Title: Specified Drug-Use Survey of INISYNC Combination Tablets "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"

NCT Number: NCT03555565

Statistical analysis plan Approve Date: 26-MAR-2019

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

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

Statistical Analysis Plan

(Analyses for tabulation for Periodic Safety Update Report)

Product name : INISYNC Combination Tablets

Sponsor : Takeda Pharmaceutical Company Limited

Seal

Date

Version 3 prepared on March 26, 2019

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List of Terms and Abbreviations

- INISYNC: INISYNC Combination Tablet is abbreviated as INISYNC.
- Adverse drug reaction (ADR), etc.: ADR, etc. is an abbreviation of ADR/infection. ADRs, etc. refer to all adverse events (AEs) other than those assessed by the investigator to be "not related" to INISYNC. In this document, "adverse drug reactions/infections" is used in titles, and "ADRs, etc." is used in the text and tables.
- Causal relationship of "related" to INISYNC: Events whose causal relationship to INISYNC has been assessed "related" or is "unassessable" shall be handled as "related", and events whose causal relationship to INISYNC has been assessed "not related" shall be handled as "not related."
- Survey periods:
    - 1st survey period: April 16, 2016 to October 15, 2016
    - 2nd survey period: October 16, 2016 to April 15, 2017
    - 3rd survey period: April 16, 2017 to October 15, 2017
    - 4th survey period: October 16, 2017 to April 15, 2018
    - 5th survey period: April 16, 2018 to April 15, 2019
    - 6th survey period: April 16, 2019 to April 15, 2020
    - 7th survey period: April 16, 2020 to September 27, 2020

- Description of the drug use-results survey and pre-approval clinical study

  In this statistical analysis plan, the drug use-results survey and pre-approval clinical study will be described respectively as follows:

Study/Survey	Description
Specified Drug Use-Results Survey "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"	Long-term
A phase 3, multicenter, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy and safety of 25 mg of SYR-322 combined with metformin hydrochloride 500 mg once daily in patients with type 2 diabetes mellitus and inadequate glycemic control despite treatment with 25 mg of SYR-322 in addition to diet and/or exercise therapy	CCT-001

- Patients with the CRF uncollected: Enrolled patients for whom the CRF has not been collected
- Patients with the CRF collected: Enrolled patients for whom the CRF has been collected
- Patients with the CRF locked: Patients for whom the CRF has been collected and locked by the data lock point
- Patients with the CRF unlocked: Patients for whom the CRF has been collected but has not been locked by the data lock point

Analysis set

"Safety analysis set" is established as an analysis set in this survey and is defined as follows:

Safety analysis set

The "safety analysis set" is defined as "all INISYNC-treated patients evaluable for safety with no major protocol violation." Patients for whom the CRF has been locked will be excluded from the safety analysis set if any of the following criteria is met:

- Not treated with INISYNC
- Treated before the contract period
- Registered out of the enrollment period
- Registered 15 days or more after INISYNC treatment
- Unknown presence or absence of AEs
- Withdrawal of consent

See the statistical analysis plan of each study for the analysis sets of pre-approval clinical studies.

1 Number of Surveyed Sites, Number of Enrolled Patients, and Patient Composition

1.1 Disposition of Patients

Survey to be analyzed:	Long-term	
Patients included in analysis:	All enrolled patients (enrolled patients)	
Analysis items:	Enrolled patients	
	Surveyed sites	
	Patients with the CRF uncollected	
	Reason for failure to collect	[Being under follow-up, personnel relocation of the investigator, health reasons of the investigator, other]
	Patients with the CRF collected	
	Patients with the CRF unlocked	
	Patients with the CRF locked	
	Patients excluded from safety evaluation*	
	Reason for exclusion (multiple tabulation)	[Not treated with INISYNC, treated before the contract period, registered out of the enrollment period, registered 15 days or more after INISYNC treatment, unknown presence or absence of AEs, withdrawal of consent]
	Safety analysis set	
Analysis methods:	For the aforementioned analysis items, analysis will be performed as described below, and a patient composition diagram will be prepared.	
	For enrolled patients, the number of surveyed sites will also be calculated. One site with different departments will be counted as one site in the survey.	
	The number "0" shall be indicated if there are no patients corresponding to the reasons for exclusion.	
	* "Patients excluded from safety evaluation" are patients with the CRF locked who have been excluded from the safety analysis set.	
	(1) Frequency tabulation	

