Janssen Research & Development *

Statistical Analysis Plan

An Open-Label Study to Evaluate the Pharmacokinetics (PK) of Darunavir (DRV) and Cobicistat (COBI) After a Single-Oral Administration of Darunavir/Cobicistat Fixed-Dose Combination Tablet in Healthy Japanese Adult Subjects

Protocol TMC114FD1HTX4002; Phase IV

TMC114 + JNJ-48763364-AAA (Prezcobix®, (Darnavir/Cobicistat))

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	alanine aminotransferase
AUC_{last}	area under the plasma concentration-time curve from time zero to time the last quantifiable time, calculated by linear trapezoidal summation
AUC_{∞}	area under the plasma concentration-time curve from time zero to infinite time
BMI	body mass index
BQL	Below quantifiable limit
C_{last}	concentration at last quantifiable time point
C_{max}	maximum plasma concentration
COBI	Cobicistat
CV	coefficient of variation
DRV	Darunavir
ECG	electrocardiogram
FDC	Fixed-dose combination
HIV	human immunodeficiency virus
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PT	preferred term
RBC	red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{1/2,term}$	terminal elimination half-life
t_{max}	time to reach the maximum plasma concentration
WBC	white blood cell
λ_z	elimination rate constant associated with the terminal phase

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses of Protocol TMC114FD1HTX4002.

1.1. Trial Objectives

Primary Objective

The primary objective is to evaluate the PK of Darunavir (DRV) and Cobicistat (COBI) after a single oral administration of Prezcobix DRV and COBI fixed-dose combination tablet, to healthy Japanese adult subjects.

Secondary Objectives

The secondary objective is to evaluate the safety after a single oral administration of Prezcobix to healthy Japanese adult subjects.

1.2. Trial Design

This is a single center open-label, single oral dose study in healthy Japanese adult subjects. The study consists of 3 phases; a screening phase from Day -21 to Day -2, an in-patient phase from Day -1 to Day 4 (dosing day is Day 1), and a follow-up assessment phase scheduled 7 to 10 days after the intake of the study drug or at the time of early withdrawal.

1.3. Statistical Hypotheses for Trial Objectives

No formal statistical hypothesis testing is planned for this study. This study is designed to collect PK data in Japanese subjects after a single oral administration of Prezcobix under a fed condition.

1.4. Sample Size Justification

Eight subjects will be enrolled in the study to ensure that at least 6 subjects complete the study assessments up to Day 4. Based on a previous study, TMC114IFD1003, the maximum observed value of between subject coefficient of variation (CV) for C_{max}, AUC_{last} and AUC_{∞} for DRV and COBI after intake of DRV and COBI as a Fixed-dose combination (FDC) tablet under fed conditions were 35% for DRV and 44% for COBI in healthy non Japanese adult subjects. Using an estimate of approximately 40% for between subject CV and a sample size of 6 subjects, the true mean C_{max}, AUC_{last} and AUC_{∞} for each component of DRV and COBI are estimated to be within 73% to 137% of the observed geometric means with 90% confidence.

1.5. Randomization and Blinding

As this is an open study, blinding procedures are not applicable. No randomization is planned in this study. All the subjects will be assigned to the same treatment.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

The evaluations are described in "Time and Events Schedule" of the protocol and the allowance are described below.

Analysis time point		**Allowance**	**Physical Examination**	**Vital Signs** [a), b)]	**12-lead ECG** [a)]	**Clinical Labs** [c)]
Screening		Day -21 to Day -2	X	X	X	X
Day -1		Within Day-1	X	X	X	X
Day 1	Predose	Within Day1 and before intake of Prezcobix	X	X	X	
	3 hr	Within Day1 and +/- 30 min.		X	X	
Day 2		Within Day 2	X	X	X	X
Day 4		Within Day 4	X	X	X	X
End-of-Study (Day 7 -10)		Within the day Day 7 -10	X	X	X	X

a) When blood samples are to be collected and 12-lead ECG and/or vital signs are to be checked at the same time point, blood samples will be collected after completion of other evaluations.
b) Vital signs include respiration rate, supine blood pressure, pulse and temperature (axillary) after more than 5 minutes rest.
c) Clinical labs include hematology, biochemistry and urinalysis. Subjects will fast for at least 10 hours prior to the blood sampling for clinical labs.

Pharmacokinetics

Analysis time point		**Allowance**	**Pharmacokinetics**
Day 1	Predose	Before intake of Prezcobix	X [a)]
	0 hr		
	0.5 hr	0.4 hr to 0.6 hr	X
	1 hr	0.8 hr to 1.2 hr	X
	1.5 hr	1.25 hr to <1.75 hr	X
	2 hr	1.75 hr to <2.25 hr	X
	2.5 hr	2.25 hr to <2.75 hr	X
	3 hr	2.75 hr to 3.25 hr	X [a)]
	4 hr	3.5 hr to <4.5 hr	X
	5 hr	4.5 hr to <5.5 hr	X
	6 hr	5.5 hr to 6.5 hr	X
	9 hr	8.0 hr to <10.0 hr	X
	12 hr	10.0 hr to <14.0 hr	X
	16 hr	14.0 hr to <18.0 hr	X
	20 hr	18.0 hr to <22.0 hr	X
Day 2	24 hr	22.0 hr to 26.0 hr	X [a)]
	36 hr	30.0 hr to <42.0 hr	X
Day 3	48 hr	42.0 hr to <54.0 hr	X
	60 hr	54.0 hr to <66.0 hr	X
Day 4	72 hr	66.0 hr to 78.0 hr	X [a)]
End-of-Study (Day 7-10)/ Early Withdrawal			X [a) b)]

a) When blood samples are to be collected and 12-lead ECG and/or vital signs are to be checked at the same time point, blood samples will be collected after completion of other evaluations.
b) At the end of study or early withdrawal, sample PK will be performed for early withdrawal visit only.

2.2. Pooling Algorithm for Analysis Centers

This is a single center study; therefore, the pooling algorithm is not applicable.

2.3. Analysis Sets

The analysis sets consist of Safety analysis population and Pharmacokinetics (PK) analysis population.

2.3.1. Safety Analysis Set

Safety analysis population is defined as all subjects who received the study drug.

2.3.2. Pharmacokinetics Analysis Set

Pharmacokinetics (PK) analysis population is defined as all subjects receiving the study drug and having at least one plasma concentration data after administration

2.4. Definition of Subgroups

Not applicable.

2.5. Summary Statistics

Summary statistics for continuous variables are number of subjects, arithmetic mean (Mean), standard deviation (SD), median, minimum, and maximum.

In PK analysis, geometric mean (geo mean), coefficient of variation (CV %) and 90% confidence intervals of geo mean are also presented. The formulas for calculation are shown as following:

$$\text{Geometric mean} = \exp\left[\frac{\sum_{i=1}^{n}\log X_i}{n}\right] = \sqrt[n]{\prod_{i=1}^{n} X_i}$$

Refer to the current "Guideline for Analysis of Pharmacokinetic Data" for general rules for rounding values.

As for displaying the descriptive statistics in safety analysis, arithmetic mean and median are rounded to one more digit for display than what was used to collect the variable. SD is rounded to one more additional decimal place than that of mean. Minimum and maximum are the same number of digit for display used to collect the variable.

Categorical variables are summarized using frequency and percent. Percent is rounded to the nearest tenth.

2.6. Other Methodological Notes

Calculation for study day:

- Post-treatment study day: [The date of a respective event] − [The date of Prezcobix dose] +1
- Pre-treatment study day: [The date of a respective event during pre-dosing time] − [The date of first Prezcobix dose]

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Not applicable.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

For the demographic parameters and baseline characteristics, descriptive statistics will be calculated for the continuous variables and the categorical variables will be presented using frequency and percent.

Demographic Parameters

- Age at the time of informed consent (years)
- Sex
- Ethnicity
- Race

- Country of Site
- Height (cm) at screening
- Weight (kg) at screening
- BMI (kg/m^2)

  * Body mass index (BMI) = weight (kg) / $(height\ (m))^2$

Baseline Characteristics

- Medical History [Yes, No]
- Physical Examination [Clinically Significant, Not Clinically Significant]
  * If a subject has at least one body system with clinically significant results, the subject will be counted as having clinically significant results.
- Complications [Yes, No]
- Cigarette Use [Current, Former, Never]

4.2. Disposition Information

Study completion/withdrawal information and evaluable subjects who are included in the analysis sets will be tabulated and listed.

4.3. Treatment Compliance

Not applicable.

4.4. Extent of Exposure

Study drug administration information will be reported in listings.

4.5. Protocol Deviations

All major protocol deviations will be displayed in a listing.

4.6. Prior and Concomitant Medications

Prior therapies and concomitant medications will be reported in listings.

5. EFFICACY

Efficacy analyses will not be conducted.

6. SAFETY

6.1. Adverse Events

All AEs will be coded using MedDRA version 20.0. All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form (ICF) is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety).

All reported AEs that newly occurred after the administration of Prezcobix and those that worsened after the treatment are defined as treatment-emergent AEs (TEAE).

Adverse Event Associated with the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely.

AEs will be summarized by preferred term (PT) per system organ class (SOC) and include number (and %) of subjects reporting any AEs. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

The incidence rates of AE are calculated as a percentage of the number of subjects with AEs in Safety Analysis Population.

$$\text{Incidence Rate (\%)} = \frac{\text{The Number of Subjects with AEs}}{\text{Safety Analysis Population}} \times 100$$

For number of subjects, each subject will contribute at most one count per summarization category.

For severity, each subject with more than one AE in the same SOC/PT will be counted once by using the highest intensity (Severe> Moderate> Mild).

For the relationship with the study drug, the latest events will be counted.

Tabulations will be provided for the following information. The number (and %) of subjects will be shown in all tables.

- AE preferred terms per body system organ class
- AE preferred terms per body system organ class by severity
- AE preferred terms per body system organ class by relationship to study drug

The following AE Listings will be provided.

