Statistical Analysis Plan

Product Name	: Lipacreon® Granules 300 mg Sachets Lipacreon® Capsules 150 mg
Survey Name	: Special Drug Use-Results Survey —All-Case Surveillance in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis of the Pancreas—
Protocol No	: P12-893
Control Version	: 2.0
Preparation Date	: April 16, 2019

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1. Summary of the Survey

1.1. Purpose of the Survey

This survey will be conducted to collect information on the safety and effectiveness of Lipacreon in patients with exocrine pancreatic insufficiency due to cystic fibrosis of the pancreas, thereby obtaining information to use Lipacreon effectively and safely.

1.2. Outline of the Survey

Brand name: Lipacreon® Granules 300 mg Sachets, Lipacreon® Capsules 150 mg

Survey name: Special Drug Use-Results Survey

CF all-case surveillance: P12-893/LPC02T

Special Drug Use-Results Survey (all-case surveillance) ―All-Case Surveillance in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis of the Pancreas―

Date of approval: April 22, 2011

Date of designation: April 14, 2011

End date of the re-examination period: April 21, 2019

Survey period: August 30, 2011 through March 31, 2018

1.3. Drug Product and its Dosage and Administration

Lipacreon® Granules 300 mg Sachets

Each sachet contains 300 mg of pancrelipase.

Lipacreon® Capsules 150 mg

Each capsule contains 150 mg of pancrelipase.

The usual dosage is 600 mg/dose of pancrelipase administered orally immediately after each meal three times daily. The dosage may be adjusted according to the condition of the patient.

1.4. Target Disease

Patients with exocrine pancreatic insufficiency due to underlying cystic fibrosis of the pancreas

2. Definitions of Terms and Abbreviations

2.1. Definitions of Analysis Sets

No	Definition name	Description
1	Survey period	Reporting interval for periodic safety reports 3rd: April 14, 2012 to October 13, 2012 4th: October 14, 2012 to April 13, 2013 5th: April 14, 2013 to April 13, 2014 6th: April 14, 2014 to April 13, 2015 7th: April 14, 2015 to April 13, 2016 8th: April 14, 2016 to April 13, 2017 9th: April 14, 2017 to April 13, 2018 10th: April 14, 2018 to April 13, 2019 End date of the re-examination period April 21, 2019
2	Data lock dates	The data lock date for periodic safety reports are as follows: 3rd: October 13, 2012 4th: April 13, 2013 5th: April 13, 2014 6th: April 13, 2015 7th: April 13, 2016 8th: April 13, 2017 9th: April 13, 2018 10th: April 17, 2019 The data lock date for re-examination is as follows: April 17, 2019 At each analysis, the following case report forms will be analyzed: Periodic safety report: Case report forms whose case report form status on each data lock date is “Primary data lock” Analysis for re-examination: All case report forms whose case report form status is “Data lock”
3	Patients registered in the survey	Patients who have been able to be registered in the survey
4	Patients with available case report forms	Patients whose case report forms have been collected
5	Patients with no available case report forms	Patients whose case report forms have not been able to be collected
6	Criteria for exclusion from the safety analysis	▪ No dose received: Patients whose use of Lipacreon has not been able to be confirmed ▪ No visit made: Patients who have not visited the institution since the start date of treatment with Lipacreon
7	Patients excluded from the safety analysis	Patients meeting the criteria for exclusion from the safety analysis among the patients with available case report forms
8	Patients included in the safety analysis	Patients not meeting the criteria for exclusion from the safety analysis among the patients with available case report forms
9	Criteria for exclusion from the effectiveness analysis	▪ Cannot be determined: Patients in whom all of “nutritional endpoints, symptoms related to exocrine pancreatic insufficiency, and degree of overall improvement” after the start date of treatment are unknown/unspecified or cannot be determined
10	Patients excluded from the effectiveness analysis	Patients meeting the criteria for exclusion from the effectiveness analysis among the patients included in the safety analysis

No	Definition name	Description
11	Patients included in the effectiveness analysis	Patients not meeting the criteria for exclusion from the effectiveness analysis among the patients included in the safety analysis
12	Patients not completing the 52-week treatment	Patients who have discontinued treatment before Week 48 among the patients included in the effectiveness analysis
13	Patients included in the effectiveness analysis (patients completing the 52-week treatment)	Patients who have completed the 52-week treatment among the patients included in the effectiveness analysis

LPC02T will target all patients, even those who have transferred to another department or hospital. If the same patient is registered multiple times at different institutions or departments, overlapped registrations will be linked to each other and counted as “1 patient.” All case report forms/follow-up case report forms collected at the individual departments/institutions will be regarded as separate volumes for the same patient and the data included in the case report forms will be handled accordingly. Evaluation time points will be calculated with the first “start date of treatment” being deemed as the starting point.

Details will be determined depending on the actual case.

2.2. Definitions of Analysis Items

No	Definition name	Description
1	Start date of treatment with Lipacreon (start date of the observation period)	Earliest start date of treatment recorded in the "2. Status of Use of Lipacreon" column
2	End date of treatment with Lipacreon (safety)	Latest end date of treatment recorded in the "2. Status of Use of Lipacreon" column However, if there is a record with no date because the end date of treatment is "Ongoing," "March 31, 2018" will be deemed as the end date of treatment with Lipacreon.
3	End date of treatment with Lipacreon (effectiveness rate)	With the start date of treatment being deemed as Day 1, Day 364 will be determined to be the end date of treatment. However, if the duration of treatment with Lipacreon is fewer than 364 days, the latest end date of treatment recorded in the "2. Status of Use of Lipacreon" column will be deemed as the end date of treatment.
4	Mean daily dose (safety)	Total dose (mg)/Duration of treatment (not including any rest periods) (mg/day)
5	Mean daily dose (effectiveness rate)	With the start date of treatment with Lipacreon being deemed as Day 1, the mean daily dose will be calculated by dividing the total dose (mg) until Day 364 by 364 days (or the number of days of any rest periods subtracted from 364)
6	Duration of use of Lipacreon (safety)	The actual number of days Lipacreon was administered will be calculated. Any rest period will not be included and "Treatment compliance" will not be taken into account.
7	Duration of use of Lipacreon (effectiveness rate)	With the start date of treatment with Lipacreon being deemed as Day 1, the actual number of days Lipacreon was administered until Day 364 will be calculated. Any rest period will not be included and "Treatment compliance" will not be taken into account.
8	Concomitant drugs (safety)	Among the drugs recorded in the "3. Status of Use of Concomitant Drugs" column, any drug that has a recorded duration of use, meets the condition (its start date of use is between the start date of treatment with Lipacreon and the end date of treatment with Lipacreon [safety]) (including its continued use at the time of the start of treatment with Lipacreon), and is used for reasons other than "treatment of any adverse event" will be deemed as a concomitant drug. (This is because it will not be possible to obtain correct results if any drug used to treat an adverse event is included when determining whether any difference in the incidence of adverse drug reactions exists between when any concomitant drug is used or not used)
9	Concomitant drugs (effectiveness rate)	Among the drugs recorded in the "3. Status of Use of Concomitant Drugs" column, any drug that has a recorded duration of use, meets the condition (its start date of use is between the start date of treatment with Lipacreon and the end date of treatment with Lipacreon [effectiveness rate]) (including its continued use at the time of the start of treatment with Lipacreon), and is used for reasons other than "treatment of any adverse event" will be deemed as a concomitant drug. (This is because it will not be possible to obtain correct results if any drug used to treat an adverse event is included when determining whether any difference in the incidence of adverse drug reactions exists between when any concomitant drug is used or not used)

