Statistical Analysis Plan: Mock-up Tables and Figures

Version 1.0, 08-SEP-2022

Protocol Number: Careseng 1370-01

A Phase I Dose-Escalation Study in Healthy Volunteers to Evaluate the Safety and Tolerability Profiles of Careseng 1370

Protocol version: 5.0, 18SEP2020
Sponsor: [redacted]

Table of Contents

1 Statistical Changes from Study Protocol

The statistical analysis methods will follow study protocol version 5.0, (18SEP2020), exceptions and clarifications are described below:

1.1 Visit Adjustment

Visit 11 is final visit or early withdrawal visit, refer to 14.3 for detail of visit adjustment

1.2 Analysis Populations

According to the protocol, only Intent-to-treat (ITT) population was defined for analyses of primary and secondary endpoints.

> Section 10.2.1 Analysis Population:
> Intent-to-treat (ITT) population:
> – Volunteers receive any Careseng 1370

For maximal tolerated dose (MTD) determination, a MTD-Evaluable Population is defined as below according to protocol section 3.1 "Volunteers Enrollment" on DLT analysis.

> MTD-Evaluable Population:
> 1. A subset of ITT population
> 2. Experiences DLT OR completes DLT observation period with at least 80% of study drug compliance and has exposed to Careseng 1370 for at least 4 days (level A, B, and C), OR completes DLT observation period with 100% of study drug compliance (level D).

1.3 Treatment Compliance

Treatment compliance is defined as below in protocol section 5.6:

> Volunteer's compliance will be assessed by the following formula:
> $$\frac{\text{\# of sachets of study drug actually administered}}{\text{Total \# of sachets of study drug assigned at that level}} \times 100\%$$

The parameters of compliance calculation are not well-defined in the protocol. The formula to derive treatment compliance and relevant parameters are adjusted as below:

$$\text{Treatment Compliance} = \frac{\text{\# of sachets of study drug actually administered}}{\text{Dose Level [Sachet/Day]} \times \text{Treatment Duration [Days]}} \times 100\%$$

- Treatment Duration [Days] = the last dosing date - the first dosing date + 1.

1.4 Pharmacokinetic Analysis

Pharmacokinetic parameters will be analyzed by Mithra Biotechnology Inc. All pharmacokinetic parameters data will be provided to sponsor directly, no data handling, data listing nor statistical analysis on such data will be done by A2 Healthcare.

> 2.2 Endpoints
> 2.2.2 Secondary endpoints
> 2 Pharmacokinetic parameters of marker ingredient in Careseng 1370, 20(S)-protopanaxadiol (PPD) and its metabolites

3 Protocol Versions and Protocol Amendments

The first subject was enrolled on 14AUG2020, and the last subject is expected to be dismissed on MAR2022. Amendments relevant to important statistical-related changes are summarized in table below, and Table/Figure/Listing programming will be based on the latest version of protocol.

Summary of important statistical-related changes for protocol version V4.0
Additional time points for PK blood sampling for Dose level B and C
Summary of important statistical-related changes for protocol version V5.0
Addition of 1 lower dose cohort (level D), and the corresponding information

4 Mock-up Tables and Figures

The Mock-up “TABLES and FIGURES” is planned according to ICH E3, in which relevant CSR section is 14. The words shadowed below are to be adjusted or repeated upon real data, or just for notification.

Columns {Label, Dose Level} will be included in the table with the analyzed population specified. In the mock table below, only the Label with one dose level column were presented to show the descriptive/inferential statistics to be displayed in the final tabulation.

Instructions and Abbreviations:

(1) Site ID □:

Site ID	Full Name
1	Taipei Medical University Hospital (TMUH)

(2) Dose Level:
- A (1 sachet/day): Careseng 1370 1 sachet before breakfast for consecutive 5 days
- B (2 sachets/day): Careseng 1370 1 sachet before breakfast and 1 sachet before lunch for consecutive 5 days
- C (3 sachets/day): Careseng 1370 1 sachet before breakfast and 2 sachets before lunch for consecutive 5 days
- D (1 sachet/day): Careseng 1370 1 sachet before breakfast on 1st, 3rd and 5th days (modified cohort)

(3) Population
- Intention-to-Treat (ITT) Population:
  - Volunteers receive any Careseng 1370
- Maximum Tolerated Dose (MTD)-Evaluable Population:
  - 1. A subset of ITT population
  - 2. Experiences DLT OR with at least 80% of study drug compliance and has exposed to Careseng 1370 for at least 4 days

(4) For Visit Name (in Tables and Figures) and Visit Code (in Subject Data Listing):

Visit No.	Visit Description	Visit Day	Visit Name	Visit Code
1	Visit 1 Screening Visit	-14 ~ -1	Visit 1 (Screening)	V01
2	Visit 2 Hospitalization: Day -1 to Day 1	1	Visit 2 (Day 1)	V02D01
3	Visit 3 Discharge: Day 2	2	Visit 3 (Day 2)	V03D02
4	Visit 4: Day 3	3	Visit 4 (Day 3)	V04D03
5	Visit 5: Day 4	4	Visit 5 (Day 4)	V05D04
6	Visit 6 Hospitalization: Day 4 to Day 5	5	Visit 6 (Day 5)	V06D05
7	Visit 7 Discharge: Day 6 *(24±2 hrs post-last dose)*	6	Visit 7 (Day 6)	V07D06
8	Visit 8 Follow-up Visit: Day 7 *(48±2 hrs post-last dose)*	7	Visit 8 (Day 7)	V08D07
9	Visit 9 Follow-up Visit: Day 8 *(72±2 hrs post-last dose)*	8	Visit 9 (Day 8)	V09D08
10	Visit 10 Follow-up Visit: Day 12±2	10 ~ 14	Visit 10 (Day 12)	V10D12
11	Visit 11 Final Visit *(Day 22±2, within 3 days after withdrawal)*	22	Visit 11 (Day 22)	V11D22
-	Unscheduled Visit	-	-	V□□.□

