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

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BBI608

Protocol

Phase 1/2 study of BBI608 combined with pemetrexed plus cisplatin in patients with malignant pleural mesothelioma

Version 3.02
5 Jan 2018

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EMERGENCY CONTACTS

Table 1 Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Medical Monitor	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor: Sumitomo Dainippon Pharma Co., Ltd.

Name of Investigational Drug: BBI608

Name of Active Ingredient: BBI608

Title of Study: Phase 1/2 study of BBI608 combined with pemetrexed plus cisplatin in patients with malignant pleural mesothelioma

Phase of Development: Phase 1/2

Planned Study Period: February 2015 to May 2018

Study Objectives:

Phase 1 part

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

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

Phase 2 part

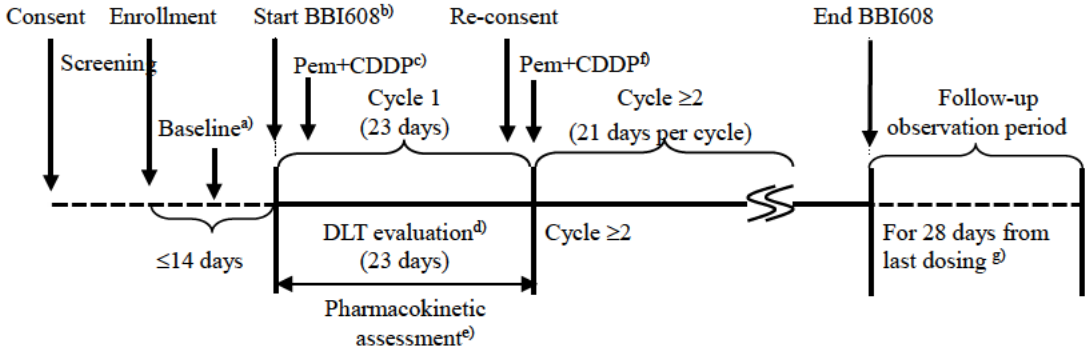
Primary: To evaluate the efficacy and safety of BBI608 combined with Pem plus CDDP in patients with MPM

Secondary: To explore biomarkers related to the efficacy of BBI608

Study Design

This clinical 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 Pem plus CDDP based on complete assessment of dose limiting toxicity (DLT) (with occurrence of DLT in no or 1 of 6 subjects).

Study Schematic for Phase 1 Part



a) Performed between Day -7 and the start of BBI608 administration.

b) In Cycle 1, Day 1 will be the first day of BBI608 administration.

c) In Cycle 1, Pem and CDDP will be administered on Day 3.

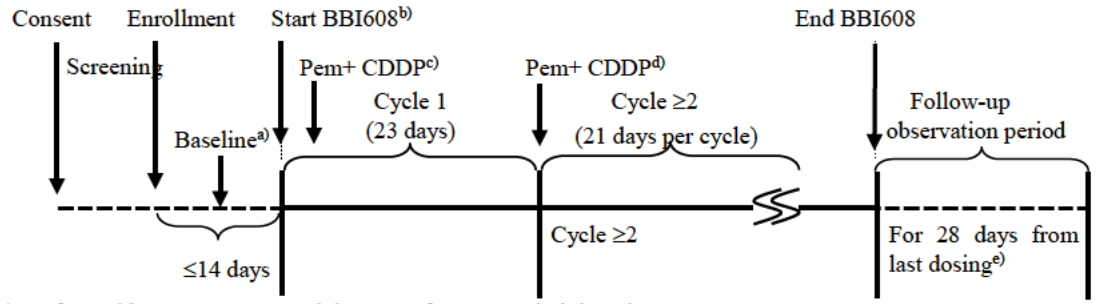
d) From Day 1 of Cycle 1 until Day 24 examination.

e) Subjects will be hospitalized for pharmacokinetic sampling (i.e., Days 1 to 4, 23 and 24 of Cycle 1), if necessary from the day before pharmacokinetic sampling.

f) In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP (or the day of administration of Pem after discontinuation of CDDP in NSCLC patients).

g) Until the examination/observation before subsequent treatment if subsequent treatment is given within 28 days after the last dose of BBI608.

Study Schematic for Phase 2 Part



a) Performed between Day -7 and the start of BBI608 administration.

b) In Cycle 1, Day 1 will be the first day of BBI608 administration.

c) In Cycle 1, Pem and CDDP will be administered on Day 3.

d) In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP.

e) Until the examination/observation before subsequent treatment if subsequent treatment is given within 28 days after the last dose of BBI608.

Number of Subjects (Planned):

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.

Sample size determination:

Phase 1 part: In line with the 3 + 3 design, the sample size is set at 3 with a maximum of 6 as the number required for determination of the safety of BBI608 combined with Pem plus CDDP.

Phase 2 part: The sample size is set at 20 as the number required and feasible to explore the efficacy of BBI608 combined with Pem plus CDDP in patients with MPM.

Target Disease and Inclusion and Exclusion Criteria:

<Phase 1 part: Patients with MPM or NSCLC>

Inclusion Criteria

- Histologically confirmed diagnosis of MPM or NSCLC
  - a) Patients with MPM must meet i) and ii) below:
    - i) Treatment naïve and not indicated for surgery
    - ii) Evaluable according to the mRECIST
  - b) Patients with NSCLC must meet i) and ii) below:
    - i) Clinical stage IV [Patients with postoperative recurrence may be included if the interval since the end of adjuvant or neoadjuvant chemotherapy (or radiotherapy) is ≥ 180 days and if they did not receive Pem or CDDP.]
    - ii) Evaluable according to the RECIST 1.1
- Age ≥ 20 years at the time of consent
- Provided written voluntary consent in person to participate in this study after fully receiving and understanding information about the study, including study objectives, contents, expected pharmacological effects and foreseeable risks
- Agree to use appropriate contraception from the time of consent until 30 days after the last dose of the study drug to avoid pregnancy of the female participant or a female partner of the male participant
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 within 14 days before enrollment
- Adequate major organ functions meeting the following criteria based on latest laboratory tests within 14 days before enrollment

- Hemoglobin (Hb) ≥ 9.0 g/dL (without blood transfusion within the preceding 14 days)
- Neutrophils ≥ 1500/μL
- Platelets ≥ 100,000/μL
- AST and ALT ≤ 2.5-fold the upper limit of the normal range of the laboratory (ULN), or ≤ 5-fold ULN within 14 days before enrollment for patients with any liver metastasis
- Total bilirubin ≤ 1.5-fold ULN
- Creatinine clearance (estimated value)[Note)] ≥ 60 mL/min

Note) Creatinine clearance will be calculated using the Cockcroft-Gault formula shown below:
Estimated creatinine clearance = (140-age) × body weight / (72 × serum creatinine) (× 0.85 for females)

- Life expectancy ≥ 3 months
- Women of childbearing potential must have a negative pregnancy test (urine) at screening.

<Phase 2 part: Patients with MPM>
Inclusion Criteria

- Histologically confirmed diagnosis of MPM
- Treatment naïve and not indicated for surgery
- Evaluable according to the mRECIST
- Age ≥ 20 years at the time of consent
- Provided written voluntary consent in person to participate in this study and tumor tissue sampling after fully receiving and understanding information about the study, including study objectives, contents, expected pharmacological effects and foreseeable risks
- Agree to use appropriate contraception from the time of consent until 30 days after the last dose of the study drug to avoid pregnancy of the female participant or a female partner of the male participant
- ECOG PS 0 or 1 within 14 days before enrollment
- Adequate major organ functions meeting the following criteria based on latest laboratory tests within 14 days before enrollment
- Hemoglobin (Hb) ≥ 9.0 g/dL (without blood transfusion within the preceding 14 days)
  - Neutrophils ≥ 1500/μL
  - Platelets ≥ 100,000/μL
  - AST and ALT ≤ 2.5-fold ULN, or ≤ 5-fold ULN within 14 days before enrollment for patients with any liver metastasis
  - Total bilirubin ≤ 1.5-fold ULN
  - Creatinine clearance (estimated value)[Note)] ≥ 60 mL/min

  Note) Creatinine clearance will be calculated using the Cockcroft-Gault formula shown below:
  Estimated creatinine clearance = (140-age) × body weight / (72 × serum creatinine) (× 0.85 for females)
- Life expectancy ≥ 3 months
- Women of childbearing potential must have a negative pregnancy test (urine) at screening

<For both Phase 1 and 2 parts>
Exclusion Criteria:

- Have received any of the following treatments “a)” to “c)” for the primary disease before enrollment in this study
  a) Chemotherapy and surgical therapy (MPM only. excluding surgical biopsy)
  b) Radiotherapy, with the exception of palliative irradiation for pain control or symptomatic relief performed within 14 days before enrollment
  c) Hormonal therapy, immunotherapy, thermotherapy, surgical therapy (NSCLC only. excluding surgical biopsy), or other antitumor treatments performed within 21 days before enrollment

- Any brain metastasis requiring treatment or symptomatic
- Presence of multiple active cancers at registration (i.e., synchronous multiple primary cancers, or metachronous multiple primary cancers with a disease-free period of ≤5 years, with the exception of curatively treated local carcinoma in situ or submucosal carcinoma)
- Presence of Crohn's disease or ulcerative colitis, or have a history of extensive resection of the small intestine
- Presence of significant 12-lead ECG abnormality within 28 days before enrollment
- History of myocardial infarction within 6 months before enrollment
- Current use of antiarrhythmic medication, with the exception of anticoagulant therapy for atrial fibrillation
- Presence of any uncontrolled concurrent disease (e.g., active infection, unstable angina, significant respiratory disease)
- Known hypersensitivity to Pem, CDDP or other drugs containing platinum
- Pregnant or possibly pregnant women, or women planning to breastfeed between the first dose of BBI608 to 30 days after the last dose of BBI608
- Have received any other investigational drug within 28 days before enrollment in this study
- Possible inability to swallow BBI608 for certain reasons such as dysphagia
- Previously received BBI608
- Inappropriate for participation in the study for other reasons in the opinion of the investigator or subinvestigator

Protocol Treatment, Study Drugs, Dosage and Mode of Administration:

Protocol treatment is defined as BBI608 in combination with Pem plus CDDP.