- All AEs
- Death
- Serious AEs without death

6.2. Clinical Laboratory Tests

Laboratory parameters will be summarized and graphically presented. The parameters of interest, units, and ranges are as follows:

Hematology Panel

Parameter	Unit	Normal Range
Hemoglobin	g/dL	Male: 13.5 - 17.5, Female: 11.5 - 15.0
Hematocrit	%	Male: 39.7 - 52.4, Female: 34.8 - 45.0
Red Blood Cell (RBC) Count	$x10^4/\mu L$	Male: 430 - 570, Female: 380 - 500
Mean Corpuscular Hemoglobin (MCH)	pg	28.0 - 34.0
MCH Concentration (MCHC)	%	30.2 - 35.1
Mean Corpuscular Volume (MCV)	fL	85 - 102
White Blood Cell (WBC) Count	/uL	3300- 9000
Basophils/Leukocytes	%	0.0 - 2.0
Eosinophils/Leukocytes	%	0.0 - 8.0
Lymphocytes/Leukocytes	%	18.0 - 49.0
Monocytes/Leukocytes	%	2.0 - 10.0
Neutrophils/Leukocytes	%	40.0 - 75.0
Platelet Count	$x10^4/\mu L$	14.0 - 34.0

Serum Chemistry Panel

Parameter	Unit	Normal Range
Sodium	mEq/L	137 - 147
Potassium	mEq/L	3.5 - 5.0
Chloride	mEq/L	98 - 108
Blood Urea Nitrogen (BUN)	mg/dL	8.0 - 20.0
Creatinine	mg/dL	Male: 0.61 - 1.04, Female: 0.47 - 0.79
Glucose	mg/dL	70 - 109
Aspartate Aminotransferase (AST)	U/L	10 - 40
Alanine Aminotransferase (ALT)	U/L	5 - 45
Gamma-glutamyltransferase (GGT)	U/L	Male: ≤80, Female: ≤30
Total Bilirubin	mg/dL	0.2 - 1.2
Direct Bilirubin	mg/dL	0.0 - 0.2
Indirect Bilirubin	mg/dL	0.2 - 1.0
Creatinine Clearance (Ccr)	mL/min	70≤
Alkaline Phosphatase (ALP)	U/L	100 - 325
Creatinine Phosphokinase (CPK)	U/L	Male: 60 - 270, Female: 40 - 150
Lactic Acid Dehydrogenase (LDH)	U/L	120 - 240
Uric Acid	mg/dL	Male: 3.8 - 7.0, Female: 2.5 - 7.0
Calcium (corrected for albumin)	mg/dL	8.4 - 10.4
Phosphate	mg/dL	2.5 - 4.5
Serum Albumin	g/dL	3.8 - 5.2
Total Protein	g/dL	6.7 - 8.3
Total Cholesterol	mg/dL	120 - 219
High-density Lipoprotein (HDL) Cholesterol	mg/dL	Male: 40 - 85, Female: 40 - 95
Low-density Lipoprotein (LDL) Cholesterol	mg/dL	65 - 139
Triglycerides	mg/dL	30 - 149
Magnesium	mg/dL	1.9 - 2.5

Urinalysis

Parameter		Unit	Normal Range	Values
Dipstick	pH		5.0 - 7.5	
	Glucose		-	-, 1+, 2+, 3+, 4+
	Protein		-	-, +-, 1+, 2+, 3+
	Blood		-	-, +-, 1+, 2+, 3+
	Ketones		-	-, +-, 1+, 2+, 3+
Sediment	RBC	/HPF	≤4	<1, 1-4, 5-9, 10-19, 20-29, 30-49, 50-99, >=100
	WBC	/HPF	≤4	<1, 1-4, 5-9, 10-19, 20-29, 30-49, 50-99, >=100
	Squamous Epithelial Cell	/HPF	≤4	<1, 1-4, 5-9, 10-19, 20-29, 30-49, 50-99, >=100
Specific gravity			1.006 - 1.030	

For Laboratory parameters marked abnormal limits are defined as follows:

Hematology Panel

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Hemoglobin[1], Low (g/dL; mmol/L)[2] ≥13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to <10.0 5.57 to <6.19	7.0 to <9.0 4.34 to <5.57	<7.0 <4.34
Hemoglobin[1], Low (g/dL; mmol/L)[2] ≥13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to <9.5 5.25 to <5.88	6.5 to <8.5 4.03 to <5.25	<6.5 <4.03
Absolute Lymphocyte Count, Low (cell/mm3; cells/L) >5 years of age (not HIV infected)	600 to <650 0.600 x 10^9 to <0.650 x 10^9	500 to <600 0.500 x 109 to <0.600 x 10^9	350 to <500 0.350 x109 to <0.500 x 10^9	<350 <0.350 x 10^9
Platelets, Decreased (cells/mm3; cells/L)	100,000 to <124,999 100.000 x 10^9 to <124.999 x 10^9	50,000 to <100,000 50.000 x 10^9 to <100.000 x 10^9	25,000 to <50,000 25.000 x 10^9 to <50.000 x 10^9	<25,000 <25.000 x 10^9
WBC, Decreased (cells/mm3; cells/L) >7 days of age	2,000 to 2,499 2.000 x 10^9 to 2.499 x 10^9	1,500 to 1,999 1.500 x 10^9 to 1.999 x 10^9	1,000 to 1,499 1.000 x 10^9 to 1.499 x 10^9	<1,000 <1.000 x 10^9

1: Male and female sex are defined as sex at birth.
2: The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Serum Chemistry Panel

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Albumin, Low (g/dL; g/L)	3.0 to <LLN 30 to <LLN	≥2.0 to <3.0 ≥20 to <30	<2.0 <20	NA
Alkaline Phosphatase, High	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
ALT or SGPT, High Report only one	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
AST or SGOT, High Report only one	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Direct Bilirubin[3], High >28 days of age	NA	NA	>ULN	>ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High >28 days of age	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to < 5.0 x ULN	≥5.0 x ULN
Calcium, High (mg/dL; mmol/L) ≥7 days of age	10.6 to <11.5 2.65 to <2.88	11.5 to <12.5 2.88 to <3.13	12.5 to <13.5 3.13 to <3.38	≥13.5 ≥3.38
Calcium, Low (mg/dL; mmol/L) ≥7 days of age	7.8 to <8.4 1.95 to <2.10	7.0 to <7.8 1.75 to <1.95	6.1 to <7.0 1.53 to <1.75	<6.1 <1.53
Creatine Kinase, High	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	>1.3 to 1.8 x ULN OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5 x ULN OR Increase of 1.5 to <2.0 x above baseline	≥3.5 x ULN OR Increase of ≥2.0 x above baseline
Creatinine Clearance[4] or eGFR, Low Report only one	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from baseline	<60 to 30ml/min or ml/min/1.73 m^2 OR ≥30 to <50% decrease from baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from baseline or dialysis needed
Glucose (mg/dL; mmol/L) Fasting, High Nonfasting, High	110 to 125 6.11 to <6.95 116 to 160 6.44 to <8.89	>125 to 250 6.95 to <13.89 >160 to 250 8.89 to <13.89	>250 to 500 13.89 to <27.75 >250 to 500 13.89 to <27.75	>500 ≥27.75 >500 ≥27.75
Glucose, Low (mg/dL; mmol/L) ≥1 month of age	55 to 64 3.05 to 3.55	40 to <55 2.22 to <3.05	30 to <40 1.67 to <2.22	<30 <1.67
Magnesium[5], Low (mEq/L; mmol/L)	1.2 to <1.4 0.60 to <0.70	0.9 to <1.2 0.45 to <0.60	0.6 to <0.9 0.30 to <0.45	<0.6 <0.30
Phosphate, Low (mg/dL; mmol/L) >14 years of age	2.0 to < LLN 0.81 to < LLN	1.4 to < 2.0 0.65 to < 0.81	1.0 to <1.4 0.32 to <0.65	<1.0 <0.32
Potassium, High (mEq/L; mmol/L)	5.6 to <6.0 5.6 to <6.0	6.0 to <6.5 6.0 to <6.5	6.5 to <7.0 6.5 to <7.0	≥7.0 ≥7.0

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Potassium, Low (mEq/L; mmol/L)	3.0 to <3.4 3.0 to <3.4	2.5 to <3.0 2.5 to <3.0	2.0 to <2.5 2.0 to <2.5	<2.0 <2.0
Sodium, High (mEq/L; mmol/L)	146 to <150 146 to <150	150 to <154 150 to <154	154 to <160 154 to <160	≥160 ≥160
Sodium, Low (mEq/L; mmol/L)	130 to <135 130 to <135	125 to <130 125 to <135	121 to <125 121 to <125	≤120 ≤120
Uric Acid, High (mg/dL; mmol/L)	7.5 to <10.0 0.45 to <0.59	10.0 to <12.0 0.59 to <0.71	12.0 to <15.0 0.71 to <0.89	≥15.0 ≥0.89

3: Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as grade 2, if <10% of the total bilirubin.
4: Use the applicable formula (Cockcroft-Gault in mL/min or Schwatrz in mL/min/1.73m2).
5: To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Urinalysis

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	NA
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Baseline laboratory evaluations are defined as the last evaluation done before the study drug administration.

On-treatment evaluations will be those performed after the study drug administration to the completion of study/withdrawal date.

The following analyses will be performed. Tables and figures:

For continuous parameters (hematology, biochemistry, and pH, specific gravity in urinalysis):

- Descriptive statistics at each scheduled time point on actual value and changes from baseline. (Use the analysis time points defined in 2.1)
- Shift from pre- versus post-treatment cross-tabulations (with classes for low, normal, high ranges and using the analysis time points defined in 2.1)
- Line plots of individual observed values at each scheduled time point (Use all the time points observed)
- Line plots of Mean and SD at each scheduled time point (Use the analysis time points defined in 2.1)

For qualitative parameters (urinalysis except for pH and specific gravity):

- Tabulation of baseline and values at each scheduled time point (Use the analysis time points defined in 2.1)
- Shift from pre- versus post-treatment cross-tabulations and using the analysis time points defined in 2.1)

The following analyses will be performed. Listing:

- Listing of subjects with laboratory results
- Listing of subjects with any laboratory results outside the normal range
- Listing of subjects with any markedly abnormal laboratory results

6.3. Vital Signs and Physical Examination Findings

Vital Signs:

The following measurements will be analyzed:

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse Rate (beats per minute)
- Temperature [Axilla] (°C)
- Respiratory Rate (breaths per minute)

Baseline vital sign evaluations are defined as the last evaluation done before the study drug administration.

On-treatment evaluations will be those performed after the study drug administration to the completion of study/withdrawal date.

