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Statistical Analysis Plan

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Product Name: Samsca
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1. Definition

1.1. Terms

Terms	Definition
Adverse event	An adverse event refers to any undesirable medical occurrence that has happened to a patient who has been administered a pharmaceutical product, and it does not necessarily only refer to those with a causal relationship with the administration of the said pharmaceutical product. In other words, an adverse event refers to any undesirable, unintended sign (for example, abnormal clinical test values), symptom, or disease that is temporally related to the use of a pharmaceutical product, regardless of whether there is a causal relationship with the said pharmaceutical product. For the notation of organ-specific major classifications and symptom names, etc., the latest version of "MedDRA/J" at the time of reporting is used.
Adverse Drug Reaction (ADR)	Among the adverse events, those that have been determined to have an undeniable causal relationship with this drug (excluding "no causal relationship"). For the notation of organ classification and symptom names, the latest version of "MedDRA/J" at the time of reporting is used.
Serious adverse event	1. Death 2. Disability: A state indicating the manifestation of functional impairment to the extent that it interferes with daily life. 3. Risk of death: Symptoms that may lead to death: Cases where the patient was exposed to the risk of death when ADRs or infectious diseases occurred. This does not imply a hypothetical meaning that if the ADRs or infectious diseases were more severe, it could have led to death. 4. Risk of disability: Symptoms that may lead to disability: Depending on the patient's constitution, it refers to symptoms that may lead to functional impairment to the extent that it interferes with daily life. 5. Hospitalization or extension of hospital stay: Symptoms requiring hospitalization or extension of hospital stay for treatment: Cases where hospitalization or extension of hospital stay was required for the treatment of ADRs or infectious diseases. It does not include hospitalization or extension of hospital stay for testing. Also, hospitalization for observation of the course of ADRs or infectious diseases that are healing or improving does not apply. 6. Serious as per 1-5: Symptoms that are serious in accordance with 1 to 5: Refers to serious symptoms that require measures to prevent outcomes like those in 1 to 5. 7. Congenital anomalies, etc.: Congenital diseases or abnormalities in future generations: Cases suspected of causing abnormalities in newborns due to exposure to drugs before or during pregnancy apply. For the notation of organ classification and symptom names, the latest version of "MedDRA/J" at the time of reporting is used.
Start date of administration of this drug	The first administration start date as described in the administration status of Samsca (hereinafter referred to as "this drug").
End date of administration of this drug	The last administration end date as described in the administration status of this drug.

Terms	Definition
Supplement of the end date of administration of this drug	In the administration status of this drug, if the administration end date of this drug in the final record of the same Case Report Form (CRF) number is blank or a non-existent date, the administration end date of this drug is supplemented in the following order of priority. - If the "start date of administration of this drug in the final record" is less than or equal to the "end date of the observation period", then the "end date of the observation period". - If the "start date of administration of this drug in the final record" is greater than the "end date of the observation period" and less than or equal to the "last recorded survey confirmation date", then the "last recorded survey confirmation date".
Period until the manifestation of adverse events (or ADRs)	Calculate using the following formula. Adverse event (or ADR) onset date - start date of administration of this drug +1.
Baseline	Data of the initiation date of this drug administration. However, if there is no data on the initiation date of this drug, use the data closest to the initiation date before administration.

1.2. Cases for Analysis

The unit for the cases to be analyzed is primarily based on the "Patient's Unique Number".

Terms	Definition
Registered cases	Cases registered with a date up to the data cut-off date, and the registration status is "Registered" or "Registered (No Survey)".
Continuing cases from clinical trials	Among the registered cases, cases that were registered with "Participation in Clinical Trials" as "Yes" on the registration form. In the same case, if the registration content is different, prioritize "Yes" over "No" and "Unknown".
Unknown cases (Cases where participation in clinical trials is unknown)	Among the registered cases, cases that were registered with "Participation in Clinical Trials" as "Unknown" on the registration form.
Post-marketing cases	Among the registered cases, cases that were registered with "Participation in Clinical Trials" as "No" on the registration form. In the same case, if the registration content is different, prioritize "No" over "Unknown".
Number of registered cases targeted for CRF collection	Among the registered cases, the number of cases where the first CRF was generated.
Unrecovered CRF cases	Among the target registered cases for CRF collection, cases where the CRF has not been collected.
Unobtained CRF cases	Among the target registered cases for CRF collection, cases where the CRF has not been obtained.
Recovered CRF cases	Among the target registered cases for CRF collection, cases where the CRF has been collected and the data has been fixed.
Cases excluded from safety analysis	Among the post-marketing cases of the CRF collection, cases that fall under the following items. However, even if it is a continuous case from a clinical trial, if it falls under the following 2), it will be treated as a case excluded from the safety analysis. 1) Cases where the drug has not been administered 2) Cases where the details of the administration status cannot be confirmed because the administration status of the drug is not described
Cases subject to safety analysis	Among the post-marketing cases of the CRF collection, cases excluding those excluded from the safety analysis.

