Non-Interventional Study Protocol

B3271007

TRASTUZUMAB BS for Intravenous Infusion 60 mg [Pfizer]

TRASTUZUMAB BS for Intravenous Infusion 150 mg [Pfizer]

General Investigation

(Unresectable Advanced/Recurrent HER2-Overexpressing Gastric Cancer)

Statistical Analysis Plan

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

Version: 2.0

Author: PPD

Date: 14-FEB-2025

TABLE OF CONTENTS

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

1. AMENDMENTS FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0 20-AUG-2019 PPD Before Enrollment	First version
2.0 14-FEB-2025 PPD Ongoing	Since this study was terminated before the target sample size of 100 patients was reached, the descriptions based on the assumption that the target sample size was to be reached were reviewed as follows: 5.4. Subgroups ▪ Subgroup analyses of safety are to be performed on age, hepatic function disorder, renal impairment, and pregnancy (female only), and other subgroups were deleted. ▪ The subgroups established for the efficacy analysis were deleted. 8.2.3.1.4. Safety specifications ▪ The tabulations by change in administration of this drug and outcome were deleted. 8.2.4.2. Exploratory analysis ▪ Since the whole section of "8.2.4.2. Subgroup analysis" was deleted, the section number of "Exploratory analysis" was changed from 8.2.4.3 to 8.2.4.2.
	5.3. Other Analysis Sets ▪ The safety analysis set consisting of consented patients and the efficacy analysis set consisting of consented patients were added.
	8.2. Statistical Analysis ▪ Analysis populations were added for each analysis item.
	8.2.1.1. Patient disposition ▪ The analysis population was changed to CRF-locked patients.
	8.2.1.2. Discontinuation status ▪ Categories of the timing of discontinuation were added. ▪ The denominators for the calculation of the proportion of discontinued patients and the proportion of patients by reason for discontinuation were added.
	8.2.2.1. Patient characteristics ▪ The method for calculating the duration of the target disease was added.
	8.2.2.2. Administration status of this drug ▪ For the total number of doses, the analysis of continuous data was changed to the analysis of categorical data, and categories were added.
	8.2.3.1.3. Details of adverse reactions ▪ Change in administration of this drug was added. ▪ A change was made to the priorities of "change in administration of this drug" and "outcome" in case of a same adverse reaction (of the same PT) occurring more than once in the same patient.

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
	8.2.3.1.5. Status of occurrence of adverse reactions in patients excluded from the safety analysis set ▪ The description about the preparation of a listing was deleted.
	8.2.3.2. Adverse events ▪ The section itself was newly added.
	9. LISTINGS ▪ The analysis population was specified as CRF-locked patients. ▪ The description about the preparation of a listing of patients excluded from the safety analysis set experiencing adverse reactions and a listing of administration status was deleted.
	Other description modifications such as correction/omissions of typographical errors and were made.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the general investigation of TRASTUZUMAB BS for Intravenous Infusion 60 mg [Pfizer] and TRASTUZUMAB BS for Intravenous Infusion 150 mg [Pfizer] (hereinafter referred to as this drug). In this document, texts cited from the protocol are indicated in *italics*.

2.1. Study Design

This study is an open-label, multicenter, one arm prospective observational cohort study in patients with unresectable advanced/recurrent gastric cancer who have been confirmed to have HER2 overexpression receiving this drug. To confirm the safety and efficacy of this drug under the actual use. The start of observation is defined as the first date of the administration of this drug (Day 1), and the observation period lasts until 28 days after the last dose within 24 weeks from the start of administration, the first dose of this drug administered more than 24 weeks after the start of administration, or the start of the next treatment, whichever comes first. Safety specifications are cardiac disorder, infusion reactions, haematotoxicity, interstitial pneumonia/lung disorder, hepatic failure/liver disorder, coma, cerebrovascular disorder, brain oedema, renal disorder, infection and tumour lysis syndrome which are important identified risks. Planned sample size is 100 patients as the safety analysis set (SAS). Rationale for sample size is as follows.

＜Rationale for sample size＞
By accumulating data from 100 patients, it is possible to detect AEs with a true incidence of 3% or higher in at least 1 patient with a probability of approximately 95% in a general investigation.