(5) Full term for 'Protocol Deviation Code':

Code	Full Term
	<To be added upon real data in final tabulation>

(6) For clinical relevance

CS: abnormal and clinically significant	LLN: lower limit of normal range
NCS: abnormal but not clinically significant	ULN: upper limit of normal range

(7) For Transition of Clinical Relevance

Relieved	CS (Medical History or Adverse Event) at baseline to Normal / NCS at visit.
Unchanged	Including Normal at baseline to NCS at visit, NCS at baseline to Normal at visit.
Worsened (Medical History)	Normal / NCS at baseline to CS (Medical History) at visit
Worsened (Adverse Event)	Normal / NCS / CS (Medical History) at baseline to CS (Adverse Event) at visit

(8) Abbreviations of statistics

N: number of non-missing values
Missing: number of missing values
Mean: mean of values
SD: standard deviation of values
Q1: 25% quartile of values
Q3: 75% quartile of values
Median: median of values
IQR: inter-quartile-range (IQR=Q3-Q1)
Min: minimum of values
Max: maximum of values
CI: confidence interval

14 TABLES AND FIGURES

- *The texts in shaded Italic are for programming note.*
- *Column of Study Site includes {Site 1: TMUH}*
- *Column of Dose Level includes {A (1 sachet/day), B (2 sachets/day), C (3 sachets/day), D (1 sachet/day), Total} as appropriate*
- *Description in <…> will be presented according to data values.*

14.1 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS

14.1.1 Screen Failures and Subject Disposition by Study Site

Population: All Screened Subjects / Eligible Subjects

Characteristics	Study Site
.All Screened Subjects	
n	XXX
Eligible Subjects	XXX (XXX.X%)
Screening Failures	XXX (XXX.X%)
<Screen Failure Reason 1>	XXX (XXX.X%)
<Screen Failure Reason 2>	XXX (XXX.X%)
<Screen Failure Reason 3>	XXX (XXX.X%)
…	XXX (XXX.X%)
.Population of Eligible Subjects	
n	XXX
ITT	XXX (XXX.X%)
MTD-Evaluable	XXX (XXX.X%)
Non-MTD-Evaluable	XXX (XXX.X%)
<Reason 1>	XXX (XXX.X%)
<Reason 2>	XXX (XXX.X%)
...	XXX (XXX.X%)
Non-ITT	XXX (XXX.X%)
.Dose Level of Eligible Subjects	
n	XXX
A (1 sachet/day)	XXX (XXX.X%)
B (2 sachets/day)	XXX (XXX.X%)
C (3 sachets/day)	XXX (XXX.X%)
D (1 sachet/day)	XXX (XXX.X%)
. Protocol Deviation of Eligible Subjects	
n	XXX
Major Protocol Deviation	XXX (XXX.X%)
<Protocol Deviation 1>	XXX (XXX.X%)
<Protocol Deviation 2>	XXX (XXX.X%)
...	
Minor Protocol Deviation	XXX (XXX.X%)
<Protocol Deviation 1>	XXX (XXX.X%)
<Protocol Deviation 2>	XXX (XXX.X%)
...	...

ITT: Intent-to-Treat population, MTD-Evaluable: Maximum Tolerated Dose-Evaluable Population (subset of ITT)

14.1.2 Study Visits, Study Termination, Subject Disposition and Protocol Deviation

Population: Intent-to-Treat Population

Characteristics	Dose Level
. Study Termination	
n	XXX
Study Completed	XXX (XXX.X%)
Study Not Completed	XXX (XXX.X%)
Withdrew consent	XXX (XXX.X%)
Protocol issue	XXX (XXX.X%)
…	XXX (XXX.X%)
. Study Duration [days]	
n (Missing)	XXX
Mean (SD)	XXX (XXX)
Median (IQR)	XXX (XXX)
Q1~Q3	XXX~XXX
Min~Max	XXX~XXX
.Population	
n	XXX
MTD-Evaluable	XXX (XXX.X%)
Non-MTD-Evaluable	XXX (XXX.X%)
<Reason 1>	XXX (XXX.X%)
<Reason 2>	XXX (XXX.X%)
...	XXX (XXX.X%)
.Protocol Deviation	
n	XXX
Major Protocol Deviation	XXX (XXX.X%)
<Protocol Deviation 1>	XXX (XXX.X%)
<Protocol Deviation 2>	XXX (XXX.X%)
...	
Minor Protocol Deviation	XXX (XXX.X%)
<Protocol Deviation 1>	XXX (XXX.X%)
<Protocol Deviation 2>	XXX (XXX.X%)
...	...
. Study Visits Completed, Adjusted Visits Completed	
N	XXX
Visit 1 (Screening)	XXX (XXX.X%)
Visit 2 (Day 1)	XXX (XXX.X%)
Visit 3 (Day 2)	XXX (XXX.X%)
Visit 4 (Day 3)	XXX (XXX.X%)
Visit 5 (Day 4)	XXX (XXX.X%)
Visit 6 (Day 5)	XXX (XXX.X%)
Visit 7 (Day 6)	XXX (XXX.X%)
Visit 8 (Day 7)	XXX (XXX.X%)
Visit 9 (Day 8)	XXX (XXX.X%)
Visit 10 (Day 12)	XXX (XXX.X%)
Visit 11 (Day 22)	XXX (XXX.X%)

