Official title: A Phase I/II Clinical Study of BBI608 in Combination With Pemetrexed and Cisplatin in Adult Patients With Malignant Pleural Mesothelioma

NCT number: NCT02347917

Document date: 2018/1/18

Statistical Analysis Plan

A Study of BBI608 in Combination With Pemetrexed and Cisplatin in Adult Patients With Malignant Pleural Mesothelioma

Protocol number: D8807005

Sumitomo Dainippon Pharma, Co., Ltd.

Version: 1
Date: 2018/1/18

Author:

[redacted] Date

Author:

[redacted] Date

Approved by:

[redacted] Approval Date

Approved by:

[redacted] Approval Date

Approved by:

[redacted] Approval Date

Version History

Version	Author	Approval date	Approver	Reason of changes
1	[redacted]	[redacted]	[redacted]	

Content

1. Introduction

This statistical analysis plan (SAP) describes the rules and convention to be used in the presentation and analysis for study D8807005. It describes, in detail, the data and variables to be summarized and analyzed, including specifics of the statistical analyses to be performed. This analysis plan is based on the protocol with Amendment 3.02 dated 12 September 2017.

2. List of abbreviations and definitions of terms

Abbreviation	Term
95%CI	95% confidential interval
ADR	adverse drug reaction
AE	adverse event
AUC	area under the concentration-time curve
BLQ	below limit of quantitation
CDDP	cisplatin
C_{max}	maximum drug concentration
C_{min}	minimum drug concentration
CR	complete response
DCR	disease control rate
DLT	dose limited toxicity
ECOG PS	Eastern Cooperative Oncology Group performance status
LLOQ	lower limit of quantification
Max	maximum
Min	minimum
MPM	Malignant pleural mesothelioma
MRT	mean residence time
MST	median survival time
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NE	not evaluable
NSCLC	Non-small cell lung cancer
OS	overall survival
PD	progressive disease
Pem	Pemetrexed
PFS	progression free survival

PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SD	standard deviation
$t_{1/2}$	terminal elimination half-life
t_{max}	time to reach maximum plasma concentration
ULOQ	upper limit of quantification
WHO-DD	WHO Drug Dictionary
λz	terminal elimination rate constant

3. Change from analyses planned in the protocol

Following analyses valuables are added to analysis plan in the protocol.

- Treatment compliance and intensity
- One-year overall survival rate
- Duration of response and disease control
- H-Score and Total percent positive as biomarker analysis
- Adverse event by first onset
- ECOG PS

For efficacy analysis, the subgroup analysis by treatment duration is removed from analysis plan in the protocol.

4. Study synopsis

4.1 Study design

This study consists of Phase 1 part and Phase 2 part, both using a multicenter, open-label, uncontrolled design. The study will proceed to Phase 2 part only after Phase 1 part demonstrates the tolerability of BBI608 in combination with Pemetrexed (Pem) plus cisplatin (CDDP) based on complete assessment of dose limiting toxicity (DLT) (with occurrence of DLT in no or 1 of 6 subjects).

4.2 Objectives

4.2.1 Phase 1 part

Primary objective

To evaluate the safety, tolerability and pharmacokinetics of BBI608 combined with Pem plus CDDP in patients with malignant pleural mesothelioma (MPM) or non-small cell lung cancer (NSCLC).

Secondary objective
To evaluate the efficacy of BBI608 combined with Pem plus CDDP.

4.2.2 Phase 2 part

Primary objective
To evaluate the efficacy and safety of BBI608 combined with Pem plus CDDP in patients with MPM.

Secondary objective
To explore biomarkers related to the efficacy of BBI608.

4.3 Protocol treat

(1) BBI608

BBI608 will be orally administrated at a dose of 480 mg twice daily (morning and evening) (daily dose, 960 mg). Each dose will be taken at either 1 hour before or 2 hours after a meal, with dosing intervals of approximately 12 hours. On Day 1 of Phase 1 part, however, only the morning dose will be administrated.

(2) Pemetrexed (Pem)

Pem, as a marketed product, will be intravenously administered at 500 mg/m^2 by drip infusion over 10 minutes on Day 1 of each treatment cycle (except for Cycle 1, in which Pem will be given on Day 3). Each infusion of Pem will start ≥4 hours after a dose of BBI608. Premeditation with folic acid and vitamin B12 should be given to reduce occurrence of serious adverse drug reactions, with reference to the package insert for Pem.

(3) Cisplatin (CDDP)

CDDP, as a marketed product, will be intravenously administered at 75 mg/m^2 by drip infusion over ≥2 hours. Each infusion of CDDP will start at 30 to 50 minutes after a dose of Pem. To reduce nephrotoxicity of CDDP, fluid infusion, diuretic therapy, and other treatments should be given, with reference to the package insert for CDDP.

4.4 Protocol period

4.4.1 Treatment period

Each cycle consists of 21 days (with the exception of cycle 1 which consists of 23 days). No restriction is set on the number of cycles. Administration of BBI608 will be

started within 14 days after enrollment.

4.4.2 DLT evaluation period

The DLT evaluation period is defined as the period following administration of BBI608 on Day 1 of Cycle 1 until Day 24 pre-dose examination. DLT will be assessed in Phase 1 part only.

4.4.3 Follow-up observation period

The follow-up observation period is defined as the period from the day of the last dose of BBI608 until the examination/observation 28 days later or until the examination/observation before subsequent treatment if subsequent treatment is given within 28 days after the last dose of BBI608.

4.4.4 Patient outcome investigation

Patient outcome investigation will be conducted 6 months and 1 year after last subject's treatment start date. Additional patient outcome investigation will be conducted after 1 year since last subject's treatment start date by sponsor requirement.

4.5 Schedule of assessments

The clinical study schedule is shown in Table 1 (Phase 1 part) and Table 2 (Phase 2 part). Schedule of imaging is shown in Table 3 (Phase 1 and 2 parts). Pharmacokinetic study schedule is shown in Table 4. The day of the first dose of BBI608 is defined as Day 1 by each cycle.