- BBI608

  BBI608 will be orally administered 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 administered.

- Pemetrexed (Pem)

  Pem, for which a marketed product will be used, 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). Meanwhile, Pem will be administered with an interval of at least 4 hours after BBI608 dosing in Cycle 1 of phase 1 part only. 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.

- 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.

Duration of Treatment:

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.

In Cycle 1, Day 1 will be the first day of BBI608 administration. From Cycle 2 onward, Day 1 will be the day of administration of Pem and CDDP (or the day of administration of Pem after discontinuation of CDDP in NSCLC patients in Phase 1 part).

Protocol treatment will be continued in the following manner:

- Protocol treatment with the three drugs should be repeated as long as possible; no restriction is set on the number of cycles.
- If an adverse event associated with either Pem or CDDP is judged to require treatment discontinuation, both Pem and CDDP should be discontinued, while BBI608 will be

continued as long as possible. For NSCLC patients, however, only CDDP may be discontinued at the discretion of the investigator or subinvestigator.

- Even after assessment of PD according to the RECIST 1.1 or mRECIST, administration of BBI608 may be continued until the treatment is no longer clinically beneficial to the patient in the opinion of the investigator or subinvestigator for certain reasons such as intolerable adverse events or further progression of the primary disease.

Reference Treatment, Dosage and Mode of Administration: Not applicable

Concomitant Medications and Therapies:

<Prohibited concomitant medications and therapies>

- Anticancer chemotherapy (other than Pem and CDDP as the components of protocol treatment), radiotherapy, hormonal therapy, immunotherapy, thermotherapy, surgical therapy, or other therapies for cancer
- Other investigational drugs, post-marketing clinical study drugs, or drugs unapproved in Japan
- Therapies with immunosuppressive effects (e.g., systemic steroids), with the exception of intermittent use for antiemesis, use at a less-than-immunosuppressive dose for malaise or appetite loss, or prophylactic use after onset of rash.
- Until the end of the DLT evaluation period in Phase 1 part, prophylactic use of granulocyte colony stimulating factor (G-CSF) products

Study Endpoints:

Phase 1 part

<Safety endpoints>

Adverse events and adverse drug reactions, DLT, vital signs, body weight, laboratory test values, 12-lead ECG, chest X-ray, and ECOG PS

<Efficacy endpoints>

Tumor response, progression-free survival (PFS), overall survival (OS), respiratory function tests (vital capacity [VC], forced vital capacity [FVC], forced expiratory volume in the first second [FEV1])

<Pharmacokinetic endpoints>

BBI608 pharmacokinetic parameters of the following:

Maximum plasma concentration (C_{max}), minimum 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 ($AUC_{0-\infty}$), time to maximum plasma concentration (t_{max}), terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), mean residence time (MRT)

Phase 2 part

<Efficacy endpoints>

PFS, OS, tumor response (response rate [RR], disease control rate [DCR]), respiratory function tests (VC, FVC, FEV1)

<Safety endpoints>

Adverse events and adverse drug reactions, vital signs, body weight, laboratory test values, 12-lead ECG, chest X-ray, ECOG PS

<Other endpoints>

Biomarkers (β-catenin, phospho-STAT3 (p-STAT3), merlin)

Statistical Methods:

<Analysis sets>

- Safety and efficacy: A set of all subjects who received the investigational drug.
- DLT evaluation: A set of subjects who received the investigational drug in Phase 1 part, who had a ≥ 80% BBI608 treatment compliance rate during the DLT evaluation period, and who experienced DLT during the DLT evaluation period
- Pharmacokinetics: A set of subjects who received BBI608 with the post-dose plasma BBI608 concentration data available for at least one time point.

<Efficacy analytical items>

- Tumor response: Best overall response
- PFS: Time from BBI608 administration to documented PD (as assessed according to the mRECIST or RECIST 1.1) or death, whichever is earlier
- OS: Time from BBI608 administration to death from any cause
- Respiratory function tests: VC, FVC, FEV1

Table 2 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			Will be performed in 6 months and 1 year 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 14) 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 this was performed on the previous day of Pem and CDDP administration, that result can be used. Meanwhile, if the administration of Pem and CDDP was discontinued, this will be performed from the next day of Pem and CDDP administration in the previous cycle in every 21 days (±7 days).
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 1 year 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]

Requirements for imaging and respiratory function tests 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.
- A baseline respiratory function test will be performed from 7 days till right before the first dose of BBI608.
- The allowable range for imaging and respiratory function tests is ±1 week. Imaging and respiratory function tests will be performed 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 is 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 because of other reason than imaging-documented worsening, imaging and respiratory function tests will be continued according to the test schedule even after discontinuation of protocol treatment until worsening is judged by an imaging test. If subsequent treatment is started before the judgment of worsening by an imaging test, imaging and respiratory function tests will be performed before subsequent treatment as far as possible, and no further imaging and respiratory function tests is required after initiation of subsequent treatment.

Table 4 Schedule of Pharmacokinetic Assessment in Phase 1 part

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 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	−20 min to BBI608	-	±5 min	±10 min	±15 min	±20 min	±20 min	−20 min to BBI608	−20 min to BBI608	-

bloodsampling	dosing							dosing	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.

Table 5 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]									
Prepare and submit tumor tissue sample			To be performed after registration corresponding to a request							
BBI608 administration, compliance			←						→	
Pem and CDDP administration, compliance				●			●			
Folic acid and vitamin B12 administration[a]		←								→
Baseline characteristics		●								
Pregnancy testing		●[g]								
Height		●								
Body weight		●		●			●[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			Will be performed in 6 months and 1 year 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 this was performed on the previous day of Pem and CDDP administration, that result can be used. Meanwhile, if the administration of Pem and CDDP was discontinued, this will be performed from the next day of Pem and CDDP administration in the previous cycle in every 21 days (±7 days).
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 1 year after last subject's treatment start date.

2. TABLE OF CONTENTS

List of Tables

List of Figures

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The abbreviations used in this protocol are shown in Table 6.

Table 6 List of Abbreviations

Abbreviation	Full Form
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
AUC_{0-12}	Area under the concentration-time curve from time zero to 12
AUC_{0-24}	Area under the concentration-time curve from time zero to 24
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
CDDP	Cisplatin
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CR	Complete response
CSC	Cancer stem cell
CT	Computed tomography
CTCAE v4.0-JCOG	Common Terminology Criteria for Adverse Events (CTCAE) version 4.0-Japanese translation by Japan Clinical Oncology Group
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose limiting toxicity
DRM	Data review meeting
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FEV1	Forced expiratory volume in 1st second
FVC	Forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IL-6	Interleukin-6
IPDs	Important protocol deviations
IRB	Institutional review board
ITT	Intention-to-Treat
λz	Terminal elimination rate constant
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

MPM	Malignant pleural mesothelioma
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NE	Not evaluable
Non-CR/Non-PD	Non-complete response /Non-progressive disease
OS	Overall survival
PD	Progressive disease
Pem	Pemetrexed
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
p-STAT3	Phospho-signal transducer and activator of transcription 3
PT	Preferred term
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RD	Recommended dose
RP2D	Recommended phase 2 dose
RR	Response rate
STAT3	Signal transducer and activator of transcription 3
SD	Stable disease
SOC	System organ class
t_{max}	Time to maximum observed concentration
$t_{1/2}$	Terminal elimination half-life
VC	Vital capacity

4. INTRODUCTION

4.1 Background

Malignant mesothelioma is difficult to diagnose and treat, and has very poor prognosis. Although it is a rare disease, the reported annual deaths from malignant mesothelioma in Japan were 710 in 2000, 911 in 2005, and 1410 in 2013,[1] showing a rapid increase in recent years. Malignant mesothelioma develops most commonly in the pleura, with malignant pleural mesothelioma (MPM) accounting for ≥ 90% of all cases of malignant mesothelioma, but also can develop in the pericardium, peritoneum, or tunica vaginalis. The most common cause is asbestos.[2] Given that the latency period from asbestos exposure and development of the disease is 25–30 years or longer, the peak prevalence of malignant mesothelioma in Japan is said to occur around 2025–2030.[3]

Trimodality therapy (consisting of surgical therapy, radiotherapy and chemotherapy) is recommended as first-choice treatment for malignant mesothelioma. Patients not indicated for trimodality therapy are treated with chemotherapy alone.[4] Currently, the only standard primary chemotherapy is the combination use of a folate metabolism inhibitor pemetrexed (Pem) and a platinum agent cisplatin (CDDP)[5],[6], but its therapeutic benefits have been unsatisfactory. Thus, new anticancer therapies with better antitumor effects on malignant mesothelioma are needed. Second and subsequent lines of treatment have no established evidence.

