncertainty of information suggested from observed results and the tendency of information suggested from multiple results. The significance level is not provided, but a threshold may be set afterwards for the purpose of screening.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the population of patients who meet the registration criteria of this Study and are confirmed to have received at least one dose of Tygacil. However, patients meeting the following will be excluded from the safety analysis set:

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")

5.2. Effectiveness Analysis Sets

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

5.2.1. Clinical Response Analysis Set

The clinical response analysis set is defined as the population of patients in the safety analysis set for whom data for at least one clinical response evaluation (during the observation period or at the assessment of cure) were collected, and will be used for the evaluation of clinical response.

5.2.2. Bacteriological Response Analysis Set

The bacteriological response analysis set is defined as the population of patients in the safety analysis set for whom data for the evaluation of bacteriological response were collected, and will be used for the evaluation of bacteriological response and eradication rate by pathogenic strain.

5.3. Subgroups

Subgroup analyses of safety will be performed for the following patient background factors. Categories to be used as the reference for risk ratio and risk difference are underlined. Items without underlines will not be analyzed based on risk ratio and risk difference.

- Diagnostic name (deep skin infections, chronic pyoderma, secondary infections associated with trauma, thermal burns, surgical wounds, etc., secondary infection of erosion or ulcer, peritonitis, intra-abdominal abscess, cholecystitis, others)
- Patients with indications, patients without indications
- Patients with susceptible strains, patients without susceptible strains
- Presence or absence of hepatic dysfunction [absent, present]
- Presence or absence of renal dysfunction [absent, present]
- Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)

- Duration of treatment (<5 days, ≥5 to <15 days, ≥15 days)

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

- Pregnant and parturient women (pregnancy confirmed)
- Presence or absence of concomitant drugs

Subgroup analyses of effectiveness will be performed for the following patient background factors. Categories to be used as the reference for risk ratio and risk difference are underlined. Items without underlines will not be analyzed based on risk ratio and risk difference.

- Diagnostic name (deep skin infections, chronic pyoderma, secondary infections associated with trauma, thermal burns, surgical wounds, etc., secondary infection of erosion or ulcer, peritonitis, intra-abdominal abscess, cholecystitis, others)
- Patients with indications, patients without indications
- Patients with susceptible strains, patients without susceptible strains
- Presence or absence of hepatic dysfunction [absent, present]
- Presence or absence of renal dysfunction [absent, present]
- Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse drug reactions: Adverse events determined to be related to Tygacil by the physician or Sponsor
- Adverse events : All-causality adverse events
- Major investigation items : Thrombocytopenia, Hepatobiliary disorder, Pancreatitis, Diarrhea and Pseudomembranous colitis
- Clinical laboratory tests

Test values at the commencement of Tygacil treatment, during and at the end of the observation period

Test parameters: White blood cell count, platelet count, hemoglobin count, total protein, total bilirubin, AST, ALT, ALP, γ-GTP, CRP, amylase, lipase, serum creatinine, BUN, prothrombin time, activated partial thromboplastin time (APTT), urine bilirubin

6.2. Effectiveness Endpoints

6.2.1. Clinical Response

6.2.1.1. Clinical Response at the End of the Observation Period

- Effective
- Ineffective
- Indeterminate

6.2.1.2. Clinical Response (Assessment of Cure) During the Period of 28 days from the End of Tygacil Treatment

- Cure
- Ineffective
- Indeterminate

6.2.2. Bacteriological Response

6.2.2.1. Bacteriological Response at the End of the Observation Period

Bacteriological response at the end of the observation period is defined as follows.

Bacteriological effectiveness	Definition*
Eradication	The pathogenic strain was not detected from an appropriately collected specimen after administration of the antibacterial drug(s).
Presumed eradication	If clinical symptoms improved or eradicated as a result of treatment and a specimen suitable for testing can no longer be obtained from the initial focus of infection, the pathogenic strain is presumed to have eradicated.
Colonization	Evident signs and symptoms of infection eradicated as a result of treatment, but the initial pathogenic strain was detected from the same site.
Persistence	No improvement of clinical symptoms is observed, and the initial pathogenic strain was detected from the focus of infection from an appropriately collected specimen.
Presumed persistence	If no improvement of clinical symptoms is observed and isolation culture from an appropriately collected specimen was impossible or not performed, the pathogenic strain is presumed to be persisting.
Microbial substitution	The initial pathogenic strain eradicated as a result of treatment, and another new pathogenic organism was detected from the same site with evident signs and symptoms of infection.

