Non-Interventional Study Protocol

A7471048

Special Investigation for VIZIMPRO Tablets

Statistical Analysis Plan

Version: 2.0

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Date: 24-APR-2025

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0 02-SEP-2019 PPD Before Enrollment	First version
2.0 24-APR-2025 PPD Ongoing	2.1. Study Design ▪ In association with the protocol amendment, the last days of the investigation period and registration period were changed. 2.2. Study Objectives ▪ In association with the termination of the study before the target sample size was reached, explanation about the background and the revision of the evaluation method for the risk of developing interstitial lung disease was added. 5.3. Other Analysis Sets ▪ The safety analysis set consisting of consented patients and the efficacy analysis set consisting of consented patients were added. 5.4. Subgroups ▪ In association with the revision of the evaluation method for the risk of developing interstitial lung disease, the patient characteristics and factors used for subgroup analyses were limited to the specific backgrounds described in the re-examination application. 6.4. Covariates ▪ The description about the evaluation method for the risk of developing interstitial lung disease was deleted. 8.1.3. Analysis of Binary Data ▪ In association with the revision of the evaluation method for the risk of developing interstitial lung disease, the description about the calculation of risk ratios was deleted. 8.2.2.1. Patient Characteristics ▪ The tabulation items related to mutation test results were changed. ▪ In association with the revision of the evaluation method for the risk of developing interstitial lung disease, the tabulation items were changed to those corresponding to the patient characteristics used for subgroup analyses. ▪ Disease history and treatment history considered to affect the onset of interstitial lung disease were added. 8.2.2.2. Disease History ▪ The section itself was added. 8.2.2.3. Administration Status of This Drug ▪ In association with the addition of Section 8.2.2.2 “Disease History,” the section number was changed from Section 8.2.2.2 to Section 8.2.2.3. 8.2.3. Safety Analysis ▪ The safety analysis set consisting of consented patients was added to the analysis sets. ▪ The description about the evaluation method for the risk of developing interstitial lung disease was deleted.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
	8.2.3.1.3. Details of Adverse Reactions 8.2.3.1.4. Timing of Onset of Adverse Reactions ▪ In association with the revision of the evaluation method for the risk of developing interstitial lung disease, these sections themselves were deleted.
	8.2.3.1.3. Status of Occurrence of Adverse Reactions in Patients Excluded from the Safety Analysis Set ▪ In association with the deletion of the two preceding sections, the section number was changed. ▪ The section title was changed from "Status of Occurrence of Adverse Reactions by Inclusion/Exclusion in the Safety Analysis Set" to "Status of Occurrence of Adverse Reactions in Patients Excluded from the Safety Analysis Set." 8.2.3.2.1. All Adverse Events ▪ The section itself was deleted because adverse events would be tabulated in Section 8.2.3.2 "Adverse Events." ▪ The safety analysis set consisting of consented patients was used as the analysis set. ▪ The method of tabulation of serious adverse events was added. 8.2.3.2.2. Serious Adverse Events ▪ The section itself was deleted because adverse events would be tabulated in Section 8.2.3.2 "Adverse Events." 8.2.3.3.1. Pregnancy ▪ The tabulation method for patients excluded from the safety analysis set was deleted. 8.2.3.3.2. Drug Therapy for Interstitial Lung Disease 8.2.3.3.3. Surgical History 8.2.3.3.4. Prior Radiotherapy ▪ In associated with the termination of the study before the target sample size was reached, these sections themselves were deleted. 8.2.3.4. Subgroup Analysis 8.2.3.5. Exploratory Analysis ▪ In association with the revision of the evaluation method for the risk of developing interstitial lung disease, some of the tabulation methods were deleted. 8.2.4.1. Best Overall Response ▪ The efficacy analysis set consisting of consented patients was used as the analysis set. 8.2.4.2. Subgroup Analysis ▪ In associated with the termination of the study before the target sample size was reached, the section itself was deleted. 9. LISTINGS ▪ The listings that were not to be prepared were deleted. 10.1. Example of Tables of Risk Ratios for Adverse Reactions Occurring in Subgroups ▪ The example of tables was deleted in association with the revision of the evaluation method for the risk of developing interstitial lung disease. Other description modifications were made.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the special investigation (Study 7471048) (hereinafter referred to as this study) for VIZIMPRO Tablets (dacomitinib hydrate) (hereinafter referred to as this drug). In this document, texts cited from the protocol are indicated in *italics*.