Table 1 Schedule of Assessments in Phase 1 Part

	Screening [f]	Baseline [f]	Treatment period (23 days in Cycle 1; 21 days in Cycle ≥2)												Discontinuation	Follow-up observation period
			Cycle 1								Cycle 2		Cycle ≥3		At the time of discontinuation as far as possible	28 days after the last dose
Day in each cycle	Day −14 to enrollment	Day −7 to dosing	1	2	3	4	10	17	23	24 [m]	1 [o]	15	1	15		
Allowable range (days)		−	−	0	0	0	±2	±2	0	0	−	±2	−	±2	−	+7
Informed consent, Re-consent	● [g]								● [l]							
Hospitalization [a]			←	—	—	→			←	→						
BBI608 administration, compliance			←	—	—	—	—	—	—	—	—	—	—	→		
Pem and CDDP administration, compliance					●						●		●			
Folic acid and vitamin B12 administration [b]		←	—	—	—	—	—	—	—	—	—	—	—	→		
Baseline characteristics		●														
Pregnancy testing		● [i]														
Height		●														
Body weight [c]		●			●					● [n]	● [p]		● [p]		●	● [r]
Vital signs [c], [d]		●	● [k]		●		●	●		● [n]	● [p]	● [q]	● [p]	● [q]	●	● [r]
ECOG PS [c]	●	● [j]			●		●	●		● [n]	● [p]	● [q]	● [p]	● [q]	●	● [r]
Hematology tests [c]	●	● [j]			●		●	●		● [n]	● [p]	● [q]	● [p]	● [q]	●	● [r]
Biochemistry tests [c]	●	● [j]			●		●	●		● [n]	● [p]	● [q]	● [p]	● [q]	●	● [r]
Urinalysis [c]	●	● [j]			●		●	●		● [n]	● [p]	● [q]	● [p]	● [q]	●	● [r]
12-Lead ECG	● [h]														●	● [r]
Chest X-ray		●								● [n]	As required					● [r]

	Screening [f]	Baseline [f]	Treatment period (23 days in Cycle 1; 21 days in Cycle ≥2)												Discontinuation	Follow-up observation period
			Cycle 1								Cycle 2		Cycle ≥3		At the time of discontinuation as far as possible	28 days after the last dose
Day in each cycle	Day −14 to enrollment	Day −7 to dosing	1	2	3	4	10	17	23	24 [m]	1 [o]	15	1	15		
Allowable range (days)		–	–	0	0	0	±2	±2	0	0	–	±2	–	±2	–	+7
Pharmacokinetic blood sampling [e]			●	●	●	●			●	●[n]						
Imaging	●		See Table 3													
Respiratory function tests		●	See Table 3													
Adverse events monitoring			←	—	—	—	—	—	—	—	—	—	—	—		→
Patient outcome investigation			Continued until 6 months after last subject's treatment start date [s]													

Pem = Pemetrexed. CDDP = Cisplatin

a) Subjects will be hospitalized to undergo pharmacokinetic sampling (i.e., Days 1 to 4, 23 and 24 of Cycle 1), if necessary from the day before pharmacokinetic sampling. All other study procedures may be performed on an outpatient basis.

b) For subjects with a diagnosis of NSCLC or MPM indicated for Pem plus CDDP combination therapy, with reference to the package insert for Pem, folic acid will be given from ≥ 7 days before the initial dose of Pem. In addition, vitamin B12 will be intramuscularly administered once ≥ 7 days before the initial dose of Pem, and repeated every 9 weeks during Pem therapy and until 22 days after the last dose of Pem. Premeditation with folic acid and vitamin B12 in routine care before consent to this study is acceptable.

c) Performed before Pem administration if it is the day of Pem and CDDP administration.

d) Blood pressure, pulse rate and body temperature (axillary) will be measured.

e) See Table 3 (page 15) for specific time points of blood sampling.

f) If multiple measurements are available, the last or later measurement obtained during the period will be used. Available data obtained within the allowable range from routine care before consent to this study may be alternatively used.

g) Written consent must be obtained before screening examination.

h) Available data obtained within 28 days before enrollment may be alternatively used.

i) Performed within 3 days before the start of study treatment.

j) If screening examination was performed within 7 days before the start of BBI608 administration, the results from screening examination may be used as baseline data. If screening examination was performed > 7 days before the start of BBI608 administration, baseline data should be newly obtained before the start of BBI608 administration.

k) Performed after BBI608 administration.

l) If treatment is continued to Cycle ≥ 2, written re-consent should be obtained between Day 17 and the start of Cycle 2 therapy.

m) Cycle 1 treatment is given for 23 days; data up to Day 24 examination will be regarded Cycle 1 data.
n) Performed before BBI608 administration.
o) If Day 1 of Cycle 2 is the same day as Day 24 of Cycle 1, the procedures scheduled for Day 1 of Cycle 2 will be omitted with the exception of "BBI608 administration, compliance" and "Pem and CDDP administration, compliance."
p) If these were performed on the day of before Pem and CDDP administration, the data may be alternatively used. If Pem and CDDP were discontinued, these will be performed every 21 days (± 7 days) starting the day following the end of the last cycle.
q) Not required if Pem and CDDP were discontinued.
r) If subsequent treatment is started during the follow-up observation period, these will be performed before subsequent treatment. Available data obtained within 14 days before the start of subsequent treatment may be alternatively used.
s) If judged necessary by the sponsor, patient outcome investigation may be continued beyond 6 months after last subject's treatment start date.

Table 2 Schedule of Assessments in Phase 2 Part

	Screening[d]	Baseline[d]	Treatment period (23 days in Cycle 1; 21 days in Cycle ≥2)						At discontinuation	Follow-up observation period
			Cycle 1				Cycle ≥2		At the time of discontinuation as far as possible	28 days after the last dose
Day in each cycle	Day −14 to enrollment	Day −7 to dosing	1	3	10	17	1	15		
Allowable range (days)		−	−	0	±2	±2	−	±2		+7
Consent	●[e]									
Tumor tissue sampling			As required after enrollment							
BBI608 administration, compliance			←						→	
Pem and CDDP administration, compliance				●			●			
Folic acid and vitamin B12 administration[a]	←									→
Baseline characteristics		●								
Pregnancy testing		●[g]								
Height		●								
Body weight[b]		●		●			●[j]		●	●[l]
Vital signs[b, c]		●	●[i]	●	●	●	●[j]	●[k]	●	●[l]
ECOG PS[b]	●	●[h]		●	●	●	●[j]	●[k]	●	●[l]
Hematology[b]	●	●[h]		●	●	●	●[j]	●[k]	●	●[l]
Biochemistry[b]	●	●[h]		●	●	●	●[j]	●[k]	●	●[l]
Urinalysis[b]	●	●[h]		●	●	●	●[j]	●[k]	●	●[l]
12-lead ECG	●[f]								●	●[l]
Chest X-ray		●	As required							●[l]
Imaging	●		See Table 3							
Respiratory function tests		●	See Table 3							
Adverse events monitoring			←							→
Patient outcome investigation			Continued until 6 months after last subject's treatment start date[m]							

a) For subjects with a diagnosis of MPM indicated for Pem plus CDDP combination therapy, with reference to the package insert for Pem, folic acid will be given from ≥ 7 days before the initial dose of Pem. In addition, vitamin B12 will be intramuscularly administered once ≥ 7 days before the initial dose of Pem, and repeated every 9 weeks during Pem therapy and until 22 days after the last dose of Pem. Premeditation with folic acid and vitamin B12 in routine care before consent to this study is acceptable.