2 Safety Evaluation

2.1 Status of onset of pre-approval adverse drug reactions/infections (Attached Form 1-2)

Study/Survey to be analyzed:	Pre-approval clinical study (a Japanese and overseas clinical study used for safety evaluation provided in the section of "Adverse Reactions" of the package insert (CCT-001)
Patients included in analysis:	Analysis set for safety data in the QD combination group
Analysis item:	ADRs, etc.
Analysis methods:	For the aforementioned analysis item, analysis will be performed in the integrated pre-approval clinical studies as described below.

(1) Pre-approval status
   1) Number of patients included in the safety analysis set*
   2) Number of patients with ADRs, etc.
   3) Percentages of ADRs

(2) Types of ADRs, etc.
   1) Number of patients with any type of ADR, etc., percentages of ADRs, etc. (by SOC)
   2) Number of patients with any type of ADR, etc., percentages of ADRs, etc. (by PT)

ADRs, etc. shall be coded using the MedDRA/J. In terms of SOCs, ADRs shall be listed in the internationally agreed SOC order. In terms of PTs, ADRs shall be listed in the ascending order of the HLGT and PT codes for the SOC of "Investigations" or in the ascending order of the PT codes for the other SOCs.

The methods of counting events for each analysis are as follows:

[Number of patients with ADRs, etc. by the type of ADR, etc., percentages of ADRs, etc.]

- When the frequency is tabulated:

  An event of a certain SOC or PT that has developed multiple times in a same patient shall be counted as one case of the event. The number of patients included in the safety analysis set shall be the denominator for calculating the percentages of ADRs, etc.

* "Patients included in the safety analysis set" are the aforementioned "object" of the analysis.

2.2 Status of onset of adverse drug reactions/infections in post-marketing surveys, etc. (Attached Form 2)

Study/Survey to be analyzed:	Long-term
Patients included in analysis:	Safety analysis set
Analysis item:	ADRs, etc.
Analysis methods:	For the aforementioned analysis item, analysis will be performed for each post-marketing survey, etc. as described below.

(1) Status of post-marketing surveys, etc.
   1) Number of patients in the safety analysis set*
   2) Number of patients with ADRs, etc.
   3) Percentages of ADRs, etc.

(2) Types of ADRs, etc.
   1) Number of patients with any type of ADR, etc., percentages of ADRs, etc. (by SOC)
   2) Number of patients with any type of ADRs, etc., percentages of ADRs, etc. (by PT)

ADRs, etc. shall be coded using the MedDRA/J. In terms of SOCs, ADRs, etc. shall be listed in the internationally agreed SOC order. In terms of PTs, ADRs, etc. shall be listed in the ascending order of the HLGT and PT codes for the SOC of "Investigations" or in the ascending order of the PT codes for the other SOCs.

The methods of counting events for each analysis are as follows:

[Number of patients with ADRs, etc. by the type of ADR, etc., percentages of ADRs, etc.]

- When the frequency is tabulated:

  An event of a certain SOC or PT that has developed multiple times in a same patient shall be counted as one case of the event. The number of patients included in the safety analysis set shall be the denominator for calculating the percentages of ADRs, etc.

* "Patients included in the safety analysis set" are the aforementioned "object" of the analysis.

History of preparation/update (version control)

Version	Date	Person who prepared/modified the SAP	Comment
1	March 29, 2017	PPD	Version 1 was prepared.
2	February 20, 2018	PPD	Version 2 was prepared.
3	March 26, 2019	PPD	Version 3 was prepared in response to the Partial Amendment to "Style of Attachment to Periodic Safety Update Report and Description Method (dated November 28, 2017).