Recent reports increasingly describe that cancer stem cells (CSC), also called tumor-initiating cells, which are the cancer cells that have self-renewal ability, are involved in various cancer types including MPM. CSCs are now believed to play a major role in malignant tumor growth, recurrence, and metastasis.[7]-[11] Since CSCs are resistant to medications compared with non-stem cancer cells (i.e., cancer cells other than cancer stem cells), the existence of CSCs is recognized as the underlying mechanism for refractoriness.[8],[9] Thus, discovery of an effective method to eliminate CSCs is expected to lead a way to the development of curative treatment that can even prevent cancer metastasis and recurrence.

Many malignant mesothelioma cells are known to secrete interleukin-6 (IL-6) and IL-6 has been described to induce multiplication of malignant mesothelioma cells; thus, inhibition of IL-6 signaling can inhibit tumor growth.[12] In addition, signal transducer and activator of transcription 3 (STAT3), which is a transcription factor downstream of IL-6, is known to be highly expressed in malignant mesothelioma cells.[13] Abnormal expression and activation of the STAT3 signal transduction pathway are reported in various cancer types,[14] with significant correlation between its expression status and prognosis for colorectal cancer, gastric cancer, head and neck cancer, breast cancer, ovarian cancer.[15]-[19] Inactivation of the STAT3 signal transduction pathway by gene targeting or other methods has shown inhibition of cancer growth, survival, and metastasis.[14]

BBI608 is a novel, small-molecule compound targeting CSCs being developed for anticancer treatment. BBI608 inhibits the STAT3 signal transduction pathway, and therefore can inhibit self-renewal and survival of CSCs, thus inducing apoptosis of both CSCs and non-stem cancer cells. STAT3 is overexpressed in malignant mesothelioma, including MPM. Thus, BBI608 can be a useful treatment option for patients with MPM, and therefore the present study was planned.

4.2 Study Conduct Rationale

4.2.1 Nonclinical Studies

BBI608 showed potent proliferation inhibitory activity against CSCs, but little proliferation inhibitory activity against normal hematopoietic stem cells. Various cancer cells with active STAT3 were sensitive to BBI608, compared with cancer cells with inactive STAT3. BBI608 showed *in vitro* cytotoxic activity against various human cancer cell lines, including lung cancer and MPM. Also *in vivo* studies using xenograft mouse models of human cancers such as colorectal cancer showed potent antitumor activity with favorable tolerability. Furthermore, a mouse model of metastatic tumors demonstrated potent anti-metastatic activity.

In vitro studies using cytochrome P450 (CYP) isoforms showed that BBI608 had moderate inhibitory activity against 1A2, 2D6 and 2C19 (IC_{50}: 0.25, 0.25, and 0.5 μM, respectively) and relatively low inhibitory activity against 2C9 and 3A4 (IC_{50}: 2.5 and 5 μM, respectively).

4.2.2 Clinical Studies

4.2.2.1 Overseas Clinical Studies

(1) Study 101

Study 101 was the first-in-human Phase 1 study of BBI608 conducted in the US and Canada from [redacted]. The study objective was to evaluate the safety and pharmacokinetics of BBI608 monotherapy using the dose-escalation design in patients with advanced solid tumors, and determine the recommended phase 2 dose (RP2D). The efficacy was evaluated in patients with advanced colorectal cancer in the RP2D expansion cohort.

BBI608 was well tolerated, and adverse events were mostly mild. Common adverse events were grade 1 or 2 transient diarrhea, nausea and vomiting. Grade 3 adverse events were fatigue, transient diarrhea, abdominal colic, nausea, anorexia, and hypophosphatemia. The most common adverse event was diarrhea. Most events of diarrhea were mild, occurred within the first week of treatment, and resolved with treatment after a median duration of 2 days. These events of diarrhea were likely osmotic in etiology.

In terms of tumor response, SD for ≥ 12 weeks was observed in 46% of evaluable patients.

(2) Other clinical studies

In addition to the above study, the following overseas clinical studies are ongoing:

- A Phase Ib/II study of BBI608 combined with paclitaxel in adult patients with advanced malignancies (Study 201)
- A Phase II study of BBI608 combined with cetuximab, panitumumab or capecitabine in patients with advanced colorectal cancer (Study 224)
- A Phase Ib study of BBI608 combined with standard chemotherapies in patients with advanced gastrointestinal cancer (Study 246)

All adverse events reported from these studies have been essentially consistent with the adverse events reported earlier, and no adverse events raised particular issues.

4.2.2.2 Japanese Clinical Studies

(1) Study D8801001

Study D8801001 is an ongoing, phase 1, open-label, uncontrolled study with dose titration using the 3 + 3 design in Japanese patients with advanced solid cancers to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of BBI608. BBI608 is administered orally at 480 mg/day, 960 mg/day or 1440 mg/day in two divided doses (at 12-hour intervals), either 1 hour before or 2 hours after a meal.

DLT evaluation was completed for all cohorts by [redacted]. Cohort 1 (480 mg/day) was performed in 3 patients with colorectal cancer, and all 3 patients completed the DLT evaluation without experiencing any DLT. Cohort 2 (960 mg/day) was performed in 4 patients with colorectal cancer, and all 4 patients completed the DLT evaluation period without experiencing any DLT. In Cohort 3 (1440 mg/day), 1 of 3 colorectal cancer patients who were administered the drug experienced DLT (grade 3 decreased appetite). Therefore, 2 colorectal cancer patients and 1 adrenal cancer patient were added to evaluate DLT. One of 3 additional patients experienced a serious adverse event (grade 2 acute enteritis, not related to the study drug); thus, the treatment was discontinued due to the subject's intention on Day 6. Accordingly, 1 colorectal cancer patient was added and the DLT evaluation period was completed. 3 patients who were applicable to DLT evaluation did not experience DLT.

As of [redacted], adverse drug reactions reported in 2 or more patients were diarrhoea (66.7%, 8/12 patients) as well as nausea, vomiting, and decreased appetite (25.0% each, 3/12 patients each), and gastrointestinal adverse drug reactions have been common. Most adverse drug reactions were

grade 1 or 2, and the only grade ≥3 adverse drug reactions were diarrhoea and decreased appetite in 1 patient in Cohort 3. About half of adverse drug reactions occurred within the first 4 days of BBI608 therapy. Compared with common adverse events in non-Japanese patients in overseas clinical studies, i.e., grade 1 or 2 transient diarrhoea, nausea, vomiting or other gastrointestinal adverse events, adverse events in Japanese patients showed no particular differences. One patient in Cohort 2 discontinued treatment during the DLT evaluation period after experiencing adverse events of nausea, vomiting, dehydration, worsening of anorexia, delirium, of renal failure, which were attributed by the investigator to either progression of the primary disease or opioid use for the control of symptoms associated with the primary disease.

Pharmacokinetic data were compared between Japanese patients and non-Japanese patients. Although the sample size differed between the two populations, the plasma concentrations in Japanese patients were within the range of variation of plasma concentrations in non-Japanese patients. Also, the distribution of maximum observed concentration (C_{max}) and area under the concentration-time curve from time zero to 24 (AUC_{0-24}) indicated no substantial difference in the extent of exposure between Japanese patients and non-Japanese patients.

(2) Study D8806004

Study D8806004 is an ongoing phase 1 study in patients with unresectable/recurrent gastric cancer with disease progression after one or more chemotherapy regimens, to determine the safety, tolerability and pharmacokinetics of BBI608 combined with paclitaxel (80 mg/m^2 intravenously three times a week in 4-week cycles). BBI608 is orally administered at a dose of 480 mg twice daily (12-hour intervals) (daily dose, 960 mg/day), at either 1 hour before or 2 hours after a meal. As of [redacted], 6 patients received the investigational drug and 1 patient remains on treatment.

In terms of the safety, no DLT occurred in 6 patients assessed for DLT. No serious adverse events occurred during the DLT evaluation period. Adverse drug reactions reported in 2 or more patients were diarrhoea and anorexia. Almost all adverse drug reactions were grade 1. About half of adverse drug reactions occurred within the first 4 days of BBI608 therapy.