No	Definition name	Description
10	Digestive enzyme preparations	Drugs corresponding to the following codes: Codes that begin with 2331 or 2339 *Excluding the code corresponding to Lipacreon
11	Adverse events	All events recorded in the “4. Adverse Event” column
12	Relationship with Lipacreon	The relationship with Lipacreon will be assessed as “Related” if the “causal relationship with Lipacreon” is “related,” “possibly related,” or “cannot be determined,” and as “Not related” if the “causal relationship with Lipacreon” is “unrelated.”
13	Adverse drug reactions	Among adverse events, any event whose “causal relationship with Lipacreon” is assessed as “Related” If the same adverse event (preferred term [PT]) occurs repeatedly and is recorded multiple times, any event related with Lipacreon will be counted.
14	Serious adverse events	Among adverse events, any event whose “causal relationship with Lipacreon” is recorded and whose “seriousness” is “Serious” If the same adverse event (PT) occurs repeatedly and is recorded multiple times, any serious event will be counted.

2.3. Definitions of Patient Demographic Factors and Indicators of Treatment Status

No	Patient demographic factor	Description
1	Sex	Male, female, unknown/unspecified
2	Pregnancy status	Not pregnant, currently pregnant, unknown/unspecified
3	Breastfeeding status	Not breastfeeding, currently breastfeeding, unknown/unspecified
4	Age category-1	<15 years old, ≥15 years old, unknown/unspecified
5	Age category-2	<6 years old, ≥6 years old and <12 years old, ≥12 years old and <18 years old, ≥18 years old, unknown/unspecified
6	Age	Actual value
7	Body height category-1	<140 cm, ≥140 cm and <150 cm, ≥150 cm and <160 cm, ≥160 cm and <170 cm, ≥170 cm and <180 cm, ≥180 cm, unknown/unspecified
8	Body height	Actual value
9	Body weight category-1	<30 kg, ≥30 kg and <40 kg, ≥40 kg and <50 kg, ≥50 kg and <60 kg, ≥60 kg and <70 kg, ≥70 kg and <80 kg, ≥80 kg, unknown/unspecified
10	Body weight	Actual value
11	BMI category-1	<18.5, ≥18.5 and <25, ≥25, unknown/unspecified
12	BMI	Actual value Body weight / (Body height/100)**2 The value will be indicated to two decimal places rounded from three decimals.
13	Inpatient/outpatient category	Inpatient, outpatient, unknown/unspecified
14	Presence or absence of concurrent diseases	Absent, present, unknown/unspecified
15	Presence or absence of concurrent hepatic impairment	Absent, present, unknown/unspecified
16	Presence or absence of concurrent renal impairment	Absent, present, unknown/unspecified
17	Presence or absence of concurrent respiratory disease	Absent, present, unknown/unspecified
18	Presence or absence of other concurrent diseases	Absent, present, unknown/unspecified
19	Presence or absence of previous diseases	Absent, present, unknown/unspecified
20	Presence or absence of allergy history	Absent, present, unknown/unspecified
21	Presence or absence of previous drugs	Absent, present, unknown/unspecified
22	Presence or absence of concomitant digestive enzyme preparations	Absent, present, unknown/unspecified
No	Indicator of treatment status	Description
23	Dosage form	Granule, capsule, granule + capsule, unknown/unspecified

No	Patient demographic factor	Description
24	Duration of treatment (safety) (excluding any rest period)	≤28 days, >28 days and ≤56 days, >56 days and ≤84 days, >84 days and ≤168 days, >168 days and ≤252 days, >252 days and ≤336 days, >336 days and ≤364 days, >364 days and ≤2 years, >2 years and ≤3 years, >3 years and ≤4 years, >4 years and ≤5 years, >5 years and ≤6 years, >6 years and ≤7 years, unknown/unspecified In the summarization for the occurrence status of adverse events and adverse drug reactions, the duration of treatment in a patient experiencing an adverse event or adverse drug reaction will be determined based on the number of days until the initial onset date of the event (including the date of onset).
25	Duration of treatment (effectiveness rate) (excluding any rest period)	≤28 days, >28 days and ≤56 days, >56 days and ≤84 days, >84 days and ≤168 days, >168 days and ≤252 days, >252 days and ≤336 days, >336 days and ≤364 days, unknown/unspecified
26	Duration of treatment (safety) (excluding any rest period)	Actual value
27	Duration of treatment (effectiveness rate) (excluding any rest period)	Actual value until Day 364 excluding any rest periods
28	Total dose (safety)	Categories will be determined based on the distribution of actual data.
No	Indicator of treatment status	Description
29	Total dose (effectiveness rate)	Categories will be determined based on the distribution of actual data.
30	Total dose (safety)	Actual value of the total dose during the duration of use of Lipacreon (safety)
31	Total dose (effectiveness rate)	Actual value of the total dose during the duration of use of Lipacreon (effectiveness rate)
32	Reason for dose change (safety) (multiple answers are allowed)	Reason for dose change during the duration of use of Lipacreon (safety) Unsatisfactory therapeutic effect, occurrence of an adverse event, patient's request, other
33	Reason for dose change (effectiveness rate) (multiple answers are allowed)	Reason for dose change during the duration of use of Lipacreon (effectiveness rate) Unsatisfactory therapeutic effect, occurrence of an adverse event, patient's request, other
34	Treatment compliance (safety) (multiple answers are allowed)	Treatment compliance during the duration of use of Lipacreon (safety) Good, half, poor, unknown/unspecified
35	Treatment compliance (effectiveness rate) (multiple answers are allowed)	Treatment compliance during the duration of use of Lipacreon (effectiveness rate) Good, half, poor, unknown/unspecified
36	Initial daily dose (mg/day)	The initial daily dose will be determined based on the daily dose on the start date of treatment with Lipacreon. <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified

No	Patient demographic factor	Description
37	Mean daily dose (safety) (mg/day)	The mean daily dose will be determined based on the mean daily dose (safety). <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified The mean daily dose for each dose observation period will be determined based on the mean daily doses during the individual periods shown below. Dose observation periods: At the start of treatment: Day 1 At Week 2: Day 2 to Day 14 At Week 4: Day 15 to Day 28 At Week 8: Day 29 to Day 56 At Week 16: Day 57 to Day 112 At Week 24: Day 113 to Day 168 At Week 32: Day 169 to Day 224 At Week 40: Day 225 to Day 280 At Week 48: Day 281 to Day 336 At Week 52: Day 337 to Day 364 At Year 2: Day 365 to Day 728 At Year 3: Day 729 to Day 1092 At Year 4: Day 1093 to Day 1456 At Year 5: Day 1457 to Day 1820 At Year 6: Day 1821 to Day 2184 At Year 7: Day 2185 to Day 2400