Attachment 1 Comparison Table for Changes

<Statistical Analysis Plan (modified from Version 1 prepared on March 29, 2017 to Version 2 prepared on February 20, 2018)>

Page	Old	New	Reason for Change
3	Patients with the CRF locked: Patients for whom the CRF has been collected and locked at least once by the data lock point Patients with the CRF unlocked: Patients for whom the CRF has been collected but has never been locked by the data lock point	Patients with the CRF locked: Patients for whom the CRF has been collected and locked by the data lock point Patients with the CRF unlocked: Patients for whom the CRF has been collected but has not been locked by the data lock point	Modified in accordance with the EDC system used in the survey.
4	Analysis set • Not treated with INISYNC • Treated before the contract period • Registered out of the enrollment period • Registered 15 days or more after INISYNC treatment • Unknown presence or absence of AEs	Analysis set • Not treated with INISYNC • Treated before the contract period • Registered 15 days or more after INISYNC treatment • Unknown presence or absence of AEs	Modified for description adjustment.
5	1.1 Disposition of Patients		Added.

Page	Old	New	Reason for Change
6	2.1 List of the adverse drug reactions/infections in the specified drug use-results survey (Attached Form 2) 2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2)		Details of the survey added. The methods for counting the pre-approval study sites clarified.

<Statistical Analysis Plan (modified from Version 2 prepared on February 20, 2018 to Version 3 prepared on March 26, 2019)>

Page	Old	New	Reason for Change
3	List of Terms and Abbreviations Serious adverse events	(Deleted)	Tabulation of serious adverse events (old version of Attached Form 2-2) deleted in response to the amendment to the notification about periodic safety update report.
4	Safety population	Safety analysis set	Modified in accordance with the description in the protocol. In order to conform the descriptions in the results of analyses to the description "number of patients in the safety analysis set" in the notification of amendment, an explanatory note for the difference in the description of the object of analysis was provided in each analysis.
4, 5		"Registered out of the enrollment period" and "Withdrawal of consent" added.	Registered out of the enrollment period: On [redacted], the system prevents registration out of the enrollment period. On the other hand, the system cannot prevent and may cause "enrollment out of the enrollment period" on [redacted], which is used in the study. This was revealed after finalization of Version 2 of the SAP.

Page	Old	New	Reason for Change
			Withdrawal of consent: Added to the EDC system as a new option for a reason of exclusion.
6, 7	2.1 List of adverse drug reactions/infections in the specified drug use-results survey (Attached Form 2) 2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2)	2.1 Status of onset of pre-approval adverse drug reactions/infections (Attached Form 1-2) 2.2 Status of onset of adverse drug reactions/infections in post-marketing surveys, etc. (Attached Form 2)	Modified in response to the amendment to the notification about periodic safety update report. [Details of the change] Old version of Attached Form 2: Divided into “Status of onset of pre-approval adverse drug reactions/infections (Attached Form 1-2)” in the integrated pre-approval clinical studies and “Status of onset of adverse drug reactions/infections in post-marketing surveys, etc. (Attached Form 2)” for each post-marketing survey. Descriptions of the terms adjusted. (Deleted) Number of surveyed sites, number of ADRs Old version of Attached Form 2-2: (Deleted)

Statistical Analysis Plan

(Analyses for tabulation for Periodic Safety Update Report)

Product name : INISYNC Combination Tablets

Sponsor : Takeda Pharmaceutical Company Limited

Seal

Date

Version 2 prepared on February 20, 2018

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2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2) 7
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List of Terms and Abbreviations

- INISYNC: INISYNC Combination Tablet is abbreviated as INISYNC.
- Adverse drug reaction (ADR), etc.: ADR, etc. is an abbreviation of ADR/infection. ADRs, etc. refer to all adverse events (AEs) other than those assessed by the investigator to be "not related" to INISYNC. In this document, "adverse drug reactions/infections" is used in titles, and "ADRs, etc." is used in the text and tables.
- Serious adverse event (SAE):
  - Clinical studies conducted before approval: AEs considered "serious"
  - Surveys: AEs assessed "serious" by the investigator. Events included in the MedDRA code list in Takeda Medically Significant AE List will be handled as serious even if assessed by the investigator to be "not serious."
- Causal relationship of "related" to INISYNC: Events whose causal relationship to INISYNC has been assessed "related" or is "unassessable" shall be handled as "related", and events whose causal relationship to INISYNC has been assessed "not related" shall be handled as "not related."
- Survey periods:
  - 1st survey period: April 16, 2016 to October 15, 2016
  - 2nd survey period: October 16, 2016 to April 15, 2017
  - 3rd survey period: April 16, 2017 to October 15, 2017
  - 4th survey period: October 16, 2017 to April 15, 2018
  - 5th survey period: April 16, 2018 to April 15, 2019
  - 6th survey period: April 16, 2019 to April 15, 2020
  - 7th survey period: April 16, 2020 to September 27, 2020
- Description of the survey and pre-approval clinical study