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

2.2. Study Objectives

To confirm the safety and efficacy of this drug under the actual use.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for the evaluation report on the risk management plan will be performed periodically. At the time of interim analyses, only the analyses necessary for the evaluation report on the risk management plan among the statistical analyses specified in this plan will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

4. HYPOTHESES AND DECISION RULES

If any statistical test is conducted, it will be considered as exploratory result.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the full analysis set that is as close as possible to all patients treated with this drug. More specifically, the safety analysis set is defined as the population of patients registered or reported, excluding those who meet any one of the following conditions:

1. The case report form could not be collected at all (Description in the report: "Case report form not collected")
2. There was a violation or deficiency in the contract (Description in the report: "Contract violation/deficiency")
3. There was a violation of registration (Description in the report: "Registration violation")
4. Administration of the target drug is not reported at all (Description in the report: "No administration information")
5. Information on adverse events is not reported at all - Patient made a hospital visit(s) after the first prescription day but no description of information (Description in the report: "No adverse event information - No description")

The "Guidance for Criteria for Inclusion/Exclusion in Analysis Sets and Data Handling in Drug Use Investigations" will be followed for the details of each criterion. If more than one condition for exclusion is met, priority will be given to the condition with a lower number above and the relevant condition will be described in the report.

5.2. Efficacy Analysis Set

The efficacy analysis set is defined as the population of patients in the safety analysis set, excluding those who meet any one of the following conditions. If more than one condition for exclusion is met, priority

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

will be given to the condition with a lower number below and the relevant condition will be described in the report.

1. Disease is not under investigation (Description in the report; "Disease not under investigation")

2. Efficacy evaluation is not reported at all (Description in the report: "No efficacy information")

5.3. Other Analysis Sets

5.3.1. Safety analysis set consisting of consented patients

It refers to the analysis population consisting of only consented patients for the external dissemination and publication of study results among the patients in the safety analysis set.

5.3.2. Efficacy analysis set consisting of consented patients

It refers to the analysis population consisting of only consented patients for the external dissemination and publication of study results among the patients in the efficacy analysis set.

5.4. Subgroups

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

- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Hepatic function disorder [absent, present]
- Renal impairment [absent, present]

For disease names (PT) corresponding to hepatic function disorder/renal impairment, the latest "procedure for extraction of hepatic function disorder/renal impairment" will be followed.

- Pregnancy (female only) [absent, present] (including pregnancy occurring after the start of administration of this drug)

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reactions: Adverse events assessed as related to this drug by the physician
- Adverse events: Adverse events of any causality
- Serious adverse events or adverse reactions: Adverse events or adverse reactions assessed as serious by the physician
- *Safety specifications: Important identified risks*
    - *Cardiac disorder*

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

- *Infusion reaction*
- *Haematotoxicity*
- *Interstitial pneumonia/lung disorder*
- *Hepatic failure/liver disorder*
- *Coma, cerebrovascular disorder, brain oedema*
- *Renal disorder*
- *Infection*
- *Tumour lysis syndrome*

Events determined to be infusion reaction by the physician will be tabulated. Events to be handled as safety specifications other than infusion reaction will be specified separately.

6.2. Efficacy Endpoints

The physician in charge will evaluate the efficacy of this drug based on the best overall response using the efficacy assessment items in the "Guidelines on New Response Evaluation Criteria in Solid Tumors: Revised RECIST guideline (Version 1.1)" at the end of the observation period or at discontinuation. The total proportion of patients with complete response (CR) or partial response (PR) will be evaluated as a response rate (%).

6.3. Other Endpoints

Other endpoints include the following laboratory test values:

Laboratory tests: CEA, CA19-9, QT, QTc, LVEF (assessed by echocardiography or MUGA scan)

6.4. Covariates

There are no covariates identified from clinical study data, etc. to date or potential covariates for the safety or efficacy of this drug.

7. HANDLING OF MISSING DATA

If the seriousness, causal relationship, action taken, and outcome of an adverse event are missing, the data will be handled as "unknown" for tabulation.

If there is no evaluation of the efficacy endpoint (best overall response), the data will be handled as missing data and will not be complemented.