2.1. Study Design

This drug blocks abnormal signals and inhibit tumor cell proliferation by irreversibly inhibiting the tyrosine kinase activity of epidermal growth factor receptor (EGFR) and mutated EGFR (e.g., deletion of exon 19, point mutation of L858R in exon 21) and other receptors of the ErbB receptor family, HER2 (ErbB2) and HER4 (ErbB4), and by irreversibly inhibiting the activity of homo and heterodimer formed by the ErbB receptor family [EGFR, HER2, ErbB3 (HER3), and HER4]. The marketing authorization of this drug was obtained in January 2019 in Japan as an indication of "EGFR mutation-positive inoperable or recurrent non-small cell lung cancer (NSCLC)".

This study is a multicenter cohort study of patients treated with this drug. The investigators complete the CRF based on the information required by the study that are extracted from medical records such as medical charts created in daily medical practice. This study will be conducted in patients with EGFR mutation-positive inoperable or recurrent NSCLC who have not received this drug.

The planned period covered by this study is as follows.

Investigation period: July 2019 to March 2026

*Registration period: July 2019 to March 2025**

**: The registration is terminated if the target number of the patients has been collected, even before the end of the registration period.*

The observation period will be 52 weeks from the first day of administration of this drug. However, the observation period will be until the date of treatment discontinuation for patients who discontinue treatment with this drug (adverse events will be reported until 28 days after the date of treatment discontinuation).

799 patients with EGFR mutation-positive inoperable or recurrent NSCLC (safety analysis set)

Rationale for the sample size

In Japanese NSCLC patients treated with single-agent dacomitinib at the starting dose of 45 mg QD, the incidence of all-causality ILD was 5.9% (6/101 patients). In order to evaluate the effect of risk factors for ILD under the actual status of use of this drug, the sample size was set so that a statistically significant relative risk can be detected between subgroups with and without risk factors. Assuming that the incidence of ILD in the low-risk and high-risk populations is 5.9% and 11.8%, respectively (equivalent to 2.0 relative risks), and that the ratio of the number of subjects in the low-risk and high-risk populations is 1: 3, the number of patients in whom risk factors can be detected under a significance level (two-sided) of

15% and a power of 80% is 799. Assuming that 10% of the enrolled patients will be excluded from the safety analysis set for some reason, the number of enrolled patients was set at 888.

2.2. Study Objectives

This study investigates the following in patients with EGFR mutation-positive inoperable or recurrent NSCLC under post-marketing actual status of use of this drug because interstitial lung disease (ILD) was observed in clinical studies of this drug and the incidence was high in Japanese patients, and ILD has also been observed with other EGFR tyrosine kinase inhibitors and it is considered as an adverse event requiring special attention.

The end of the registration period of this study was March 31, 2025. However, 40 patients were registered until that time, and the registration in this study was terminated before the target sample size of 799 patients (888 patients to be registered) was reached. As a result, the initially planned analyses to investigate risk factors are considered to be less significant. Thus, instead of performing these analyses, risk factors will be evaluated to the extent possible based on the information such as patient background of the patients developing interstitial lung disease.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for Periodic Safety Update Reports will be performed periodically. At the time of interim analyses, only the analyses necessary for the Periodic Safety Update Reports among the statistical analyses specified in this plan will be performed. In addition, the final analysis for the re-examination application will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

4. HYPOTHESES AND DECISION RULES

This study is not a confirmatory investigation. Therefore, any test will be considered as exploratory.