  In this statistical analysis plan, the survey and pre-approval clinical study will be described respectively as follows:

Study/Survey	Description
Specified Drug Use-Results Survey "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"	Long-term
A phase 3, multicenter, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy and safety of 25 mg of SYR-	CCT-001

Study/Survey	Description
322 combined with metformin hydrochloride 500 mg once daily in patients with type 2 diabetes mellitus and inadequate glycemic control despite treatment with 25 mg of SYR-322 in addition to diet and/or exercise therapy	

- Patients with no CRF collected: Enrolled patients for whom the CRF has not been collected
- Patients with the CRF collected: Enrolled patients for whom the CRF has been collected
- Patients with the CRF locked: Patients for whom the CRF has been collected and locked by the data lock point
- Patients with the CRF unlocked: Patients for whom the CRF has been collected but has not been locked by the data lock point

Analysis set

"Safety population" is established as an analysis set in this survey. This analysis set is defined as follows:

Safety population

In this document, the "safety population" is defined as "all INISYNC-treated patients evaluable for safety with no major protocol violation." Patients for whom the CRF has been locked will be excluded from the safety population if any of the following criteria is met:

- Not treated with INISYNC
- Treated before the contract period
- Registered 15 days or more after INISYNC treatment
- Unknown presence or absence of AEs

See the statistical analysis plan of each study for the analysis sets of pre-approval clinical studies.

1 Number of Surveyed Sites, Number of Enrolled Patients, and Patient Composition

1.1 Disposition of Patients

The disposition of patients has not been prepared because there were no patients with locked CRF as of the data lock point of the periodic safety update report.

Survey to be analyzed:	Long-term	
Patients included in analysis:	All enrolled patients (enrolled patients)	
Analysis items:	Enrolled patients	
	Number of surveyed sites	
	Patients with the CRF uncollected	
	Reason for failure to collect	[Being under follow-up, personnel relocation of the investigator, health reasons of the investigator, other]
	Patients with the CRF collected	
	Patients with the CRF unlocked	
	Patients with the CRF locked	
	Patients excluded from safety evaluation	
	Reason for exclusion (multiple tabulation)	[Not treated with INISYNC, treated before the contract period, registered 15 days or more after INISYNC treatment, unknown presence or absence of AEs]
	Safety analysis set	
Analysis methods:	For the aforementioned analysis items, analysis will be performed as described below, and a patient composition diagram will be prepared.	
	For enrolled patients, the number of surveyed sites will also be calculated. One site with different departments will be counted as one site in the survey.	
	The number “0” shall be indicated if there are no patients corresponding to the reasons for exclusion.	
	(1) Frequency tabulation	

2 Safety Evaluation

2.1 List of adverse drug reactions/infections in the drug use-results survey/specified drug use-results survey (Attached Form 2)

Study/Survey to be analyzed:
(1) Pre-approval clinical study (a Japanese and overseas clinical study used for safety evaluation provided in the section of "Adverse Reactions" of the package insert (CCT-001))
(2) Long-term

Patients included in analysis:
(1) Analysis set for safety data in the QD combination group
(2) Safety population

Analysis item: ADRs, etc.

Analysis methods: For the aforementioned analysis item, analysis will be performed as described below in the patients (1) and (2) in each of the pre-approval clinical study and drug use-results survey/specified drug use-results survey.

(1) Number of surveyed sites, number of surveyed patients, summary of ADRs, etc.
   1) Number of surveyed sites
   2) Number of surveyed patients
   3) Number of patients with ADRs, etc.
   4) Number of ADRs
   5) Proportion of patients with ADRs, etc.

(2) Types of ADRs, etc.
   1) Number of patients with any type of ADR, etc., proportion of patients with ADRs, etc. (by SOC)
   2) Number of patients with any type of ADR, etc., proportion of patients with ADRs, etc. (by PT)

ADRs, etc. shall be coded using the MedDRA/J. In terms of SOCs, ADRs shall be listed in the internationally agreed SOC order. In terms of PTs, ADRs shall be listed in the ascending order of the HLGT and PT codes for the SOC of "Investigations" or in the ascending order of the PT codes for the other SOCs.