b) Performed before Pem administration if it is the day of Pem and CDDP administration.

c) Blood pressure, pulse rate and body temperature (axillary) will be measured.

d) If multiple measurements are available, the last or later measurement obtained during the period will be used. Available data obtained within the allowable range from routine care before consent to this study may be alternatively used.

e) Written consent must be obtained before screening examination.

f) Available data obtained within 28 days before enrollment may be alternatively used.
g) Performed within 3 days before the start of study treatment.
h) If screening examination was performed within 7 days before the start of BBI608 administration, the results from screening examination may be used as baseline data. If screening examination was performed ≥ 7 days before the start of BBI608 administration, baseline data should be newly obtained before the start of BBI608 administration.
i) Performed after BBI608 administration.
j) If these were performed on the day of before Pem and CDDP administration, the data may be alternatively used. If Pem and CDDP were discontinued, these will be performed every 21 days (± 7 days) starting the day following the end of the last cycle.
k) Not required if Pem and CDDP were discontinued.
l) If subsequent treatment is started during the follow-up observation period, these will be performed before subsequent treatment. Available data obtained within 14 days before the start of subsequent treatment may be alternatively used.
m) If judged necessary by the sponsor, patient outcome investigation may be continued beyond 6 months after last subject's treatment start date.

Table 3 Schedule of Imaging and Respiratory function tests in Phase 1 and 2 Parts

Months	-	1				2				3				4				5				6				7				8				9	…
Weeks	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	…
Imaging	●						●						●						●						●						●				
Respiratory function tests	●						●						●						●						●						●				

[redacted]

Imaging and respiratory function tests requirements are as follows:

- For screening imaging, available imaging obtained within 14 days before enrollment may be alternatively used if the imaging conditions were in line with the RECIST 1.1 for NSCLC patients or the mRECIST for MPM patients.
- Respiratory function tests will be performed within 7 days before the start of BBI608 administration.
- The allowable range for imaging and respiratory function tests are ±1 week. Imaging and respiratory function tests will be obtained every 6 weeks from the first dose of BBI608 (Day 1 of Cycle 1) until Week 30, and then every 9 weeks from Week 31 on. The schedule of imaging and respiratory function tests are based only on Day 1 of Cycle 1, irrespective of Day 1 of Cycle 2 or any later cycle.
- If protocol treatment is discontinued because of imaging-documented worsening, no further imaging and respiratory function tests are required.
- If protocol treatment is discontinued for other reasons than imaging-documented worsening, imaging and respiratory function tests will be continued according to the imaging schedule even after discontinuation of protocol treatment. If subsequent treatment is started, imaging and respiratory function tests will be performed before subsequent treatment as far as possible, and no further imaging and respiratory function tests are required after initiation of subsequent treatment.

Table 4 Pharmacokinetic Study Schedule

Day in Cycle 1	1								2	
Time from the BBI608 morning dose on Day 1 of Cycle 1 (hr)	Pre-BBI608 dose	0	2	4	6	8	10	12	24	36
BBI608 administration [a)]		●							●	●
Allowable range for blood sampling	−2 hr to BBI608 dosing	-	±5 min	±10 min	±15 min	±20 min	±20 min	±20 min	−20 min to BBI608 dosing	-
BBI608 PK blood sampling	●		●	●	●	●	●	●	●	

Day in Cycle 1	3									4	
Time from the BBI608 morning dose on Day 3 of Cycle 1 (hr)	Pre-BBI608 dose	0	Just before Pem dose	Pem dose	Just after Pem dose	Just before CDDP dose	CDDP dose	Just after CDDP dose	12	24	36
BBI608 administration [a)]		●							●	●	●
Pem administration [b)]				●							
CDDP administration [b)]							●				
Allowable range for blood sampling	−20 min to BBI608 dosing	-	−5 min	-	+5 min [d)]	−5 min	-	+5 min [d)]	−20 min to BBI608 dosing	−20 min to BBI608 dosing	-
BBI608 PK blood sampling	●		●						●		
Pem PK blood sampling			●		●[d)]				●		
CDDP PK blood sampling			●[c)]					●[d)]		●	

Day in Cycle 1	23								24	
Time from the BBI608 morning dose on Day 23 of Cycle 1 (hr)	Pre-BBI608 dose	0	2	4	6	8	10	12	24	36
BBI608 administration [a)]		●						●	●	●
Allowable range for bloodsampling	−20 min to BBI608 dosing	-	±5 min	±10 min	±15 min	±20 min	±20 min	−20 min to BBI608 dosing	−20 min to BBI608 dosing	-
BBI608 PK blood sampling	●		●	●	●	●	●	●	●	

a) On Days 1, 3 and 23 of Cycle 1, the date and time of meal intake should be recorded. On Days 1 to 3, 22 and 23 of Cycle 1, the date and time of medication should be recorded. From Day 1 to Day 23 of Cycle 1, the number of capsules taken should be recorded.

b) On Day 3 of Cycle 1, the start time and end time of each dosing of Pem and CDDP, and of each fluid infusion before and after CDDP administration, should be recorded.

c) One blood sample will be collected just before or after Pem dose, or just before CDDP dose.

d) Within 5 minutes after the end of intravenous drip infusion of the drug.

4.6 Determination of sample size

Phase 1 part: 3 to 6 subjects evaluable for DLT.

Phase 2 part: 20 subjects given protocol treatment at least once, including 15 subjects with epithelioid histology.

5. Analysis population

5.1 Safety analysis population

The safety analysis population will consist of all subjects received the investigational drug.

5.2 DLT evaluable population

The DLT evaluable population will consist of subjects who received the investigational drug in Phase 1 part and met either of the following:

- Subjects with a ≥ 80% BBI608 treatment compliance rate during the DLT evaluation period, as calculated by the following formula:
  [Amount of BBI608 actually taken/ (480 mg × 45)] × 100 (%)
- Subjects with onset of DLT during the DLT evaluation period.

5.3 Pharmacokinetics analysis population

The pharmacokinetics analysis population will consist of subjects who received BBI608 with the post-dose plasma BBI608 concentration data available for at least one time point.