The strategy for handling data with uncompleted cleaning is described below:

- Item of missing data: The item will be handled as missing (category of categorical variables is "unknown") for both tabulation and listing.
- Item of inconsistent data: The item will be handled as missing for both tabulation and listing. However, a listing of data handling will be prepared separately.

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

- No signature: Any entry in a case report form without the signature of a contracted physician (including a case report form with the signature of an uncontracted physician only) will be handled as missing for both tabulation and listing. If there is no date of signature in the field for the date of signature or if there is inconsistency in the date entered (e.g., date before the start date of treatment, future date), the entry in the case report form will be regarded as having no signature.

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, minimum) will be calculated.

8.1.2. Analysis of categorical data

The frequency (e.g., number of patients) and proportion of data will be calculated for each category.

8.1.3. Analysis of binary data

The frequency and proportion of data will be calculated. When the confidence interval of the proportion is calculated, the two-sided 95% confidence interval (exact method) will be calculated.

8.2. Statistical Analysis

Unless otherwise specified, the analyses described in Section 8.2.1 to Section 8.2.3 will be performed on the safety analysis set, and the analyses described in Section 8.2.4 will be performed on the efficacy analysis set.

Similarly, the analyses to be performed on the safety analysis set or the efficacy analysis set will also be performed on the safety analysis set consisting of consented patients or the efficacy analysis set consisting of consented patients. However, these analyses will not be performed if each population consisting of consented patients is the same as the safety analysis set or efficacy analysis set.

8.2.1. Overview of patients

8.2.1.1. Patient disposition

For CRF-locked patients, the numbers of patients in the safety analysis set and the efficacy analysis set will be tabulated. In addition, the numbers of patients excluded from the safety analysis set and the efficacy analysis set and the number of patients by reason for exclusion will be tabulated.

8.2.1.2. Discontinuation status

The number and proportion of patients discontinuing the study during the entire study period and at each timing of discontinuation [on the day of the first dose, before the second dose, after the day of the second dose] will be tabulated. In addition, the number and proportion of patients by reason for discontinuation

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

will be tabulated. The denominator of the proportion of discontinued patients will always be the number of patients in the safety analysis set. The denominator of the proportion of discontinued patients by reason for discontinuation will be the number of patients discontinuing the study during the entire study period and at each time point of the study.

8.2.1.3. Listing of excluded patients by patient

A listing of patients excluded from the safety analysis and patients excluded from the efficacy analysis by reason for exclusion will be prepared.

8.2.2. Patient characteristics and history of treatment

8.2.2.1. Patient characteristics

The following patient characteristics will be tabulated as described in Section 8.1.

- Gender [male, female]
- Age (continuous variable)
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Body weight (continuous variable)
- Target disease [unresectable advanced/recurrent HER2-overexpressing gastric cancer, others]
- Other details of the target disease
- Duration of gastric cancer (months, continuous variable)

The duration of gastric cancer is expressed as (date of the start of administration of this drug − date of initial diagnosis of gastric cancer + 1) / 30.44.

- Target lesion [absent, present]
- ECOG PS before the start of administration of this drug [0, 1, 2, 3, 4]
- T classification [TX, T0, T1a, T1b, T2, T3, T4a, T4b]
- N classification [NX, N0, N1, N2, N3a, N3b]
- M classification [MX, M0, M1]
- Lesion site (metastatic site) [absent, present]
- Lesion site when a metastatic site is present [peritoneum, lymph node, liver, others] (including overlapping)
- Other details of the lesion site
- Family history of malignancy [absent, present, unknown]
- Hepatic function disorder [absent, present]
- Renal impairment [absent, present]
- Past history [absent, present]
- Complication [absent, present]
- History of trastuzumab product use [absent, present, unknown]
- Reason for trastuzumab product use [advanced/recurrent gastric cancer, breast cancer, others]
- Prior medication [absent, present, unknown]
- Prior therapy (non-drug therapy) [absent, present]
- Administration of prophylaxis for infusion reaction [absent, present]
- Concomitant medication [absent, present]

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

- Concomitant non-drug therapy [absent, present]
- Pregnancy (female only) [absent, present] (including pregnancy occurring after the start of administration of this drug)

The numbers and proportions of patients with past history and complications will be tabulated by system organ class (SOC) and preferred term (PT).