4.1. Statistical Hypothesis

Unless otherwise specified, any test will be two-sided and the significance level will be 5%.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set consists of a full analysis set that is as closer as possible to all patients who received this drug. More specifically, the safety analysis set is defined as the population of patients registered or reported, excluding those meeting at least 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. Administration of the drug under investigation is not reported at all (Description in the report: “No administration information”)

4. 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 revisits”)

5. Information on adverse events is not reported at all - The participant revisited 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 in Analysis Sets and Data Handling in Drug Use Investigations” will be followed for the details of each criterion. For any patient meeting more than one condition, one will be adopted in order of priority of 1, 2, 3, 4, and 5 and included in the tabulation.

5.2. Efficacy Analysis Set

The efficacy analysis set is defined as the population of patients in the safety analysis set, excluding those meeting at least one of the following conditions:

1. Efficacy evaluation is not reported at all (Description in the report: “No efficacy information”)

2. Disease is not under investigation (Description in the report; “Disease not under investigation”)

5.3. Other Analysis Sets

5.3.1. Safety Analysis Set Consisting of Consented Patients

The safety analysis set consisting of consented patients is defined as the population of patients registered or reported and providing consent for dissemination and publication of study results, excluding those meeting at least one of the conditions in Section 5.1.

5.3.2. Efficacy Analysis Set Consisting of Consented Patients

The efficacy analysis set consisting of consented patients is defined as the population of patients registered or reported, excluding those meeting at least one of the conditions in Section 5.2 from the safety analysis set consisting of consented patients.

5.4. Subgroups

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

- Age group [<15 years, ≥15 to <65 years, ≥65 years]

- Complication: Hepatic impairment [absent, present]
- Complication: Renal impairment [absent, present]

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

- Pregnancy status (female only) [absent, present]

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoint

- Safety specification: Interstitial lung disease

  Events to be handled as interstitial lung disease will be specified separately.

6.2. Efficacy Endpoint

- Best overall response (according to the "Response Evaluation Criteria in Solid Tumors Guidelines - Revised Version 1.1")

6.3. Other Endpoints

- Confirmation of survival status

6.4. Covariates

The known risk factors for drug-induced lung injury include age of ≥60 years, past pulmonary lesion (especially interstitial pneumonia), post-lung surgery patients, decreased respiratory functions, oxygen therapy, irradiation to the lung, and presence of renal disorder.

7. HANDLING OF MISSING DATA

If the seriousness, causal relationship, action taken, and outcome of interstitial lung disease are missing, the data will be handled as “unknown” for tabulation.

Any missing efficacy endpoint will not be imputed.

The strategy for handling data with uncompleted cleaning is as follows.

- 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.
- 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.

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 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 presented.

8.1.4. Analysis of Period Data (Time to Event Onset)

The median, first quartile, and third quartile will be calculated by the Kaplan-Meier method. The 95% confidence interval will be calculated using the Brookmeyer and Crowley method. In addition, Kaplan-Meier plots will be prepared.

8.2. Statistical Analysis

8.2.1. Overview of Patients

8.2.1.1. Patient Disposition

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

8.2.1.2. List of Discontinuations and Dropouts

For the safety analysis set and the efficacy analysis set, the number and proportion of discontinuations will be tabulated. In addition, the number and proportion of patients by reason for discontinuation (insufficient clinical efficacy, adverse event, death, no revisit, transfer to other hospital/department, other) will be tabulated.

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

For the safety analysis set and the efficacy analysis set, the following patient characteristics will be tabulated as described in Section 8.1.

- Gender (categorical [male, female])
- Age (continuous, categorical [<15 years, ≥15 to <65 years, ≥65 years])
- Body weight (continuous, categorical [<50 kg, ≥50 to <70 kg, ≥70 kg])
- BMI (continuous, categorical [<18.5 kg/m^2, ≥18.5 to <25.0 kg/m^2, ≥25.0 kg/m^2])
- Height (continuous)
- Disease name (categorical [EGFR mutation-positive inoperable or recurrent NSCLC, other])
- Time from the date of initial diagnosis of NSCLC to the start of administration of this drug (continuous, categorical [<6 months, ≥6 to <12 months, ≥12 to <18 months, ≥18 to <24 months, ≥24 months])
- EGFR mutation test results (categorical [positive, negative, equivocal, not performed])

If there is more than one test result, one result will be adopted in the order of positive, equivocal, and negative.