No	Indicator of treatment status	Description
38	Mean daily dose (effectiveness rate) (mg/day)	The mean daily dose will be determined based on the mean daily dose (effectiveness rate). <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified The mean daily dose for each dose observation period will be determined based on the mean daily doses during the individual periods shown below. Dose observation periods: At the start of treatment: Day 1 At Week 2: Day 2 to Day 14 At Week 4: Day 15 to Day 28 At Week 8: Day 29 to Day 56 At Week 16: Day 57 to Day 112 At Week 24: Day 113 to Day 168 At Week 32: Day 169 to Day 224 At Week 40: Day 225 to Day 280 At Week 48: Day 281 to Day 336 At Week 52: Day 337 to Day 364

No	Indicator of treatment status	Description
39	Maximum daily dose (safety) (mg/day)	The maximum daily dose will be determined based on the maximum value of the daily dose during the duration of use of Lipacreon (safety). <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified In the summarization for the occurrence status of adverse events and adverse drug reactions, the maximum daily dose in a patient experiencing an adverse event or adverse drug reaction will be determined based on the maximum daily dose until the time of initial onset of the event.
40	Maximum daily dose (effectiveness rate) (mg/day)	The maximum daily dose will be determined based on the maximum value of the daily dose during the duration of use of Lipacreon (effectiveness rate). <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified
41	Last daily dose (safety) (mg/day)	The last daily dose will be determined based on the last daily dose during the duration of use of Lipacreon (safety). <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified In the summarization for the occurrence status of adverse events and adverse drug reactions, the last daily dose in a patient experiencing an adverse event or adverse drug reaction will be determined based on the dose at the time of initial onset of the event.
42	Last daily dose (effectiveness rate) (mg/day)	The last daily dose will be determined based on the last daily dose during the duration of use of Lipacreon (effectiveness rate). <900, 900, >900 and <1800, 1800, >1800, unknown/unspecified

3. Analysis Methods

3.1. Statistical Analysis Environment

Statistical analysis software: SAS Institute Inc., SAS for Windows Version 9.2 or higher

The version of SAS used for summarization and analysis will be defined in the written statistical analysis specification.

3.2. Testing

When any test is applied, a two-sided level of significance of 5% will be used without correction for continuity or adjustment of multiplicity.

P-values will be displayed with two asterisks (**) when being larger than 0 (zero) and less than 0.01 and with one asterisk (*) when being greater than or equal to 0.01 and less than 0.05. For any unknown/unspecified value, its frequency will be displayed in the tabulation, but it will not be included in the calculation for testing.

3.3. Policy regarding Categorization

Unknown values, unspecified values, and calculation items that cannot be calculated will be summarized together as “unknown/unspecified.”

3.4. Handling of Adverse Events

In the summarization of the number of adverse events (adverse drug reactions) by PT, if the same patient experiences any adverse event (adverse drug reaction) of the same PT multiple times, each event will be counted once (number of events basis). In the summarization of the number of patients with adverse events (adverse drug reactions) by SOC or PT, if the same patient experiences any adverse event (adverse drug reaction) of the same SOC or PT multiple times, the patient will be counted once (number of patients basis).

Adverse events (adverse drug reactions) will be summarized using the “ICH International Medical Dictionary for Regulatory Activities Japanese Version (MedDRA/J)” according to the notification concerning the “ICH International Medical Dictionary for Regulatory Activities Japanese Version (MedDRA/J)” (Notification No. 0325001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, and Notification No. 0325032 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 25, 2004).

The version of the MedDRA/J used for summarization and analysis will be defined in the written statistical analysis specification.

The procedure for summarization and analysis through grouping of MedDRA terms by SOC is as follows:

- According to the LLT entered (coded) in the database, the MedDRA table of the above version will be referenced to follow the link for each adverse event and combine the LLT with the information on “PT-SOC” of the version.

- Adverse event terms will be output in the ascending order of the SOC internationally agreed order-PT codes.

3.5. Rules about Calculation Methods for Individual Items, Units, and Number of Digits Displayed

Item	Unit	Digits displayed	Calculation method, etc.
Calculation of durations (duration to discontinuation, duration to onset of adverse drug reaction, duration of treatment)	day	1	End date − Start date + 1 (including the start date) 1 year = 52 weeks = 364 days
Age	years old	1	INT ([Start date of treatment with Lipacreon − Date of birth + 1)/365.25)
P-value	-	0.001	All numbers after the third decimal place will be disregarded.
Incidence	-	0.01	
Effectiveness rate	-	0.1	Evaluation of the degree of overall improvement: Number of improved patients/(No. of improved patients + No. of unchanged patients + No. of deteriorated patients) × 100
Summary statistics	-	-	Sample size: Integral number Minimum and maximum values: Displayed in the number of digits of the raw data. Other statistics: The two lower digits of the raw data will be rounded off to display up to the lowest digit of the raw data.

3.6. Allowable Time Window for Each Evaluation Time Point

The allowable time window for each evaluation time point is as shown below. If multiple evaluation values exist within an allowable time window, the evaluation value obtained at the time point with the smallest difference in time (absolute value) from the specified evaluation date will be adopted. If the differences in time are the same, the evaluation value obtained after the specified evaluation date will be adopted. The number of days from the start date of treatment with Lipacreon will be calculated with the start date of treatment with Lipacreon being deemed as Day 1 and the date before the start of treatment with Lipacreon being deemed as −Day 1.

Nutritional endpoints, symptoms of exocrine pancreatic insufficiency:

Evaluation time point	Allowable time window[*1]	Specified evaluation date[*1]
Before the start of treatment	to Day 1	Day 1
At Week 4	Day 14 to Day 41	Day 28
At Week 8	Day 56±14	Day 56
At Week 24	Day 168±28	Day 168
At Week 52	Day 364±28	Day 364
At Year X $2 \leq X \leq 7$	364 × Day X±28	Day 364 × X
Before dose increase[*2]	Start date of dose increase – 28 days to Start date of dose increase	Start date of dose increase
At the time of discontinuation	Date of discontinuation – 28 days to Date of discontinuation, which does not correspond to any of the above	Date of discontinuation

At the time of last evaluation	Data obtained on the last date among the data obtained before Day 364 × X + 28	

Degree of overall improvement:

Evaluation time point	Allowable time window[*1]	Specified evaluation date[*1]
At Week 24	Day 168±28	Day 168
At Week 52	Day 364± 28	Day 364
At the time of discontinuation	Date of discontinuation – 28 days to Date of discontinuation, which does not correspond to any of the above	Date of discontinuation
At the time of last evaluation	All of the last dates	

*1: The allowable time window and the specified evaluation date before the start of treatment to Year X are displayed in the number of days from the start date of treatment with Lipacreon.

*2: A dose increase will be defined as a dose of ≥1800 mg/day administered.