Study Duration [days] = Date of Termination - Visit 1, or alternatively as the last visit date - Visit 1
Adjusted Visits Completed: Visits except visit 8 and visit 9 not in its visit window are shifted to corresponding scheduled visits

14.1.3 Demographic Data

Population: Intent-to-Treat Population

Characteristics	Dose Level
. Study Sites	
n (Missing)	XXX (XXX)
Site 1: TMUH	XXX (XXX.X%)
. Variable, including Age [Y/O], Baseline Body Weight [kg], Height [cm], BMI [kg/m^2]	
n (Missing)	XXX (XXX)
Mean (SD)	XXX (XXX)
Median (IQR)	XXX (XXX)
Q1~Q3	XXX~XXX
Min~Max	XXX~XXX
. Gender	
n (Missing)	XXX (XXX)
Male	XXX (XXX.X%)
Female	XXX (XXX.X%)
. Race *(multiple selection)*	
n (Missing)	XXX (XXX)
Black or African American	XXX (XXX.X%)
American Indian or Alaska Native	XXX (XXX.X%)
Asian	XXX (XXX.X%)
Native Hawaiian or Other Pacific Islander	XXX (XXX.X%)
White	XXX (XXX.X%)
Not Reported	XXX (XXX.X%)
Unknown	XXX (XXX.X%)

Age [Y/O] = int((date of informed consent – date of birth)/365.25)
BMI [kg/m^2]= Weight [kg] / (Height [cm])^2 * 10000
Baseline is Visit 2 or alternatively as Visit 1 if Visit 2 data is not available

14.1.4 General Medical History, Concurrent Disease/Status and Chest X-Ray

Population: Intent-to-Treat Population

Characteristics	Dose Level
.General Medical History	
n	XXX
At least one below	XXX (XXX.X%)
<Body System 1>	XXX (XXX.X%)
<Body System 2>	XXX (XXX.X%)
<Body System 3>	XXX (XXX.X%)
<Body System 4>	XXX (XXX.X%)
…	…
. Current Condition	
n	XXX
At least one below	XXX (XXX.X%)
<Body System 1>	XXX (XXX.X%)
<Body System 2>	XXX (XXX.X%)
<Body System 3>	XXX (XXX.X%)
<Body System 4>	XXX (XXX.X%)
…	…
. Chest X-Ray	

Characteristics	Dose Level
n (Missing)	XXX (XXX)
Normal	XXX (XX.X%)
NCS	XXX (XX.X%)
CS (Medical History)	XXX (XX.X%)
CS (Adverse Event)	XXX (XX.X%)
Not Interpretable	XXX (XX.X%)

Current condition lists the medical histories that are ongoing or with end date ≥ date of visit 2

14.1.5 Prohibited Medications, Treatments, Procedures and Foods

For Prohibited Medications, categories are Surgery, Herbal Medications, Herbal Supplements, Herbal Medicinal Food, Other. For Prohibited Foods, refer to CRF for the categories.

Population: Intent-to-Treat Population

Characteristics	Dose Level
. Prohibited Medications, Treatments, Procedures	
. Prohibited Foods	
n (Missing)	XXX (XXX)
At least one below	XXX (XXX.X%)
<Category 1>	XXX (XXX.X%)
<Category 2>	XXX (XXX.X%)
<Category 3>	XXX (XXX.X%)
<Category 4>	XXX (XXX.X%)
…	…

14.1.6 Study Drug Administration, Compliance and Exposure

Population: Intent-to-Treat Population

Characteristics	Dose Level
.Total IP Administration [sachets], Treatment Duration [days] Treatment Compliance [%], Mean Daily Dose [sachet/day]	
n (Missing)	XXX
Mean (SD)	XXX (XXX)
Median (IQR)	XXX (XXX)
Q1~Q3	XXX~XXX
Min~Max	XXX~XXX
. Treatment Compliance	
n (Missing)	XXX (XXX)
<60%	XXX (XXX.X%)
60 ~ <80%	XXX (XXX.X%)
80 ~ <100%	XXX (XXX.X%)
100 ~ <120%	XXX (XXX.X%)
≥120%	XXX (XXX.X%)

- Treatment Duration [days] = the last dosing date - the first dosing date + 1.
- Treatment Compliance [%] = Total IP Administration [sachets] / Dose Level [sachet/day] / Treatment Duration [days] * 100%
- Mean Daily Dose [sachet/day] = Total IP Administration [sachets] / Treatment Duration [days]

14.2 EFFICACY DATA

N/A

14.3 SAFETY DATA

Visit 11 is final visit or early withdrawal visit.

Safety data below except for visit 8 and visit 9 not in its visit window will be shifted to corresponding scheduled visit for analysis as in table below. If there is any data shifting, visit name will be presented as 'Adjusted Visit' for the visits reallocated to its original scheduled visit or the next visit after preceding scheduled visit.