Pharmacokinetic data showed profound inter-individual differences, but the time-course of plasma BBI608 concentrations did not show major difference between single-dose administration and multiple-dose administration in individual cycles. Between patients with total or partial gastrectomy and those without gastrectomy, the time-course of plasma BBI608 concentrations did not show major difference, either after single-dose administration or multiple-dose administration.

4.2.3 Multinational Clinical Studies

A phase 3 multinational, placebo-controlled study (Study CO.23) is ongoing in patients with previously treated advanced colorectal cancer. A phase 3, multinational, placebo-controlled, double-blind, randomized study of BBI608 combined with paclitaxel (Study 336) is ongoing in patients with advanced previously treated gastric or gastro-esophageal junction adenocarcinoma. These studies are conducted in multiple countries including Japan. All adverse events reported from these studies were essentially consistent with the adverse events reported earlier, and no adverse events raised particular issues. For Study CO.23, the protocol-specified sample size was reached, and the first interim analysis was performed, revealing that the disease control rate (DCR) did not meet the pre-established criteria. Thus, the independent safety data monitoring committee advised to discontinue enrollment of new patients and discontinuation of treatment in already enrolled patients. Enrollment of new patients was discontinued on [redacted]. Treatment was withdrawn in already enrolled approximately 280 patients, including 44 Japanese patients. The primary endpoint of overall survival (OS) is to be analyzed.

4.3 Present Investigational Plan

The present study is a phase 1/2, open-label, uncontrolled study. Phase 1 part is conducted in patients with malignant pleural mesothelioma (MPM) or non-small cell lung cancer (NSCLC) to evaluate the safety, tolerability and pharmacokinetics of BBI608 960 mg/day combined with Pem plus CDDP (protocol treatment).

Phase 2 part is conducted in patients with MPM to primarily evaluate the efficacy (based on progression-free survival [PFS] as the primary endpoint) and safety of BBI608 combined with Pem plus CDDP, and secondarily explore biomarkers related to the efficacy.

The study will proceed to Phase 2 part only after Phase 1 part demonstrates the tolerability of BBI608 combined with Pem plus CDDP based on complete assessment of DLT (with occurrence of DLT in no or 1 of 6 patients).

BBI608 will be administered at a dose of 480 mg twice daily (daily dose, 960 mg) in line with the overseas RP2D, given that there have been no particular problematic adverse events in overseas clinical studies to date and that plasma concentrations showed no profound difference between Japanese subjects and non-Japanese subjects.

NSCLC patients are included in the Phase 1 part for preliminary evaluation of the efficacy and safety because one of standard therapies is similar between MPM and NSCLC and non-clinical data on BBI608 suggest that add-on BBI608 may also be effective in treating NSCLC.

5. STUDY OBJECTIVES

5.1 Phase 1 Part

5.1.1 Primary Objective

To evaluate the safety, tolerability and pharmacokinetics of BBI608 combined with Pem plus CDDP in patients with MPM or NSCLC.

5.1.2 Secondary Objective

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

5.2 Phase 2 Part

5.2.1 Primary Objectives

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

5.2.2 Secondary Objective

To explore biomarkers related to the efficacy of BBI608.

6. STUDY ENDPOINTS

6.1 Phase 1 Part

6.1.1 Safety Endpoints

- Adverse events and adverse drug reactions, DLT
- Vital signs, 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
- PFS
- OS
- Respiratory function tests (vital capacity [VC], forced vital capacity [FVC], forced expiratory volume in the first 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 ($AUC_{0-\infty}$)
- 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])
  RR is defined as the proportion of patients with either Complete Response (CR) or Partial Response (PR). DCR is defined as the proportion of patients with CR, PR or Stable Disease (SD).
- Respiratory function tests (VC, FVC, FEV1)

6.2.2 Safety Endpoints

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

6.2.3 Other Endpoints

Biomarkers (β-catenin, phospho-STAT3 [p-STAT3], merlin)

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design

This clinical study consists of two parts: Phase 1 and Phase 2. Protocol treatment is defined as BBI608 in combination with Pem plus CDDP. Each cycle of protocol treatment consists of 21 days (with the exception of Cycle 1 which consists of 23 days). No restriction is set on the number of

cycles of protocol treatment. Phase 1 part is conducted in patients with MPM or NSCLC to evaluate the safety, tolerability and pharmacokinetics of BBI608 combined with Pem plus CDDP. Phase 2 part is conducted in patients with MPM to evaluate the efficacy and safety of BBI608 combined with Pem plus CDDP. A multicenter, open-label, uncontrolled study design is used for both Phase 1 and Phase 2 parts.

The study will proceed to Phase 2 part only after Phase 1 part demonstrates the tolerability of BBI608 combined with Pem plus CDDP based on complete assessment of DLT (with occurrence of DLT in no or 1 of 6 patients).

7.1.1 Phase 1 Part

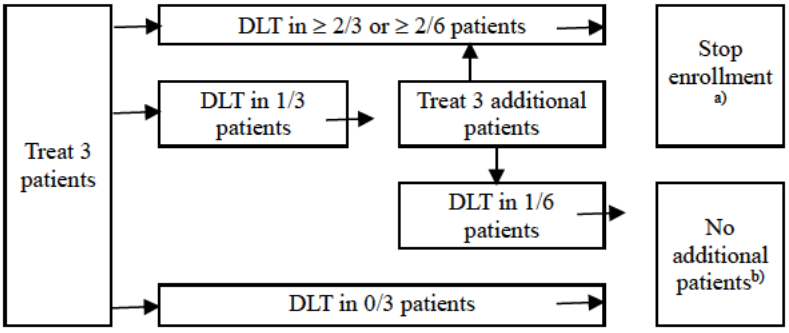
DLT is first assessed in 3 patients given BBI608 combined with Pem plus CDDP. If DLT occurs in 0/3 patients, no additional patients are enrolled. If DLT is observed in 1/3 patients, 3 additional patients are enrolled and treated. If none of the 3 additional patients experience DLT (i.e., DLT occurred in 1/6 patients), no additional patients are enrolled. Figure 1 (page 33) shows the flowchart of subject enrollment, and Figure 2 (page 33) shows the flowchart of study procedures in individual patients. Patients may be enrolled only after providing consent and being confirmed to be eligible. The procedures for enrollment are described in Section 10 (page 42). Administration of BBI608 will be started within 14 days after enrollment. If BBI608 therapy is started > 7 days after enrollment, repeat baseline examination (ECOG PS, hematology tests, biochemistry tests, and urinalysis) is required. In Cycle 1, Day 1 will be the first day of BBI608 administration, and Pem and CDDP will be administered on Day 3. DLT will be assessed from Day 1 examination to Day 24 examination. If treatment is continued to Cycle ≥ 2, re-consent should be obtained between Day 17 and the start of Cycle 2 therapy. In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP (or the day of administration of Pem after discontinuation of CDDP in NSCLC patients).

The daily dose of BBI608 will be 960 mg which will be orally administered twice daily (morning and evening). On Day 1 of Phase 1 part, only the morning dose will be administered. Pem 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 with an interval of 4 hour after BBI608 dosing on Day 3). Premedication 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. Further details are described in Section 10.1 (2) (page 44). CDDP 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 on Day 1 of each treatment cycle (with the exception of Cycle 1

in which CDDP will be given on Day 3).

The schedule of study investigations, observations and examinations is shown in Table 2 (P.10), the schedule of imaging and respiratory function tests in Table 3 (P.13), and the schedule of pharmacokinetic assessment in Table 4 (P.14), and the schedule of BBI608, Pem and CDDP co-administration in Figure 3 (P.34).

Figure 1 Flowchart of Enrollment of Additional Subjects

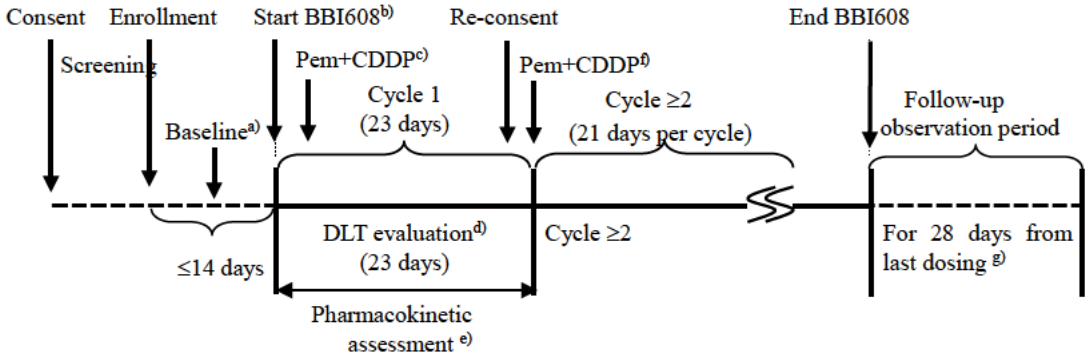


DLT: dose limiting toxicity (Section 10.5.1, page 50)

a) If DLT occurs in ≥ 2/3 or ≥ 2/6 patients, the sponsor will discuss with the investigator to decide whether or not to continue already ongoing treatment in subjects currently in the study. As necessary, the sponsor will seek opinion of the Data and Safety Monitoring Board.

b) If judged necessary by the sponsor, additional patients may be enrolled after discussion with a coordinating investigator etc.

