



Title: Treatment preference for weekly DPP-4 inhibitors versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus < TRINITY >

NCT Number: NCT03231709

Statistical analysis plan Approve Date: 15-Mar-2018

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Note; This document was translated into English as the language on original version was Japanese.

**Treatment preference
for weekly DPP-4 inhibitors versus daily DPP-4 inhibitors
in patients with type 2 diabetes mellitus
(TRINITY)**

(Protocol number: Trelagliptin-4003)

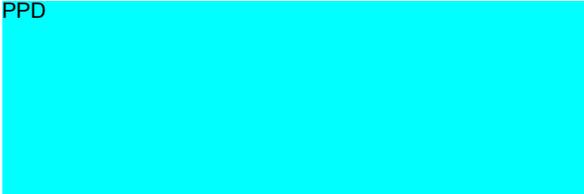
Statistical Analysis Plan

(Ver.2.0: 15 Mar 2018)

Sponsor: Takeda Pharmaceutical Company Limited

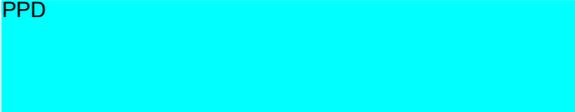
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PPD



Biostatistics Manager:

PPD

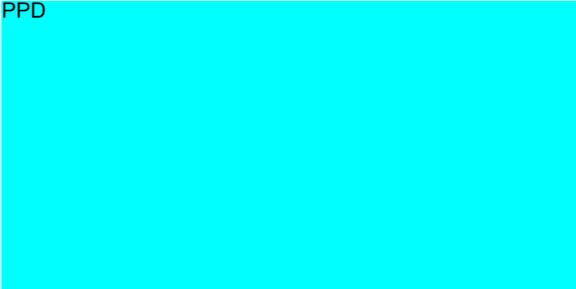


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1. DEFINITIONS of TERMS

- MedDRA: Medical Dictionary for Regulatory Activities
- PT: Preferred Term
- SOC: System Organ Class
- TEAE: Treatment-Emergent Adverse Event
- Summary Statistics: Number of Subjects, Mean, SDs, Maximum values, Minimum values, and Quartiles
- DTSQ: Diabetes Treatment Satisfaction Questionnaire

2. ANALYSIS SET

- Full Analysis Set
The subjects who were randomized and given at least one dose of the study drug
- Safety Analysis Set
The subjects who were given at least one dose of the study drug

3. CONSIDERATIONS on STATISTICAL ANALYSIS

3.1. Adjustments for Covariates

Adjustment for covariates is not performed.

3.2. Handling of Dropouts or Missing Data

Missing values will not be complemented.

3.3. Criteria for Interim Analysis and Early Stopping

Interim analysis will be not performed.

3.4. Multicenter Study

Analyses for consideration of medical institution will not be performed.

3.5. Multiple Comparisons/Multiplicity

It does not adjust multiplicity.

3.6. Examination of Subgroups

Subgroup analysis will not be performed.

3.7. Considerations for Creating Analysis Results

- Confidence Coefficient
95% (two-sided estimation)
- Significance Level
The level of significance should be 5%.
- Summary Statistics
Number of Subjects, mean, SDs, Maximum values, Minimum values, and Quartiles
- Display Digit
 - [Mean, Confidence Coefficient, Quartiles]
Round statistics off to the 1 digits lower than significant digits of the data.
 - [Standard Deviation]
Round statistics off to the 2 digits lower than significant digits of the data.
 - [Minimum and Maximum Values]
Display the data at the significant digits.
 - [Proportion, Percentage]
Round off 2 decimal places and display up to 1 decimal place.
 - [p-value]
Round off 5 decimal places and display up to 4 decimal places. However, when the p-value is less than 0.0001, it is expressed as "p <0.0001".

3.8. Time Window

For each inspection, observation and evaluation item, evaluable data is handled according to the following table. Administration of the study medicine starts from the day after completion of all the examination of Week 0. The date of the first dose is defined as "Day 1" and the day before of the first dose is defined as "Day -1". The criteria of adoption of data on the data obtained after discontinuation in discontinued subjects are as follows.

- HbA1c (NGSP) :
If data up to 14 days after the last dose is included in a time window, it is treated as data of that visit.
- DTSQ treatment satisfaction and Medication Compliance:
As long as the criteria for the analysis set is satisfied, if an evaluation date is included in a time window, it is treated as data of that visit.