- EGFR mutation test method showing a positive test result (categorical [therascreen® EGFR mutation detection kit RGQ “Qiagen,” cobas® EGFR mutation detection kit v2.0, other, no test method showing a positive test result, test not performed])
- Target lesion (categorical [absent, present])
- T classification (categorical [TX, T0, Tis, T1mi, T1a, T1b, T1c, T2a, T2b, T3, T4])
- N classification (categorical [NX, N0, N1, N2, N3])
- M classification (categorical [M0, M1a, M1b, M1c])
- Metastatic site (categorical [absent, liver, lymph node, bone marrow, bone, brain, adrenal gland, skin, peritoneum, other])
- Histopathological diagnosis (categorical [replacement adenocarcinoma, acinar adenocarcinoma, papillary adenocarcinoma, micropapillary adenocarcinoma, adenocarcinoma in situ, solid adenocarcinoma, special type adenocarcinoma, minimally invasive adenocarcinoma, unclassified adenocarcinoma, atypical adenomatous hyperplasia, squamous cell carcinoma, large cell carcinoma, adenosquamous cell carcinoma, other, not performed])

- ECOG PS (categorical [0, 1, 2, 3, 4, not performed])
- Smoking history (categorical [absent (non-smoker), past (ex-smoker), present (smoker), unknown])
- Brinkman index (continuous, categorical [0, >0 to <200, ≥200 to <400, ≥400])
- History of occupational/environmental exposure to asbestos, pneumoconiosis, etc. (categorical [absent, present, unknown])
- Oxygen administration for treatment of respiratory disease (categorical [absent, present, unknown])
- Number of prior therapies for NSCLC (including EGFR-TKI) (categorical [0,1, 2, 3, 4, ≥5])
- History of drug therapy for NSCLC (categorical [absent, present])
- History of drug therapy for NSCLC (EGFR-TKI) (categorical [absent, present])
- History of previous drug therapy for NSCLC
    - EGFR-TKI (1) (categorical [absent, present])
    - EGFR-TKI (2) (categorical [absent, afatinib, gefitinib, erlotinib, osimertinib])
    - Chemotherapy (categorical [absent, present])
    - History of other specific drug therapy (by therapeutic class [subclass]) (categorical [absent, present])
- Past illness (categorical [absent, present])
- Past illness: Interstitial lung disease (categorical [absent, present])
- Past illness: Lung lesion (excluding interstitial lung disease) or decreased respiratory function (categorical [absent, present])

The disease name (PT) corresponding to lung lesion (excluding interstitial lung disease) or decreased respiratory function should be asthma/bronchospasm (SMQ narrow), respiratory failure (SMQ narrow), or "chronic obstructive pulmonary disease."

- Complication: (categorical [absent, present])
- Complication: Interstitial lung disease (categorical [absent, present])
- Complication: Lung lesion (excluding interstitial lung disease) or decreased respiratory function (categorical [absent, present])
- Complication: Hepatic impairment (categorical [absent, present])
- Complication: Renal impairment (categorical [absent, present])

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

- History of surgery for NSCLC (categorical [absent, present])
- Prior radiotherapy for NSCLC (categorical [absent, present])

8.2.2.2. Disease History

For the safety analysis set, the numbers and proportions of patients with past illness and complications will be tabulated by system organ class (SOC) and preferred term (PT).