For vital signs parameters, normal range limits (indicators) are defined as follows:

Parameter	Unit	Normal range limits
SBP	mmHg	90 - 140
DBP	mmHg	60 - 90
Pulse Rate	beats per minute	50 - 100
Temperature	°C	36 - 38
Respiratory Rate	breaths per minute	12 - 20

For vital signs marked abnormal limits are defined as follows:

Abnormality Code	Vital Signs parameter		
	Pulse	DBP	SBP
	Abnormalities on actual values		
Abnormally low	≤45 bpm	≤50 mmHg	≤90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	>140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥100 mmHg - < 110 mmHg	≥160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg
Abnormally high	≥120bpm	-	-

The following analyses will be performed. Tables and figures:

- Descriptive statistics at each scheduled time point on actual value and changes from baseline. (Use the analysis time points defined in 2.1)
- Shift from pre- versus post-treatment cross-tabulations (with classes for low, normal, high ranges and using the analysis time points defined in 2.1)
- Tabulation of percentage of subjects with values beyond clinically important limits at each scheduled time point (Use the analysis time points defined in 2.1)
- Line plots of individual observed values at each scheduled time point (Use all the time points observed)
- Line plots of Mean and SD at each scheduled time point (Use the analysis time points defined in 2.1)

The following analyses will be performed. Listings:

- Listing of subjects with vital signs results
- Listing of subjects with any vital signs results outside the normal range
- Listing of subjects with any markedly abnormal vital sign results

Physical Examination:

Physical examination findings will be summarized at each scheduled at time point.

Baseline physical examination findings are defined as the last evaluation done before the study drug administration.

On-treatment evaluations will be those performed after the study drug administration to the completion of study/withdrawal date.

The following analysis will be performed. Tables:

- Tabulation of baseline and values at each scheduled time point (Use the analysis time points defined in 2.1)
- Shift from pre- versus post-treatment cross-tabulations and using the analysis time points defined in 2.1)

The following analyses will be performed. Listings:

- Listing of results (presence of abnormal findings) of physical examinations

6.4. Electrocardiogram

Overall ECG interpretation will be summarized at each scheduled at time point.

Baseline 12-lead ECG evaluations are defined as the last evaluation done before the study drug administration.

On-treatment evaluations will be those performed after the study drug administration to the completion of study/withdrawal date.

The following analyses will be performed. Tables:

- Shift from pre- versus post-treatment cross-tabulations of overall ECG interpretation [Normal, Abnormal, Unevaluable]

The following analyses will be performed. Listings:

- Listing of overall ECG interpretation

6.5. Other Safety Parameters

Not applicable.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Concentrations and PK parameters for DRV and COBI will be summarized. Concentrations will be also presented graphically. The parameters of interest and units are as follows (but not limited):

C_{max}	ng/mL	Maximum plasma concentration
C_{last}	ng/mL	Concentration at last quantifiable time point
t_{max}	h	Time to reach the maximum plasma concentration
AUC_{last}	h*ng/mL	Area under the plasma concentration-time curve from time zero to time the last quantifiable time, calculated by linear trapezoidal summation
λ_z	1/h	Elimination rate constant associated with the terminal phase (including λ_z lower and λ_z upper). In the case the following criteria are not met, λ_z, AUC_{∞} and $t_{1/2,\ term}$ will be excluded from the descriptive statistics. • The number of data points used for calculation of $\lambda_z \geq 3$. • Adjusted coefficient of determination (R^2_{adj}) for the regression of $\lambda_z \geq 0.9000$. • $t_{1/2,\ term} \times 1.5 < \lambda_z$ upper - λ_z lower.
AUC_{∞}	h*ng/mL	Area under the plasma concentration-time curve from time zero to infinite time. In the case following value ($\%AUC_{\infty,ex}$) > 20 %, AUC_{∞} will be excluded from the descriptive statistics. $\%AUC_{\infty,ex} = \frac{AUC_{\infty} - AUC_{last}}{AUC_{\infty}} \times 100$
$t_{1/2,\ term}$	h	Terminal elimination half-life. $t_{1/2,term} = \frac{\log_e 2}{\lambda_z}$
Vz/F	mL	Apparent volume of distribution at the terminal phase after extravascular administration
CL/F	mL/h	Apparent total body clearance of drug at the terminal phase after extravascular administration

Following rules will be applied for descriptive statistics.

- The plasma DRV and COBI concentrations collected outside the visit time window allowance will be excluded from the calculation of descriptive statistics.
- Below quantifiable limit (BQL) will be substituted with 0.
- The number subject displayed as "N" on summary tables will be the number of subject whose plasma concentrations are measured (include BQL) or PK parameters are calculated.
- When more than half (>50%) of plasma DRV and COBI concentrations are BQL at each scheduled time point, mean, median, and minimum will be shown as 'BQL', and SD, and %CV will be shown as 'NC' (not-calculated). If all plasma DRV and COBI concentrations are BQL, maximum will also be shown as 'BQL'. If a minimum concentration is substituted to '0', 'BQL' will be presented as minimum.
- When number of plasma DRV and COBI concentrations is equal to or less than 2, only N and mean will be calculated and SD, %CV, median, minimum and maximum will be shown as 'NC' regardless of the proportion of BQL.

Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg. incomplete administration of the study drug; subject vomited after receiving study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

Based on actual sampling times, PK parameters will be estimated using a non-compartmental analysis method with WinNonlin® (Version 6.4). The detail procedure is written in "ATTACHMENTS" of this document.

The following analyses will be performed. Tables and figures:

- Descriptive statistics of plasma DRV and COBI concentrations at each sampling time point (Use the analysis time points defined in 2.1)
- Descriptive statistics of PK parameters of DRV and COBI
- Line plots of arithmetic mean and SD of plasma DRV and COBI concentration time profiles (Use the analysis time points defined in 2.1)
- Line plots of arithmetic mean and SD of plasma DRV and COBI concentration time profiles with a log scale (values of 10^{-1}, 10^{0}, 10^{1}, 10^{2}, 10^{3}, 10^{4}) on the Y axis (Use the analysis time points defined in 2.1)
- Line plots of individual plasma DRV and COBI concentration time profiles (Use all the time points observed)
- Line plots of individual plasma DRV and COBI concentration time profiles with a log scale (values of 10^{-1}, 10^{0}, 10^{1}, 10^{2}, 10^{3}, 10^{4}) on the Y axis (Use all the time points observed)

The following analyses will be performed. Listings:

- Listing of individual plasma DRV and COBI concentrations at each sampling time point
- Listing of PK parameters of DRV and COBI

7.2. Immune Response

Not applicable.

7.3. Pharmacodynamics

Not applicable.

7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

8. HEALTH ECONOMICS

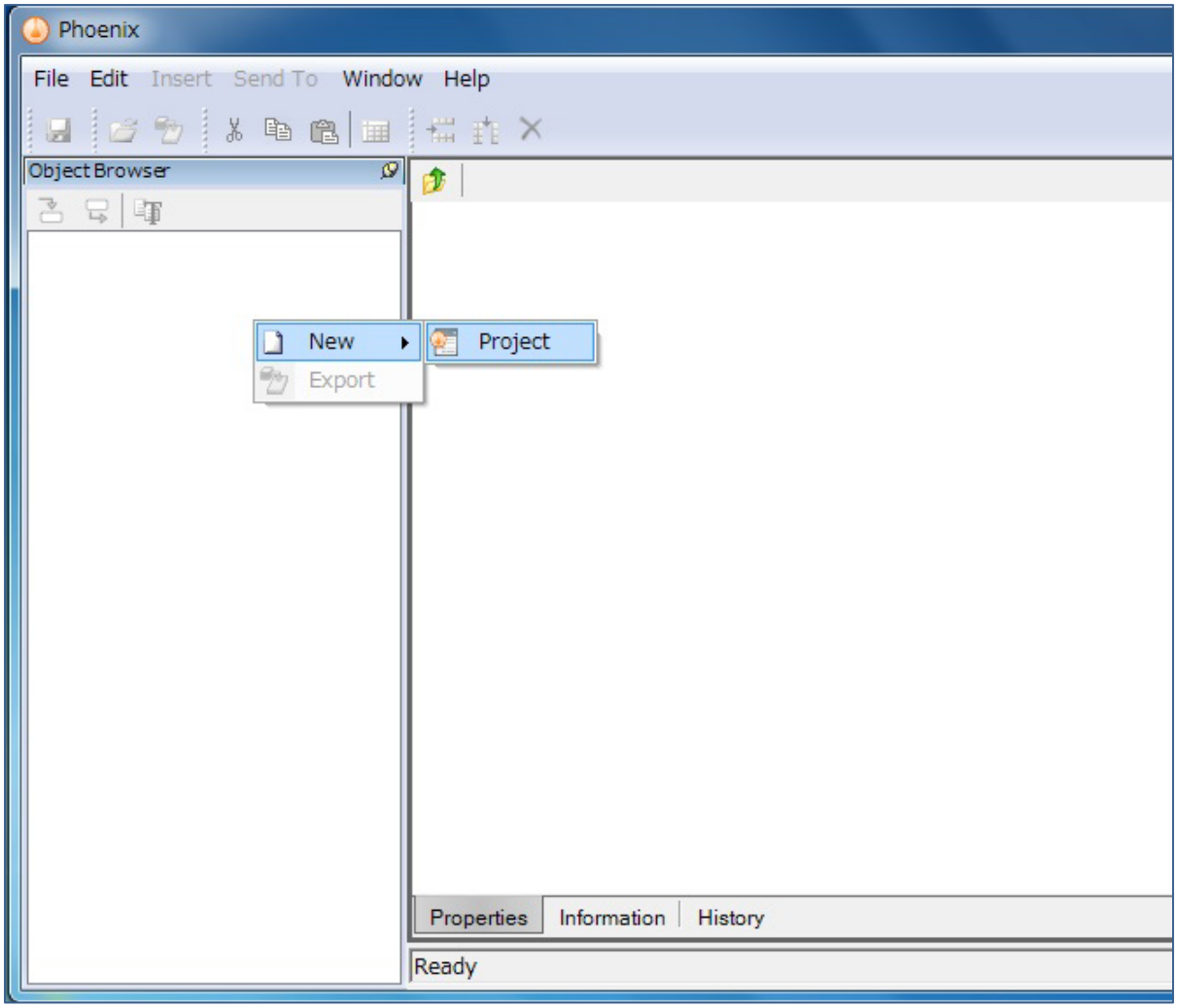
Not applicable.