4. Statistical Analyses

4.1. Summarization of Patient Composition

4.1.1. Summarization of patient composition

Patients for summarization: Patients registered in the survey, patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients completing the 52-week treatment)

4.1.1.1. Breakdown of patients concerning institution information

For patients registered in the survey, patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients completing the 52-week treatment), the number of institutions surveyed, the total number of patients, the mean number of patients, the largest number of patients, the smallest number of patients, and the constituent ratios of the individual patients will be calculated by founder of each survey-participating institution (Table 1.1.1.1).

The number and constituent ratio of patients with available case report forms will be calculated by department (Table 1.1.1.2).

4.1.1.2. Breakdown of discontinued patients

For patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients completing the 52-week treatment), the number of the individual patients will be presented by reason for discontinuation and observation period category (Table 1.1.2).

No	Item name	Description
1	Observation period category	≤28 days, >28 days and ≤56 days, >56 days and ≤112 days, >112 days and ≤168 days, >168 days and ≤224 days, >224 days and ≤280 days, >280 days and ≤364 days, >364 days and ≤728 days, >728 days and ≤1092 days, >1092 days and ≤1456 days, >1456 days and ≤1820 days, >1820 days and ≤2184 days, >2184 days and ≤2400 days

4.1.1.3. Breakdown of patient composition

The following will be presented: the number of institutions surveyed, the number of patients registered in the survey, the number of patients with available case report forms, the number of patients with no available case report forms, the number of patients included in the safety analysis, the number of patients excluded from the safety analysis, the number of patients included in the effectiveness analysis, the number of patients excluded from the effectiveness analysis, the number of patients included in the effectiveness analysis (patients completing the 52-week treatment), and the number of patients not completing the 52-week treatment. For patients excluded from the safety analysis and patients excluded from the effectiveness analysis, the number of the individual patients will be presented by reason for exclusion (Figure 1.1.3.1).

In addition, the number of patients with available case report forms will be presented by separate volume (Figure 1.1.3.2).

For patients with multiple reasons for exclusion among the patients excluded from the safety analysis or patients excluded from the effectiveness analysis, a list of patients will be prepared (Table 1.1.3.1, Table 1.1.3.2).

For patients excluded from the safety analysis, lists of reported adverse events will be prepared by SOC, PT, seriousness, and presence/absence of relationship (Table 1.1.3.3).

For discontinued patients, a list of patients will be prepared by survey-participating institution (Table 1.1.3.4).

No	Item name	Contents to be displayed
1	Survey-participating institution	-
2	Department name	-
3	Patient number	-
4	Age	Actual value
5	Sex	Male, female
6	Start date of treatment	-
7	End date of treatment	-
8	Number of days from the start of treatment to discontinuation	-
9	Reason for discontinuation	Occurrence of an adverse event, unsatisfactory therapeutic effect, patient's refusal to receive Lipacreon, no visit, worsening of cystic fibrosis of the pancreas, other For "other," a specific reason for discontinuation will be presented.
10	Name of the adverse event as the reason for discontinuation	-
11	Seriousness	Non-serious, serious
12	Causal relationship with Lipacreon	Related, possibly related, unrelated, cannot be determined
13	Outcome	Resolved, resolving, not resolved, sequelae, fatal, unknown
14	Date of onset	-
15	Number of days to onset	-
16	Inclusion/exclusion of patient in the safety analysis	Included, excluded
17	Inclusion/exclusion of patient in the effectiveness analysis	Included, excluded

4.1.2. Distribution of patients by patient demographic factors

– Patients for summarization: Patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients completing the 52-week treatment)

4.1.2.1. Distribution of patient demographic factors

For patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients

completing the 52-week treatment), the number and percentage of the individual patients will be calculated for each of the demographic factors defined in Section 2.3. In addition, for age, body height, body weight, and BMI, summary statistics will be calculated (Table 1.2.1).

4.1.3. Distribution of patients by indicator of treatment status

– Patients for summarization: Patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients completing the 52-week treatment)

4.1.3.1. Distribution of patients by indicator of treatment status

For patients with available case report forms, patients included in the safety analysis, patients included in the effectiveness analysis, and patients included in the effectiveness analysis (patients completing the 52-week treatment), the number and percentage of the individual patients will be calculated for each of the indicators of treatment status defined in Section 2.3. In addition, for the number of days of treatment (excluding any rest period) and the total dose, summary statistics will be calculated (Table 1.3.1).

4.2. Summarization concerning Safety

4.2.1. Occurrence status of adverse events and adverse drug reactions

– Patients for summarization: Patients included in the safety analysis

4.2.1.1. Occurrence status of adverse events

For patients included in the safety analysis, the number of patients with adverse events, the percentage of patients with adverse events (with the number of patients included in the safety analysis being the denominator), and the number of reported adverse events will be calculated by SOC, PT, seriousness, and causal relationship with Lipacreon (Table 2.1.1.1). The number of patients with adverse events and the number of reported adverse events will be counted as described in Section 3.4. In addition, seriousness and causal relationship with Lipacreon by patient will be determined first for “Serious” events and “Related” events.

The breakdown of patients with serious events will be calculated (Table 2.1.1.2).

4.2.1.2. Time of onset of adverse events and adverse drug reactions

For patients included in the safety analysis, the number of patients with adverse events, serious adverse events, adverse drug reactions, and serious adverse drug reactions, and the number of the individual events will be calculated by SOC, PT, and time of onset. In addition, the number of patients with adverse events, serious adverse events, adverse drug reactions, and serious adverse drug reactions, the percentage of patients with the individual events (with the number of patients included in the safety analysis being the denominator), and the smallest and largest numbers of days to onset will be calculated by SOC and PT (Table 2.1.2.1 to Table 2.1.2.4). In the summarization based on the number of patients, time of onset will be determined based on the event with the shortest duration to onset among the events of the same SOC (PT).

No	Item name	Description
1	Time of onset	≤28 days, >28 days and ≤56 days, >56 days and ≤112 days, >112 days and ≤168 days, >168 days and ≤224 days, >224 days and ≤280 days, >280 days and ≤364 days, >364 days and ≤728 days, >728 days and ≤1092 days, >1092 days and ≤1456 days, >1456 days and ≤1820 days, >1820 days and ≤2184 days, >2184 days and ≤2400 days

4.2.1.3. Treatment with Lipacreon and outcomes of adverse events and adverse drug reactions

For patients included in the safety analysis, a cross summarization of treatment with Lipacreon by outcome will be performed for adverse events, serious adverse events, adverse drug reactions, and serious adverse drug reactions (Table 2.1.3.1.1 to Table 2.1.3.1.4).

For adverse events, serious adverse events, adverse drug reactions, and serious adverse drug reactions, the number of patients with the individual events, the percentage of patients with the individual events (with the number of patients included in the safety analysis being the denominator), and the number of the individual events will be calculated by SOC, PT, and treatment with Lipacreon (Table 2.1.3.2.1 to Table 2.1.3.2.4). In the summarization on the number of patients basis, treatment with Lipacreon will be determined in the following order of priority, discontinued > suspended > dose reduced > continued > developed after discontinuation, among the events of the same SOC (PT).