Bacteriological effectiveness	Definition*
Superinfection	A new microorganism may emerge with the initial pathogenic strain persisting. If clinical findings of infection or findings of infection on testing persist or exacerbate in association with such emergence, it will be considered as superinfection.
Relapse	A case where the eradication of the pathogenic strain is proven, but the same pathogenic strain was subsequently detected from a specimen from the same infection site. It will be mainly used for the evaluation at the assessment of relapse compared to the time of assessment of cure.
Not evaluable	None of the above assessments could be made, for instance, bacteriological testing was not performed for various reasons.

*: The definitions above are those specified in case report form.

6.2.2.2. Eradication Rate by Pathogenic Strain

The rate of eradication of pathogenic strains is based on the survival of strains detected before Tygacil treatment in bacteriological testing. The survival of strains is defined as follows.

- Eradication: The pathogenic strain detected at the commencement of treatment was not detected after treatment (the amount of strain is "-") or no specimens could be collected.
- Persistence: The pathogenic strain detected at the commencement of treatment was detected from a specimen after treatment.
- Not evaluable: Bacteriological testing 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 Tygacil, there are no covariates identified from clinical study data thus far obtained or potential covariates.

7. HANDLING OF MISSING DATA

If there is no measured value at each evaluation time point for clinical laboratory test values and effectiveness endpoints, the value will be handled as missing and will not be complemented.

When the seriousness/outcome of adverse events and action taken with Tygacil 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 patients for whom the case report form was collected, 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 completed the Study, 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 bacteriological response will be tabulated. In addition, the number of patients excluded from the analysis of safety, clinical response, and bacteriological 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 bacteriological response analysis set, the number and proportion of cured patients and discontinued patients, and the number 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, clinical response, and bacteriological response will be prepared.

8.2.2. Patient background and treatment history of Tygacil

- **Patient background**

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

- Gender [male, female]
- Age (continuous)
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Age [≥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 [<40 kg, ≥40 to <50 kg, ≥50 to <60 kg, ≥60 to <70 kg, ≥70 kg, not measured]
- Body weight (continuous)
- BMI [<18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35 to <40, ≥40]
- BMI (continuous)
- Diagnostic name [deep skin infections, chronic pyoderma, secondary infections associated with trauma, thermal burns, surgical wounds, etc., secondary infection of erosion or ulcer, peritonitis, intra-abdominal abscess, cholecystitis, others]
- Details of diagnostic name “others”
- Diagnostic name* [patients with indications, patients without indications]
- Susceptible strains** [patients with susceptible strains, patients without susceptible strains, unknown]
- Severity [mild, moderate, severe, unknown]
- Hepatic dysfunction [absent, present, unknown]

- Renal dysfunction [absent, present, unknown]
- Presence or absence of concurrent illness of diseases or syndromes other than hepatic and renal dysfunction [absent, present]
- Presence or absence of the past medical history of diseases or syndromes other than hepatic and renal dysfunction [absent, present]

If a patient has more than one infection, multiple diagnostic names will be counted. Also, for the diagnostic name "others," multiple diagnostic names will be counted. As for diagnostic name,* patients with at least one diagnostic name falling under indications specified in the package insert will be considered as patients with indications, and patients with only diagnostic names other than the indications will be considered as patients without indications.

As for susceptible strains,** patients for whom pathogenic strains detected before Tygacil treatment in bacteriological testing include at least one susceptible strain will be considered as patients with susceptible strains. Patients for whom pathogenic strains do not include susceptible strains at all will be considered as patients without susceptible strains. "Unknown" is defined as cases such as when pathogenic strains could not be detected.

In the safety analysis set, the number and proportion of the following patients will be tabulated by Preferred Term (PT) of MedDRA.

- Past medical history
- Concurrent illness

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

- Pregnant and parturient women (pregnancy confirmed)
- Concomitant medications
- Non-drug concomitant therapies
- Prior treatment

- **Status of treatment of Tygacil**

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

- Duration of treatment [<5 days, ≥5 to <15 days, ≥15 days]
- Duration of treatment (continuous)
- Total dose (continuous)
- Initial dose (continuous)
- Mean dose from the second administration (continuous)

A tabulation will be performed also in subgroups of children (<15 years) and adults (≥15 years). In addition, a listing will also be prepared because the dose may be on a body weight basis in children.