ATTACHMENTS

Procedure for non-compartment analysis using WinNonLin version 6.4

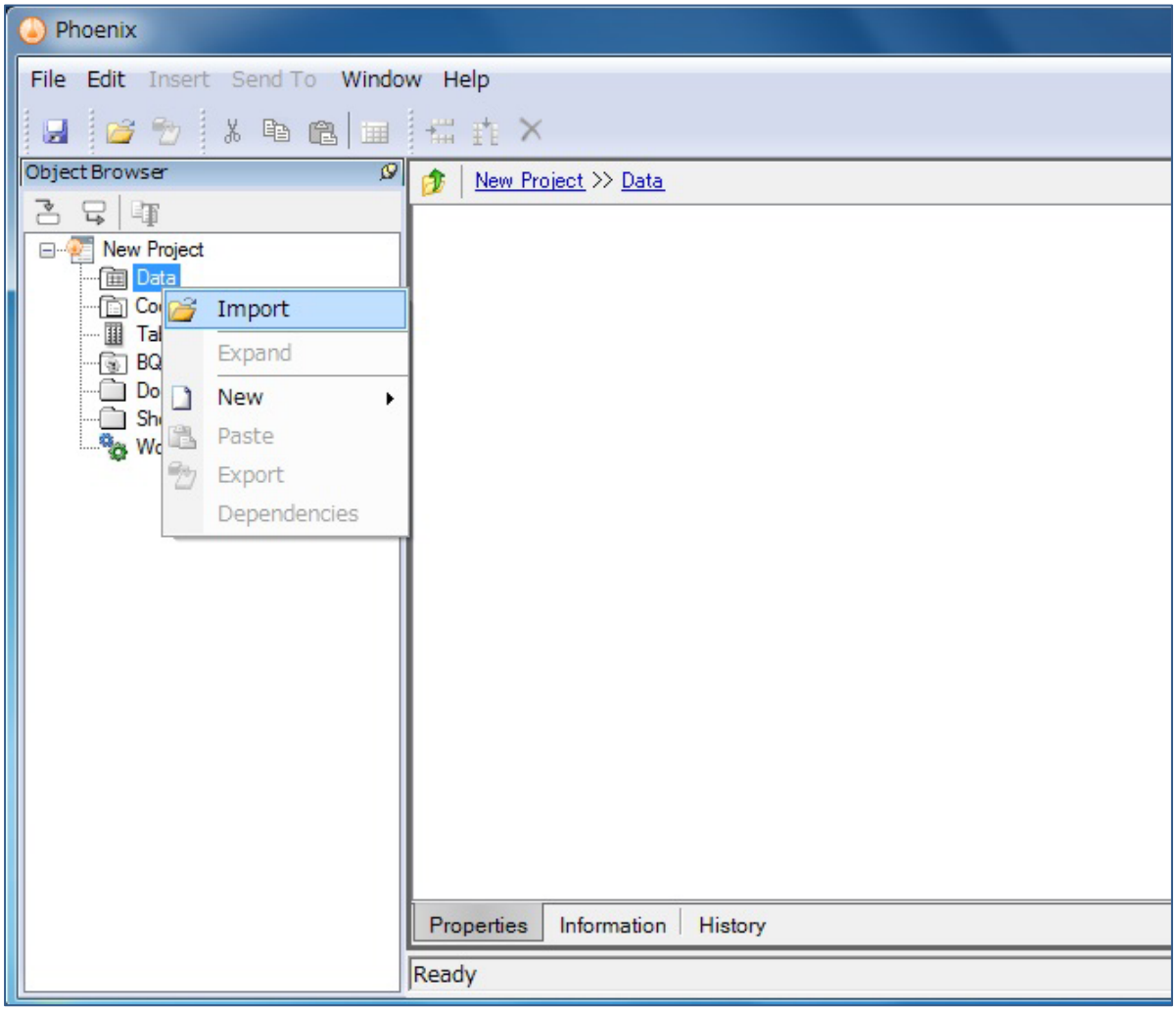
Starting a new project

- Right click and select "New" and "project" in "ObjectBrowser".

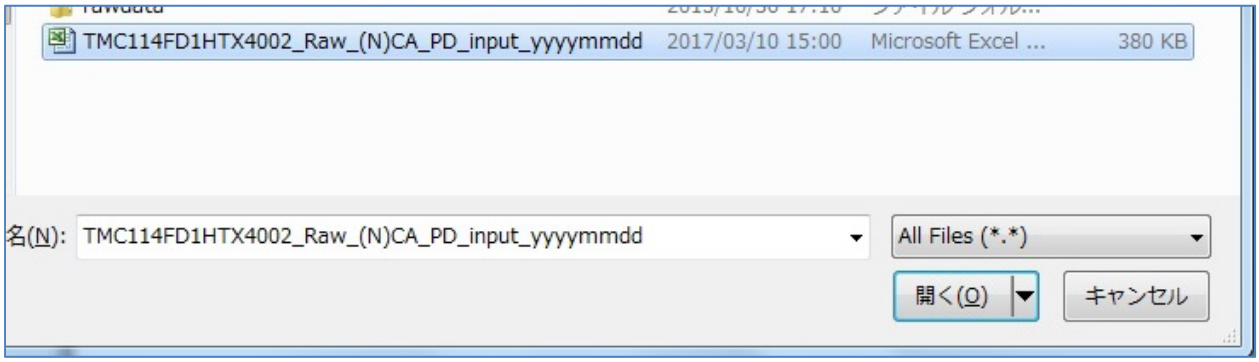


Loading data

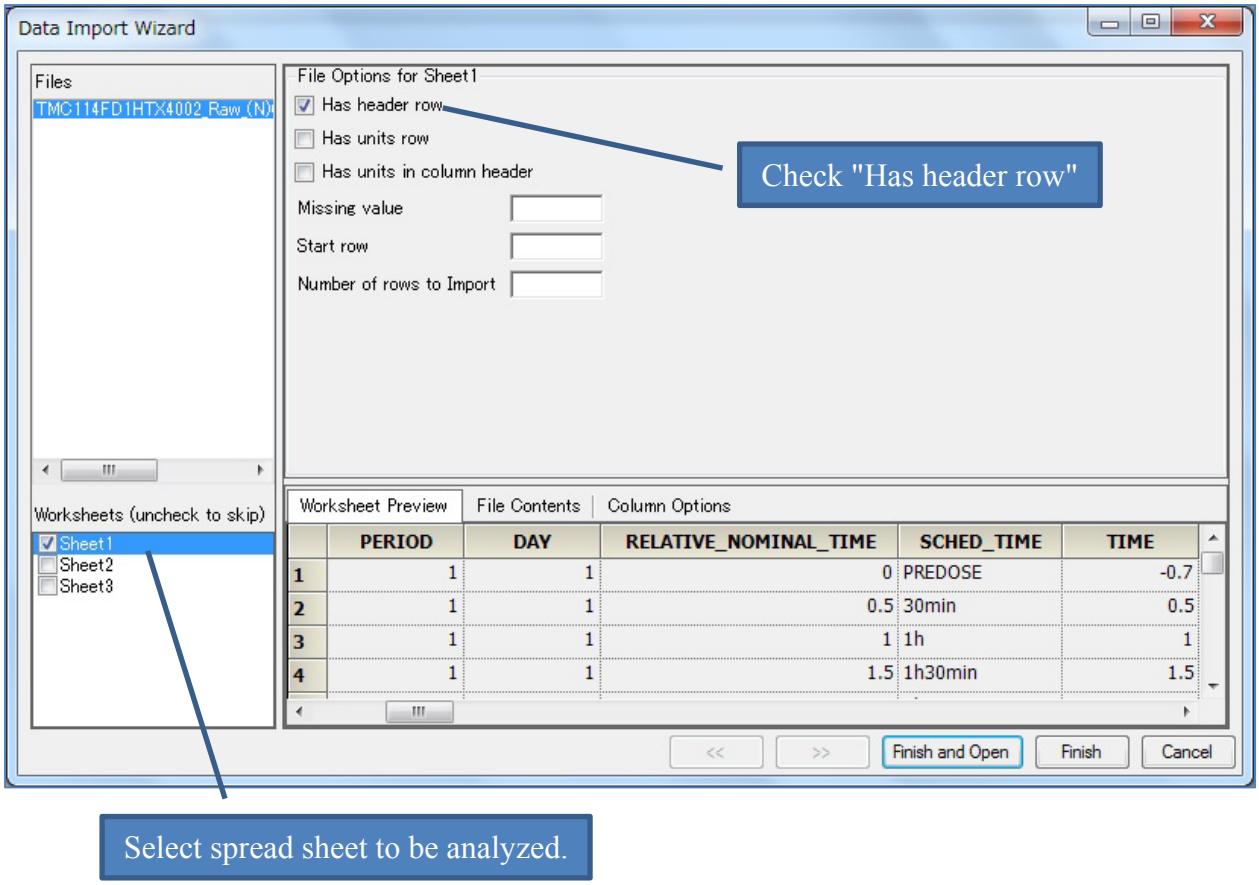
- Right click "Data" and select "Import".



- Select NCA input file and open.