5.4 Efficacy analysis population (modified ITT population: mITT population)

Subjects who received the investigational drug.

6. Safety and efficacy endpoints

6.1 Phase 1 part

6.1.1 Safety endpoints

- Adverse event, adverse drug reaction and DLT
- Vital signs and body weight
- Laboratory test values
- 12-lead ECG
- Chest X-ray
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

6.1.2 Efficacy endpoints

- Tumor response (Response rate [RR], Disease control rate [DCR])
- Duration of response
- Duration of disease control
- PFS
- OS
- Respiratory function tests (Vital capacity [VC], Forced vital capacity [FVC], Forced expiratory volume in 1st second [FEV1])

6.1.3 Pharmacokinetic endpoints

BBI608 pharmacokinetic parameters of the following:

- Maximum observed plasma concentration (C_{max})
- Minimum observed plasma concentration (C_{min})
- Area under the plasma concentration-time curve from time zero to 12 hours (AUC_{0-12})
- Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24})
- Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$)
- Percent of $AUC_{0-\infty}$ due to extrapolation from last non-zero data time to infinity (AUC% extrapolated)
- Time to maximum observed plasma concentration (t_{max})
- Terminal elimination rate constant (λz)
- Terminal elimination half-life ($t_{1/2}$)
- Mean residence time (MRT)

6.2 Phase 2 part

6.2.1 Efficacy endpoints

6.2.1.1 Primary endpoint

- PFS

6.2.1.2 Secondary endpoints

- OS
- Tumor response (Response rate [RR], Disease control rate [DCR])
- Duration of response
- Duration of disease control
- Respiratory function tests (Vital capacity [VC], Forced vital capacity [FVC],

Forced expiratory volume in the first second [FEV1])

6.2.2 Safety endpoints

- Adverse event and adverse drug reaction
- Vital signs and body weight
- Laboratory test values
- 12-lead ECG
- Chest X-ray
- ECOG PS

6.2.3 Other endpoints

- Biomarkers (pSTAT3 Nuclear Tumor, Beta-catenin Nuclear Tumor, Merlin Tumor)

7. General data handling

7.1 Definition and data handling

Detailed data handling will be defined before database lock.
Order of data handling process is as follows; 1) Determine the data excluded from analysis. 2) Determine analysis visit and baseline.

7.1.1 Data excluded from the analyses

7.1.1.1 Upper/Lower limit of quantification (ULOQ/LLOQ)

Where applicable, the upper limit of quantification (ULOQ) will be substituted for chemistry, hematology, urinalysis, and urine microscopic values that are greater than the ULOQ. Similarly, if the value is below the lower limit of quantification (LLOQ), then the LLOQ will be substituted.

7.1.1.2 Vomiting

When the subject experiences vomiting within 8 hours after the dose of BBI608 in the morning at Day 1, Day 3, Day 23 and Day 24 whose all plasma concentrations data will be excluded from analysis in principle. The handling of plasma concentrations data with vomited subject will be decided in blinded data review meeting.

7.1.1.3 Violation from blood sampling time

In case that the error in blood sampling time for BBI608, the plasma concentration data will be not included the calculation of summary statistics by nominal time point, but

will be used to calculate PK parameters with actual time.

Planned time point	Allowable range of blood sampling time	Reference time point
Day 1, 2 hours	Reference time point + 2 hour ± 6 min	BBI608 administration at Day 1
Day 1, 4 hours	Reference time point + 4 hour ± 12 min	BBI608 administration at Day 1
Day 1, 6 hours	Reference time point + 6 hour ± 18 min	BBI608 administration at Day 1
Day 1, 8 hours	Reference time point + 8 hour ± 24 min	BBI608 administration at Day 1
Day 1, 10 hours	Reference time point + 10 hour ± 30 min	BBI608 administration at Day 1
Day 1, 12 hours	Reference time point + 12 hour ± 36 min	BBI608 administration at Day 1
Day 2, 24 hours	Reference time point + 24 hour ± 72 min and BBI608 pre-dose at Day 2 morning	BBI608 administration at Day 1
Day 23, 2 hours	Reference time point + 2 hour ± 6 min	BBI608 administration at Day 23
Day 23, 4 hours	Reference time point + 4 hour ± 12 min	BBI608 administration at Day 23
Day 23, 6 hours	Reference time point + 6 hour ± 18 min	BBI608 administration at Day 23
Day 23, 8 hours	Reference time point + 8 hour ± 24 min	BBI608 administration at Day 23
Day 23, 10 hours	Reference time point + 10 hour ± 30 min	BBI608 administration at Day 23
Day 23, 12 hours	Reference time point + 12 hour ± 36 min and BBI608 pre-dose at Day 23 evening	BBI608 administration at Day 23
Day 24, 24 hours	Reference time point + 24 hour ± 72 min and BBI608 pre-dose at Day 24 morning*	BBI608 administration at Day 23

* Confirm the blood sampling time at Day 24 (24 hours) in blinded data review meeting.

Summarize the PK concentration at Day 3 and Day 4 for BBI608, Pem and CDDP used by reporting time point from EDC.

7.1.1.4 Others

If there are considerable issues to detect analysis population and data handling for analysis data, study team members will discuss carefully in blinded data review meeting (BDRM).

For the listing, all values are presented using the numbers reported in the CRF.

7.1.2 Definition of visit

7.1.2.1 Baseline

Baseline values will be the values measured between Day -7 and Day 1 in cycle 1 (before BBI608 administration). If there are two or more values measured before the first dose of BBI608, the value which was evaluated the nearest day of first dose will be baseline value. If the value which was evaluated before Day -7 will be handled as baseline value, study team member should be discuss in blinded data review meeting.

7.1.2.2 Study Day

The day of the first dose of BBI608 is defined as Day 1 of study day.

7.1.2.3 Visit windows and termination window

Visit windows (analysis window) will not be used for this study. Instead, all analyses will use the scheduled visits recorded on the CRF including termination visit. This rule will be applied all efficacy and safety endpoints to be analyzed.

7.1.3 Handling of missing data

7.1.3.1 Safety endpoints

Missing data will not be imputed.

For laboratory samples that are not evaluable, the corresponding laboratory records will not be used in analyses and only be listed as part of the listings. Non-evaluable records will be determined prior to database lock and provided separately from this SAP.

7.1.3.2 Efficacy endpoints

Any individual missing item in any scale will not be imputed.

7.1.3.3 Others

7.1.3.3.1 Partial date

If partial dates of “Date of Diagnosis of Primary Cancer” in cancer history are reported, impute first date of the month/first month of the year. Partial dates for others will not be imputed.