Terms	Definition
Cases excluded from efficacy analysis	Among the cases subject to safety analysis, cases that fall under the following items. 1) Cases where the purpose of use is not "suppression of ADPKD progression with a rapid kidney volume increase in patients with increased kidney volume" 2) Cases where the efficacy evaluation items have not been measured after the administration of the drug, or there is no efficacy data measured within the allowable range at each evaluation time
Cases subject to efficacy analysis	Among the cases subject to safety analysis, cases excluding those excluded from the efficacy analysis.

1.3. Evaluation Period and Evaluation Range

The following formula is used to calculate the number of days.

Number of days = [Observation Day] - [Start Day of Administration] + 1 (The same day is considered as the first day)

Furthermore, the pre-administration value adopts the "start date of administration". However, if there is no data for the "start date of administration", the data closest to the start date of administration will be adopted. This pre-administration value is used as the baseline.

The "clinical test values" and "progression of renal function, etc." will adopt the data from the final volume and final SEQ if there is the same date among the data with test values.

Evaluation Period	Standard Number of Days	Permissible Range
Pre-administration	One day before the start of administration	Within 0 days
Start date of administration	Start date of administration	Day 1

1.4. Matters Concerning Statistical Analysis Output

1.4.1. Summary Statistics

Calculate the mean, standard deviation, minimum value, median, and maximum value.

1.4.2. Significance Level and Confidence Interval of the Test

The significance level of the test is set at a two-tailed 5%, and the confidence level of the confidence interval is set at a two-tailed 95%.

1.4.3. Display Digits

The display digits (valid digits) for each clinical test value item shall be as per the table below.

Classification	Item Name	Unit	Display Digits*
Transition of Kidney volume	Total Kidny Volume of Both Sides	mL	0.001
Transition of Renal Function, etc.	Height	cm	0.1
	Weight	kg	0.01
	Serum Creatinine Value	mg/dL	0.01

	e-GFR	mL/min/1.73m^2	0.001
	Creatinine Clearance	mL/min	0.1
Hematological Biochemical Examination	AST(GOT)	IU/L	0.1
	ALT(GPT)	IU/L	0.1

* The number of digits displayed after rounding off.

1.4.3.1. Minimum Value, Maximum Value

Display up to the significant digits of the data.

1.4.3.2. Ratio, Percentage

Round to the second decimal place and display up to the first decimal place. However, in the case of the incidence rate of side effects, round to the third decimal place and display up to the second decimal place.

1.4.3.3. p Value

Round to the fourth decimal place and display up to the third decimal place.However, if the p-value is <0.001, display it as p<0.001.

1.4.4. Software

The following software will be used for analysis:

- SAS 9.4 or later
- Microsoft Excel 2016 or later

1.4.5. Sample Code

1.4.5.1. Estimation of cumulative incidence over time using the Kaplan-Meier method and creation of a dataset for graphing.

```
proc lifetest data =[input dataset] alpha = 0.05 method = KM plots = (s, lls) outs = [output dataset1];
    strata [strata variable] ;
    time [time variable] * [censoring variable] (0) ;
run ;
proc means data = [output dataset1] max noprint;
    class [strata variable] ;
    var SURVIVAL ;
    output out = [output dataset2] min = [min output variable] ;
run;
data [output dataset2] ;
    set [output dataset2] ;
    if [strata variable] ^= . ;
run;
```

```
data [output dataset1] ;
    merge [output dataset1] [output dataset2] ;
    by [strata variable] ;
    if SURVIVAL = . then SURVIVAL = [min output variable] ;
run;
data [graph output dataset] ;
    set [output dataset1] ;
    [rate output variable] = 1 – SURVIVAL ;
    output ;
    if _CENSOR_ = 1 then do;
       [rate output variable] = [rate output variable] + 0.025 ;
       output ;
       [rate output variable] = [rate output variable] – 0.025 ;
       output ;
    end ;
run;
```