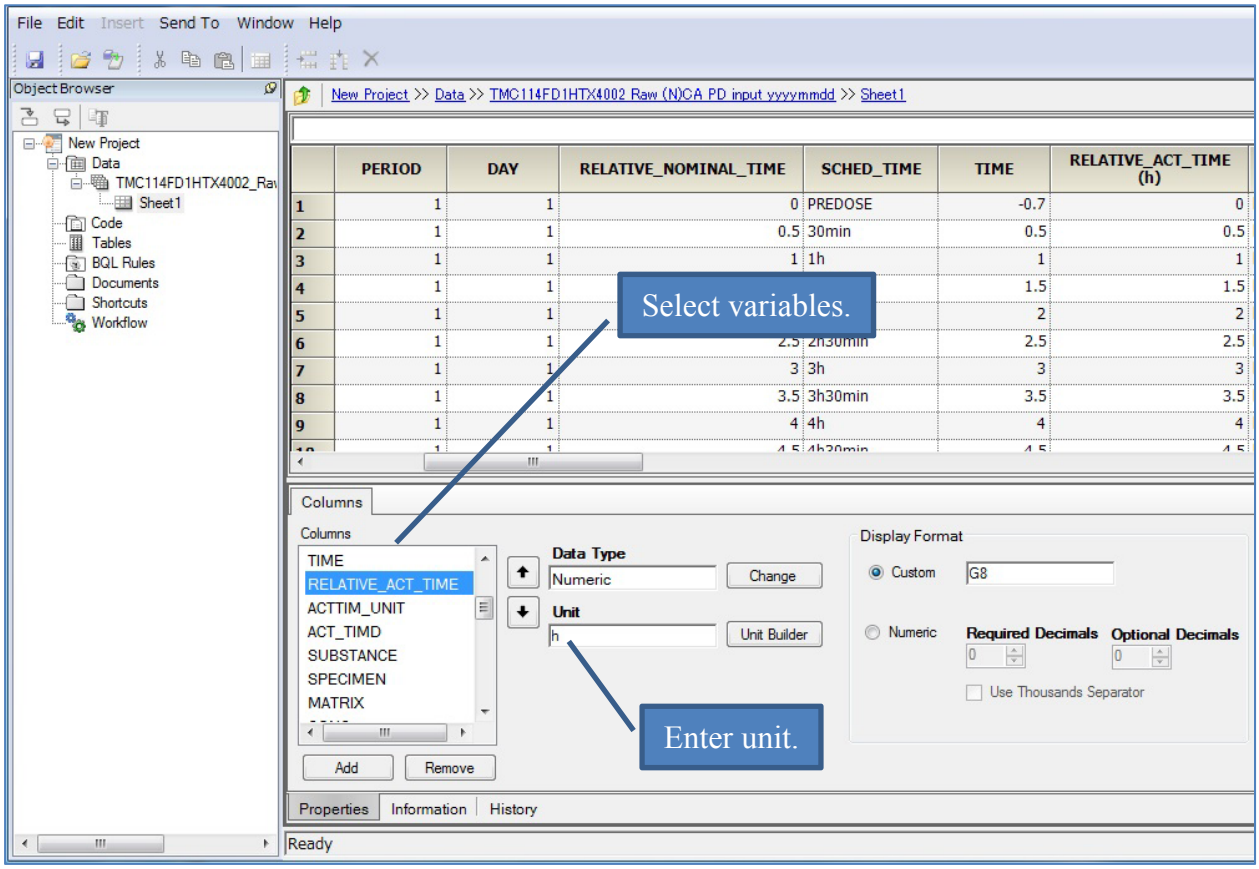


- Confirm following check boxes in "Data Import Wizard" and click "Finish and Open".



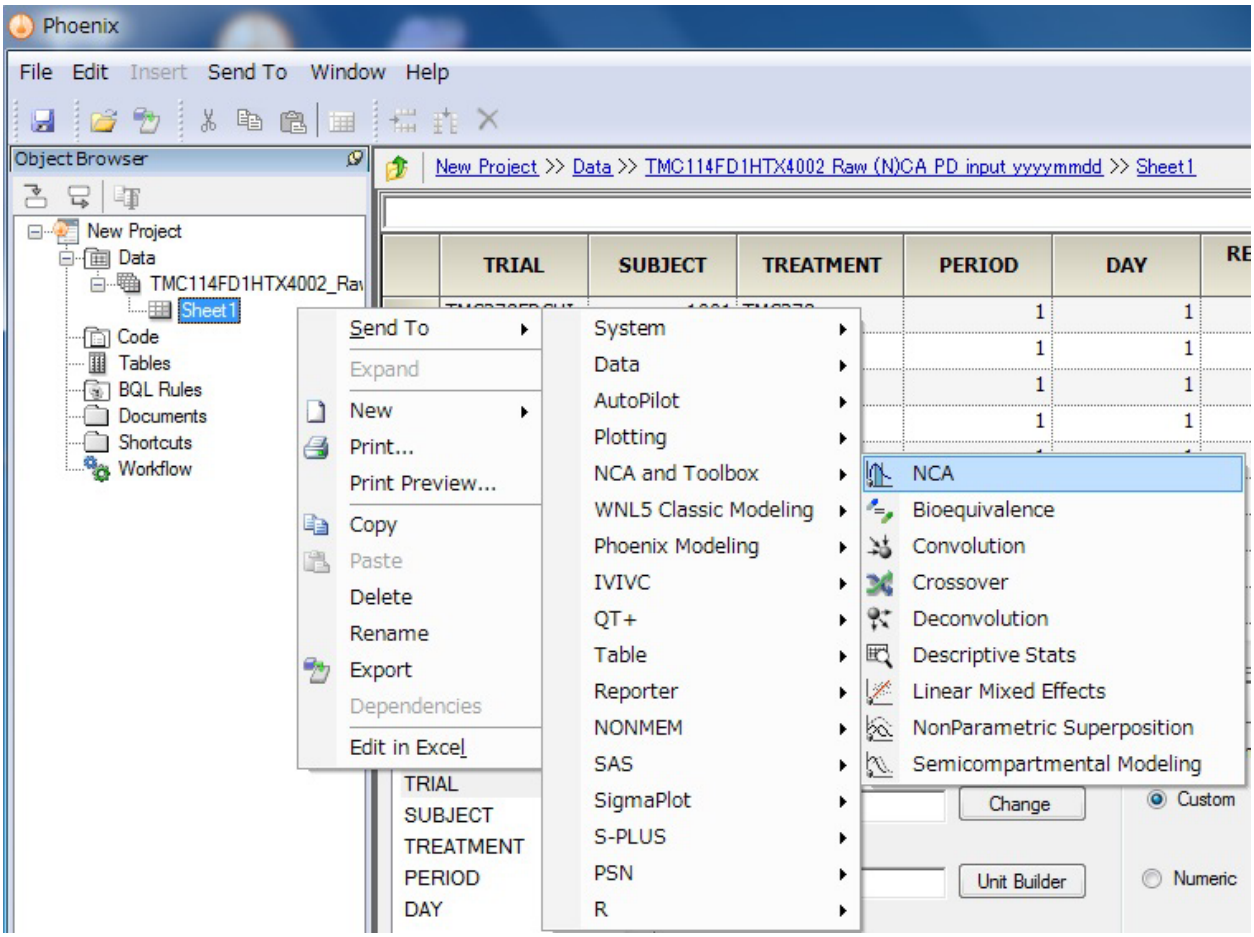
Setting unit

- Select variables and enter their units.
- "h" for RELATIVE_ACT_TIME
- "ng/mL" for CONC
- "mg" for CONTAINS_DOSE



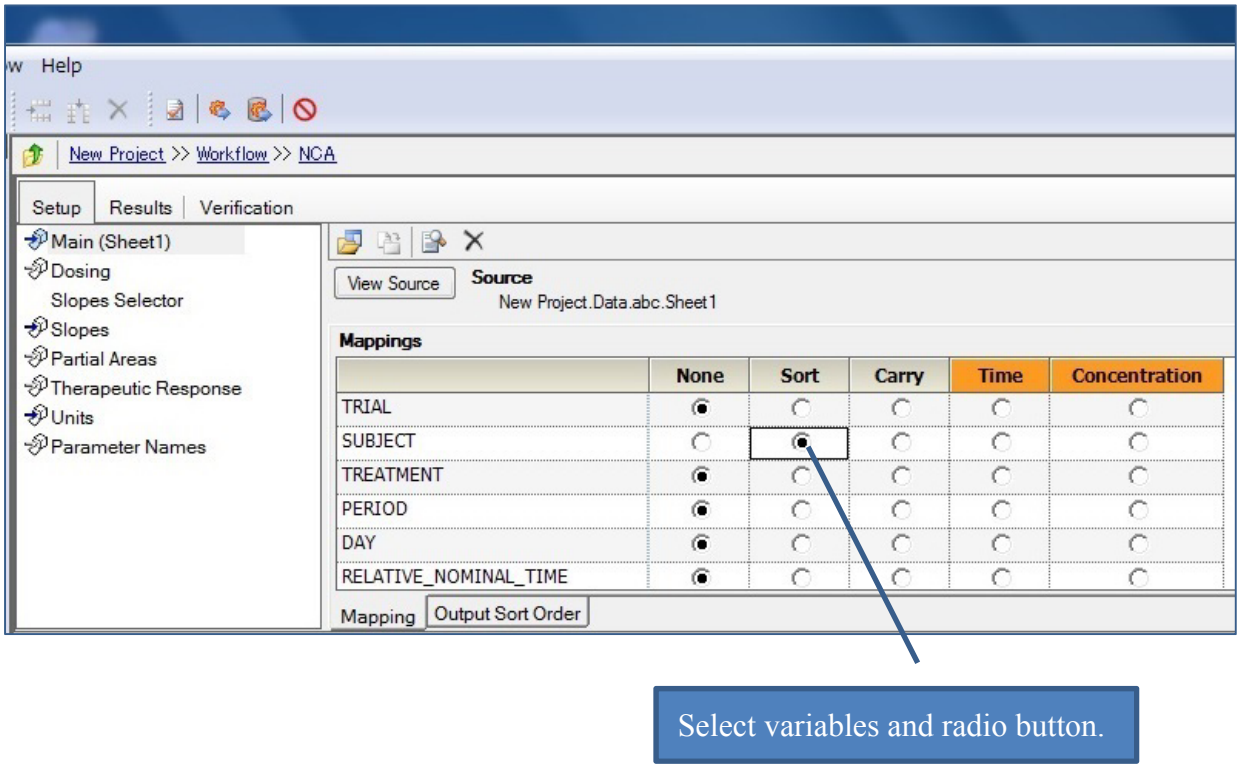
Model

- Right click spread sheet name and select settings as shown below.