For adverse events, serious adverse events, adverse drug reactions, and serious adverse drug reactions, the number of patients with the individual events, the percentage of patients with the individual events (with the number of patients included in the safety analysis being the denominator), and the number of the individual events will be calculated by SOC, PT, and outcome (Table 2.1.3.3.1 to Table 2.1.3.3.4). In the summarization on the number of patients basis, outcome will be determined in the following order of priority, fatal > with sequelae > not resolved > resolving > resolved > unknown, among the events of the same SOC (PT).

No	Item name	Description
1	Treatment with Lipacreon	Continued, dose reduced, suspended, discontinued, developed after discontinuation
2	Outcome	Resolved, resolving, not resolved, sequelae, fatal, unknown

4.2.1.4. Time to “resolved” or “resolving” of adverse events and adverse drug reactions

For patients included in the safety analysis, the number of patients with adverse events, serious adverse events, adverse drug reactions, and serious adverse drug reactions, the percentage of patients with the individual events (with the number of patients included in the safety analysis being the denominator), the number of the individual events, and the smallest and largest number of days to “resolved” or “resolving” will be calculated by SOC, PT, and time to “resolved” or “resolving” (Table 2.1.4.1 to Table 2.1.4.4). In the summarization on the number of patients basis, time to “resolved” or “resolving” will be determined based on the event with the longest time to “resolved” or “resolving” among the events of the same SOC (PT).

No	Item name	Description
1	Time to “resolved” or “resolving”	<28 days, ≥28 days and <56 days, ≥56 days and <84 days, ≥84 days and <112 days, ≥112 days

4.2.1.5. List of patients experiencing adverse events

A list of patients experiencing adverse events will be prepared (Table 2.1.5.1).

No	Item name	Contents to be displayed
Records concerning patient demographics		
1	Patient number	
2	Sex	Male, female
3	Pregnancy status	Absent, present
4	Age	Actual value
5	Inpatient/outpatient category	Inpatient, outpatient
6	Presence or absence of concurrent hepatic impairment	Absent, present
7	Presence or absence of concurrent renal impairment	Absent, present
8	Presence or absence of concurrent respiratory disease	Absent, present
9	Other concurrent diseases (disease name)	-
10	Presence or absence of previous diseases	Absent, present
11	Previous disease name	-
12	Presence or absence of allergy history	Absent, present
13	Concomitant drug name	-
14	Presence or absence of discontinuation	Absent, present
15	Reason for discontinuation	-
Records concerning treatment with Lipacreon		
16	Number of days of treatment (day)	-
17	Total dose (mg)	-
18	Maximum daily dose (mg/day)	-
19	Last daily dose (mg/day)	-
20	Duration of treatment until initial onset of adverse drug reactions (day)	-
21	Total dose until initial onset of adverse drug	-

No	Item name	Contents to be displayed
	reactions (mg)	
22	Daily dose at initial onset of adverse drug reactions (mg/day)	-

Records concerning adverse events		
23	Adverse event name	-
24	Date of onset	-
25	Number of days to onset	-
26	Seriousness	Non-serious, serious
27	Treatment with Lipacreon	Continued, dose reduced, suspended, discontinued, developed after discontinuation
28	Outcome	Resolved, resolving, not resolved, sequelae, fatal, unknown
29	Date of outcome	-
30	Number of days to “resolved” or “resolving”	-
31	Causal relationship with Lipacreon	Related, possibly related, unrelated, cannot be determined
32	Possible factors other than Lipacreon	None, concomitant drug, primary disease, concurrent diseases, other

Patient number lists will be prepared for the following: Patients with adverse drug reactions; patients with adverse drug reactions whose outcome is “not resolved,” “with sequelae,” “fatal,” or “unknown;” patients who have adverse drug reactions after the completion of treatment; pediatric (aged <15 years) patients with adverse drug reactions; pregnant patients with adverse drug reactions (those who are pregnant during the duration of treatment with Lipacreon); patients with adverse drug reactions who have hepatic impairment; patients with adverse drug reactions who have renal impairment; and patients with adverse drug reactions who have respiratory disease (Table 2.1.5.2).

4.2.2. Status of treatment with Lipacreon in patients included in the safety analysis

– Patients for summarization: Patients included in the safety analysis

4.2.2.1. Change over time in the mean daily dose

For patients included in the safety analysis, the number and percentage of patients by mean daily dose category (mg/day) will be calculated for each dose observation period (Table 2.2.1).

No	Item name	Description
1	Dose observation period	At the start of treatment, at Week 2, at Week 4, at Week 8, at Week 16, at Week 24, at Week 32, at Week 40, at Week 48, at Week 52, at Year 2, at Year 3, at Year 4, at Year 5, at Year 6, at Year 7, at the last evaluation time point
2	Mean daily dose for each dose observation period (mg/day)	<900, 900, >900 and <1800, 1800, >1800

4.2.2.2. Changes in the dose

For patients included in the safety analysis, the number and percentage of patients by dose increase and decrease pattern will be calculated (Table 2.2.2).

No	Item name	Description
1	Dose increase and decrease pattern	Not changed, increased, decreased, other Not changed: Certain daily dose throughout the duration of treatment with Lipacreon excluding any rest period Increased: Initial daily dose = Lowest daily dose < Maximum daily dose = Last daily dose Decreased: Initial daily dose = Maximum daily dose > Lowest daily dose = Last daily dose Other: Dose increase and decrease patterns other than the above Initial daily dose: Daily dose at the start of treatment with Lipacreon Minimum daily dose: Lowest daily dose during the duration of treatment with Lipacreon excluding any rest period Maximum daily dose: Highest daily dose during the duration of treatment with Lipacreon excluding any rest period Last daily dose: Daily dose at the end of treatment with Lipacreon

4.2.2.3. Maximum daily dose and last daily dose

For patients included in the safety analysis, a cross summarization of the maximum daily dose by the last daily dose will be performed (Table 2.2.3).

4.2.3. Examination of factors possibly affecting the incidence of adverse drug reactions

– Patients for summarization: Patients included in the safety analysis

4.2.3.1. Incidence of adverse drug reactions by patient demographics

For patients included in the safety analysis, the number of patients, the percentage of patients, the number of patients with adverse drug reactions, the number of adverse drug reactions, and the percentage of patients with adverse drug reactions will be calculated for each of the demographic factors and indicators of treatment status defined in Section 2.3. In addition, for items that are unordered categorical variables, their independence from the incidence of adverse drug reactions will be tested using a Fisher's exact, and for items that are ordered variables (e.g., duration of treatment), their independence from the incidence of adverse drug reactions will be tested using a Kruskal-Wallis test to detect factors possibly affecting the incidence of adverse drug reactions (Table 2.3.1.1).

For demographic factors and indicators of treatment status that are found statistically significant in Table 2.3.1.1, lists of reported adverse drug reactions by category will be prepared (Table 2.3.1.2.X).