7.1.4 Prior and Concomitant medications

7.1.4.1 Prior medications

Prior medications are defined as medications that were taken before start of study drug.

7.1.4.2 Concomitant medications

Concomitant medications are defined as medications that of administration period were overlapped with study drug administration period.

7.2 Statistical methodology

7.2.1 Software

All PK parameter estimation will be carried out using Phoenix® WinNonlin® (version

6.3 or a more recent version).
Computations for all of the results will be performed using SAS version 9.4 or higher computer software package, unless otherwise specified.

7.2.2 Summary statistics

Categorical parameters will be summarized by presenting the number and percentage of subjects in each category.–
Continuous parameters will be summarized using n, mean, standard deviation (SD), median, minimum (min), and maximum (max) values. Coefficient of variation (CV%), geometric mean and geometric CV% will be added for the summary of plasma concentration. Coefficient of variation and geometric CV% will be displayed at the one decimal place.
Geometrics mean and geometric CV% are calculated by following SAS code.

```
ods listing close ;
proc ttest data=[dataset] dist=lognormal ;
   var [variable] ;
   ods output statistics=[dataset] ;
run ;
ods listing ;
```

7.2.3 Significant level and p value, confidential interval

Since no statistical test will be performed, level of significance will not be set.

7.2.4 Multiple comparison/Multiplicity

Not apply the statistical method for multiplicity in this study.

7.2.5 Definition of terms

Definition of each item is presented below. For a derived variable, the computed value is used for the analysis without rounding, in general. Rounding is just made when the result is presented in tables or listings.

- Study day (relative day from the date of the first dose of BBI608):
  Assessment date – the date of the first dose of BBI608 + 1 (On or after the date of the first dose of BBI608)
  Assessment date – the date of the first dose of BBI608 (Before the date of the first dose of BBI608)
- Month: 365.25/12=30.4375 day

- Week: 7 day
- Disease duration (month): (Date of Informed consent − Date of diagnosis of primary cancer + 1)/30.4375
- Treatment compliance of BBI608 (%): See 8.5.1
- Treatment intensity of BBI608 (%), Pem/CDDP: See 8.5.1
- Mean daily dose (mg/day): See 8.5.4
- Modal daily dose (mg/day): See 8.5.5

8. Analysis of subjects

8.1 Disposition of subjects

The following will be summarized for entire study and separately for Phase 1 part and Phase 2 part:

- Number of enrolled subjects
- Number of start BBI608 administration subjects
- Number of discontinued subjects during DLT evaluation period (Phase 1 part only)
- Number of subjects completing DLT evaluation period (Phase 1 part only)
- Number of discontinued subjects after administration
- Number of subject completing survival follow-up observation period
- Number of discontinued subjects before survival follow-up observation period

Reason for discontinuation will be summarized and listed for entire study and separately for Phase 1 part and Phase 2 part. A listing of cause of death and survival follow-up will be provided.

8.2 Important Protocol Deviation

Important protocol deviations will be detected at BDRM and listed.

8.3 Analysis population

The number of subjects within each analysis population will be summarized for entire study and separately for Phase 1 part and Phase 2 part.

- Safety analysis population
- DLT evaluable population (Phase 1 part only)
- Pharmacokinetic (PK) analysis population (Phase 1 part only)
- modified ITT (mITT) population

8.4 Demographic and other baseline characteristics

In each analysis population, and separately for Phase 1 part, Phase 2 part and Phase 2 part (including subjects with MPM in Phase 1 part), summary statistics will be calculated for following demographics and baseline charactertistics:

- Sex: Male/Female
- Age (year): summary statistics
- Ethnicity: Not Hispanic or Latino
- Race: Asian
- Weight (kg): summary statistics
- ECOG PS: 0, 1, 2≤
- Disease Classification (NSCLC): Stage I, Stage II, Stage IIIA, Stage IIIB, Stage IV
- Disease Classification (MPM): Stage I, Stage II, STAGE III, Stage IV
- Primary cancer: Malignant Pleural Mesothelioma (MPM), Non-Small Cell Lung Cancer (NSCLC)
- Tissue Classification (MPM): Epithelioid, Sarcomatoid, Biphasic, Other
- Tissue Classification (NSCLC): Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma, Other
- Metastasis: Yes, No
- Disease duration (month): summary statistics

Output Phase 1 part only in PK and DLT evaluate population.

8.5 Measurements of treatment compliance

In safety analysis, DLT evaluable, PK analysis population and mITT population, and separately for Phase 1 part, Phase 2 part and Phase 2 part (including subjects with MPM in Phase 1 part), summary tables will be provided.
The calculation will be conducted in DLT evaluation period in DLT evaluable and PK analysis populations for Phase 1 part only.

8.5.1 Treatment compliance and intensity

Treatment compliance of BBI608 and treatment intensity of BBI608 and Pem/CDDP will be summarized and listed.
Treatment compliance/intensity will be calculated as follows:

<u>BBI608</u>

- Overall treatment compliance (%) of BBI608: 100×(total number of actual

ingested capsules)/(total number of prescribed capsules)
- Overall treatment intensity (%) of BBI608: 100×(total number of actual ingested capsules)/(12×study duration-6), where phase 1 part subject
  Overall treatment intensity (%) of BBI608: 100×(total number of actual ingested capsules)/(12×study duration), where phase 2 part subject
- Treatment intensity (%) of BBI608 at DLT evaluation period: 100×(total number of actual ingested capsules at DLT evaluation period)/270
- Study duration: Date of last administration of BBI608 – Date of first administration of BBI608 + 1

Pem
- Overall treatment intensity (%) of Pem: 100×[total amount of actual injected pemetrexed (mg/m^2)]/[total time of injected pemetrexed×500 (mg/m^2)]

CDDP
- Overall treatment intensity (%) of CDDP: 100×[total amount of actual injected cisplatin (mg/m^2)]/[total time of injected cisplatin×75 (mg/m^2)]

8.5.2 Duration of exposure
Duration of exposure by month of BBI608 will be summarized and listed.
Duration of exposure by day of BBI608 will be summarized for DLT evaluable population and listed.
Count the number of subject and percentage who received both of Pem and CDDP more than or equal 6 cycles.

8.5.3 Cumulative dose
Cumulative dose of BBI608, Pem and CDDP will be summarized and listed.

8.5.4 Mean daily dose
Mean daily dose of BBI608 will be listed.
Mean daily dose will be calculated as follows:
- Overall mean daily dose (mg/day) = Cumulative dose of BBI608/Study duration

8.5.5 Modal daily dose
Modal daily dose of BBI608 in phase 2 part will be listed.

If subject has two or more most frequent daily doses, handle the highest dose as modal daily dose.