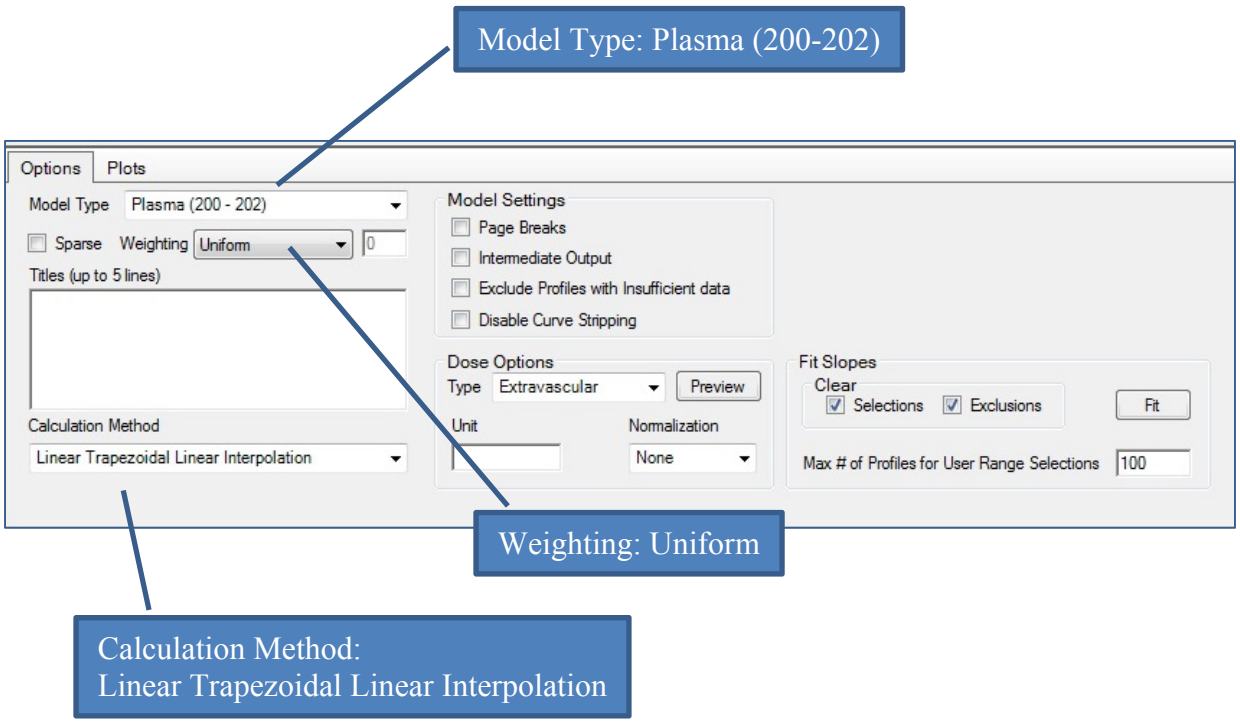
Variables

- Select "Main" in "Setup" tab and identify how input variables are used.
- SUBJECT and SUBSTANCE: Sort
- RELATIVE_ACT_TIME: Time
- CONC: Concentration
- Other: None



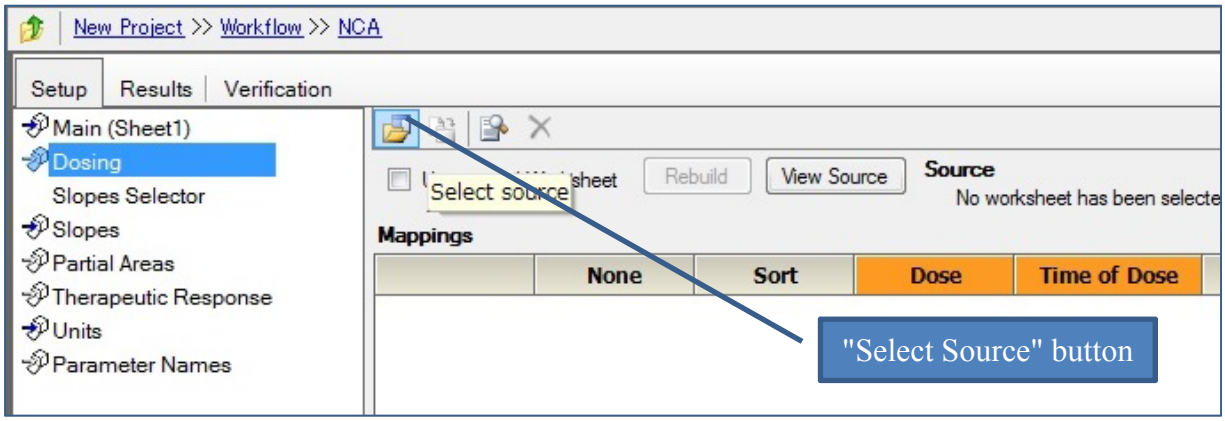
Options

- Confirm following settings.
- Model Type: Plasma (200-202)
- Weighting: Uniform
- Calculation Method: Linear Trapezoidal Linear Interpolation
- Dose Options Type: Extravascular

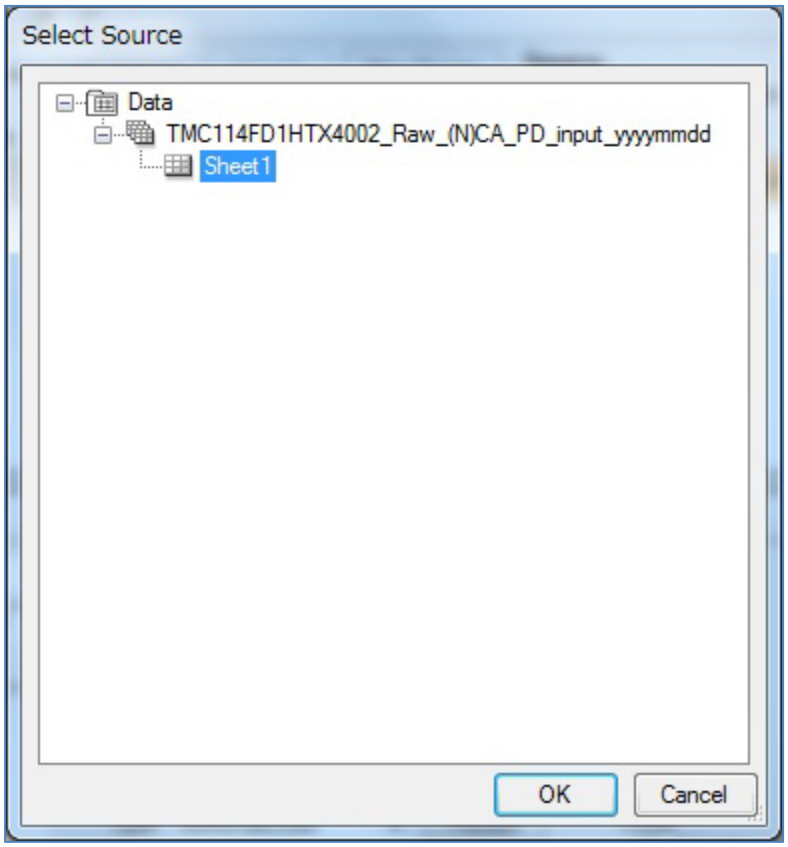


Dosing

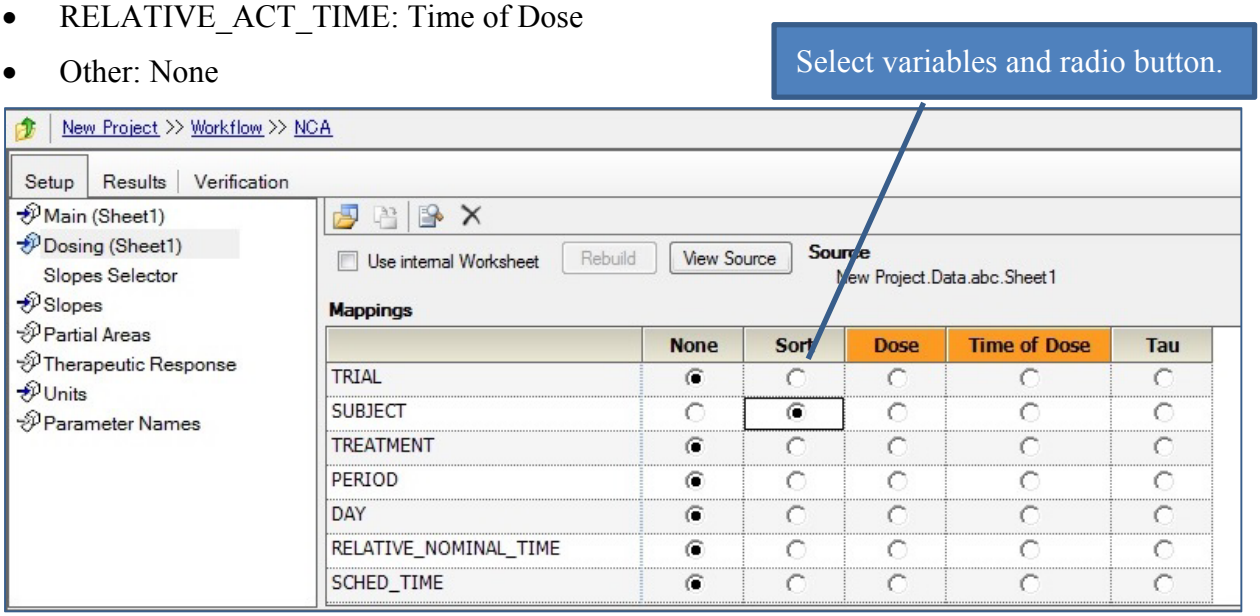
- Select "Dosing" in "Setup" tab.
- Click "Select source" button and open "Select Source" dialog.



- Click spread sheet name.

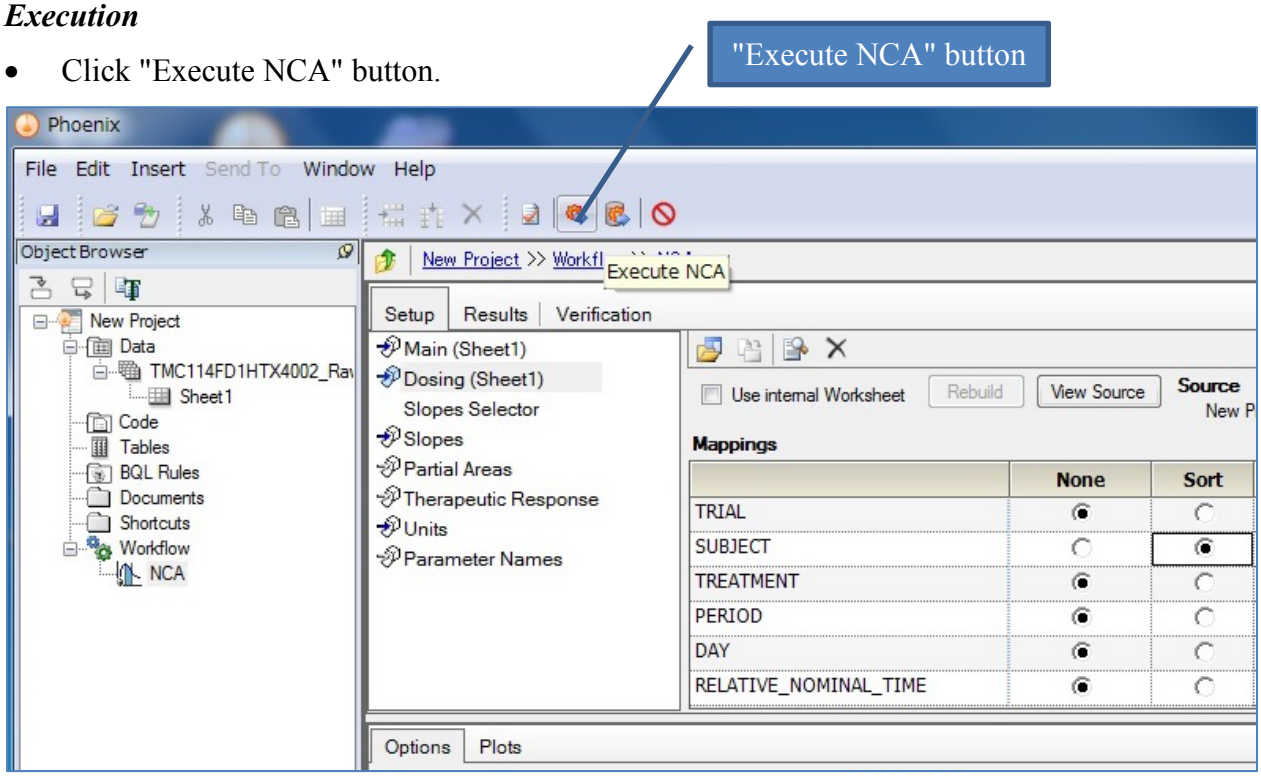


- Identify how input variables are used.
- SUBJECT and SUBSTANCE: Sort
- CONTAINS_DOSE: Dose
- RELATIVE_ACT_TIME: Time of Dose
- Other: None