8.2.2.3. Administration Status of This Drug

For the safety analysis set, the administration status of this drug will be tabulated for the following:

- Period of administration (≤13 weeks, >13 to ≤26 weeks, >26 to ≤39 weeks, >39 to ≤52 weeks, >52 weeks [ongoing])
- Mean daily dose (unit: mg/day)
- Reason for change/interruption (adverse event, other)

The period of administration is defined as the period from the first date of administration to the last date of confirmation of administration in this study, including the non-treatment period. The mean daily dose will be calculated using the following formula:

$$\text{MDD (mg/day)} = \text{aCD (mg)}/\text{DR (days)}.$$

Here, MDD is the mean daily dose, aCD is the total dose during the administration period excluding the non-treatment period, and DR is the number of days of administration excluding the non-treatment period.

8.2.3. Safety Analysis

The analyses described in this section will be performed on the safety analysis set unless other analysis sets are specified. Analyses, other than those to be performed only on the safety analysis set consisting of consented patients in Section 8.2.3.2, will be performed on the safety analysis set consisting of consented patients as necessary.

Adverse reactions and adverse events occurring between the start date of administration of this drug and the end date of the observation period (or 28 days after the day of discontinuation of administration) will be summarized in listings. All events reported in this study will be included in the listings. For the safety tabulations and analyses (Section 8.2.3.1, Section 8.2.3.2, and Section 8.2.3.3) among the safety analyses in this section, the occurrence of interstitial lung disease will be determined based on the investigator's assessment.

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.

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.

8.2.3.1.3. 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.

8.2.3.2. Adverse Events

For the safety analysis set consisting of consented patients, the number and proportion of patients with adverse events will be tabulated by seriousness for each SOC and PT. If the same adverse reaction (of the same PT) occurs more than once in the same patient and both serious and non-serious events are reported, the event will be regarded as serious.

For the safety analysis set consisting of consented patients, the number and proportion of patients with serious adverse events of CTCAE Grade 5 will be tabulated.

8.2.3.3. Other Endpoints

8.2.3.3.1. Pregnancy

For female patients in the safety analysis set, the presence or absence of pregnancy during the observation period of this study will be tabulated.

8.2.3.3.2. Laboratory Test Values

A listing of laboratory test values will be prepared.

8.2.3.3.3. Survival

The numbers and proportions of patients surviving or death on the end date of the observation period will be calculated. In addition, the number and proportion of patients will be calculated by reason for death.

Survival time will be summarized using the Kaplan-Meier method. Patients surviving at the end of the observation period will be censored at the end date of the observation period.

8.2.3.4. Subgroup Analysis

For each of the factors specified in Section 5.4, the number and proportion of patients experiencing interstitial lung disease will be tabulated.

8.2.3.5. 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

For the efficacy analysis set and the efficacy analysis set consisting of consented patients, the numbers and proportions of patients with each best overall response will be calculated. In addition, the efficacy rate (proportion of patients with a best overall response of CR or PR) and its two-sided 95% confidence interval (exact method) will be calculated. For the calculation of the efficacy rate, patients not reporting a best overall response will be considered to have achieved a best overall response other than CR or PR.

9. LISTINGS

The following listings will be prepared:

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

In addition, a form necessary for reexamination application (PSEHB/PED Notification No. 1128-2 dated November 28, 2017 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) will be prepared.

- Attached Form 2 (Status of occurrence of adverse reactions/infections up to the time of approval)
- Attached Form 12 (Status of occurrence of adverse reactions/infections in the additional pharmacovigilance plan)
- Attached Form 15 (Status of occurrence of adverse reactions/infections in the post-marketing surveillance, etc.)
- Attached Form 16 (Overview of patients in the post-marketing surveillance, etc.)

Furthermore, a form necessary for Periodic Safety Update Reports (PSEHB/PED Notification No. 1128-5 and PSEHB/SD Notification No. 1128-4, dated November 28, 2017 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) will be prepared for Periodic Safety Update Reports.

- Attached Form 1-2 (Status of occurrence of adverse reactions/infections up to the time of approval)
- Attached Form 2 (Status of occurrence of adverse reactions/infections in the post-marketing surveillance, etc.)