The duration of treatment is from the initial day of administration in this Study to the last confirmed day of administration, including the period during which Tygacil is suspended.

- **Reasons for judging patients as the target of Tygacil treatment**

In the safety analysis set, reasons for judging patients as the target of treatment will be tabulated.

8.2.3. Safety Analysis

8.2.3.1. Adverse Drug Reactions

- **Adverse drug reactions**

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

- **Serious adverse drug reactions**

The number and proportion of patients with serious adverse drug reactions will be tabulated by SOC and PT. Also by duration of infusion, the number and proportion of patients with serious adverse drug reactions will be tabulated by SOC and PT.

- **Adverse drug reactions**

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

- Seriousness [serious, non-serious]
- Expected/unexpected [Expected, unexpected]
- Time to onset [<12 hours, ≥12 to <24 hours, ≥24 hours to <5 days, ≥5 to <15 days, ≥15 days]
- Duration of infusion [30 minutes, 60 minutes, others]
- Intervention [discontinuation, temporarily discontinued, dose reduction, none]
- Outcome [not recovered, recovered with sequela, recovering, resolved/recovered, unknown]

If the same adverse event (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 taken with Tygacil for the adverse events are reported, one of discontinuation, temporarily discontinued, dose reduction, or none, in descending order of precedence, will be adopted.
- Outcome: The outcome of the last occurring event will be used.

- **Major investigation items**

For the following adverse drug reactions considered as major investigation items, the number and proportion of patients with events will be tabulated.

- Thrombocytopenia
- Hepatobiliary disorder
- Pancreatitis
- Diarrhea and pseudomembranous colitis

Events to be handled as each major investigation item will be identified using MedDRA SMQs.

- **The adverse drug reactions by patients of included/exclueded in 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 events will be tabulated 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

- **Clinical Laboratory Test Values**

The by-patient plots of each Clinical laboratory test value against the number of days from the commencement of Tygacil treatment will be prepared. The following time plots will also be prepared.

- Time plots of white blood cell count, hemoglobin count, and platelet count in patients with thrombocytopenia (major investigation item, adverse drug reaction) and patients without thrombocytopenia
- Time plots of ALT, AST, ALP, γ-GTP, total bilirubin, and urine bilirubin in patients with hepatobiliary disorder (major investigation item, adverse drug reaction) and patients without hepatobiliary disorder
- Time plots of amylase and lipase in patients with pancreatitis (major investigation item, adverse drug reaction) and patients without pancreatitis
- If a new adverse drug reaction related to laboratory test is observed at a high incidence, time plots of the laboratory test parameter in patients with the adverse drug reaction and patients without the adverse drug reaction
- For laboratory test parameters showing a high incidence as adverse events in clinical studies (total protein, serum creatinine, prothrombin time, and APTT), time plots of the laboratory test parameter in patients with adverse drug reactions related to the parameter and patients without adverse drug reactions related to the parameter

- **Bacteriologic culture for Clostridium difficile and antigen test**

In patients who experienced diarrhea, the number and proportion of patients who underwent bacteriologic culture for Clostridium difficile and antigen test will be calculated.

8.2.3.4. Subgroup Analysis

The number and proportion of patients who experienced at least one adverse drug reaction will be tabulated for each factor specified in Section 5.3. To evaluate the relationship between patient background factors and the development of adverse drug reactions, the examination based on risk ratio and risk difference specified in Section 8.1.3 will be performed.

The same analysis will be performed for serious adverse drug reactions.

8.2.3.5. Exploratory Analysis

The following exploratory analysis will be performed for factors affecting safety.

- Logistic regression analysis using the presence or absence of development of major investigation items (adverse drug reactions) with an incidence of ≥ 10% as an objective variable and factors such as patients background and baseline values of related laboratory test parameters as explanatory variables
- The number and proportion of patients with adverse drug reactions (by SOC and PT) will be tabulated by cumulative dose of Tygacil immediately before the onset of adverse drug reactions.