Adjusted Visit	Laboratory Assessment†	Physical Examination	Body Weight	Vital Signs	12-Lead Electrocardiogram
• Baseline	N Baseline is Visit 1 (Screening), no need to present statistics for Baseline additionally	N.	Y Baseline is Day 1 , or alternatively as Visit 1 if Day 1 data are not available.	Y Baseline is Day 1 Pre-dose, or alternatively as Visit 1 if Day 1 Pre-dose data are not available.	Y Baseline is Day 1 Pre-dose, or alternatively as Visit 1 if Day 1 Pre-dose data are not available.
• Visit 1 (Screening)	Y	Y	Y	Y	Y
• Visit 2 (Day 1)	Y (8 hours post-first dose)	Y (Pre-dose), (8 hours post-first dose)	Y	Y (Pre-dose), (1 hour post-first dose), (4 hours post-first dose), (8 hours post-first dose)	Y (Pre-dose), (1 hour post-first dose), (4 hours post-first dose), (8 hours post-first dose), (12 hours post-first dose)
• Visit 3 (Day 2)	Y	Y	Y	Y	Y (Pre-dose), (1 hour post-first dosing post-first dosing)
• Visit 4 (Day 3)	Y	Y	Y	Y	Y (Pre-dose), (1 hour post-first dosing)
• Visit 5 (Day 4)	Y	Y	Y	Y	Y (Pre-dose), (1 hour post-first dosing)
• Visit 6 (Day 5)	Y (Pre-dose), (4 hours post dosing)	Y (Pre-dose), (4 hours post dosing)	Y	Y (Pre-dose), (4 hours post dosing)	Y (Pre-dose), (1 hour post-first dose), (4 hours post-first dose), (8 hours post-first dose), (12 hours post-first dose)
• Visit 7 (Day 6)	Y	Y	Y	Y	Y
• Visit 8 (Day 7)	N	N	N	N	N
• Visit 9 (Day 8)	N	N	N	N	N
• Visit 10 (Day 12)	Y	Y	Y	Y	Y
• Visit 11 (Day 22)	Y	Y	Y	Y	Y

Y denotes that the Visit is performed in the corresponding tables.
N denotes that the Visit is not performed in the corresponding tables.
† **Visit 1, 3, 7, 11 only for immunology**

14.3.1 Treatment Emergent Adverse Event – Subject Based Analyses

For 14.3.1.4, population will include ITT and MTD-Evaluable population.

14.3.1.1 Treatment Emergent AE – Summary

Population: Intent-to-Treat Population / MTD-Evaluable Population

Characteristics [Event#:Subj#]	Treatment
Repeat Population: Intent-to-Treat Population, MTD-Evaluable Population	
n	XXX
Subjects with AE	XXX : XXX (XXX.X%)
Subjects with Treatment-Related AE	XXX : XXX (XXX.X%)
Subjects with DLT	XXX : XXX (XXX.X%)
Subjects with Grade ≥3 AE	XXX : XXX (XXX.X%)
Subjects with Grade ≥3 Treatment-Related AE	XXX : XXX (XXX.X%)
Subjects with AE Leading to Action Taken	XXX : XXX (XXX.X%)
Subjects with AE Leading to Drug withdrawn	XXX : XXX (XXX.X%)
Subjects with SAE	XXX : XXX (XXX.X%)
Subjects with Death SAE	XXX : XXX (XXX.X%)
Subjects with SUSAR	XXX : XXX (XXX.X%)
Subjects with Death SUSAR	XXX : XXX (XXX.X%)

Subject with multiple events are counted as one incidence.
Treatment-Related is defined as Definitely Related, Probable Related, or Possibly Related

Programmer's Notes:
Repeat Population only when the two populations are not identical

14.3.1.2 Treatment Emergent AE – Subjects with AE

14.3.1.3 Treatment Emergent AE – Subjects with Treatment-Related AE

14.3.1.4 Treatment Emergent AE – Subjects with DLT

[For 14.3.1.2-3] Population: Intent-to-Treat Population
[For 14.3.1.4] Population: Intent-to-Treat Population / MTD-Evaluable Population

Characteristics [Event#:Subj#]	Dose Level
Repeat Population: Intent-to-Treat Population, MTD-Evaluable Population (Applied for 14.3.1.4)	
. By MedDRA SOC and Preferred Term	
n	XXX
At least one below	XXX : XXX (XXX.X%)
<MedDRA Body System 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)
…	XXX : XXX (XXX.X%)
<MedDRA Body System 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)

For each MedDRA (version 23.0) SOC or Preferred Term, Subject with multiple events are counted as one incidence.
[For 14.3.1.3] Treatment-Related is defined as Definitely Related, Probable Related, or Possibly Related

Programmer's Notes:
Repeat Population only when the two populations are not identical
Sorted in descending order of Subject No, Event No. of Total column by MedDRA Body System first, and then MedDRA Preferred Term.

14.3.1.5 Treatment Emergent AE – Subjects with Grade ≥3 AE

14.3.1.6 Treatment Emergent AE – Subjects with Grade ≥3 Treatment-Related AE

Population: Intent-to-Treat Population

Characteristics [Event#:Subj#]	Dose Level
. By Severity Grade, MedDRA SOC and Preferred Term	
n	XXX
At least one below	XXX : XXX (XXX.X%)
Grade ≥3, Grade 4, Grade 5	XXX : XXX (XXX.X%)
<MedDRA Body System 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)
…	XXX : XXX (XXX.X%)
<MedDRA Body System 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)

[For 14.3.1.6] Treatment Related is defined as Definitely Related, Probable Related, or Possibly Related

Programmer's Notes:
Sorted in descending order of Subject No, Event No. of Total column by MedDRA Body System first, and then MedDRA Preferred Term for each Grade Level

14.3.1.7 Treatment Emergent AE – Subjects with AE Leading to Action Taken

Population: Intent-to-Treat Population

Characteristics [Event#:Subj#]	Dose Level
. By Action Taken, MedDRA SOC and Preferred Term	
n	XXX
At least one below	XXX : XXX (XXX.X%)
Drug interrupted, Drug withdrawn	XXX : XXX (XXX.X%)
<MedDRA Body System 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)
<MedDRA Body System 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)

Programmer's Notes:
Sorted in descending order of Subject No, Event No. of Total column by Action Taken first, then MedDRA Body System, and then MedDRA Preferred Term