1.4.5.2. Linear Mixed Effects Model

```
proc mixed data = [input dataset] ;
    class [pre-post treatment group variable] [case number variable] ;
    model [objective variable] = [pre-post treatment group variable] [time (year) variable] [pre-post
treatment group variable]*[time (year) variable]
                                [case number variable] [case number variable]* [time (year) variable] / s cl ;
    random INT [time (year) variable] / type = un sub = [case number variable] s gcorr ;
    parms / pdata = covpe noiter ;
run ;
```

Note: [pre-post treatment group variable] and [case number variable] are categorical values, [time (year) variable] is a continuous value.

The INT in the random statement is specified as is, meaning the intercept. The intercept and slope vary between individuals.random.

2. Statistical Analysis

2.1. Case Composition

2.1.1. Excluded Cases

A list of case numbers and reasons for exclusion will be created for cases excluded from safety analysis and efficacy analysis.

2.2. Patient Background Factors and Treatment Factors

【Analysis Target】

The target for the safety analysis will be aggregated.

【Analysis Method】

For each item of patient background factors and treatment factors shown in Table 1, the number of cases and composition ratio will be calculated by category. Summary statistics will be calculated for continuous variables (Age, e-GFR (pre-administration), creatinine clearance (pre-administration), total kidney volume on both sides (pre-administration)).

For patient background factors, the information described in the final volume of CRF will be adopted as a rule, and the first volume will be adopted depending on the item. For treatment factors and clinical test values, the information described in all collected volumes will be adopted.

The pre-dose creatinine clearance (Ccr) is calculated using the pre-dose serum creatinine value for cases with pre-dose values, using the following formula[1]:

- For men: Ccr = {(140-age) x weight(kg)} / {72 x serum creatinine value(mg/dL)}
- For women: Ccr = {(140-age) x weight(kg)} / {72 x serum creatinine value(mg/dL)} x 0.85

The pre-dose e-GFR is prioritized according to the physician's notation. If there is no physician's notation, it is calculated for cases with pre-dose values using the following formula[2]:

- For men: e-GFR = (194 x serum creatinine value(mg/dL)^-1.094 x age^-0.287)
- For women: e-GFR = (194 x serum creatinine value(mg/dL)^-1.094 x age^-0.287) x 0.739

The height-corrected total kidney volume on both sides is calculated using the following formula:

- Total kidney volume on both sides (mL) ÷ (height(cm) ÷ 100)

Table1. Distribution of Cases by Patient Background Factors and Treatment Factors

Item Name	Category	Aggregation Method
Gender	1. Male 2. Female 3. Unknown	Frequency Tabulation Final Subdivision Adoption of CRF
Age	1. Under 15 years old 2. 15 years old and above but under 65 3. 65 years old and above 4. Unknown	Summary statistics, Frequency tabulation Adopt the date of birth from the final volume of the CRF, and calculate the age from the start date of this drug administration. If the date of birth in the final volume of the CRF is blank or non-existent, adopt the age from

Item Name	Category	Aggregation Method
		the first volume of the CRF.
e-GFR (Before Administration) (mL/min/1.73m^2)	1. Less than 15 2. 15 to less than 30 3. 30 to less than 45 4. 45 to less than 60 5. 60 to less than 90 6. 90 and above 7. Unknown	Summary statistics, Frequency tabulation Full volume adoption Prioritize physician's notes, calculate if there are no physician's notes.
Bilateral Total Kidney Volume (Pre-administration)(mL) * Cases with data up to 3 months (92 days) before the administration of Samusca.	1. Less than 750 2. 750 to less than 1500 3. 1500 to less than 3000 4. 3000 to less than 4500 5. 4500 to less than 6000 6. 6000 and above 7. Unknown	Summary statistics, Frequency tabulation Full volume adoption