The methods of counting for each analysis are as follows:

[Number of surveyed sites]

For the pre-approval clinical study, a same site shall be counted as one site, and the total number of study sites shall be counted. One site with different departments will be counted as one site in the survey.

[Number of surveyed patients]

The number of patients to be analyzed shall be counted.

[Number of ADRs, etc.]

The total number of cases shall be counted.

[Number of patients with ADRs, etc. by the type of ADR, etc., proportion of patients with ADRs, etc.]

- When the frequency is tabulated by SOC:

  An event of a same SOC that has developed multiple times in a same patient shall be counted as one ADR, etc. of the SOC. The number of surveyed patients shall be the denominator for calculating the proportion of patients with ADRs, etc.

- When the frequency is tabulated by PT:

  An event of a same PT that has developed multiple times in a same patient shall be counted as one ADR, etc. of the PT. The number of surveyed patients shall be the denominator for calculating the proportion of patients with ADRs, etc.

2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2)

Study/Survey to be analyzed:	(1) Pre-approval clinical study (a Japanese and overseas clinical study used for safety evaluation provided in the section of "Adverse Reactions" of the package insert (CCT-001))
	(2) Long-term
Patients included in analysis:	(1) Analysis set for safety data in the QD combination group
	(2) Safety population
Analysis item:	SAEs
Analysis methods:	For the aforementioned analysis item, analysis will be performed as described below in the patients (1) and (2) in each of the pre-approval clinical study and drug use-results survey/specified drug use-results survey.

(1) Number of surveyed sites, number of surveyed patients, summary of SAEs

1) Number of surveyed sites
2) Number of surveyed patients
3) Number of patients with SAEs
4) Number of SAEs
5) Proportion of patients with SAEs

(2) Types of SAEs

1) Number of patients with any type of SAE, proportion of patients with SAEs (by SOC)

2) Number of patients with any type of SAE, proportion of patients with SAEs (by PT)
3) Number of patients with SAEs whose causal relationship to INISYNC has been assessed “not related” (by PT)

SAEs shall be coded using the MedDRA/J. In terms of SOCs, SAEs shall be listed in the internationally agreed SOC order. In terms of PTs, SAEs shall be listed in the ascending order of the HLGT and PT codes for the SOC of “Investigations” or in the ascending order of the PT codes for the other SOCs.

The methods of counting for each analysis are as follows:

[Number of surveyed sites]

For the pre-approval clinical study, a same site shall be counted as one site, and the total number of study sites shall be counted. One site with different departments will be counted as one site in the survey.

[Number of surveyed patients]

The number of patients to be analyzed shall be counted.

[Number of serious SAEs]

The total number of SAEs shall be counted.

[Number of patients with SAEs by the type of SAE, proportion of patients with SAEs]

- When the frequency is tabulated by SOC:
  An event of a same SOC that has developed multiple times in a same patient shall be counted as one SAE of the SOC. The number of surveyed patients shall be the denominator for calculating the proportion of patients with SAEs.
- When the frequency is tabulated by PT:
  An event of a same PT that has developed multiple times in a same patient shall be counted as one SAE of the PT. When an event of a same PT has developed in a same patient multiple times and the causal relationship has been assessed “related” to INISYNC in one case but has been assessed “not related” in another case, the event shall be counted as one SAE that is “related” to INISYNC. The number of surveyed patients shall be the denominator for calculating the proportion of patients with SAEs.

History of preparation/update (version control)

Version	Date	Person who prepared/modified the SAP	Comment
1	March 29, 2017	PPD	Version 1 was prepared.
2	February 20, 2018	PPD	Version 2 was prepared.