14.3.1.8 Treatment Emergent AE – Subjects with SAE

14.3.1.9 Treatment Emergent AE – Subjects with SUSAR

SUSAR: Suspected Unexpected Serious Adverse Reaction (Unexpected Treatment Related SAE)

Population: Intent-to-Treat Population

Characteristics [Event#:Subj#]	Dose Level
. By SAE Criteria, MedDRA SOC and Preferred Term	
n	XXX
At least one below	XXX : XXX (XXX.X%)
<SAE Criterion>	XXX : XXX (XXX.X%)
<MedDRA Body System 1>	
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)
	XXX : XXX (XXX.X%)
<MedDRA Body System 2>	
<MedDRA Preferred Term 1>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 2>	XXX : XXX (XXX.X%)
<MedDRA Preferred Term 3>	XXX : XXX (XXX.X%)
	XXX : XXX (XXX.X%)

SAE Criteria 'F/L/H' and 'F/L' will be counted as 'F' only, and 'L/H' as 'L', where F=Fatal (Death), L=Life threatening, H=Require hospitalization or prolongation of existing hospitalization.

Programmer's Notes:
SAE Criterion: {Any SAE Criterion, Requires or Prolongs Hospitalization, death, …}
Sorted in descending order of Subject No, Event No. of Total column by SAE Criterion, MedDRA Body System, and MedDRA Preferred Term

14.3.2 Laboratory Examination – Hematology

14.3.2.1 Hematology – <Hematology Item 1 and Unit>

14.3.2.2 Hematology – <Hematology Item 2 and Unit>

14.3.2.3 Hematology – <Hematology Item 3 and Unit>

14.3.2.4 …

14.3.3 Laboratory Examination – Biochemistry

14.3.3.1 Biochemistry – <Biochemistry Item 1 and Unit>

14.3.3.2 Biochemistry – <Biochemistry Item 2 and Unit>

14.3.3.3 Biochemistry – <Biochemistry Item 3 and Unit>

14.3.3.4 …

14.3.4 Laboratory Examination – Urinalysis

14.3.4.1 Urinalysis – pH

14.3.4.2 Urinalysis – Protein <Unit>

14.3.4.3 Urinalysis – RBC <Unit>

14.3.4.4 Urinalysis – WBC <Unit>

14.3.4.5 Urinalysis – Casts <Unit>

Data '<a', '≤a', '>a', '≥a' will be estimated as 'a' for analysis.

14.3.5 Laboratory Examination – Immunology

14.3.5.1 Immunology – CD3 <Unit>

14.3.5.2 Immunology – CD4 <Unit>

14.3.5.3 Immunology – CD8 <Unit>

14.3.5.4 Immunology – CD16 <Unit>

14.3.5.5 Immunology – CD19 <Unit>

14.3.5.6 Immunology – CD56 <Unit>

<For continuous Laboratory Examination >

Population: Intent-to-Treat Population

Characteristics	Dose Level
. (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Mean (SD)	XXX (XXX)
Median (IQR)	XXX (XXX)
Q1~Q3	XXX~XXX
Min~Max	XXX~XXX
n (Missing)	XXX (XXX)
Normal	XXX (XX.X%)
NCS	XXX (XX.X%)
CS (Medical History)	XXX (XX.X%)
CS (Adverse Event)	XXX (XX.X%)
. (Adjusted) Visits - Baseline, see visit table below 14.3	
n (Missing)	XXX (XXX)
Mean (SD)	XXX (XXX)
Median (IQR)	XXX (XXX)
Q1~Q3	XXX~XXX
Min~Max	XXX~XXX
95% CI (WI)	XXX~XXXwt
. Baseline to (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Relieved	XXX (XX.X%)
Unchanged	XXX (XX.X%)
Worsened (Medical History)	XXX (XX.X%)
Worsened (Adverse Event)	XXX (XX.X%)

- For CI (WI, within group), t denotes by using one sample t-test, w denotes CI of median (determined by Shapiro-Wilk normality test)
- Refer to [Instructions and Abbreviations] of title pages for Transition of Clinical Relevance

Programmer's Notes:
Present 'Baseline' as Visit 1 (Screening).

<For categorical urinalysis data>

Population: Intent-to-Treat Population

Characteristics	Dose Level
. (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
<Value 1>	XXX (XX.X%)
<Value 2>	XXX (XX.X%)
<Value 3>	XXX (XX.X%)
n (Missing)	XXX (XXX)
Normal	XXX (XX.X%)
NCS	XXX (XX.X%)
CS (Medical History)	XXX (XX.X%)
CS (Adverse Event)	XXX (XX.X%)
Baseline to (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
<Value 1>	XXX (XX.X%)
<Value 2>	XXX (XX.X%)
<Value 3>	XXX (XX.X%)
Baseline to (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Relieved	XXX (XX.X%)
Unchanged	XXX (XX.X%)
Worsened (Medical History)	XXX (XX.X%)
Worsened (Adverse Event)	XXX (XX.X%)

- Refer to [Instructions and Abbreviations] of title pages for Transition of Clinical Relevance

Programmer's Notes:
Present 'Baseline' as Visit 1 (Screening).