When there are multiple data that can be evaluated at the same visit, the one with the closest inspection date, observation date and evaluation date to the reference implementation date is adopted. If the magnitude of the difference from the reference implementation date is the same, the later data is adopted.

The 16th week (Week 16) of the treatment period in the following analysis is handled as the visit of 8 weeks after start of administration of the study drug after switching.

[HbA1c (NGSP), DTSQ treatment satisfaction]

Visit	Reference Date	Time Allowance
Week 0 of the Treatment Period	Number of days after administration: -1	-1
Week 8 of the Treatment Period	Number of days after administration: 56	49 - 63
Week 16 of the Treatment Period	Number of days after administration: 112	105 - 119

[Medication Compliance]

Visit	Reference Date	Time Allowance
Week 8 of the Treatment Period	Number of days after administration: 56	49 - 63
Week 16 of the Treatment Period	Number of days after administration: 112	105 - 119

4. SUBJECTS, DEMOGRAPHIC and OTHER BASELINE CHARACTERISTICS

4.1. Subject Disposition

4.1.1. Study Information

Analysis Set: All subjects who were obtained informed consent

Analysis Variables:

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Show above items.

If the last administration date of the study drug is missing, the last visit date of the study is used.

4.1.2. Subject Disposition

Analysis Set: All subjects who were obtained informed consent

Analysis Variables: All subjects who were obtained informed consent, Randomized Subjects, Full Analysis Set, Safety Analysis Set

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Tabulation of subjects included in/excluded from each analysis set

4.1.3. Eligibility of Subjects

Analysis Set: All subjects who were obtained informed consent

Analysis Variables: Eligibility for the study

[Yes, No (and the reason)]

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Calculate the number of subjects and Proportions (%).

4.1.4. Treatment Exit Status

Analysis Set: Full Analysis Set

Analysis Variables: Treatment Exit Status [Complete, Incomplete (and the reason)]

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Calculate the number of subjects and Proportions (%).

4.1.5. Protocol Deviations and Analysis Datasets

4.1.5.1. Protocol Deviations

Analysis Set: Randomized Subjects

Analysis Variables: Protocol Deviations

[Major GCP Violations, Deviations of Protocol Entry Criteria, Deviations of Discontinuation Criteria, Deviations Related to Treatment Procedure or Dose, Deviations Concerning Excluded Medication or Therapy, Deviations to Avoid Emergency Risk, Deviations Related to Efficacy Evaluation, Deviations Related to Safety Evaluation, Other Deviations]

Analysis Methods: For the above analysis items, the following analysis is performed.

Summarize the number of subjects who have deviated from the protocol, classify the deviations into above category, and show the breakdown of deviations. Subjects applicable for multiple categories will be counted once in each category.

(1) Calculate the number of subjects and Proportions (%).

4.1.5.2. Datasets for Analyses

Analysis Set: Randomized Subjects

Analysis Variables: Subjects excluded from analysis datasets [Reason of exclusion]

Inclusion of Subjects

Full Analysis Set [Adopted]

Safety Analysis Set [Adopted]

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate the number of subjects and Proportions (%) in each analysis set about handling for subjects (and reasons for exclusion). Subjects applicable for multiple categories in reason for excluded will be counted once in each category.
- (2) Calculate the number of subjects and proportions (%) of adopted subjects of each analysis set in randomized subjects.

4.2. Demographics and Other Baseline Characteristics

4.2.1. Distribution of Demographics Items

Analysis Set: Full Analysis Set

Analysis Variables:

Age (years old) [Min<= - <65, 65<= - <75, 75<= - <=Max]

Gender [Male, Female]

Height (cm)

[Min<= - <150, 150<= - <160,
160<= - <170, 170<= - <=Max]

Weight (kg)

[Min<= - <50.0, 50.0<= - <60.0,
60.0<= - <70.0, 70.0<= - <80.0,
80.0<= - <=Max]

BMI (kg/m²)

[Min<= - <18.5, 18.5<= - <25.0,
25.0<= - <=Max]

Duration of Diabetes

[3 Years or More, Less than 3 Years]

Work Status [Worker, Unemployed]

Alcohol Intake History

[Regular Drinker, Occasional Drinker, Non-Drinker]

Smoking Habits [Yes, No]

Experience of Educational Hospitalization on DM

[Yes, No]

Presence of Cohabiter

[Living Alone, Living Together]

Compliance with DPP-4 Inhibitors During 4 weeks before the Start of Treatment Period

[90 Percent or More, Less than 90 Percent]

Number of Oral Drugs per Day at the Beginning of the Treatment Period

[1 or 2 Tablet(s), 3 - 5 Tablets, 6 Tablets or More]

Complication of Metabolic Syndrome

[Yes, No]

HbA1c (NGSP) Level at the Time of Informed Consent

[<7.0%, 7.0%=<-<8.0%, 8.0%=<]

DTSQ Treatment Satisfaction Level (Except for question 2 and 3) at the Time of Informed Consent

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Tabulation for discrete variables and summary statistics for continuous variables

4.2.2. Concurrent Medical Conditions

Analysis Set: Full Analysis Set

Analysis Variables: Concurrent Medical Conditions

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate the number of subjects and Proportions (%).