Figure 2 Flowchart of Study Procedures in Individual Subjects (Phase 1 Part)



a) Performed between Day -7 and the start of BBI608 administration.

b) In Cycle 1, Day 1 will be the first day of BBI608 administration.

c) In Cycle 1, Pem and CDDP will be administered on Day 3.

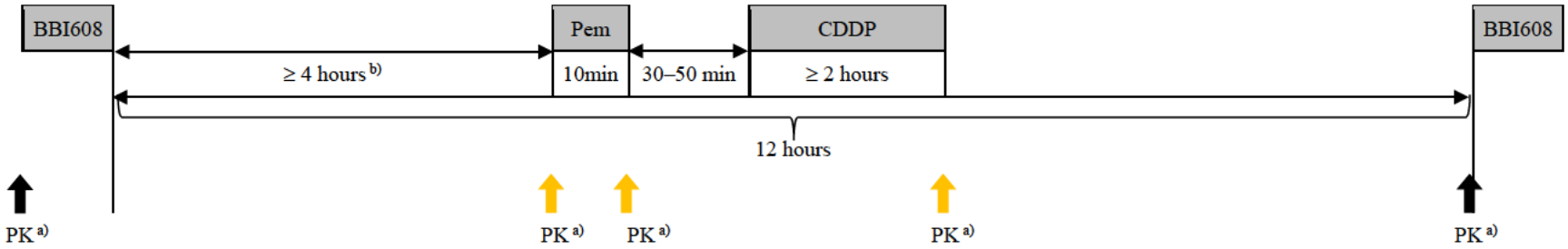
d) From Day 1 of Cycle 1 until Day 24 examination.

e) Subjects will be hospitalized for pharmacokinetic sampling (i.e., Days 1 to 4, 23 and 24 of Cycle 1), if necessary from the day before pharmacokinetic sampling.

f) In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP (or the day of administration of Pem after discontinuation of CDDP in NSCLC patients).

g) Until the examination/observation before subsequent treatment if subsequent treatment is given within 28 days after the last dose of BBI608.

Figure 3　Schedule of BBI608, Pem and CDDP Co-administration in a Day



a) Blood collection for PK will be performed in Cycle 1 of Phase 1 part only
b) Will be performed in Cycle 1 of Phase 1 part only

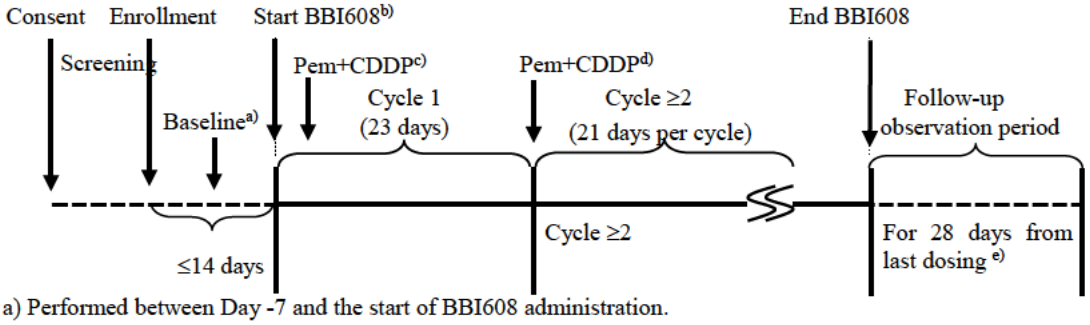
7.1.2 Phase 2 Part

Figure 4 (page 35) shows the flowchart of study procedures in individual subjects. Patients may be enrolled only after providing consent and being confirmed to be eligible. Procedures for enrollment are described in Section 10 (page 42). Administration of BBI608 will be started within 14 days after enrollment. If BBI608 therapy is started > 7 days after enrollment, repeat baseline examination (ECOG PS, hematology tests, biochemistry tests, and urinalysis) is required. In Cycle 1, Day 1 will be the first day of BBI608 administration, and Pem and CDDP will be administered on Day 3. In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP.

The daily dose of BBI608 will be 960 mg which will be orally administered twice daily (morning and evening). On Day 1 of Phase 1 part, only the morning dose will be administered. Pem 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).. Premedication 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. Further details are described in Section 10.1 (2) (page 44). CDDP 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 on Day 1 of each treatment cycle (with the exception of Cycle 1 in which CDDP will be given on Day 3).

The schedule of investigations, observations and examinations is shown in Table 5 (P.16), and the schedule of imaging and respiratory function tests in Table 3 (P.13).

Figure 4 Flowchart of Study Procedures in Individual Subjects (Phase 2 Part)



a) Performed between Day -7 and the start of BBI608 administration.
b) In Cycle 1, Day 1 will be the first day of BBI608 administration.
c) In Cycle 1, Pem and CDDP will be administered on Day 3.
d) In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP.
e) Until the examination/observation before subsequent treatment if subsequent treatment is given within 28 days after the last dose of BBI608.

7.2 Rationale

7.2.1 Rationale for the Study Design

The open-label, uncontrolled design was selected because this design will allow for evaluation of the safety, tolerability and pharmacokinetics as the objective of Phase 1 part, and also for Phase 2 part which is exploratory and does not aim to compare the efficacy of this drug and another drug.

7.2.2 Rationale for the Dosages

(1) BBI608

The dose of BBI608 in this study is set on the basis of the RP2D of BBI608 for monotherapy, pharmacokinetics in non-Japanese patients vs. Japanese patients, and metabolism of Pem and CDDP.

The RP2D of BBI608 for monotherapy was determined to be 1000 mg/day (500 mg twice daily) based on the results of an overseas phase 1 study (Study 101). Subsequently, a new formulation containing 80 mg of BBI608 was developed, and thus 960 mg/day (480 mg twice daily) was used as the dose nearest to 1000 mg/day in subsequent phase 3 study of BBI608 monotherapy and phase 3 study of combination therapy with BBI608 and paclitaxel.

Currently in Japan, a phase 1 study of BBI608 monotherapy (D8801001) is ongoing in patients with advanced solid cancers. DLT evaluation was completed for all cohorts by [redacted]. BBI608 was administered to 3 patients in Cohort 1 (480 mg/day), 4 patients in Cohort 2 (960 mg/day), and 6 patients in Cohort 3 (1440 mg/day), among whom DLT occurred in no patients except 1 patient in Cohort 3 who experienced grade 3 anorexia assessed as DLT. No serious adverse events occurred during the DLT evaluation period. Compared with common adverse events in overseas clinical studies, i.e., grade 1 or 2 transient diarrhoea, nausea, vomiting or other gastrointestinal adverse events, common adverse events in Japanese patients showed no particular differences. Comparison of the pharmacokinetics between Japanese patients and non-Japanese patients showed that the plasma concentrations in Japanese patients were within the range of variation of plasma concentrations in non-Japanese patients. Also, the distribution of C_{max} and AUC_{0-24} indicated no substantial difference in the extent of exposure between Japanese patients and non-Japanese patients.

Pem and CDDP, which are used in combination with BBI608 in this study, do not inhibit CYP1A2 as the primary enzyme involved in the metabolism of BBI608.[20),21)] Although BBI608 inhibits CYP1A2, CYP2D6, and other CYP isoforms, CYP enzymes are unlikely involved in the metabolism of Pem or CDDP, and thus the use of Pem and CDDP in combination with BBI608 are unlikely to cause drug interactions.

The recommended dose (RD) of BBI608 for use with Pem plus CDDP was considered to be similar to 960 mg/day, i.e., the RD for monotherapy, based on Japanese and overseas clinical studies. Thus, the dose of BBI608 in this study is set at the RD of 960 mg/day, for evaluation of the safety, tolerability and pharmacokinetics in patients with MPM or NSCLC patients in Phase 1 part, as well as the efficacy and safety in patients with MPM in Phase 2 part.

For the method of BBI608 administration, twice daily oral administration at intervals of approximately 12 hours was selected with reference to data from ongoing Japanese and overseas studies.

For the duration of treatment, daily administration will be continued until discontinuation due to adverse events etc., given that BBI608 has little inhibitory effects on normal hematopoietic stem cells and nonclinical studies and Japanese and overseas clinical studies have shown favorable tolerability of BBI608. Moreover, for patients with MPM, no second-line or subsequent therapies with established evidence exist and no standard therapies are available for subsequent treatment. For this reason, protocol treatment may be continued until the treatment is no longer clinically beneficial to the patient in the opinion of the investigator or subinvestigator.

The duration of each cycle is set at 21 days (with the exception of Cycle 1 which consists of 23 days) because this study will use Pem and CDDP that require at least 20 days of dosing intervals and are administered on the first day of each 21-day cycle.