14.3.6 Physical Examination

14.3.6.1 Physical Examination – All Abnormalities

Population: Intent-to-Treat Population

Characteristics	Dose Level
. (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
At least one below	XXX (XXX.X%)
<Body System 1>	XXX (XXX.X%)
CS (Medical History)	XXX (XXX.X%)
CS (Adverse Event)	XXX (XXX.X%)
<Body System 2>	XXX (XXX.X%)
CS (Medical History)	XXX (XXX.X%)
CS (Adverse Event)	XXX (XXX.X%)
<Body System 3>	XXX (XXX.X%)
CS (Medical History)	XXX (XXX.X%)
CS (Adverse Event)	XXX (XXX.X%)
…	…

14.3.7 Vital Signs and Body Weight

14.3.7.1 Vital Signs – Body Temperature [degree C]

14.3.7.2 Vital Signs – Respiratory Rate [breaths/min]

14.3.7.3 Vital Signs – Systolic Blood Pressure [mmHg]

14.3.7.4 Vital Signs – Diastolic Blood Pressure [mmHg]

14.3.7.5 Vital Signs – Heart/Pulse Rate [beats/min]

14.3.7.6 Body Weight [kg]

Use the layout <For continuous Laboratory Assessment>, clinical relevance {Normal, NCS, CS (Medical History), CS (Adverse Event)} analysis will be only presented for 14.3.7.1, 2, 3, 5.

Footnote "For Body Weight, uncheck of Clinical Relevance 'CS' will be recoded as 'Normal / NCS' for analysis".
Footnote "Baseline is Visit 2 (Day 1, Pre-dose) or alternatively as Visit 1 (Screening) if Visit 2 (Day 1, Pre-dose) data are not available".
Footnote for weight "Baseline is Visit 2 (Day 1) or alternatively as Visit 1 (Screening) if Visit 2 (Day 1) data are not available".

14.3.8 12-Lead Electrocardiogram (EKG)

14.3.8.1 Electrocardiogram - Overall Interpretation

Population: Intent-to-Treat Population

Characteristics	Dose Level
. (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Normal	XXX (XX.X%)
NCS	XXX (XX.X%)
CS (Medical History)	XXX (XX.X%)
CS (Adverse Event)	XXX (XX.X%)
. Baseline to (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Relieved	XXX (XX.X%)
Unchanged	XXX (XX.X%)
Worsened (Medical History)	XXX (XX.X%)
Worsened (Adverse Event)	XXX (XX.X%)

- Baseline is Visit 2 (Day 1, Pre-dose) or alternatively as Visit 1 (Screening) if Visit 2 (Day 1, Pre-dose) data are not available.
- Refer to [Instructions and Abbreviations] of title pages for Transition of Clinical Relevance

14.3.8.2 Electrocardiogram - Sinus Rhythm

Population: Intent-to-Treat Population

Characteristics	Dose Level
. (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Normal	XXX (XX.X%)
Abnormal	XXX (XX.X%)
. Baseline to (Adjusted) Visits, see visit table below 14.3	
n (Missing)	XXX (XXX)
Normal to Abnormal	XXX (XX.X%)
No Change	XXX (XX.X%)
Abnormal to Normal	XXX (XX.X%)

- Baseline is Visit 2 (Day 1, Pre-dose) or alternatively as Visit 1 (Screening) if Visit 2 (Day 1, Pre-dose) data are not available.

14.3.8.3 Electrocardiogram - Ventricular Rate [beats/min]

14.3.8.4 Electrocardiogram - PR Interval [msec]

14.3.8.5 Electrocardiogram - QRS Interval [msec]

14.3.8.6 Electrocardiogram - QT Interval [msec]

14.3.8.7 Electrocardiogram - QTc Interval [msec]

Use the layout <For continuous Laboratory Assessment>, excluding clinical relevance {Normal, NCS, CS (Medical History), CS (Adverse Event)} analysis

Footnote "Baseline is Visit 2 (Day 1, Pre-dose) or alternatively as Visit 1 (Screening) if Visit 2 (Day 1, Pre-dose) data are not available".

Statistical Analysis Plan: Mock-up Subject Data Listings

Version 1.0, 08-SEP-2022

Protocol Number: Careseng 1370-01

A Phase I Dose-Escalation Study in Healthy Volunteers to Evaluate the Safety and Tolerability Profiles of Careseng 1370

Protocol version: 5.0, 18SEP2020
Sponsor: [redacted]

The Mock-up "Subject Data Listings" is planned according to ICH E3, in which relevant CSR section is 16.2. The words shadowed below are for notifications, or to be revised, or variables/format/footnotes to be included.

All listing will be sorted by (1) Eligibility {Eligible subjects by dose level, Screen failures} (2) Subject ID (3) Visit No. (4) Item No.

Instructions and Abbreviations:

(1) Subject ID contains Screening Number and Subject Number (S□□□-□□□) for eligible subject and Screening Number (S□□□) for non-eligible subject / screening failure.

Site ID □	1 = Taipei Medical University Hospital (TMUH)
Screening number S□□□	Assigned sequentially from S□01 for each site
Dose Level □	A = Careseng 1370 1 sachet before breakfast for consecutive 5 days B = Careseng 1370 1 sachet before breakfast and 1 sachet before lunch for consecutive 5 days C = Careseng 1370 1 sachet before breakfast and 2 sachets before lunch for consecutive 5 days
Subject Number □□□:	Assigned sequentially from □01 for dose level □ for each site

(2) DP/AG:

D denotes dose level

A: Careseng 1370 1 sachet before breakfast for consecutive 5 days
B: Careseng 1370 1 sachet before breakfast and 1 sachet before lunch for consecutive 5 days
C: Careseng 1370 1 sachet before breakfast and 2 sachets before lunch for consecutive 5 days
D (1 sachet/day) (modified cohort): Careseng 1370 1 sachet before breakfast on 1st, 3rd and 5th days