Analysis variables will be coded using the MedDRA dictionary and be summarized into SOC and PT. SOCs will be sorted in alphabetical order, then PTs will be sorted in frequency order. The method of accounting for the frequency is as follows.

[Method of Accounting for the Frequency]

Within each summary, subjects with one or more events within a level of SOC term is counted only once in that level. Similarly, subjects with one or more events within a level of PT term is counted only once in that level.

4.2.3. Prior and Concomitant Medication

Analysis Set: Full Analysis Set

Analysis Variables: Prior Medication, Concomitant Medication

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate the number of subjects and Proportions (%).
 Analysis variables will be coded using the WHO (World Health Organization) Drug and be summarized into Preferred Name. Coded medications will be sorted in frequency order. Medications used more than once within a subject will be counted only once for the subject.

5. EFFICACY EVALUATIONS

5.1. Primary Endpoint and the Analytical Methods

5.1.1. Treatment Preference (Treatment Selection Rate)

Analysis Set: Subjects in Full Analysis Set from whom preference for treatment was interviewed

Analysis Variables: Patient preference for treatment interviewed from the subjects using the standardized questions

Visit: End of Treatment Period

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate the treatment selection rate (%) for each treatment group and all subjects in the analysis set
- (2) Applying the Mainland-Gart test, the treatment selection rates for once-weekly DPP-4 inhibitor and daily DPP-4 inhibitor are compared by p-value.

Fisher's exact test for the following 2×2 table is performed and p-value will be calculated for subjects who selected either one (excluding subjects who selected "Neither good" nor "Neither wanted").

	(\times , \circ) Prefer to the second treatment.	(\circ , \times) Prefer to the first treatment.
T-A	xx	xx
A-T	xx	xx

- (3) As sensitivity analysis, performed the same analysis as (1) - (2) on the subjects in the Full Analysis Set who were administered both of Trelagliptin and Alogliptin at

least once and were interviewed the treatment preference.

5.2. Secondary Endpoints and the Analytical Methods

5.2.1. Patient Preference by Background Factors

Analysis Set: Subjects in Full Analysis Set from whom preference for treatment was interviewed

Analysis Variables: Patient preference for treatment interviewed from the subjects using the standardized questions

Visit: End of Treatment Period

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate the treatment selection rate (%) for each treatment group and all subjects in the analysis set by background factors.
- (2) Regarding the ratio (odds) of the selection rate of once-weekly dosing of DPP-4 inhibitor to the selection rate of once-daily dosing of DPP-4 inhibitor by each background factor, the odds ratio between the background factor and their both sides 95 % confidence interval are calculated for all subjects in the analysis set (treatment group are combined).

5.3. Other Endpoints and the Analytical Methods

5.3.1. DTSQ Treatment Satisfaction for Each Study Drug at 8 Weeks after Start of Each Study Drug Administration

Analysis Set: Full Analysis Set

Analysis Variables: DTSQ Treatment Satisfaction *1

DTSQ Treatment Satisfaction (each item)

Visit: 8 weeks after start of administration of each study drug

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate summary statistics for each study drug.

*1 Evaluated with the total points of questions 1, 4, 5, 6, 7, and 8

Items that refer to blood glucose levels (questions 2 and 3) are excluded in order to prevent the assessment of satisfaction from being influenced by the blood

glucose level-related part.

5.3.2. HbA1c (NGSP) for Each Study Drug at 8 Weeks after Start of Each Study Drug Administration

Analysis Set: Full Analysis Set

Analysis Variables: HbA1c (NGSP)

Visit: 8 weeks after start of administration of each study drug

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate summary statistics for each study drug.