The duration of follow-up observation period is set at 28 days on the basis that the $t_{1/2}$ of BBI608 was approximately 8 hours in the phase 1 study of BBI608 monotherapy (Study 101) and 28 days would be adequate for safety evaluation after the end of the treatment.

(2) Pem and CDDP

Pem and CDDP will be administered in accordance with their approved dose and administration in Japan. Specifically, Pem will be intravenously administered at 500 mg/m^2 by drip infusion over 10 minutes on Day 1 of each treatment cycle, while CDDP will be intravenously administered at 75 mg/m^2 by drip infusion over ≥2 hours on Day 1 of each treatment cycle, with the exception of Cycle 1 in which these drugs will be administered on Day 3 to allow for determination of adverse events associated with BBI608.

7.2.3 Rationale for the Study Population

This study will enroll patients with MPM and patients with NSCLC, which are the patient populations indicated for the Pem plus CDDP combination chemotherapy.

7.2.4 Rationale for the Endpoints

1) Efficacy endpoints

For MPM, assessment of the treatment efficacy requires measurement of the thickness of the tumor lesion in the pleura and thus tumor response will be assessed using the mRECIST designed to measure pleura lesion thickness. For NSCLC, tumor response will be assessed using the RECIST 1.1 typically used in the assessment of treatment efficacy on solid tumors. Tumor response and PFS are used because these are widely used as surrogate endpoints in the assessment of efficacy of anticancer drugs. OS is employed for exploratory analysis of OS prolongation in this study with a small sample size. FVC and other respiratory function tests are used because FVC has been described as an indicator of disease progression or improvement in patients with malignant pleural mesothelioma.[22)]

2) Safety endpoints

Commonly used safety endpoints are employed.

3) Pharmacokinetic endpoints

Commonly used parameters for pharmacokinetic evaluation are employed.

4) Other endpoints

β-catenin, p-STAT3 and merlin are employed for exploratory analysis of the effects of these parameters on the efficacy of BBI608.

7.3 Planned Study Period

February 2015 to May 2018

8. SELECTION OF SUBJECTS

8.1 Inclusion Criteria

8.1.1 Phase 1 Part

Patients must fulfil all of the following criteria to be included in this study:

1) Histologically confirmed diagnosis of MPM or NSCLC
   a) Patients with MPM must meet i) and ii) below:
      i) Treatment naïve and not indicated for surgery
      ii) Evaluable according to the mRECIST
   b) Patients with NSCLC must meet i) and ii) below:
      i) Clinical stage IV [Patients with postoperative recurrence may be included if the interval since the end of adjuvant or neoadjuvant chemotherapy (or radiotherapy) is ≥ 180 days and if they did not receive Pem or CDDP.]
      ii) Evaluable patients according to the RECIST 1.1
2) Age ≥ 20 years at the time of consent
3) Provided written voluntary consent in person to participate in this study after fully receiving

and understanding information about the study, including study objectives, contents, expected pharmacological effects and foreseeable risks

4) Agree to use appropriate contraception from the time of consent until 30 days after the last dose of the study drug to avoid pregnancy of the female participant or a female partner of the male participant
5) ECOG PS 0 or 1 within 14 days before enrollment
6) Adequate major organ functions meeting the following criteria based on latest laboratory tests within 14 days before enrollment
   - Hemoglobin (Hb) ≥ 9.0 g/dL (without blood transfusion within the preceding 14 days)
   - Neutrophils ≥ 1500/μL
   - Platelets ≥ 100,000/μL
   - AST and ALT ≤ 2.5-fold the upper limit of the normal range of the laboratory (ULN), or ≤ 5-fold ULN for patients with any liver metastasis
   - Total bilirubin ≤ 1.5-fold ULN
   - Creatinine clearance (estimated value)[Note)] ≥ 60 mL/min

     Note) Creatinine clearance will be calculated using the Cockcroft-Gault formula shown below: Estimated creatinine clearance = (140-age) × body weight / (72 × serum creatinine) (× 0.85 for females)
7) Life expectancy ≥ 3 months
8) Women of childbearing potential must have a negative pregnancy test (urine) at screening.

8.1.2 Phase 2 Part

1) Histologically confirmed diagnosis of MPM
2) Treatment naïve and not indicated for surgery
3) Evaluable according to the mRECIST
4) Age ≥ 20 years at the time of consent
5) Provided written voluntary consent in person to participate in this study and tumor tissue sampling after fully receiving and understanding information about the study, including study objectives, contents, expected pharmacological effects and foreseeable risks
6) Agree to use appropriate contraception from the time of consent until 30 days after the last dose of the study drug to avoid pregnancy of the female participant or a female partner of the male participant
7) ECOG PS 0 or 1 within 14 days before enrollment
8) Adequate major organ functions meeting the following criteria based on latest laboratory tests within 14 days before enrollment
   - Hemoglobin (Hb) ≥ 9.0 g/dL (without blood transfusion within the preceding 14 days)
   - Neutrophils ≥ 1500/μL
   - Platelets ≥ 100,000/μL

- AST and ALT ≤ 2.5-fold ULN, or ≤ 5-fold ULN for patients with any liver metastasis
- Total bilirubin ≤ 1.5-fold ULN
- Creatinine clearance (estimated value)[Note)] ≥ 60 mL/min

Note) Creatinine clearance will be calculated using the Cockcroft-Gault formula shown below:
Estimated creatinine clearance = (140-age) × body weight / (72 × serum creatinine) (× 0.85 for females)

9) Life expectancy ≥ 3 months
10) Women of childbearing potential must have a negative pregnancy test (urine) at screening

8.2 Exclusion Criteria

For both Phase 1 and 2 parts, patients meeting any of the following criteria will be excluded from this study:

1) Have received any of the following treatments "a)" to "c)" for the primary disease before enrollment in this study
   a) Chemotherapy and surgical therapy (MPM only. excluding surgical biopsy)
   b) Radiotherapy, with the exception of palliative irradiation for pain control or symptomatic relief performed within 14 days before enrollment
   c) Hormonal therapy, immunotherapy, thermotherapy, surgical therapy (NSCLC only. excluding surgical biopsy), or other antitumor treatments performed within 21 days before enrollment
2) Any brain metastasis requiring treatment or symptomatic
3) Presence of multiple active cancers at registration (i.e., synchronous multiple primary cancers, or metachronous multiple primary cancers with a disease-free period of ≤5 years, with the exception of curatively treated local carcinoma in situ or submucosal carcinoma)
4) Presence of Crohn's disease or ulcerative colitis, or have a history of extensive resection of the small intestine
5) Presence of significant 12-lead ECG abnormality within 28 days before enrollment
6) History of myocardial infarction within 6 months before enrollment
7) Current use of antiarrhythmic medication, with the exception of anticoagulant therapy for atrial fibrillation
8) Presence of any uncontrolled concurrent disease (e.g., active infection, unstable angina, significant respiratory disease)
9) Known hypersensitivity to Pem, CDDP or other drugs containing platinum
10) Pregnant or possibly pregnant women, or women planning to breastfeed between the first dose of BBI608 to 30 days after the last dose of BBI608
11) Have received any other investigational drug within 28 days before enrollment in this study
12) Possible inability to swallow BBI608 for certain reasons such as dysphagia
13) Previously received BBI608

14) Inappropriate for participation in the study for other reasons in the opinion of the investigator or subinvestigator

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1 Description of Investigational Drug

The following investigational drug is used in this study:

Name of investigational drug: BBI608 Capsules 80 mg

Dosage form and strength: Hard capsules, each containing 80 mg of BBI608

9.2 Investigational Drug Packaging and Labeling

9.2.1 Package Description

Each bottle of the investigational drug contains 84 capsules of BBI608 Capsules 80 mg.

9.2.2 Labeling Description

Each bottle of the investigational drug is labeled with the following information: statement of “For use in a clinical trial”, investigational substance code (BBI608), lot number, expiration date, storage condition, sponsor’s name and address.

9.3 Investigational Drug Storage

Store in a tight, light-resistant container at 2 to 25°C.

9.4 Dispensing of Investigational Drug

The investigator or subinvestigator will dispense the investigational drug to each subject in light of the inpatient/outpatient status of the subject so that the subject can take the protocol-specified amount of the investigational drug. Subjects treated as outpatients should be given adequate explanation about the handling of the investigational drug as well as instructions on how to store and take the drug appropriately.

9.5 Investigational Drug Accountability

After the study contract is signed between the sponsor and the medical institution, the sponsor will deliver the investigational drug to the investigational drug manager. The investigational drug manager of the medical institution will store and manage the investigational drug according to the written procedures for management of the investigational drug, and prepare the investigational drug accountability log to keep track of the use of the investigational drug. The investigational drug must not be used for other purposes than this study.

9.6 Investigational Drug Handling and Disposal

The investigational drug manager of the medical institution will handle the investigational drug according to the written procedures for handling of the investigational drug. Any investigational drug unused or returned from the subjects must be returned to the sponsor from the investigational drug manager according to the written procedures for management of the investigational drug. If the investigational drug is inadvertently discarded or lost at the medical institution, the investigational drug manager will document it in the investigational drug accountability log and report it to the sponsor.