4.3. Summarization concerning Effectiveness

4.3.1. Examination of factors possibly affecting effectiveness rates

– Patients for summarization: Patients included in the effectiveness analysis and patients included in the effectiveness analysis (patients completing the 52-week treatment)

4.3.1.1. Degree of overall improvement

For patients included in the effectiveness analysis, the number and percentage of patients by evaluated overall improvement at Week 24, Week 52, and the time of last evaluation will be calculated (Table 3.1.1.1).

For patients included in the effectiveness analysis (patients completing the 52-week treatment), the number and percentage of patients by evaluated overall improvement at Week 24 and Week 52 will be calculated (Table 3.1.1.2).

For patients included in the effectiveness analysis or patients included in the effectiveness analysis (patients completing the 52-week treatment), a list of patients concerning the degree of overall improvement will be prepared for patients with special background (children, pregnant women and nursing mothers, hepatic impairment, renal impairment, respiratory disease). Item to be output will be determined according to the analysis table and figure output plan (Table 3.1.1.3.1, Table 3.1.1.3.2, Table 3.1.1.3.3, Table 3.1.1.3.4, Table 3.1.1.3.5, Table 3.1.1.4.1, Table 3.1.1.4.2, Table 3.1.1.4.3, Table 3.1.1.4.4, and Table 3.1.1.4.5).

4.3.1.2. Examination of factors possibly affecting effectiveness rates

For patients included in the effectiveness analysis or patients included in the effectiveness analysis (patients completing the 52-week treatment), the following will be calculated: the number and percentage of patients for each of the patient demographic factors and indicators of treatment status (effectiveness rate) defined in Section 2.3., the number of patients by degree of overall improvement (improved, unchanged, deteriorated), the number of patients evaluated for the degree of overall improvement (excluding those for whom the degree of overall improvement cannot be determined), effectiveness rate, and the number of patients for whom the degree of overall improvement cannot be determined. In addition, as with the examination of factors possibly affecting the incidence of adverse drug reactions (Section 4.2.3.1.), the effects of individual items on effectiveness rates will be evaluated using a Fisher's exact test or a Kruskal-Wallis test. In addition, the effects of individual items on effectiveness (improved, unchanged, deteriorated) will be evaluated using a Mantel Haenszel test and an extended Mantel-Haenszel test to detect items possibly affecting effectiveness (Table 3.1.2.1, Table 3.1.2.2).

4.3.2. Nutritional endpoints

– Patients for summarization: Patients included in the effectiveness analysis and patients included in the effectiveness analysis (patients completing the 52-week treatment)

4.3.2.1. Changes over time in the nutritional endpoints

For patients included in the effectiveness analysis or patients included in the effectiveness analysis (patients completing the 52-week treatment), summary statistics for the actual measurement values of the nutritional endpoints by evaluation time point and changes in the nutritional endpoints from the start of treatment will be calculated. In addition, a paired t-test will be used to identify the presence or absence of any change in the nutritional endpoints from the start of treatment (Table 3.2.1.1, Table 3.2.1.2).

In addition, a line graph of the change in the mean value of each nutritional endpoint will be prepared (Figure 3.2.1.1, Figure 3.2.1.2).

No	Item name	Description
1	Nutritional endpoints	Body height (cm), body weight (kg), BMI, serum total protein (g/dL), albumin (g/dL), total cholesterol (mg/dL), triglycerides (mg/dL), hemoglobin (g/dL)

4.3.3. Symptoms of exocrine pancreatic insufficiency

– Patients for summarization: Patients included in the effectiveness analysis and patients included in the effectiveness analysis (patients completing the 52-week treatment)

4.3.3.1. Changes over time in the symptoms of exocrine pancreatic insufficiency

For patients included in the effectiveness analysis or patients included in the effectiveness analysis (patients completing the 52-week treatment), the changes over time in the symptoms of exocrine pancreatic insufficiency by evaluation time point will be displayed.

For steatorrhea, diarrhea, bad stool odor, anorexia, and abdominal bloating, the number of patients with or without each symptom and by pattern of change from the start of treatment will be calculated. In addition, a McNamara test will be used to confirm the equivalence in the patterns of change.

Summary statistics for the actual measurement values of the frequency of defecation by evaluation time point and changes in the frequency of defecation from the start of treatment will be calculated. In addition, a paired t-test will be used to identify the presence or absence of any change in the frequency of defecation from the start of treatment (Table 3.3.1.1, Table 3.3.1.2).

No	Item name	Description
1	Symptoms of exocrine pancreatic insufficiency	Discrete data: Steatorrhea, diarrhea, bad stool odor, anorexia, abdominal bloating Continuous data: Frequency of defecation (times/day)

4.4. Patients Excluded from the Analysis and Patients with Special Background

4.4.1. List of patient numbers of patients excluded from the analysis and patients with special background

– Patients for summarization: Patients excluded from the safety analysis, patients excluded from the effectiveness analysis, and patients included in the safety analysis

4.4.1.1. Selection of patients excluded from the safety analysis

Patients excluded from the safety analysis will be selected by reason for exclusion and the following items will be presented (Table 4.1.1).

No	Reason for exclusion	Items to be displayed
1	No dose received	Registration number
2	No visit made	Registration number, reason for discontinuation of the survey, date of discontinuation of the survey, start date of treatment, end date of treatment

4.4.1.2. Selection of patients excluded from the effectiveness analysis

Patients excluded from the effectiveness analysis will be selected by reason for exclusion and the following items will be presented (Table 4.1.2).

No	Reason for exclusion	Items to be displayed
1	Cannot be determined	Registration number

4.4.1.3. Selection of patients with special background

Among the patients included in the safety analysis, patients with special background will be selected and their registration numbers will be presented (Table 4.1.3).

No	Special background	Description
1	Children	Patients aged <15 years
2	Pregnant women and nursing mothers	Pregnant patients
3	Hepatic impairment	Patients with concurrent hepatic impairment
4	Renal impairment	Patients with concurrent renal impairment
5	Respiratory disease	Patients with concurrent respiratory disease

4.5. Patients with Cystic Fibrosis of the Pancreas

4.5.1. Occurrence of events associated with cystic fibrosis of the pancreas

– Patients for summarization: Patients included in the safety analysis

4.5.1.1. Occurrence of events associated with cystic fibrosis of the pancreas

For patients included in the safety analysis, a list of reported events associated with cystic fibrosis of the pancreas will be prepared (Table 5.1.1).

4.5.2. List of patients with cystic fibrosis of the pancreas

– Patients for summarization: Patients with available case report forms

4.5.2.1. List of patients with cystic fibrosis of the pancreas

A list of patients with cystic fibrosis of the pancreas will be prepared (Table 5.2.1.1 to Table 5.2.1.3).