The number and proportion of patients will be tabulated for the following:

- Breakdown of prior medications
- Breakdown of prior therapies (non-drug therapies)
- Breakdown of concomitant medications
- Breakdown of concomitant non-drug therapies

8.2.2.2. Administration status of this drug

The administration status of this drug will be tabulated for the following:

- Reason for use [first-line therapy, second-line therapy, others]
- Duration of continued treatment (days, continuous variable)
- Total number of doses [1, 2, ≥3]

The duration of continued treatment is defined as the period from the first date of administration to the last date of confirmation of administration in this study, including non-treatment period.

8.2.3. Safety analysis

Adverse reactions and adverse events occurring during the observation period will be summarized in listings. All events reported in this study will be included in the listings.

8.2.3.1. Adverse reactions

8.2.3.1.1. All adverse reactions

The number and proportion of patients with adverse reactions will be tabulated by SOC and PT and by severity (CTCAE Grade) [1, 2, 3, 4, 5]. If the same adverse reaction (of the same PT) occurs more than once in the same patient, the higher severity event will be adopted.

8.2.3.1.2. Serious adverse reactions

The number and proportion of patients with serious adverse reactions will be tabulated by SOC and PT and by severity (CTCAE Grade) [1, 2, 3, 4, 5]. If the same adverse reaction of the same PT occurs more than once in the same patient, the higher severity event will be adopted.

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

8.2.3.1.3. 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:

- Change in administration of this drug [unchanged, dose increased, dose reduced, suspended, discontinued, not applicable]
- Outcome [fatal, not resolved/not recovered, resolved/recovered with sequelae, resolving/recovering, resolved/recovered, unknown]

In the tabulation of the number of patients with events, any same adverse reaction of the same PT occurring more than once in the same patient will be handled as follows:

- Change in administration of this drug: One will be adopted in order of priority of the following actions: discontinued, suspended, dose reduced, unchanged, dose increased, not applicable.
- Outcome: One will be adopted in order of priority of the following outcomes: fatal, not resolved/not recovered, resolved/recovered with sequelae, resolving/recovering, unknown, resolved/recovered.

8.2.3.1.4. Safety specifications

The number and proportion of patients with adverse reactions corresponding to the safety specifications listed in Section 6.1 will be tabulated by SOC and PT and by severity.

8.2.3.1.5. Status of occurrence of adverse reactions in patients excluded from the safety analysis set

For patients excluded from the safety analysis set, the number of patients with adverse reactions will be tabulated by SOC and PT.

8.2.3.1.6. Subgroup Analysis

For each of the factors specified in Section 5.4, the number and proportion of patients with adverse reactions will be tabulated by severity and by SOC and PT.

8.2.3.2. Adverse events

8.2.3.2.1. Serious adverse events

For the safety analysis set consisting of consented patients, the number and proportion of patients with serious adverse events will be tabulated by SOC and PT.

8.2.3.2.2. Non-serious adverse events

For the safety analysis set consisting of consented patients, the number and proportion of patients with non-serious adverse events will be tabulated by SOC and PT.

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)

8.2.3.3. Exploratory analysis

Additional analysis may be performed as necessary. Any exploratory analysis will be reported only when providing results giving important interpretation.

8.2.4. Efficacy analysis

8.2.4.1. Best overall response

The number and proportion of patients with each best overall response will be calculated, and the number of patients with response and response rate (%) will be calculated, along with a 95% confidence interval.

8.2.4.2. Exploratory analysis

Additional analysis may be performed as necessary. Any exploratory analysis will be reported only when providing results giving important interpretation.

9. LISTINGS

For CRF-locked patients, the following listings will be prepared:

- Listing of patients
- Listing of patients experiencing adverse reactions
- Listing of patients experiencing serious adverse reactions
- Listing of deaths
- Listing of laboratory test values

In addition, the following table corresponding to the attached form of the evaluation report on the drug risk management plan will be prepared:

- Attached Form 15 (Status of occurrence of adverse reactions/infections in the post-marketing surveillance, etc.)

10. REFERENCES

Guidelines on New Response Evaluation Criteria in Solid Tumors (RECIST guideline) - Revised version 1.1 - Japanese translation JCOG version ver. 1.0.

090177e1a35fd148\Approved\Approved On: 12-Dec-2025 08:32 (GMT)