2.3. Safety-related Aggregation

2.3.1. Manifestation Status of ADRs and Infectious Diseases

2.3.1.1. Manifestation status of adverse events, ADRs, and infectious diseases in post-marketing surveilances, etc., and manifestation status of ADRs and infectious diseases in additional drug safety monitoring plans

【Analysis Target】

Safety analysis target cases

【Analysis Method】

As shown in Table 2, the number of safety analysis target cases and the number of cases of adverse events, etc., are aggregated for the usage performance survey, and the manifestation rate of adverse events, etc., is calculated. In addition, frequency aggregation is performed separately for SOC and PT, and the manifestation rate is calculated.

*Display order: SOC international agreement order, PT code ascending order

Table 2. Overview of the manifestation of ADRs and infectious diseases

Item Name	Definition content
Causal Relationship	Adopt the causality determined by the physician.
Severity	Adopt the severity determined by the physician.
Case Number	The case numbers used to count the number of survey cases and the number of cases with ADRs, etc., are as follows: ADPKD: Patient-specific number (BaseEntryNO)
Number of Cases Subject to Safety Analysis	Aggregate the number of cases for safety analysis.
Number of Cases with ADRs, etc.	If multiple ADRs occur in the same case, count it as one case.
Incidence Rate of ADRs, etc.	Number of cases with ADRs / Number of cases for safety analysis x 100
Major Classification by Organ	MedDRA SOC (name)
Basic or Subordinate Terms	MedDRA PT (name)

Item Name		Definition content
Incidence Rate by SOC, PT		SOC : Number of cases with ADRs / Number of cases for safety analysis x 100 PT : Number of cases with ADRs / Number of cases for safety analysis x 100
ADPKD	Usage Performance Survey (Post-Marketing Cases)	Target all cases for safety analysis.
Examination Item Name1		Name assigned from safety review items.
Examination Item Name2		Name assigned from safety review items. If there is a name different from the examination item name 1, output it.

2.3.2. List of serious adverse events in post-marketing surveillance, List of serious ADRs in post-marketing surveillance

【Analysis Target】

Safety analysis target cases

【Analysis Method】

As shown in Table 3, for the post-marketing surveillance, the number of survey cases and the number of cases with serious adverse events are aggregated, and the incidence rate of serious adverse events is calculated. In addition, frequency aggregation by SOC and PT is performed, and the incidence rate is calculated. In the PT-specific aggregation, events where the causal relationship has been denied (unrelated) are also aggregated, but if there are events that are related and events where the causal relationship has been denied in the same PT in the same case, the related events are prioritized and not counted as events where the causal relationship has been denied.

In addition, similar aggregation is performed for serious ADRs, but aggregation of events where the causal relationship has been denied is not performed in the PT-specific aggregation.

*Display order: SOC international agreement order, PT code ascending order

Table 3. Overview of the Occurrence Status of Serious Adverse Events

Item Name	Definition content
Severity	Adopt the severity determined by the physician.
Causal Relationship	Adopt the causality determined by the physician.
Case Number	The case numbers used to count the number of survey cases and the number of cases with ADRs, etc., are as follows: ADPKD: Patient-specific number (BaseEntryNO)
Number of Cases investigated	Aggregate the number of cases for safety analysis.
Number of cases with adverse event occurrence	If multiple serious adverse events occur in the same case, it is counted as one case.
Incidence Rate of adverse event, etc.	Number of cases with adverse event occurrence / Number of cases subject to safety analysis x 100
Major Classification by Organ	MedDRA SOC (name)
Basic or Subordinate Terms	MedDRA PT (name)

Item Name		Definition content
Incidence Rate by SOC, PT		SOC : Number of cases with ADRs / Number of cases for safety analysis x 100 PT : Number of cases with ADRs / Number of cases for safety analysis x 100
ADPKD	Usage Performance Survey (Post-Marketing Cases)	Target all cases for safety analysis.
Examination Item Name1		Name assigned from safety review items.
Examination Item Name2		Name assigned from safety review items. If there is a name different from the examination item name 1, output it.

2.3.2.1. Duration until ALT and AST exceed the upper limit of the reference value

【Analysis Target】

Cases where ALT has increased from before administration and are subject to safety analysis, or cases where AST has increased from before administration and are subject to safety analysis.