Example

- Treatment duration (daily dose): 50 days (160 mg/day), 40 days (480 mg/day), 50 days (960 mg/day)
- Modal daily dose: 960 mg/day

8.6 Prior and Concomitant medications

Prior and concomitant medications will be coded to ATC (Anatomical Therapeutic Chemical) classification and Drug Name using WHO Drug Dictionary (WHODrug) version September, 2014.

Prior and concomitant medications will be provided by level 3 ATC classification and preferred name using frequencies and percentages in the Safety and mITT analysis population separately for Phase 1 part, Phase 2 part and Phase 2 part (including subjects with MPM in Phase 1 part).

9. Analysis of efficacy assessment

All analysis for efficacy will be performed in mITT analysis population.

9.1 Definition of efficacy endpoint

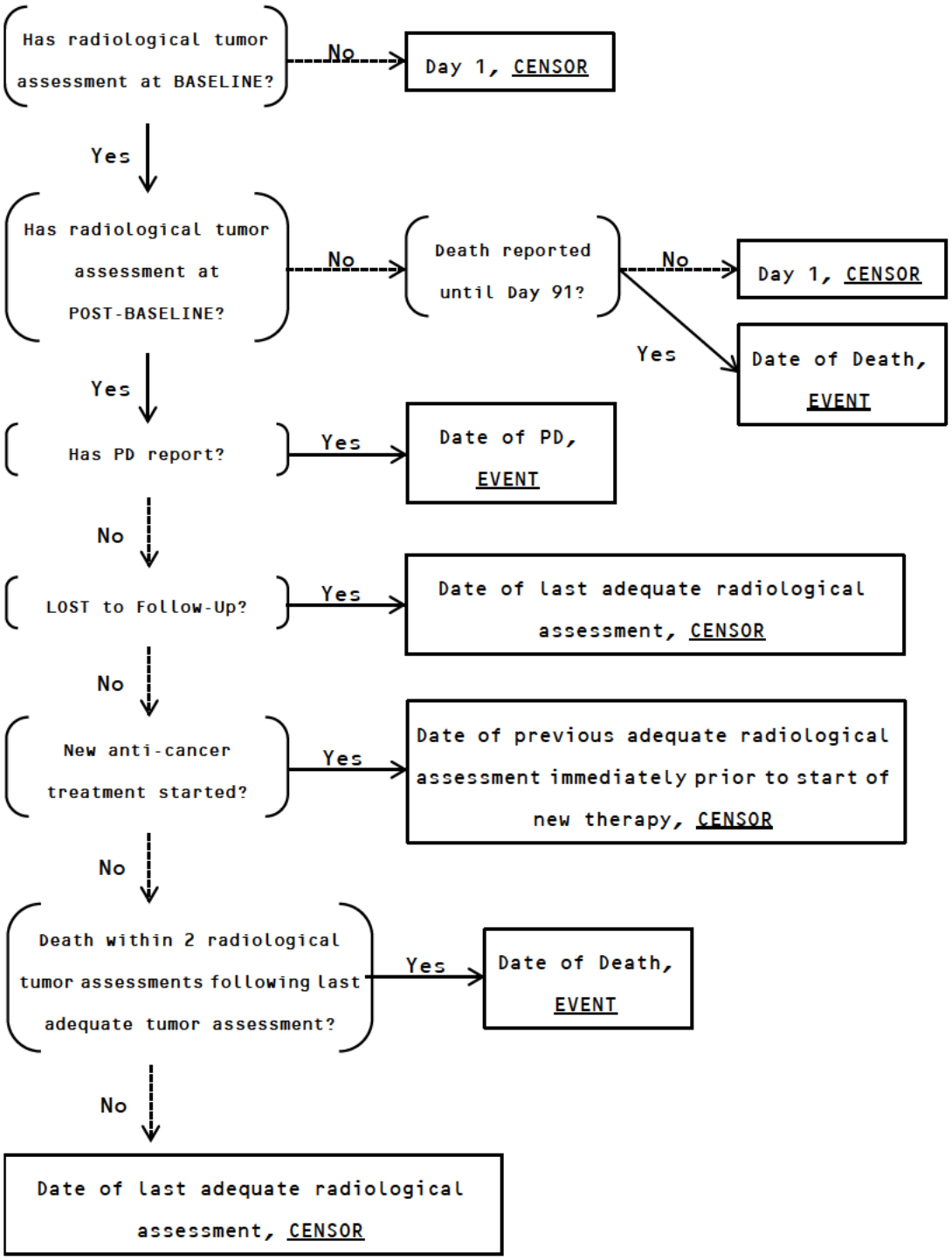
9.1.1 Progression Free Survival (PFS)

PFS time is defined as the time from the date of enrollment until the date of first radiographic documentation of progression as defined by RECIST (Version 1.1), or death due to any cause, whichever is first.

The following table summarizes the censoring rules for the PFS analysis:

Situation	Date of Event or Censor	Event / Censor
No baseline radiological tumor assessment available	Day 1	Censored
No post baseline radiological tumor assessment available and no death reported until Day 91	Day 1	Censored
No post baseline radiological tumor assessment available but death reported until Day 91	Date of Death	Event
No tumor progression (per RECIST 1.1) and no death reported within 2 radiological tumor assessments following last adequate radiological tumor assessment	Date of last adequate radiological tumor assessment	Censored

No tumor progression (per RECIST 1.1) but death reported within 2 radiological tumor assessments following last adequate radiological tumor assessment	Date of death	Event
New anticancer treatment started and no tumor progression	Date of previous adequate radiological assessment immediately prior to start of new therapy	Censored
No tumor progression (per RECIST 1.1) and subject lost to follow-up or withdrawal of consent	Date of last adequate radiological Assessment	Censored


Has radiological tumor assessment at BASELINE?
No
Day 1, CENSOR
Yes
Has radiological tumor assessment at POST-BASELINE?
No
Death reported until Day 91?
No
Day 1, CENSOR
Yes
Date of Death, EVENT
Yes
Has PD report?
Yes
Date of PD, EVENT
No
LOST to Follow-Up?
Yes
Date of last adequate radiological assessment, CENSOR
No
New anti-cancer treatment started?
Yes
Date of previous adequate radiological assessment immediately prior to start of new therapy, CENSOR
No
Death within 2 radiological tumor assessments following last adequate tumor assessment?
Yes
Date of Death, EVENT
No
Date of last adequate radiological assessment, CENSOR

9.1.2 Overall Survival (OS)

OS is defined as the time from BBI608 administration to death from any cause. Subjects alive at final observation or lost to follow-up will be censored at their last contact (i.e., visit or telephone) date.