No	Item name	Contents to be displayed
Records concerning patient demographics Table 5.2.1.1		
1	Patient number	-
2	Institution name Department name	-
3	Inclusion/exclusion in the safety analysis Inclusion/exclusion in the effectiveness analysis	Safety: XX Effectiveness: XX
4	Sex Date of birth Age	Male, female 88/88/8888 88
5	Inpatient/outpatientPatient identification number	Inpatient, outpatient XXXXXXXXX
6	Concurrent disease	-
7	Previous disease	-
8	Allergy history	-
9	Previous drug	-
10	Dose, duration of treatment	8888 mg, Capsule: 8888/88/88 to 8888/88/88 8888 mg, Granule: 8888/88/88 to 8888/88/88
11	Number of days of treatment Date of discontinuation Reason for discontinuation	888 88/88/8888 XXXXXX
12	Concomitant drug: Digestive enzyme preparations	-
13	Concomitant drug: Other concomitant drugs	-
14	Presence or absence of adverse events Presence or absence of serious adverse events Presence or absence of events associated with cystic fibrosis of the pancreas	Present, absent Present, absent Present, absent
15	Degree of overall improvement (at the time of last evaluation)	Improved, unchanged, deteriorated, cannot be determined

No	Item name	Contents to be displayed
Records concerning nutritional endpoints/symptoms of exocrine pancreatic insufficiency Table 5.2.1.2		
1	Patient number	-
2	Sex Date of birth Age	Male, female 88/88/8888 88
3	No.	-
4	Nutritional endpoints/ PEI symptoms	Body height, body weight, BMI, serum total protein, albumin, total cholesterol, triglycerides, hemoglobin, steatorrhea, frequency of defecation, bad stool odor, anorexia, abdominal bloating
5	Unit	Body height: cm Body weight: kg BMI: kg/m^2 Serum total protein: g/dL Albumin: g/dL Total cholesterol: mg/dL Triglycerides: mg/dL Hemoglobin: g/dL Steatorrhea: - Frequency of defecation: times/day Bad stool odor: - Anorexia: - Abdominal bloating: -
6	Data by evaluation time point	Date of test, test values, and normal/abnormal assessment by evaluation time point

No	Item name	Contents to be displayed
Records concerning adverse events Table 5.2.1.3		
1	Registration number	-
2	Separate volume	-
3	Date of onset	88/88/8888
4	LLT	-
5	LLT name	-
6	PT	-
7	PT name	-
8	SOC	-
9	SOC name	-
10	Presence or absence of treatment of the event	Present, absent
11	Date of outcome	88/88/8888
12	Outcome	Resolved, resolving, not resolved, sequelae, fatal, unknown

4.6. Attached Forms

4.6.1. Attached forms

– Patients for summarization: Patients with available case report forms

4.6.1.1. List of reported adverse drug reactions and infections [Attached Form 2]

The occurrence of adverse drug reactions and infections will be summarized.

Line

No	Item name	Description
1	Number of institutions surveyed	The same institution name will be regarded as 1 institution.
2	Number of patients surveyed	The separate volume for each reporting interval will be counted as the number of patients. If only 1 separate volume is locked, 1 separate volume will be regarded as 1 patient. If 2 separate volumes are locked at the same time, 2 separate volumes will be regarded as 1 patient. The total number of patients surveyed will be counted as the number of patients irrespective of separate volumes.
3	Number of patients with adverse drug reactions and number of adverse drug reactions	Adverse drug reactions corresponding to the number of patients surveyed (or each reporting interval) will be counted as the number of patients. If the same adverse drug reaction (PT) occurs repeatedly and is recorded multiple times, the adverse drug reaction will be summarized in the row of the period in which the firstly completed separate volume is counted. In addition, adverse drug reactions corresponding to the number of patients surveyed (total) will be counted as the number of patients.
4	Percentage of patients with adverse drug reactions	= Number of patients with adverse drug reactions / number of patients included in the safety analysis × 100
5	System organ class	MedDRA SOCs will be used. If the same patient experiences any adverse drug reaction (MedDRA SOC) multiple times, the patient will be counted once. Adverse drug reactions will be displayed in the SOC internationally agreed order.
6	Event name	MedDRA PTs will be used. If the same patient experiences any adverse drug reaction (MedDRA PT) multiple times, each event will be counted once. Adverse drug reactions will be displayed in the order of PT codes.

Row

No	Item name	Description
1	Survey period	See Section 2.1.

An unknown adverse drug reaction will be displayed with an asterisk (*) on its left side.

Novelty information (unknown or known) will be included in the information on MedDRA coding information provided by Mylan EPD G.K. Based on the novelty information, it will be determined whether an adverse drug reaction is unknown or not.

4.6.1.2. List of reported serious adverse events [Periodic safety report, Attached Form 2-2; Re-examination, Attached Form 10]

The occurrence of serious adverse events will be summarized. A list of serious adverse events will be prepared only for LPC02T.

The occurrence of serious adverse events will be summarized, as with Attached Form 2.

According to Appendix 2 (Attached Form 2-2) of the Notification No. 0325001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW and Notification No. 0325006 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW dated March 25, 2005, the number of unrelated serious adverse events will be summarized and displayed in [brackets] by MedDRA PT code.

4.6.1.3. Summary list of patients surveyed [Re-examination, Attached Form 3]

A summary list of patients surveyed will be prepared at the time of summarization for the re-examination.

Contents to be output will be specified separately in the written statistical analysis specification.

4.7. Additional Summarization for the Re-examination

– Patients for summarization: Patients with available case report forms and patients included in the safety analysis

4.7.1.1. Occurrence of adverse drug reactions and infections up to the time of approval [Re-examination, Attached Form 2 (New notification)]

The occurrence of adverse drug reactions and infections in the patients included in the safety analysis up to the time of approval will be summarized.

Line

No	Item name	Description
1	Number of patients included in the safety analysis	The number of patients included in the safety analysis will be counted.
2	Number of patients with adverse drug reactions	Adverse drug reactions reported up to the time of approval will be counted as the number of patients. If the same adverse drug reaction (PT) occurs repeatedly and is recorded multiple times, the adverse drug reaction will be counted once. Any event occurring beyond Week 52 will be excluded from the summarization for Attached Form 2.
3	Percentage of patients with adverse drug reactions	= Number of patients with adverse drug reactions / number of patients included in the safety analysis × 100
4	System organ class	MedDRA SOCs will be used. If the same patient experiences any adverse drug reaction (MedDRA SOC) multiple times, the patient will be counted once. Adverse drug reactions will be displayed in the order of SOC codes.
5	Event name	MedDRA PTs will be used. If the same patient experiences any adverse drug reaction (MedDRA PT) multiple times, each event will be counted once. Adverse drug reactions will be displayed in the order of PT codes.

4.7.1.2. Occurrence of adverse drug reactions and infections reported in post-marketing surveillance, etc. [Re-examination, Attached Form 15 (New notification)]

The occurrence of adverse drug reactions and infections in the patients included in the safety analysis reported in post-marketing surveillance, etc. will be summarized, as with Attached Form 2 (New notification).

4.7.1.3. Summary list of patients surveyed [Re-examination, Attached Form 16 (New notification)]

A summary list of patients surveyed will be prepared at the time of summarization for the re-examination.

Contents to be output will be specified separately in the written statistical analysis specification.