The investigational drug manager will submit a copy of the investigational drug accountability log to the sponsor after the end of treatment with the investigational drug. The sponsor will check the consistency between the investigational drug accountability log and the number of the investigational drug unused or returned from the subjects and the entries in the eCRF. Any inconsistency should be immediately investigated and addressed as necessary by the investigator or subinvestigator.

The sponsor will retrieve any unused investigational drug in principle before the expiration date as a measure to ensure that no subjects receive the investigational drug after the expiration date. If the retrieval is after the expiration date, the investigational drug manager of the medical institution will separately store the expired investigational drug from the non-expired investigational drug.

10. TREATMENT OF SUBJECTS

1) The investigator or subinvestigator will assign a Subject Identification Code to each of the individuals who have provided the informed consent.
2) The investigator or subinvestigator will assess the eligibility of subjects against the inclusion and exclusion criteria before enrollment.
3) Individual subjects are enrolled according to the procedures in Figure 5 (page 44). For enrollment of subjects meeting the eligibility, the investigator, subinvestigator or clinical research coordinator will facsimile the “Subject Enrollment Form” to the sponsor. The sponsor will confirm the eligibility of each subject based on the “Subject Enrollment Form” and facsimile the “Enrollment Confirmation Form” to the investigator or subinvestigator to notify the result of enrollment assessment and Subject Number for the subject.
4) Hospitalization (Phase 1 part only)
   The investigator or subinvestigator will admit the subject to the study site for pharmacokinetic sampling (i.e., Days 1 to 4, 23 and 24 of Cycle 1), if necessary from the day before pharmacokinetic sampling.
5) Confirmation of eligibility just before BBI608 administration

Just before the start of BBI608 administration, the investigator and subinvestigator will confirm the following:

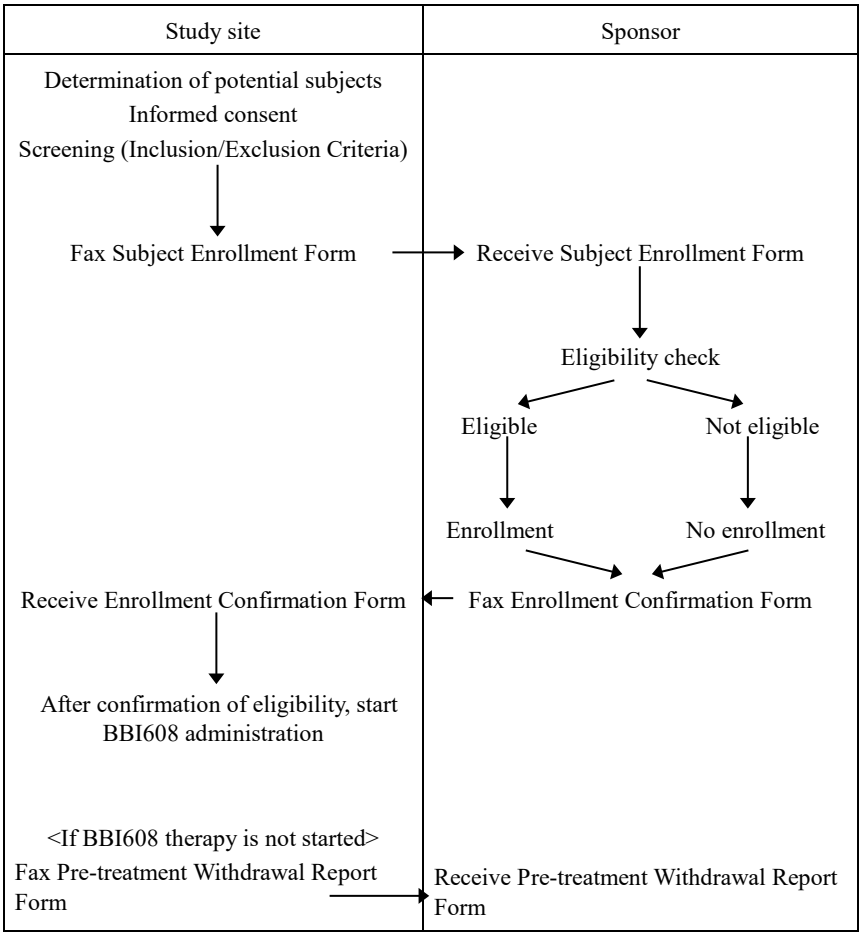
- Completion of baseline examination specified in the study schedule (Table 2 on page 10 orTable 5 on page 16)
- No presence of any new test findings obtained after the last eligibility assessment that would require exclusion of the subject according to the inclusion or exclusion criteria.

6) Any discontinuation before the start of BBI608 administration

If the subject is discontinued from the study between enrollment and the start of BBI608 administration, the investigator, subinvestigator or clinical research coordinator will facsimile the “Pre-treatment Withdrawal Report Form” to the sponsor to notify the withdrawal. The sponsor will take the withdrawal procedure.

Where to contact for Subject Enrollment:
Group 2, Oncology Clinical Development Office
Sumitomo Dainippon Pharma Co., Ltd.
Address: 1-17-10 Kyobashi, Chuo-ku, Tokyo 104-0031
Office hours: 9:00–18:00, Monday through Friday (Closed on Saturdays, Sundays, national holidays, and from December 29 to January 4)
Fax: 03-5159-2946
Tel: 03-5159-2518

Figure 5 Subject Enrollment Procedures



10.1 Study Medication

(1) BBI608

BBI608 will be orally administered 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 administered. Subjects should be advised to drink an adequate amount of fluid when taking BBI608.

(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). Meanwhile, Pem will be administered with an interval of at least 4 hours after BBI608 dosing in Cycle 1 of phase 1 part only. Premeditation with folic acid and vitamin B12 should be given as described below to reduce occurrence of serious adverse drug reactions, with reference to the package insert for Pem.

1) Folic acid

Folic acid (as a marketed product) will be orally administered at 0.5 mg once daily, starting ≥ 7 days before the initial dose of Pem. When Pem therapy is discontinued or completed, folic acid administration will be continued until 22 days after the last dose of Pem as far as possible.

2) Vitamin B12

A dose of vitamin B12 (as a marketed product) 1 mg will be intramuscularly administered ≥ 7 days before the initial dose of Pem. Vitamin B12 dosing will then be repeated every 9 weeks during Pem therapy and until 22 days after the last dose of 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.

10.2 Criteria for Protocol Treatment Modification

When discontinuation of Pem or CDDP is required by an adverse event etc. in the opinion of the investigator or subinvestigator, both Pem and CDDP should be discontinued, while only BBI608 will be continued. When discontinuation of BBI608 is required, the subject will be withdrawn from the study. For NSCLC patients in Phase 1 part, however, only CDDP may be discontinued at the discretion of the investigator or subinvestigator.[23)]

(1) BBI608

Possible adverse events associated with BBI608 include gastrointestinal disorders (nausea, diarrhoea, abdominal colic) and fatigue on the basis of previous clinical studies. If any adverse event occur and treatment suspension or dose reduction is judged required, the following <Method of treatment suspension and dose reduction (Recommendations)> shall be referred.

<Method of treatment suspension and dose reduction (Recommendations)>

Table 7 (page 46) shows BBI608 dosage modifications, and Table 8 (page 47) summarizes recommended interventions for management of adverse events.

Adverse events will be graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, Japanese translation by Japanese Clinical Oncology Group (NCI CTCAE v4.0-JCOG). For a subject experiencing multiple adverse events for which recommended measures differ, the lowest recommended dose should be selected.

BBI608 therapy should be suspended if a subject experiences an intolerable grade 2, or grade 3/4 adverse event. Once the adverse event improves to a tolerable level (grade ≤2 or baseline or better), BBI608 therapy will be resumed at the previous dose level or the dose reduced by at least one level, and a supportive therapy will be performed, according to the patient's condition. However, if ≥ 5 days are required for improvement to a tolerable level (grade ≤ 2 or baseline or better) or if the adverse event recurs immediately after resumption of BBI608 therapy despite use of supportive therapy, the dosage level should be reduced by at least one level.

<Method of dose increase after dose reduction>

After dose reduction, the dose may be reincreased up to 480 mg as tolerated at the discretion of the investigator or subinvestigator.

<Acceptable duration of treatment suspension>

Treatment may be suspended as long as the percentage of treated days is ≥ 50%. The denominator for calculation of the percentage of treated days will be "23 days" immediately following the first dose of BBI608, and subsequently "21 days" irrespective of administration of Pem and CDDP. For example, the acceptable duration of treatment suspension is up to 11 days during the first 23 days, and then up to 10 days during every 21 days. When the percentage of treated days has become or is anticipated to become < 50%, the protocol treatment in the subject will be discontinued. Days of missing doses are regarded as untreated days.