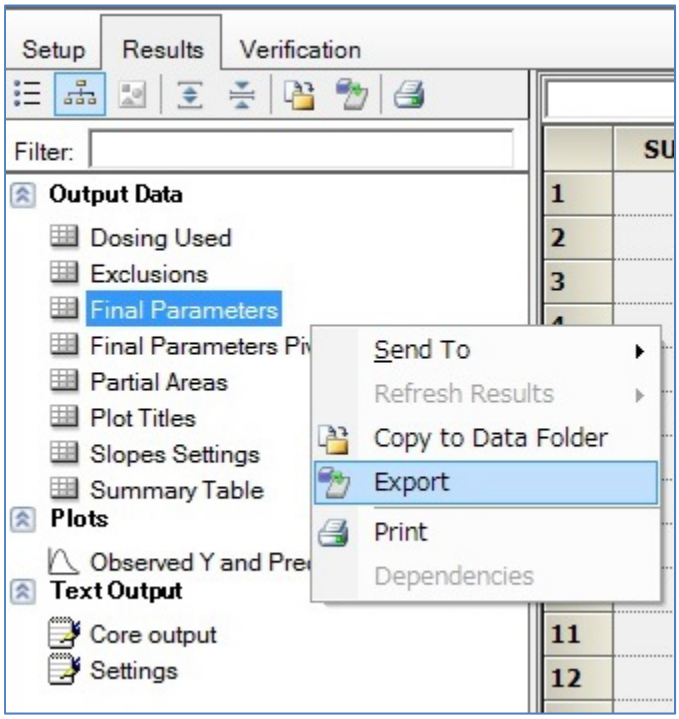
Execution

- Click "Execute NCA" button.

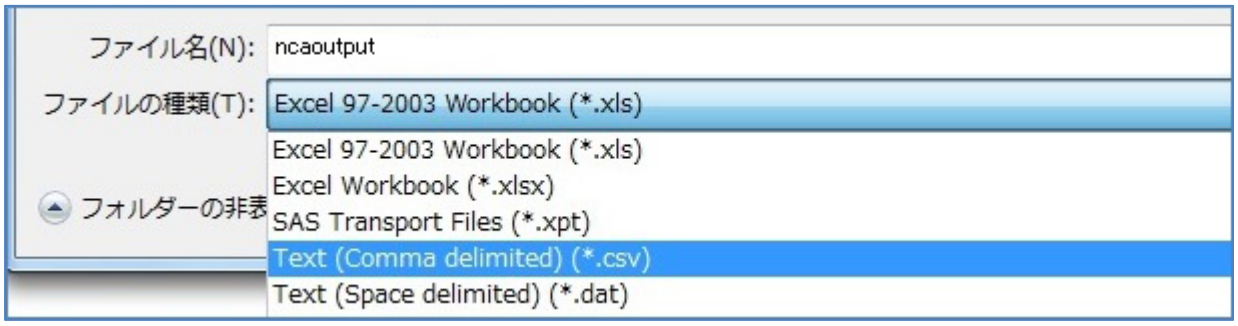


Saving analysis results

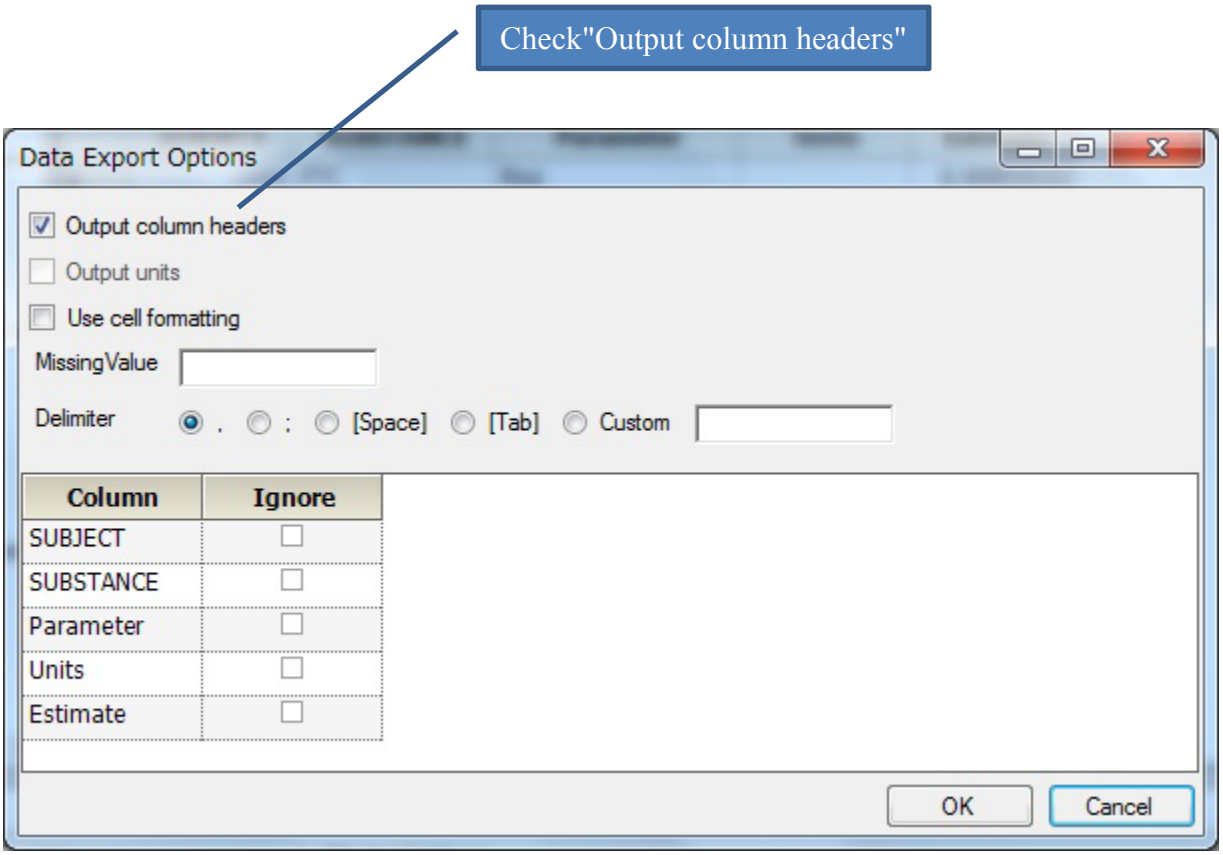
- Right click "Final Parameters" in "Results" tab and select "Export".



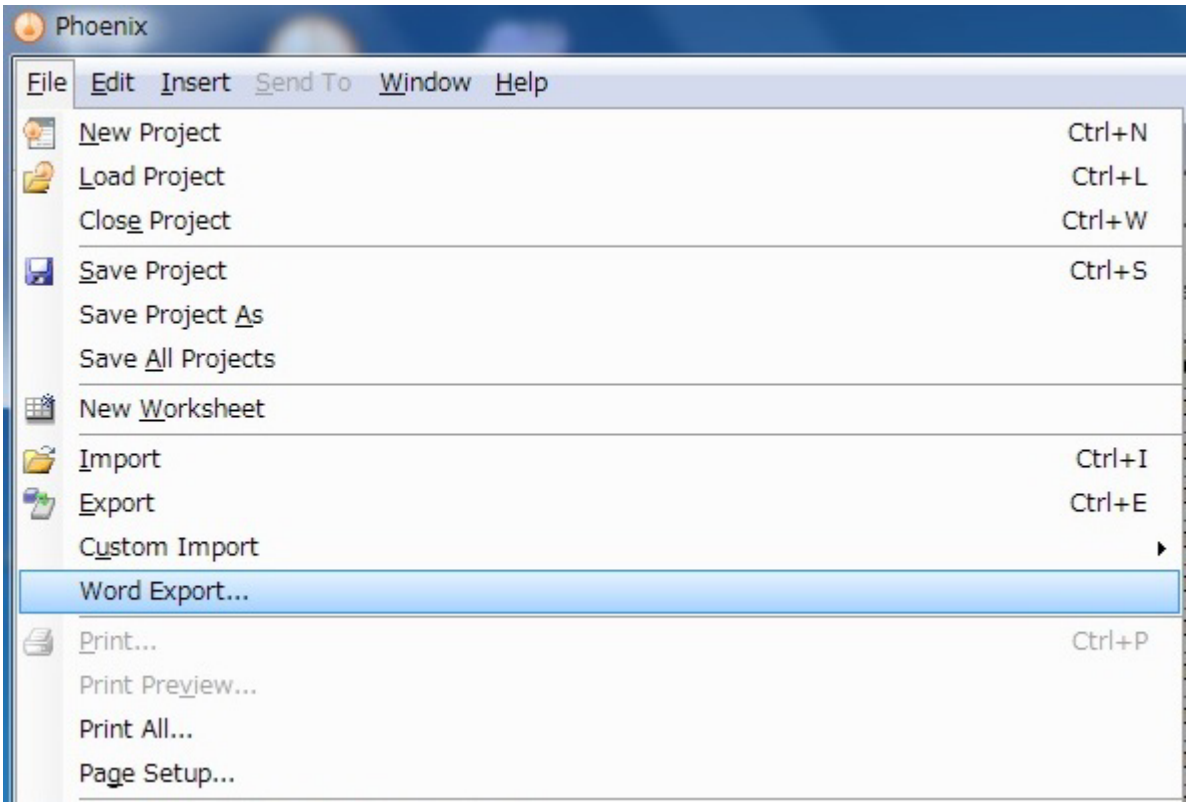
- Save as "ncaoutput.csv".