P denotes population

I: intent-to-treat (ITT) population
- Volunteers receive any Careseng 1370

M: Maximum Tolerated Dose (MTD)-Evaluable Population, satisfying
1. A subset of ITT population
2. Experiences DLT OR with at least 80% of study drug compliance and has exposed to Careseng 1370 for at least 4 days

A denotes age in Y/O

Age = int((date of informed consent – date of birth)/365.25)

G denotes gender

M: male
F: female

(3) Date format: YYYY-MM-DD

(4) For Visit Name (in Tables and Figures) and Visit Code (in Subject Data Listing):

Visit No.	Visit Description	Visit Day	Visit Name	Visit Code
1	Visit 1 Screening Visit	-14 ~ -1	Visit 1 (Screening)	V01
2	Visit 2 Hospitalization: Day -1 to Day 1	1	Visit 2 (Day 1)	V02D01
3	Visit 3 Discharge: Day 2	2	Visit 3 (Day 2)	V03D02
4	Visit 4: Day 3	3	Visit 4 (Day 3)	V04D03
5	Visit 5: Day 4	4	Visit 5 (Day 4)	V05D04
6	Visit 6 Hospitalization: Day 4 to Day 5	5	Visit 6 (Day 5)	V06D05
7	Visit 7 Discharge: Day 6 *(24±2 hrs post-last dose)*	6	Visit 7 (Day 6)	V07D06

Visit No.	Visit Description	Visit Day	Visit Name	Visit Code
8	Visit 8 Follow-up Visit: Day 7 *(48±2 hrs post-last dose)*	7	Visit 8 (Day 7)	V08D07
9	Visit 9 Follow-up Visit: Day 8 *(72±2 hrs post-last dose)*	8	Visit 9 (Day 8)	V09D08
10	Visit 10 Follow-up Visit: Day 12±2	10 ~ 14	Visit 10 (Day 12)	V10D12
11	Visit 11 Final Visit *(Day 22±2, within 3 days after withdrawal)*	22	Visit 11 (Day 22)	V11D22
-	Unscheduled Visit	-	-	V□□.□

(5) For the visit/assessment days and hour (like AE Onset Day), they were derived by formula below
Day/Hour = [visit/assessment date/time – the first treatment date/time + 1] , if date/hour ≧ 1st dosing date/time,
Day/Hour = [visit/assessment date/time – the first treatment date/time] , if date/hour < 1st dosing date/time,
Duration in days/hours = [end date/time – onset date/time + 1] if end date/time is active
Duration in days/hours = [end date/time – onset date/time] if end date/time is inactive

(6) Full term for 'Protocol Deviation Code':

Code	Full Term
	<To be added upon real data in final tabulation>

(7) Full term for Laboratory Measurements:

- Hematology

Test code of SDTM	Test of SDTM	Test in section 14
HGB	Hemoglobin	Hemoglobin
HCT	Hematocrit	Hematocrit (Hct)
RBC	Erythrocytes	RBC
WBC	Leukocytes	WBC
NEUTLE	Neutrophils/Leukocytes	Neutrophils
LYMLE	Lymphocytes/Leukocytes	Lymphocytes
MONOLE	Monocytes/Leukocytes	Monocytes
EOSLE	Eosinophils/Leukocytes	Eosinophils
BASOLE	Basophils/Leukocytes	Basophils
NEUT	Neutrophils	Absolute neutrophil Count (ANC)
LYM	Lymphocytes	Lymphocyte Count
PLAT	Platelets	Platelet
INR	Prothrombin Intl. Normalized Ratio	International normalized ratio (INR)
APTT	Activated Partial Thromboplastin Time	Activated partial thromboplastin time (APTT)

- Biochemistry

Test code of SDTM	Test of SDTM	Test in section 14
AST	Aspartate Aminotransferase	AST, SGOT
ALT	Alanine Aminotransferase	ALT, SGPT
ALB	Albumin	Albumin
ALP	Alkaline Phosphatase	Alkaline Phosphatase (ALP)
BILI	Bilirubin	Total bilirubin
CREAT	Creatinine	Creatinine
UREAN	Urea Nitrogen	Blood urea nitrogen (BUN)
CRP	C Reactive Protein	C-reaction protein (CRP)
PROT	Protein	Total protein
GGT	Gamma Glutamyl Transferase	Gamma-glutamyl transferase (γ -GT)

Test code of SDTM	Test of SDTM	Test in section 14
GLUC	Glucose	Blood Glucose
URATE	Urate	Uric Acid
CHOL	Cholesterol	Total Cholesterol
TRIG	Triglycerides	Triglyceride (TG)
SODIUM	Sodium	Sodium (Na)
K	Potassium	Potassium (K)
CA	Calcium	Calcium (Ca)
MG	Magnesium	Magnesium
PHOS	Phosphate	Phosphorus
AMYLASE	Amylase	Amylase
LIPASET	Lipase	Lipase

- Urinalysis

Test code of SDTM	Test of SDTM	Test in section 14
PH	pH	pH
PROT	Protein	Protein
RBC	Erythrocytes	RBC
WBC	Leukocytes	WBC
CASTS	Casts	Casts

- Immunology

Test code of SDTM	Test of SDTM	Test in section 14
CD3	CD3+	CD3+
CD3CD4	CD3+/CD4+	CD3+/CD4+
CD3CD8	CD3+/CD8+	CD3+/CD8+
CD19	CD19+	CD19+
CD16CD56	CD16+/CD56+	CD16+/CD56+
CD4CD8	CD4/CD8 Ratio	CD4/CD8 Ratio

(8) For Serial No.,
- H[X][X][X]: Serial No. of General Medical History,
- C[X][X][X]: Serial No. of Concomitant Medication
- A[X][X][X]: Serial No. of Adverse Event
- CO[X][X]: Serial No. of Comment