5. Other

5.1. Implementation of Additional Analysis

Any necessary analysis other than the analyses specified in this statistical analysis plan will be implemented after discussion with Mylan EPD G.K.

5.2. Tables and Figures Prepared at the Time of Periodic Safety Reporting

At the time of periodic safety reporting, summarization will be performed for Attached Form 2 and Attached Form 2-2.

6. List of Tables and Figures

Table title	Periodic safety reporting	Re-examination
LPC02T_01_Patient composition.xls		
Table 1.1.1.1 Number of institutions surveyed and patients with available case report forms by founder of each institution surveyed		○
Table 1.1.1.2 Number of patients with available case report forms by department		○
Table 1.1.2 Breakdown of discontinued patients		○
Figure 1.1.3.1 Diagram of patient composition		○
Figure 1.1.3.2 Diagram of patient composition (Follow-up survey)		○
Table 1.1.3.1 List of patients with overlapping reasons for exclusion (patients excluded from the safety analysis)		○
Table 1.1.3.2 List of patients with overlapping reasons for exclusion (patients excluded from the effectiveness analysis)		○
Table 1.1.3.3 List of adverse events reported in patients excluded from the safety analysis		○
Table 1.1.3.4 List of discontinued patients		○
Table 1.2.1 Patient demographic		○
Table 1.3.1 Status of use of Lipacreon		○
LPC02T_02_Safety.xls		
Table 2.1.1.1 List of reported adverse events by seriousness and relationship		○
Table 2.1.1.2 Breakdown of serious patients		○
Table 2.1.2.1 List of reported adverse events by time of onset		○
Table 2.1.2.2 List of reported serious adverse events by time of onset		○
Table 2.1.2.3 List of reported adverse drug reactions by time of onset		○
Table 2.1.2.4 List of reported serious adverse drug reactions by time of onset		○
Table 2.1.3.1.1 Treatment with Lipacreon and outcome of adverse events		○
Table 2.1.3.1.2 Treatment with Lipacreon and outcome of serious adverse events		○
Table 2.1.3.1.3 Treatment with Lipacreon and outcome of adverse drug reactions		○
Table 2.1.3.1.4 Treatment with Lipacreon and outcome of serious adverse drug reactions		○
Table 2.1.3.2.1 List of reported adverse events by treatment with Lipacreon		○
Table 2.1.3.2.2 List of reported serious adverse events by treatment with Lipacreon		○
Table 2.1.3.2.3 List of reported adverse drug reactions by treatment with Lipacreon		○
Table 2.1.3.2.4 List of reported serious adverse drug reactions by treatment with Lipacreon		○
Table 2.1.3.3.1 List of reported adverse events by outcome		○
Table 2.1.3.3.2 List of reported serious adverse events by outcome		○
Table 2.1.3.3.3 List of reported adverse drug reactions by outcome		○
Table 2.1.3.3.4 List of reported serious adverse drug reactions by outcome		○
Table 2.1.4.1 List of reported adverse events by time to “resolved” or “resolving”		○
Table 2.1.4.2 List of reported serious adverse events by time to “resolved” or “resolving”		○
Table 2.1.4.3 List of reported adverse drug reactions by time to “resolved” or “resolving”		○
Table 2.1.4.4 List of reported serious adverse drug reactions by time to “resolved” or “resolving”		○
Table 2.1.5.1 List of patients with adverse events		○
Table 2.1.5.2 List of patient numbers of adverse drug reactions		○
Table 2.2.1 Change over time in the mean daily dose		○

Table title	Periodic safety reporting	Re-examination
Table 2.2.2 Changes in the dose		○
Table 2.2.3 Maximum daily dose and last daily dose		○
Table 2.3.1.1 Incidence of adverse drug reactions by patient demographics		○
Table 2.3.1.2.X List of adverse drug reactions showing significant difference by patient demographics		○
LPC02T_03_Effectiveness.xls		
Table 3.1.1.1 Degree of overall improvement (patients included in the effectiveness analysis)		○
Table 3.1.1.2 Degree of overall improvement (patients included in the effectiveness analysis [patients completing the 52-week treatment])		○
Table 3.1.1.3.1 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis): Children		○
Table 3.1.1.3.2 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis): Pregnant women and nursing mothers		○
Table 3.1.1.3.3 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis): Hepatic impairment		○
Table 3.1.1.3.4 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis): Renal impairment		○
Table 3.1.1.3.5 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis): Respiratory disease		○
Table 3.1.1.4.1 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis [patients completing the 52-week treatment]): Children		○
Table 3.1.1.4.2 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis [patients completing the 52-week treatment]): Pregnant women and nursing mothers		○
Table 3.1.1.4.3 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis [patients completing the 52-week treatment]): Hepatic impairment		○
Table 3.1.1.4.4 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis [patients completing the 52-week treatment]): Renal impairment		○
Table 3.1.1.4.5 Degree of overall improvement in patients with special background (patients included in the effectiveness analysis [patients completing the 52-week treatment]): Respiratory disease		○
Table 3.1.2.1 Degree of overall improvement and effectiveness rate (patients included in the effectiveness analysis)		○
Table 3.1.2.2 Degree of overall improvement and effectiveness rate (patients included in the effectiveness analysis [patients completing the 52-week treatment])		○
Table 3.2.1.1 Change over time in the nutritional endpoints (patients included in the effectiveness analysis)		○
Figure 3.2.1.1 Change over time in the nutritional endpoints (patients included in the effectiveness analysis)		○
Table 3.2.1.2 Change over time in the nutritional endpoints (patients included in the effectiveness analysis [patients completing the 52-week treatment])		○
Figure 3.2.1.2 Change over time in the nutritional endpoints (patients included in the effectiveness analysis [patients completing the 52-week treatment])		○
Table 3.3.1.1 Change over time in the symptoms of exocrine pancreatic insufficiency (patients included in the effectiveness analysis)		○
Table 3.3.1.2 Change over time in the symptoms of exocrine pancreatic insufficiency (patients included in the effectiveness analysis [patients completing		○

Table title	Periodic safety reporting	Re-examination
the 52-week treatment])		
LPC02T_04_Patient selection.xls		
Table 4.1.1 Selection of patients excluded from the safety analysis		○
Table 4.1.2 Selection of patients excluded from the effectiveness analysis		○
Table 4.1.3 Selection of patients with special background		○
LPC02T_05_Cystic fibrosis of the pancreas.xls		
Table 5.1.1 Occurrence of events associated with cystic fibrosis of the pancreas		○
Table 5.2.1.1 List of patients with cystic fibrosis of the pancreas 1		○
Table 5.2.1.2 List of patients with cystic fibrosis of the pancreas 2		○
Table 5.2.1.3 List of patients with cystic fibrosis of the pancreas 3		○
LPC02T_06_Attached form .xls		
Attached Form 2	○	○
Attached Form 2-2_LPC02T	○	○
Attached Form 3		○
LPC02T_07_Additional summarization for re-examination.xls		
Attached Form 2 (New notification)		○
Attached Form 15 (New notification)		○
Attached Form 16 (New notification)		○

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