9.1.3 Response Rate (RR)

RR is defined as the proportion of subjects with either Complete Response (CR) or Partial Response (PR).

9.1.4 Disease Control Rate (DCR)

DCR is defined as the proportion of patients with CR, PR or Stable Disease (SD).

9.1.5 Duration of response

Duration of response is calculated as follows:
Duration of response (month) = (the first date of PD evaluation or death – the first date of CR or PR evaluation)/30.4375

9.1.6 Duration of disease control

Duration of disease control is calculated as follows:
Duration of disease control (month) = (the first date of PD evaluation or death – the first date of BBI608 administration)/30.4375

9.2 Phase 1 part

Data from MPM patients and NSCLC patients will be combined for efficacy analysis.

9.2.1 Tumor response

The best overall response according to RECIST 1.1 or mRECIST, RR and DCR will be summarized.
Duration of response and duration of disease control will be summarized.

9.2.2 Progression Free Survival (PFS)

Survival curve of PFS will be displayed by Kaplan-Meier method. Median survival time (MST) of PFS will be calculated.

9.2.3 Overall Survival (OS)

Survival curve of OS will be displayed by Kaplan-Meier method. MST of OS will be calculated.

9.2.4 Respiratory Function Tests

The measurement of respiratory function tests (vital capacity [VC], forced vital capacity [FVC] and forced expiratory volume in 1st second [FEV1]) and their change from baseline will be summarized by visit.

9.3 Phase 2 part

The efficacy data from MPM subjects in Phase 1 part will be included in the Phase 2 part efficacy analysis.

9.3.1 Primary endpoints

Survival curve of PFS will be displayed by Kaplan-Meier method. MST of PFS and the 95%CI will be calculated. In addition, 6-month PFS rate and the 95%CI will be calculated.

9.3.2 Secondary endpoints

- Survival curve of OS will be displayed by Kaplan-Meier method. MST of OS and the 95%CI will be calculated. In addition, 1-year OS rate and the 95%CI will be calculated.
- The best overall response according to RECIST 1.1 or mRECIST, RR and DCR will be summarized.
- Duration of response and duration of disease control will be summarized.
- Scatter plots biomarker vs. PFS and OS by all MPM subject and epithelioid subject will be provided.
  Biomarker: H-score and Total percent positive of pSTAT3 Nuclear Tumor, Bete-catenin Nuclear Tumor and Merlin Tumor.
  H score of pSTAT3 Nuclear Tumor is calculated by [Percent Tumor Staining 1] + [Percent Tumor Staining 2] * 2 + [Percent Tumor Staining 3] * 3

The measurement of respiratory function tests (vital capacity [VC], forced vital capacity [FVC] and forced expiratory volume in 1st second [FEV1]) and their change from baseline will be summarized by visit.

9.3.3 Subgroup analysis

Subgroup analysis will be performed for MPM subjects according to tissue classification (epithelioid, sarcomatoid, biphasic) for following:

- Survival curve of PFS will be displayed by Kaplan-Meier method. MST of PFS, 6-month PFS rate and their 95%CI will be calculated.

- Survival curve of OS will be displayed by Kaplan-Meier method. MST of OS, 1-year OS rate and their 95%CI will be calculated.
- The best overall response according to RECIST 1.1 or mRECIST, RR and DCR will be summarized.
- Duration of response and duration of disease control will be summarized.
- The measurement of respiratory function tests (vital capacity [VC], forced vital capacity [FVC] and forced expiratory volume in 1st second [FEV1]) and their change from baseline will be summarized by visit.

10. Analysis of Safety assessment

Safety will be analyzed using the safety analysis population, and the data will be summarized for the entire study and separately for Phase 1 part, Phase 2 part and Phase 2 part (including MPM subjects in Phase 1 part).

10.1 Adverse Events

Adverse event (AE) is defined as all adverse events reported in CRF. Adverse drug reaction (ADR) is defined as an event whose relationship to study medication is NOT "not related" and "unlikely".

10.1.1 Overall summary of AEs

The number and percentage of subjects with following will be calculated.

- AE/ADR
- AE/ADR leading to death
- serious AE/ADR
- AE/ADR leading to drug withdraw (BBI608/Pem/CDDP)
- AE/ADR leading to drug interrupt (BBI608/Pem/CDDP)
- AE/ADR leading to dose reduced (BBI608/Pem/CDDP)

The listing of survival follow up will be reported.

10.1.2 Summary of AE by MedDRA

The number and percentage of subjects with AE/ADR using MedDRA SOC and PT will be calculated. The similar table by severity (grade) will be reported.

10.1.3 Summary of AE by onset

The number and percentage of subjects with AE onset each following exposure intervals using MedDRA SOC and PT will be calculated.

a. 1-3 days, 4-7 days, 8-14 days, 15-24 days
b. 1-28 days, 29-56 days, 57-84 days, 85-112 days, 113-140 days, 141-168 days, 169-196 days, 197days-, Overall

Denominators for exposure intervals will be based on the number of subjects who were exposed as of the first day of the interval.
If subject has two or more same AE in same exposure interval, count up as one subject.

10.1.4 Summary of AE by first onset

The number and percentage of subjects with first onset event of each AE will be calculated. The exposure interval will be used same with "10.1.3 Summary of AE by onset".

10.2 DLT evaluation

Tables and lists regarding DLT evaluation will be provided using DLT evaluable population for subjects in Phase 1 part.
The number and percentage of subjects with DLT for DLT evaluate population will be calculated. Adverse events which are met definition of DLT but are not handled as DLT will be listed.

10.3 Clinical laboratory evaluation

10.3.1 Summary of hematology and biochemistry

Summary statistics for observed value and change from baseline will be calculated by analysis visit.
The line chart by individual will be displayed.

10.3.2 Summary of urinalysis

Urinalysis tests with categorical results will be summarized by analysis visit and shift table will be displayed at baseline and post-baseline worst case.

10.3.3 Summary of CTCAE grade

The results of laboratory parameters will be graded according to NCI CTCAE v4.03 (See chapter 13). The CTCAE grading will be performed based on only observed value without considering any clinical symptoms or findings. The highest grade will be defined as the maximum grade throughout the study and decided for each laboratory parameter.

a. The number of percentage of subjects with the highest grade by laboratory parameters will be calculated. Denominators of percentage will be based on the

number of subjects who have at least one graded observed value besides baseline assessment.

b. The shift from baseline grade to highest grade at post-baseline will be produced to show the number of subjects with corresponding changes.
c. Listing will be provided by subjects and laboratory parameters.