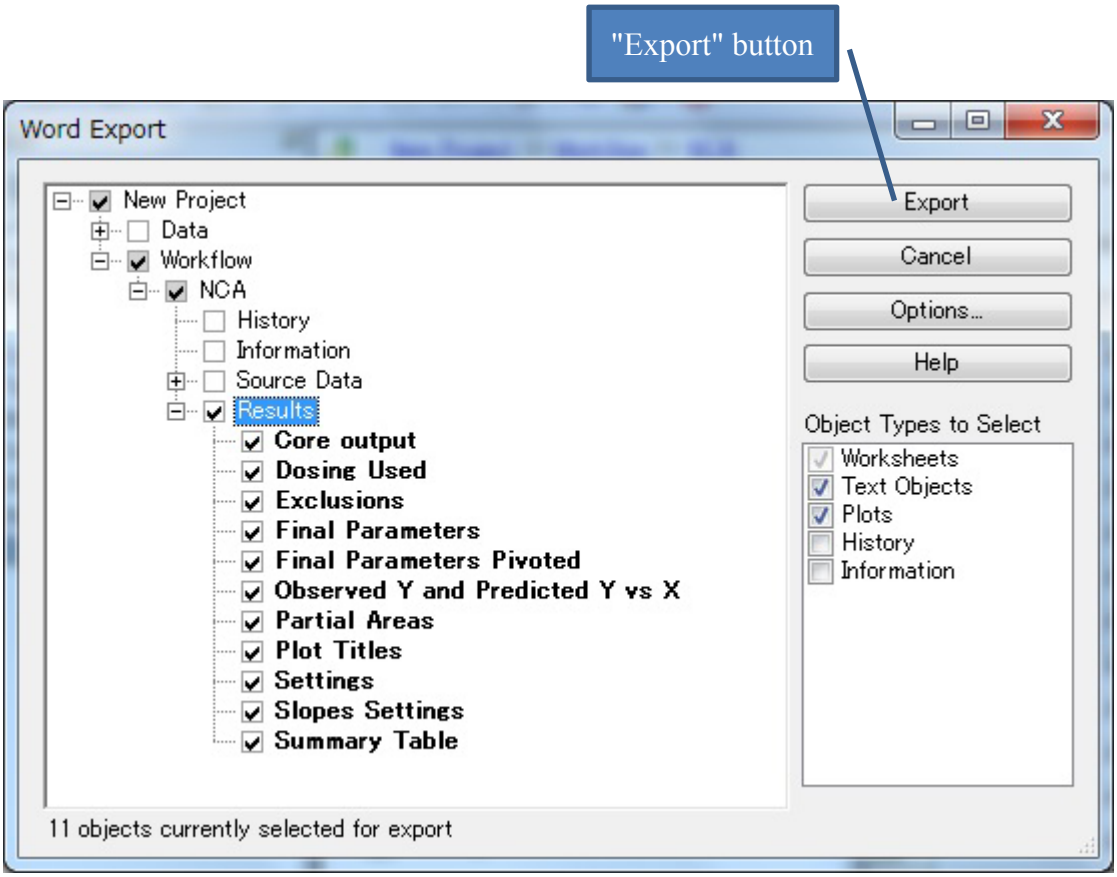
- Confirm following check box in "Data Export Options" and click "OK".



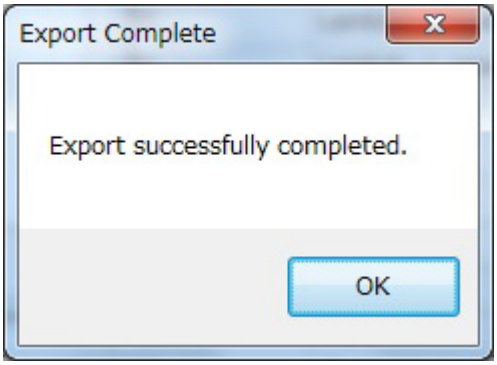
- Left click "File" and select "Word Export".



- Select items as shown below and click "Export" button in "Word Export" dialog.



- Click "OK".



- Save created word file as "xxxx.doc".

Quality control of PK parameters

- Confirm all items that listed on the check list.
- See "Mappings" section in exported word file to check variable and dosing settings.

```
/********************************* Begin Mappings *********************************/
Main : New Project.Data.abc.Sheet2
        Sort : SUBJECT, SUBSTANCE
        Carry :
        Time : RELATIVE_ACT_TIME [h]
        Concentration : CONC [ng/mL]

Dosing : New Project.Data.abc.Sheet2
        Sort : SUBJECT, SUBSTANCE
        Dose : CONTAINS_DOSE [mg]
        Time of Dose : RELATIVE_ACT_TIME [h]
        Tau :

Slopes : (Internal)

Partial Areas : <None>

Therapeutic Response : <None>

Units : (Internal)

Parameter Names : <None>

/********************************* End Mappings  *********************************/
```

- See the section that follows "Mappings" section in exported word file to check options.

```
Phoenix Build 6.4.0.768
Plasma Model
Title =
Linear Trapezoidal Linear Interpolation
Sparse = False
Dose Type = Extravascular
Dose Unit = mg
Weighting = Uniform Weighting; 0
Dose Normalization = None
Exclude Insufficient Profiles = False
Slope Settings
        SUBJECT=[redacted]  SUBSTANCE=DRV,  Start  Time=36,  End  Time=72,  Exclusions=,
```

- See "Settings" section in exported word file to check subject level settings

WinNonlin 6.4

SUBJECT=[redacted],SUBSTANCE=DRV

Date: 2/21/2017

Time: 19:44:30

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

6.4.0.768

Core Version 04Jun2007

Settings

Model: Plasma Data, Extravascular Administration

Number of nonmissing observations: 20

Dose time: 0.00

Dose amount: 800.00

Calculation method: Linear Trapezoidal with Linear Interpolation

Weighting for lambda_z calculations: Uniform weighting

Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
h	ng/mL	ng/mL	ng/mL	h*ng/mL	h*h*ng/mL	
0.0000	0.0000			0.0000	0.0000	
0.5000	37.90			9.475	4.738	

Check lists for PK parameters

Overall settings

Variable settings (See "Mappings" section in exported word file)		
Sort	SUBJECT, SUBSTANCE	☐
Carry	none	☐
Time	RELATIVE_ACT_TIME [h]	☐
Concentration	CONC [ng/mL]	☐
Dosing settings (See "Mappings" section in exported word file)		
Sort	SUBJECT, SUBSTANCE	☐
Dose	CONTAINS_DOSE [mg]	☐
Time of Dose	RELATIVE_ACT_TIME [h]	☐
Tau	none	☐
Options (See the section that follows "Mappings" section in exported word file)		
Model type	Plasma	☐
Calculation method	Linear Trapezoidal with Linear Interpolation	☐
Dose options type	Extravascular	☐
Dose unit	mg	☐
Weighting	Uniform weighting	☐

Checked all items ☐	Date:
	Signature:

Approval by CRO PaB Representative	Date:
	Signature:

Subject level settings

Subject ID	Dose time		Dose amount (DRV)		Dose amount (COBI)	
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐
	0	☐	800 mg	☐	150 mg	☐

Checked all items ☐	Date:
	Signature:

Approval by CRO PaB Representative	Date:
	Signature:

PK parameters to be used for this study

WinNonLin parameter name	WinNonLin's Definition	SDTM PPTEST	SDTM PPSTRESU	Note
AUC_%Extrap_obs	Percentage of AUCINF_obs due to extrapolation from Tlast to infinity. $= \frac{\text{AUCINF\_obs} - \text{AUClast}}{\text{AUCINF\_obs}} \times 100$	AUC %Extrapolation Obs	%	Parameter to check validity of AUC.
AUCINF_obs	AUC from Dosing_time extrapolated to infinity, based on the last observed concentration (obs). $= \text{AUClast} + \frac{\text{Clast}}{\lambda z}$	AUC Infinity Obs	h*ng/mL	Written as "AUC_{∞}" in clinical protocol.
AUClast	Area under the curve from the time of dosing (Dosing_time) to the last measurable (positive) concentration.	AUC to Last Nonzero Conc	h*ng/mL	Written as "AUClast" in clinical protocol.
Clast	Concentration corresponding to Tlast.	Last Nonzero Conc	ng/mL	Written as "Clast" in clinical protocol.
Cl_F_obs	Total body clearance for extravascular administration. = Dose/AUCINF_obs.	Total CL Obs by F	mL/h	
Cmax	Maximum observed concentration, occurring at Tmax. If not unique, then the first maximum is used.	Max Conc	ng/mL	Written as "Cmax" in clinical protocol.
Dosing_time	Time of the last administered dose (assumed to be zero unless otherwise specified).			
HL_Lambda_z	Terminal half-life = ln(2) / λ_z	Half-Life Lambda z	h	Written as "$t_{1/2}$" in clinical protocol.
Lambda_z	First order rate constant associated with the terminal (log-linear) portion of the curve. Estimated by linear regression of time vs. log concentration. If "No_points_lambda_z" < 3, Lambda_z is not be calculated by WinNonLin.	Lambda z	1/h	Written as "λ_z" in clinical protocol.
Lambda_z_lower	Lower limit on Time for values to be included in the calculation of λ_z.	Lambda z Lower Limit	h	Parameter to check validity of λ_z
Lambda_z_upper	Upper limit on Time for values to be included in the calculation of λ_z.	Lambda z Upper Limit	h	Parameter to check validity of λ_z.
No_points_lambda_z	Number of points used in the computation of λ_z. Time point for Cmax is excluded by WinNonLin.	Number of Points for Lambda z		Parameter to check validity of λ_z.
Rsq_adjusted	Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z.	R Squared Adjusted		Parameter to check validity of λ_z.
Tlast	Time of last measurable (positive) concentration.		h	

WinNonLin parameter name	**WinNonLin's Definition**	**SDTM PPTEST**	**SDTM PPSTRESU**	**Note**
Tmax	Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.	Time of CMAX	h	Written as "t_{max}" in clinical protocol.
Vz_F_obs	Volume of distribution based on the terminal phase. $= \frac{\text{Dose}}{\lambda z \times \text{AUCINF\_obs}}$	Vz Obs by F	mL	