(9) For clinical relevance,
- NCS denotes ‘abnormal but not clinically significant’
- CS denotes ‘abnormal and clinically significant’

(10) General abbreviations

Code	Full Term
A, NA, N/A	Not Applicable
U, UK, U/K	Unknown
O, OG, O/G	Ongoing
D, ND, N/D	Not Done
M, MS, M/S	Missing
MH	Medical History
AE	Adverse Event
CM	Concomitant Medication
INC[X][X]	Inclusion Criterion [X][X]
EXC[X][X]	Exclusion Criterion [X][X]

16.2 Subject Data Listings

16.2.1 Discontinued Subjects

16.2.1.1 Screen Failures
Screening failure reasons and criteria (IE)

16.2.1.2 Study Termination of Eligible Subjects
First Treatment Date/Day,
Last Treatment Date/Day,
Study Termination Date, Study Duration [days] (Refer to table 14.1.2 for formula),
Status (Study Completed or Not Completed),
Primary Discontinued Reason and Description.

16.2.1.3 Visit Dates and Inform Consent Date
Including visit status and fasting status

16.2.1.4 Visit Adjustment
(If any)

16.2.1.5 Unscheduled Visit Dates
(If any)

16.2.1.6 Protocol Versions Applied

16.2.2 Protocol Deviations

16.2.2.1 Inclusion / Exclusion Criteria
Including visit and protocol version if there is related protocol amendment.

16.2.2.2 Protocol Deviations
Including Subject ID / Severity / Code / Description / Population to be excluded,

† according to ICH E9 section '5.2.2 Per Protocol Set', protocol violations may include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data.

16.2.2.3 Non Protocol Deviation Findings

16.2.3 Eligible Subjects Excluded from the Safety/Efficacy Analysis

16.2.3.1 Eligible Subjects Excluded from ITT Population

16.2.3.2 Eligible Subjects Excluded from MTD-Evaluable Population

16.2.4 Demographic Data and Baseline Characteristics

16.2.4.1 Demographic Data
Including re-screen status, preceding Screening No., body height, baseline weight and BMI

16.2.4.2 General Medical History
Identifier of current condition included
Footnote: Current condition lists the medical histories that are ongoing or with end date ≥ date of visit 1

16.2.4.3 Chest X-ray

16.2.5 Concomitant Medications, Treatments, Procedures and Prohibited Foods

16.2.5.1 Medication History &Concomitant Medications

16.2.5.2 Prohibited Foods

16.2.6 Study Drug Administration, Compliance and Exposure

16.2.6.1 Study Drug Compliance and Exposure
Including Total IP Administration [Sachets], Treatment Duration [Days], Treatment Compliance [%], Mean Daily Dose [Sachet / day]
Refer to table 14.1.6 for the definition

16.2.6.2 Drug Accountability

16.2.7 Adverse Event (AE) and Serious Adverse Event (SAE)

16.2.7.1 Pre-Treatment AE

16.2.7.2 Treatment Emergent AE

Variables: In addition to event description and general AE profiles (Before / After doseing, onset date, resolution date, severity, relationship to study treatment, action taken to study treatment, seriousness, outcome), the Subject data listing will also present the MedDRA System Organ Class and preferred term, onset day, and AE duration [days]

Footnote:

- ***Onset Day = onset date – the first treatment dosing date + 1***
- ***AE duration [days]***
  = resolution date - onset date (while resolved)
  =study exit date – onset date (while not resolved, noted with '+')

16.2.7.3 Treatment Emergent AE – Treatment Related AE
Treatment Related is defined as Definitely Related, Probable Related, or Possibly Related

16.2.7.4 Treatment Emergent AE – DLT

16.2.7.5 Treatment Emergent AE – Grade ≥3 AE

16.2.7.6 Treatment Emergent AE – Grade ≥3 Treatment Related AE

16.2.7.7 Treatment Emergent AE – AE Leading to Action Taken

16.2.7.8 Serious Adverse Event (SAE)

16.2.7.9 Suspected Unexpected Serious Adverse Reaction (SUSAR)
(Unexpected Treatment Related SAE)

16.2.8 Laboratory Examination

16.2.8.1 Laboratory Examination – Summary in Standard Unit

16.2.8.2 Laboratory Examination – Hematology

16.2.8.3 Laboratory Examination – Biochemistry

16.2.8.4 Laboratory Examination – Urinalysis

16.2.8.5 Laboratory Examination – Immunology

16.2.8.6 Laboratory Examination – Not Done Reason and Comments

16.2.8.7 Pregnancy Test
For Female Subjects Only

16.2.9 Other Safety Measurements

16.2.9.1 Physical Examination

16.2.9.2 Physical Abnormalities

16.2.9.3 Vital Signs and Body Weight

16.2.9.4 12-Lead Electrocardiogram (EKG)
Variables: Overall interpretation, Sinus Rhythm, Ventricular Rate, PR Interval, QRS Interval, QT Interval, QTc Interval

16.2.9.5 Not Done Reason and Comments of Other Safety Measurements

16.2.10 Pharmacokinetics Sampling

PK blood sampling time points:

V02D01 Pre-Dose	*V06D05 Pre-Dose*	*V07D06 24h*
V03D02 Pre-Dose	*V06D05 0.5h*	*V08D07 48h*
V04D03 Pre-Dose	*V06D05 1h*	*V09D08 72h*
V05D04 Pre-Dose	*V06D05 2h*	
	V06D05 4h	
	V06D05 6h	
	V06D05 12h	

16.2.10.1 Blood Sampling Time

16.2.11 Comments

16.2.11.1 Comment