10.3.4 Potential Clinical Significant

The number and percentage of subjects will be calculated with potential clinical significant (PCS). PCS will be provided in the results of laboratory test listing. The criteria of PCS are shown in Chapter 12.

10.4 Vital signs and Body weight evaluation

Summary statistics for observed value and change from baseline will be calculated by analysis visit.

10.5 12-lead ECG evaluation

12-lead ECG with categorical results will be summarized by analysis visit.
The shift from baseline to worst result at post-baseline will be produced to show the number of subjects. (Order of results: Normal > Abnormal [NCS] > Abnormal [CS])

10.6 ECOG PS evaluation

ECOG PS with categorical results will be summarized by analysis visit and shift table will be displayed at baseline and post-baseline worst case.

10.7 Chest X-ray evaluation

Chest X-ray with categorical results will be listed.

11. Analysis of Pharmacokinetics assessment

All analysis for PK evaluation will be performed for pharmacokinetics analysis population.

11.1 Handling of data

Actual sampling time will be used for calculating PK parameters of plasma concentration. The pre-dose sampling time will be set to zero, and will also be reported as such (i.e. if the actual pre-dose time is -0.5 h, report the pre-dose time as 0 h for PK analysis). For PK parameters and summary statistics, all below limit of quantitation

(BLQ: less than 5.00 ng/mL for BBI608, less than 10.0 ng/mL for pemetrexed, less than 25.0 ng/mL for cisplatin) values will be set to zero.

11.1.1 Reporting conventions

For the listing, λz, $t_{1/2}$ and MRT will be rounded to three decial places, t_{max} and AUC% extrapolated will be rounded to two decimal places, and C_{min} will be rounded to one decimal place, and AUCs, C_{max}, and number of points for λz will be rounded to integer.

11.2 Method of PK parameter estimation

The following PK parameters will be estimated from the BBI608 concentration data at Day 1 and Day 23 in Cycle 1 and the actual post-dose time.

- C_{max}: Maximum observed plasma concentration will be obtained directly from the concentration-time data.
- AUC_{0-t}: Area under the concentration-time curve up to the nominal sampling point (=12 and 24 h) will be calculated by linear trapezoidal method.
- $AUC_{0-\infty}$: Area under the concentration-time curve up to the last non-zero observed concentration time point (AUC_{0-last}) will be calculated by linear trapezoidal method, plus "foot slope" area extrapolated by λz, i.e. the observed $AUC_{0-\infty}$ will be reported.
- AUC% extrapolated will be calculated as $(AUC_{0-\infty}/AUC_{0-last})/AUC_{0-\infty} \times 100$

- λz: The elimination rate constant will be determined by linear regression of logarithmic transformed concentration-time data. For the linear regression analysis, at least three observations from the last measurable observed concentration (C_{last}(obs)) up to C_{max}(exclusive), will be selected according to the "Adjusted R-square".
  In the PK parameter listing, percent of $AUC_{0-\infty}$ extrapolated and number of data points for λz will be reported as the supportive information for λz and $AUC_{0-\infty}$.
- $t_{1/2}$: Terminal half-life is will be calculaed as ln(2)/λz.
- t_{max}: Time to C_{max} will be directly observed from the concentration-time data. If more than one time points which give C_{max} exist, the one which comes first will be adopted.
- MRT: Mean residence time will be calculated as the ratio of area under the first moment of the concentration-time curve (AUMC) to observed $AUC_{0-\infty}$.
- C_{min}: Minimum observed plasma concentration during a dosing interval at the steady state.

Plasma concentration of BBI608, Pem, and CDDP by each time point will be summarized.
The following chart will be provided:

- Line chart of BBI608 concentration by individual at Day 1 and Day 23 in Cycle 1 (linear and logarithmic scale)

- Scatter plot of BBI608/Pem/CDDP concentration by individual at Day 3 in Cycle 1
- Scatter plot of BBI608 C_{max}, AUC_{0-12}, and AUC_{0-24} at Day 1 and Day 23

12. Clinical significant laboratory abnormalities

Parameter (unit)	Change	Criteria
Leukocyte count (x10^3/μL)	increase	100 < val
Leukocyte count (x10^3/μL)	decrease	val < 2
Erythrocyte count (x10^6/μL)	decrease	val ≤ 3
Hemoglobin (g/dL)	increase	ULN+4 < val
Hemoglobin (g/dL)	decrease	val < 8
Hematocrit (%)	decrease	Male: val ≤ 37, Female: val ≤ 32
Platelets (x10^4/μL)	increase	70 ≤ val
Platelets (x10^4/μL)	decrease	val < 5
Neutrophil count (x10^9/L)	decrease	val < 1
Lymphocyte count (x10^9/L)	increase	20 < val
Lymphocyte count (x10^9/L)	decrease	val < 0.5
Protein (g/dL)	decrease	val < 4.5
Albumin (g/dL)	decrease	val < 2
Bilirubin (mg/dL)	increase	3×ULN < val
Aspartate Aminotransferase (U/L)	increase	5×ULN < val
Alanine Aminotransferase (U/L)	increase	5×ULN < val
Alkaline Phosphatase (U/L)	increase	5×ULN < val
Lactate Dehydrogenase (U/L)	increase	3×ULN ≤ val and 1.2×BL ≤ val
Blood Urea Nitrogen (mg/dL)	increase	30 < val
Creatinine (mg/dL)	increase	3×ULN < val
Creatinine (mg/dL)	increase	BL+4 < val
Sodium (mEq/L)	increase	155 < val
Sodium (mEq/L)	decrease	val < 130
Potassium (mEq/L)	increase	6 < val
Potassium (mEq/L)	decrease	val < 3
Chloride (mEq/L)	increase	115 < val
Chloride (mEq/L)	decrease	val < 90
Calcium (corrected) (mg/dL)	increase	12.5 < val
Calcium (corrected) (mg/dL)	decrease	val < 7
Magnesium (mg/dL)	increase	3 < val
Magnesium (mg/dL)	decrease	val < 0.9

Glucose *3	increase	BL+2 ≤ val
Blood *3	increase	BL+2 ≤ val
Protein *3	increase	BL+2 ≤ val

*3: Subjects whose baseline result is normal will be summarized.

[End of File]