5.3.3. Treatment Compliance for Each Study Drug at 8 Weeks after Start of Each Study Drug Administration

Analysis Set: Full Analysis Set

Analysis Variables: Treatment Compliance [Properly (90 Percent or More), Generally (70 Percent or More), Half (50 Percent or More), Less than Half (Less than 50 Percent)]

Visit: 8 weeks after start of administration of each study drug

Analysis Methods: For the above analysis items, the following analysis is performed.

- (1) Calculate the number of subjects and Proportions (%) for each study drug.

6. SAFETY EVALUATION

6.1. Brief Summary of Adverse Events (TEAE)

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

- 1) All of the TEAEs
- 2) TEAEs Related to Study Drug
- 3) TEAEs by Severity
- 4) TEAEs Related to Study Drug by Severity
- 5) TEAEs Leading to Discontinuation of Study Drug
- 6) Serious TEAEs
- 7) Serious TEAEs Related to Study Drug

8) Serious TEAEs Leading to Discontinuation of Study Drug

9) TEAEs Leading to Death

Analysis Methods: The following analyses are performed on TEAEs.

(1) Calculate the number of subjects and Proportions (%) by Study Drug.

Incidence rates will be calculated as following.

[Frequency of Subjects]

· Frequency by Severity

Subjects with one or more adverse events within a level of MedDRA term is counted only once in that level using the most severe incident. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

· Analyses Other Than the Above

Subjects with one or more adverse events within a level of MedDRA term is counted only once for that MedDRA term.

The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

(2) For TEAE described in the CRF, prepare a replacement table for SOP and PT. SOC's will be sorted in alphabetical order, then PT's will be sorted in frequency order.

6.2. Display of TEAE

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

- 1) All of the TEAEs
- 2) TEAEs Related to Study Drug
- 3) TEAEs by Severity
- 4) TEAEs Related to Study Drug by Severity
- 5) TEAEs Leading to Discontinuation of Study Drug
- 6) Serious TEAEs
- 7) Serious TEAEs Related to Study Drug
- 8) Serious TEAEs Leading to Discontinuation of Study Drug
- 9) TEAEs Leading to Death
- 10) Non-serious TEAE with Incidence of over 5%

Analysis Methods: For the above analysis items, the following analysis is performed by

Study drug.

- (1) Tabulation of frequencies of all adverse events about number of subjects, its proportions (%) and number of cases. Analysis variables will be coded using the MedDRA dictionary and be summarized into SOC and PT. SOC's will be sorted in alphabetical order, then PT's will be sorted in frequency order. Incidence rates will be calculated as following.

[Frequency of Subjects]

· Frequency (by SOC/PT)

Within each summary, subjects with one or more adverse events within a level of SOC term is counted only once in that level. Similarly, subjects with one or more adverse events within a level of PT term is counted only once in that level. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

· Frequency by Severity (by SOC/PT)

Subjects with one or more adverse events within a level of SOC term is counted only once in that level using the most severe incident. Subjects with one or more adverse events within a level of PT term is counted only once in that level using the most severe incident. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

7. LISTING

Following lists will be created for Full Analysis Set.

- Demographics
- Eligibility for the Study (Inclusion/Exclusion Criteria)
- Discontinuation
- Protocol Deviation
- Concurrent Disease
- Prior Medication
- Concomitant Medication
- Treatment Preference
- DTSQ

- HbA1c
- Study Drug Compliance
- Study Drug Overdose
- TEAE

8. REFERENCE

1. Byron Jones, and Michael G. Kenward, *Design and analysis of cross-over trials (Third Edition)*, New York, 2014, pp.96-100.

9. REVISION HISTORY

Ver.	Date	Author	Revised Content	Reason for Revision
1.0	2017/8/9	PPD	-	-
2.0	2018/3/15	PPD	<ul style="list-style-type: none"> • In order to clarify a part of the analysis content, description was adjusted. • Add description of “3.8. Time Window”. • Description in "4.1.5.2. Datasets for Analyses" was broken up into tabulation about the reasons for exclusion from analysis sets and tabulation about adopted subjects. • Add sensitivity analysis to "5.1.1. Treatment Preference (Treatment Selection Rate)" • Add creation of replacement table of adverse events to "6.1. Brief Summary of Adverse Events (TEAE)" • Revision of "7. LISTING" 	<p>In the process of creation of analysis result layout, some descriptions and clause titles in SAP were reconsidered so that analysis content become easy to be understood.</p> <p>As for Time Window was added by necessity.</p> <p>The sensitivity analysis of the treatment preference had been considered by the results of the data review and added.</p> <p>The contents of LISTING has been revised as it has been changed to a policy that it should cyclopaedically reflect the contents of CRF.</p>