Attachment 1 Comparison Table for Changes

<Statistical Analysis Plan (modified from Version 1 prepared on March 29, 2017 to Version 2 prepared on February 20, 2018)>

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3	Patients with the CRF locked: Patients for whom the CRF has been collected and locked at least once by the data lock point Patients with the CRF unlocked: Patients for whom the CRF has been collected but has never been locked by the data lock point	Patients with the CRF locked: Patients for whom the CRF has been collected and locked by the data lock point Patients with the CRF unlocked: Patients for whom the CRF has been collected but has not been locked by the data lock point	Modified in accordance with the EDC system used in the survey.
4	Analysis set • Not treated with INISYNC • Treated before the contract period • Registered out of the enrollment period • Registered 15 days or more after INISYNC treatment • Unknown presence or absence of AEs	Analysis set • Not treated with INISYNC • Treated before the contract period • Registered 15 days or more after INISYNC treatment • Unknown presence or absence of AEs	Modified for description adjustment.
5	1.1 Disposition of Patients		Added.

Page	Old	New	Reason for Change
6	2.1 List of the adverse drug reactions/infections in the specified drug use-results survey (Attached Form 2) 2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2)		Details of the survey added. The methods for counting the pre-approval study sites clarified.

Statistical Analysis Plan

(Analyses for tabulation for Periodic Safety Update Report)

Product name : INISYNC Combination Tablets

Sponsor : Takeda Pharmaceutical Company Limited

Seal

Date

Version 1 prepared on March 29, 2017

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2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2) 7
History of preparation/update (version control) 9

List of Terms and Abbreviations

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- Serious adverse event (SAE):
  - Clinical studies conducted before approval: AEs considered "serious"
  - Surveys: AEs assessed "serious" by the investigator. Events included in the MedDRA code list in Takeda Medically Significant AE List will be handled as serious even if assessed by the investigator to be "not serious."
- Causal relationship of "related" to INISYNC: Events whose causal relationship to INISYNC has been assessed "related" or is "unassessable" shall be handled as "related", and events whose causal relationship to INISYNC has been assessed "not related" shall be handled as "not related."
- Survey periods:
  - 1st survey period: April 16, 2016 to October 15, 2016
  - 2nd survey period: October 16, 2016 to April 15, 2017
  - 3rd survey period: April 16, 2017 to October 15, 2017
  - 4th survey period: October 16, 2017 to April 15, 2018
  - 5th survey period: April 16, 2018 to April 15, 2019
  - 6th survey period: April 16, 2019 to April 15, 2020
  - 7th survey period: April 16, 2020 to September 27, 2020
- Description of the survey and pre-approval clinical study

  In this statistical analysis plan, the survey and pre-approval clinical study will be described respectively as follows:

Study/Survey	Description
Specified Drug Use-Results Survey "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"	Long-term
A phase 3, multicenter, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy and safety of 25 mg of SYR-	CCT-001

Study/Survey	Description
322 combined with metformin hydrochloride 500 mg once daily in patients with type 2 diabetes mellitus and inadequate glycemic control despite treatment with 25 mg of SYR-322 in addition to diet and/or exercise therapy	

- Patients with the CRF uncollected: Enrolled patients for whom the CRF has not been collected
- Patients with the CRF collected: Enrolled patients for whom the CRF has been collected
- Patients with the CRF locked: Patients for whom the CRF has been collected and locked at least once by the data lock point
- Patients with the CRF unlocked: Patients for whom the CRF has been collected but has never been locked by the data lock point

Analysis set

"Safety population" is established as an analysis set in this survey. This analysis set is defined as follows:

Safety population

In this document, the "safety population" is defined as "all INISYNC-treated patients evaluable for safety with no major protocol violation." Patients for whom the CRF has been locked will be excluded from the safety population if any of the following criteria is met:

- Not treated with INISYNC
- Treated before the contract period
- Registered out of the enrollment period
- Registered 15 days or more after INISYNC treatment
- Unknown presence or absence of AEs

See the statistical analysis plan of each study for the analysis sets of pre-approval clinical studies.

1 Number of Surveyed Sites, Number of Enrolled Patients, and Patient Composition

1.1 Disposition of Patients

The disposition of patients has not been prepared because there were no patients with locked CRF as of the data lock point of the periodic safety update report.

2 Safety Evaluation

2.1 List of adverse drug reactions/infections in the drug use-results survey/specified drug use-results survey (Attached Form 2)

Study/Survey to be analyzed: (1) Pre-approval clinical study (a Japanese and overseas clinical study used for safety evaluation provided in the section of "Adverse Reactions" of the package insert (CCT-001))

Patients included in analysis: (1) Analysis set for safety data in the QD combination group

Analysis item: ADRs, etc.