8.2.4. Effectiveness Analysis

8.2.4.1. Clinical Response at the End of the Observation Period

In the clinical response analysis set, the number and proportion of patients with each clinical response at the end of the observation period will be calculated. Using the proportion of "effective" as the clinical response rate, the 95% confidence interval of clinical response rate will also be calculated. When the clinical response rate is calculated, the denominator should not include "indeterminate" patients. The analysis will be performed also by diagnostic name and by patients with indications/patients without indications.

8.2.4.2. Clinical Response at the Assessment of Cure

In the clinical response analysis set, the number and proportion (cure rate) of patients in the clinical response evaluation at the assessment of cure (during period of 28 days from the end of Tygacil treatment) and the 95% confidence interval of cure rate will be calculated. When the cure rate is calculated, the denominator should not include "indeterminate" patients. The analysis will be performed also by diagnostic name and by patients with indications/patients without indications.

8.2.4.3. Bacteriological Response at the End of the Observation Period

In the bacteriological response analysis set, the number and proportion of patients with each bacteriological response on the day of the end of the observation period will be calculated. The proportion of patients with eradication (eradicated + presumed eradicated) (eradication rate) and the 95% confidence interval of eradication rate will also be calculated. When the eradication rate is calculated, the denominator should not include indeterminate patients.

8.2.4.4. Eradication Rate by Pathogenic Strain

In the bacteriological response analysis set, the number and proportion of patients with each bacteriological response on the day of end of the observation period will be calculated by pathogenic strain. The proportion of patients with eradication (eradicated + presumed eradicated) (eradication rate) and the 95% confidence interval of eradication rate will also be calculated. When the eradication rate is calculated, the denominator should not include "not evaluable" patients.

In addition, the eradication rate by susceptibility to Tygacil (S = susceptible, I = intermediate, R = resistant) and the 95% confidence interval of eradication rate will be calculated by pathogenic strain.

8.2.4.5. Subgroup Analysis

For each factor specified in Section 5.3, the evaluation of clinical response on the day of end of the observation period and the clinical response evaluation at the assessment of cure will be performed based on risk ratio and risk difference in the clinical response analysis set. The

subgroup analysis of bacteriological response on the day of end of the observation period will be performed in the same manner in the bacteriological response analysis set.

8.2.4.6. Exploratory Analysis

The clinical response rate by susceptibility to Tygacil (S = susceptible, I = intermediate, R = resistant) and the 95% confidence interval of clinical response rate will be calculated by pathogenic strain. The cure rate will be calculated in the same manner.

For rationales for the assessment of clinical response, the number and proportion of patients will be calculated by clinical response (effective/ineffective) and for each rationale. Other rationales will be presented in a listing.

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. Listings with [Intext] specified after the table name are in a format which allows attachment to the report without change.

- Listing of patients (safety analysis set)
- Listing of patients with adverse drug reactions
- Listing of patients with adverse drug reactions (for provision of information) [Intext]
- Listing of patients with adverse drug reactions among patients excluded from the safety analysis set
- Listing of serious adverse drug reactions
- Listing of patients with adverse events
- Listing of deaths [Intext]
- Listing of patients with adverse drug reactions among patients with hepatic dysfunction [Intext]
- Listing of patients with adverse drug reactions among patients with renal dysfunction [Intext]
- Listing of events falling under major investigation items
- Listing of patients with adverse drug reactions falling under major investigation items
- Listing of patients who underwent tests related to diarrhea which developed after Tygacil treatment [Intext]
- Listing of laboratory test values
- Listing of bacteriological test results
- Listing of patients for whom the susceptibility test of pathogenic strains showed resistance to Tygacil at least once [Intext]
- Listing of reasons for administering Tygacil
- Listing of the status of administration of Tygacil
- Listing of the status of administration of Tygacil (children) [Intext]

- Listing of test findings and clinical findings contributing to the assessment of clinical response

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

- PSUR: Appendix Form 2 (Listing of occurrence of ADR and infections)
- PSUR: Appendix Form 2-2 (Listing of occurrence of serious adverse events)
- Reexamination: Appendix Form 2 (Listing of occurrence of ADR and infections)
- Reexamination: Appendix Form 3 (Listing of overview of patients)
- Reexamination: Appendix Form 10 (Listing of occurrence of serious adverse event)

10. REFERENCES

None

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