【Analysis Method】

The number of days elapsed from the start date of administration of this drug until the day when ALT or AST first became 3 times or more of the upper limit of the reference value is estimated by the Kaplan-Meier estimation method, and the cumulative exceedance rate is plotted. The termination date is the end date of administration of this drug. It also shows the At Risk (risk set) at the time.

The upper limit of the reference value is 30U/L for ALT and 30U/L for AST.

2.4. Aggregation Regarding Efficacy

2.4.1. Rate of Change in Bilateral Total Kidney volume

【Analysis Target】

Cases subject to efficacy analysis

Cases with one measurement date at baseline and before baseline are classified as the pre-administration group, and cases with one or more measurement dates during administration are classified as the post-administration group.

An analysis will be conducted on cases that fall into either the pre-administration group or the post-administration group.

【Analysis Method】

Regarding the rate of kidney volume increase

1) To reduce heterogeneity of variance and achieve linearity over time, the data of bilateral total kidney volume is log-transformed (log10). This log-transformed bilateral total kidney volume is set as the dependent variable, and a linear mixed-effects model is fitted as repeated measures data. The explanatory variables of the model are the administration group, time (years), patient, interaction of administration group and time, and interaction of patient and time as fixed effects, and the intercept and slope of the time axis for each patient as random effects. The variance-covariance matrix of the random effects is unstructured. The annual change rate and 95% confidence interval are returned to

their original scale by (10 estimated value -1) x 100.

Time (years) is calculated as "(measurement date - baseline +1) ÷ 365.25".

2) The pre-administration group calculates the rate of kidney volume change from before the baseline to the baseline, and the post-administration group calculates the rate of kidney volume change from the baseline to after the baseline. The rate of change in kidney volume is calculated using the following formula.

・Rate of kidney volume change = {((post-administration value - pre-administration value) / pre-administration value) x 100} / "period (years) from the start of administration of this drug to the measurement date"

Also, the Estimated Slope and Estimated SE are calculated for each of the pre-administration group and the post-administration group, and a graph is created. The difference in the Estimated Slope between the pre-administration group and the post-administration group and its test result are displayed as the estimated value of the parameter based on the solution of the fixed effect of the administration group and time and the p-value based on the t-distribution.

2.4.2. Change in e-GFR

【Analysis Target】

Cases subject to efficacy analysis

Cases with one measurement date at baseline and before baseline are classified as the pre-administration group, and cases with one or more measurement dates during administration are classified as the post-administration group.

Analyses targeting cases that apply to either the pre-administration group or the post-administration group (however, excluding cases that only have two points: one at baseline and one either before baseline or during administration) will be conducted.

【Analysis Method】

1) e-GFR will be treated as the dependent variable using actual values, and a linear mixed-effects model will be applied as repeated measurement data. The explanatory variables of the model are the administration group, time (years), patient, interaction of administration group and time, and interaction of patient and time as fixed effects, and the intercept and slope of the straight line over time for each patient as random effects. The variance-covariance matrix of the random effects will be unstructured.

2) The change in e-GFR from before baseline to baseline for the pre-administration group, and the change in e-GFR from baseline to after baseline for the post-administration group will be calculated. The change in e-GFR will be calculated using the following formulas:

・Pre-administration change = (Pre-baseline value - Baseline)

・Post-administration change = (Post-administration value - Baseline)

In addition, the Estimated Slope and Estimated SE will be calculated separately for the pre-administration group and the post-administration group. The difference in the Estimated Slope between the pre-administration group and the post-administration group and its test result will be displayed as the estimated parameter values based on the solution of the fixed effects of the administration group and time, and the p-value based on the t-distribution.

Reference

1. **Marc Froissart, Jerome Rossert, Christian Jacquot, Michel Paillard and Pascal Houillier: Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol 16: 763-73, 2005.**
2. **Ministry of Health, Labour and Welfare Scientific Research Grant for Intractable Diseases Policy Research Project (Intractable Diseases Policy Research Project) Research Group on Intractable Renal Disorders: Evidence-based Polycystic Kidney Disease PKD Treatment Guidelines 2020, 2020.**