Analysis methods: For the aforementioned analysis item, analysis will be performed as described below.

(1) Number of surveyed sites, number of surveyed patients, summary of ADRs, etc.
   1) Number of surveyed sites
   2) Number of surveyed patients
   3) Number of patients with ADRs, etc.
   4) Number of ADRs
   5) Proportion of patients with ADRs, etc.

(2) Types of ADRs, etc.
   1) Number of patients with any type of ADR, etc., proportion of patients with ADRs, etc. (by SOC)
   2) Number of patients with any type of ADR, etc., proportion of patients with ADRs, etc. (by PT)

ADRs, etc. shall be coded using the MedDRA/J. In terms of SOCs, ADRs shall be listed in the internationally agreed SOC order. In terms of PTs, ADRs shall be listed in the ascending order of the HLGT and PT codes for the SOC of "Investigations" or in the ascending order of the PT codes for the other SOCs.

The methods of counting for each analysis are as follows:

[Number of surveyed sites]

For the pre-approval clinical study, the total number of study sites shall be counted.

[Number of surveyed patients]

The number of patients to be analyzed shall be counted.

[Number of ADRs, etc.]

The total number of cases shall be counted.

[Number of patients with ADRs, etc. by the type of ADR, etc., proportion of patients with ADRs, etc.]

- When the frequency is tabulated by SOC:

An event of a same SOC that has developed multiple times in a same patient shall be counted as one ADR, etc. of the SOC. The number of surveyed patients shall be the denominator for calculating the proportion of patients with ADRs, etc.

- When the frequency is tabulated by PT:

  An event of a same PT that has developed multiple times in a same patient shall be counted as one ADR, etc. of the PT. The number of surveyed patients shall be the denominator for calculating the proportion of patients with ADRs, etc.

2.2 List of serious adverse events in the drug use-results survey/specified drug use-results survey/post-marketing clinical study (Attached Form 2-2)

Study/Survey to be analyzed:	(1) Pre-approval clinical study (a Japanese and overseas clinical study used for safety evaluation provided in the section of "Adverse Reactions" of the package insert (CCT-001))
Patients included in analysis:	(1) Analysis set for safety data in the QD combination group
Analysis item:	SAEs
Analysis methods:	For the aforementioned analysis item, analysis will be performed as described below.

(1) Number of surveyed sites, number of surveyed patients, summary of SAEs
   1) Number of surveyed sites
   2) Number of surveyed patients
   3) Number of patients with SAEs
   4) Number of SAEs
   5) Proportion of patients with SAEs

(2) Types of SAEs
   1) Number of patients with any type of SAE, proportion of patients with SAEs (by SOC)
   2) Number of patients with any type of SAE, proportion of patients with SAEs (by PT)
   3) Number of patients with SAEs whose causal relationship to INISYNC has been assessed "not related" (by PT)

SAEs shall be coded using the MedDRA/J. In terms of SOCs, SAEs shall be listed in the internationally agreed SOC order. In terms of PTs, SAEs shall be listed in

the ascending order of the HLGT and PT codes for the SOC of "Investigations" or in the ascending order of the PT codes for the other SOCs.

The methods of counting for each analysis are as follows:

[Number of surveyed sites]

For the pre-approval clinical study, the total number of study sites shall be counted.

[Number of surveyed patients]

The number of patients to be analyzed shall be counted.

[Number of serious SAEs]

The total number of SAEs shall be counted.

[Number of patients with SAEs by the type of SAE, proportion of patients with SAEs]

- When the frequency is tabulated by SOC:
  An event of a same SOC that has developed multiple times in a same patient shall be counted as one SAE of the SOC. The number of surveyed patients shall be the denominator for calculating the proportion of patients with SAEs.
- When the frequency is tabulated by PT:
  An event of a same PT that has developed multiple times in a same patient shall be counted as one SAE of the PT. When an event of a same PT has developed in a same patient multiple times and the causal relationship has been assessed "related" to INISYNC in one case but has been assessed "not related" in another case, the event shall be counted as one SAE that is "related" to INISYNC. The number of surveyed patients shall be the denominator for calculating the proportion of patients with SAEs.

History of preparation/update (version control)

Version	Date	Person who prepared/modified the SAP	Comment
1	March 29, 2017	PPD	Version 1 was prepared.