Table 7 BBI608 Dosage Modification Table

Dose level	Dosage
Original Dosage Level	480 mg twice daily (at intervals of 12 hours)
Modified Dosage Level 1	240 mg twice daily (at intervals of 12 hours), and gradually increased as tolerated.
Modified Dosage Level 2	80 mg twice daily (at intervals of 12 hours), and gradually increased as tolerated.
Modified Dosage Level 3	80 mg once daily, and gradually increased as tolerated.

Table 8 Recommended Supportive Therapies for Common Adverse Events with BBI608 (unless contraindicated)

Toxicity / Adverse events	Supportive treatment
Diarrhea, Abdominal colic	• Loperamide (e.g., Lopemin®) • Atropine • Butylscopolamine (Buscopan®) or hyoscyamine • Codeine phosphate
Nausea, Vomiting	• First line: Ondansetron (Zofran®) or palonosetron (Aloxi®) • Second line: Add dexamethasone (Decadron®) • Other drugs: Dimenhydrinate (Dramamine®), prochlorperazine (Novamin®), metoclopramide (Primperan®), lorazepam (Wypax®)
Fatigue	Possible supportive treatment required for concurrent gastrointestinal adverse events

(2) Pemetrexed (Pem) and cisplatin (CDDP)

1) Criteria for starting administration

On the day or the day before administration of Pem and CDDP in each cycle, the subject must be confirmed to meet the criteria in Table 9 (page 47) to receive Pem and CDDP. If the subject does not meet the criteria in Table 9 (P.47) at the start of a cycle, or the administration cannot be started due to holiday etc., the cycle will be delayed. If the administration of Pem and CDDP cannot be started within 21 days from the day after the end of the last cycle, Pem and CDDP will be withdrawn.

Table 9 Criteria for Starting Pem and CDDP Administration

Parameter	Criteria
ECOG PS	0 or 1
Neutrophil count	≥ 1500/μL
Platelet count	≥ 100,000/μL
AST and ALT	≤ 2.5-fold ULN, or ≤ 5-fold ULN for patients with any liver metastasis
Creatinine clearance (estimated value) [a)]	≥ 45 mL/min, or ≥ 60 mL/min for Cycle 1
Non-hematotoxicity	Grade ≤ 2 (or Grade ≤ 1 for peripheral nerve disorder)
Use of multivitamin product	Multivitamin 1 g administered once daily for ≥ 14 days during the 21 days preceding the next cycle administration of Pem

a) Estimated using the Cockcroft-Gault formula

2) Criteria for treatment discontinuation, suspension and dose reduction

In the following instances, administration of Pem and CDDP will be discontinued, suspended, or reduced in doses. If an adverse event is judged to require dose reduction, reduction of Pem and CDDP should be first considered, but BBI608 may be reduced as required by the adverse event. Pem and CDDP doses should not be re-increased after dose reduction.

- When an adverse event in Table 10 (page 48) to Table 13 (page 49) occurred in the previous or current cycle:

  Reduce the dose in the next cycle according to the dose reduction criteria in Table 10 (page 48) to Table 13 (page 49).
- When dose reduction of Pem and CDDP is required for the third time:

  Discontinue Pem and CDDP.
- When grade 3 or 4 hematotoxicity or non-hematotoxicity occurred after second dose reduction of Pem and CDDP:

  Discontinue Pem and CDDP.
- If grade ≥ 3 non-hematotoxicity occurred:

  Withhold Pem and CDDP until return to baseline or better. At resumption, the dose will be decided according to the criteria in Table 11 (page 49).
- When grade 3 or 4 neurotoxicity occurred:

  Discontinue Pem and CDDP.
- When creatinine clearance (estimated value) decreased to < 45 mL/min:

  Discontinue Pem and CDDP.

Table 10 Pem and CDDP Dose Modification for Hematotoxicity

Criteria	Pem and CDDP doses (mg/m^2)
Nadir neutrophil count <500/μL and Nadir platelet count ≥50,000/μL	75% of the previous dose
Nadir platelet count <50,000/μL, irrespective of nadir neutrophil count	75% of the previous dose
Nadir platelet count <50,000/μL with hemorrhage, irrespective of nadir neutrophil count	50% of the previous dose

Table 11 Pem and CDDP Dose Modification for Non-hematotoxicity (Other Than Neurotoxicity)

Criteria	Pem (mg/m^2)	CDDP (mg/m^2)
Grade 3 or 4 toxicity other than mucositis	75% of the previous dose	75% of the previous dose
Diarrhoea of any grade requiring hospitalization, or grade 3 or 4 diarrhoea	75% of the previous dose	75% of the previous dose
Grade 3 or 4 mucositis	50% of the previous dose	100% of the previous dose

Grade according to CTCAE v4.0-JCOG.

Table 32 Pem and CDDP Dose Modification for Neurotoxicity

Grade	Pem (mg/m^2)	CDDP (mg/m^2)
0-1	100% of the previous dose	100% of the previous dose
2	100% of the previous dose	50% of the previous dose

Grade according to CTCAE v4.0-JCOG.

Table 43 Pem and CDDP Dose Modification for Renal Impairment

CCr (mL/min)	Pem (mg/m^2)	CDDP (mg/m^2)
≥ 45, < 60	100% of the previous dose	75% of the previous dose

10.3 Treatment Compliance

The investigator or subinvestigator will check the drug compliance status at each visit of the subject, and collect the unused investigational drug from the subject after discontinuation of study drug administration. During the study treatment period, the following compliance data will be recorded in the eCRF.

1) BBI608

   Dates of first and last dosing, dates of starting and completing instruction for instructed dose, dates of first and last dosing with the instructed dose by subject, the number of capsules taken, and reason for change if the instructed dose is changed

2) Pem

   Dates of administration and dose (mg/m^2)

3) CDDP

   Dates of administration and dose (mg/m^2)

10.4 Treatment Period, Follow-Up Observation Period, Patient Outcome Investigation and Subsequent Treatment

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. DLT will be assessed following the start of BBI608 administration on Day 1 of Cycle 1 and until Day 24 pre-dose examination in Phase 1 part.

Protocol treatment will be continued in the following manner:

- Only in Phase 1 part, voluntary written re-consent to continue treatment should be obtained from the subject between Day 17 of Cycle 1 and the start of Cycle 2.
- Protocol treatment with the three drugs should be repeated as long as possible; no restriction is set on the number of cycles.
- If an adverse event associated with either Pem or CDDP is judged to require treatment discontinuation, both Pem and CDDP should be discontinued, while BBI608 will be continued as long as possible. For NSCLC patients, however, only CDDP may be discontinued at the discretion of the investigator or subinvestigator.[23)]
- Even after assessment of PD according to the RECIST 1.1 or mRECIST, administration of BBI608 may be continued until the treatment is no longer clinically beneficial to the patient in the opinion of the investigator or subinvestigator for certain reasons such as intolerable adverse events or further progression of the primary disease.

2) 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.

3) Patient outcome investigation

Patient outcome investigation will be continued until 6 months and 1 year after last subject's treatment start date.

4) Subsequent treatment

No restriction is set on subsequent treatment.

10.5 Definition of DLT and Enrollment of Additional Subjects (Phase 1 Part)

DLT will be assessed in Phase 1 part and not in Phase 2 part.

10.5.1 Definition of DLT

DLT is defined as an adverse event meeting any of the following that occurred during the DLT evaluation period in any subjects given BBI608 with the causal relationship to BBI608 assessed as "Definite," "Probable," or "Possible." The severity of adverse events will be graded according to the CTCAE v4.0-JCOG. The investigator and the sponsor will discuss to determine any DLT in individual subjects. As necessary, the sponsor will seek opinion of the Data and Safety Monitoring

Board to determine DLT.

- Grade 4 neutropenia persisting for ≥ 7 days
- Grade ≥ 3 febrile neutropenia persisting for ≥ 5 days
- Grade 3 thrombocytopenia requiring platelet transfusions, grade 4 thrombocytopenia
- Grade ≥ 3 non-hematotoxicity except the following:
  a) Inappetence, nausea, vomiting and electrolyte abnormality which, within 3 days of onset, improved to grade ≤ 2 or resolved after appropriate treatment
  b) Diarrhoea and fatigue which, within 5 days of onset, improved to grade ≤ 2 or resolved after appropriate treatment
- Other clinically significant signs in the opinion of the investigator

10.5.2 DLT Evaluation Period and Subjects Evaluated for DLT

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 evaluation will be performed in subjects given BBI608 who meet 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/(Protocol-specified dose* × 45)] × 100 (%)

  *Protocol-specified dose = 480 mg
- Subjects with onset of DLT irrespective of the BBI608 treatment compliance rate

10.5.3 Enrollment of Additional Subjects

Criteria for enrollment of additional subjects are as follows (see Figure 1, page 33).

- If any of the first 3 patients started on study treatment are not assessable for DLT, the patient(s) will be replaced by new patient(s).
- If DLT occurs in 0/3 patients, no additional patients are enrolled.
- If DLT occurs in 1/3 patients, 3 additional patients are enrolled.
- If DLT occurs in ≥ 2/3 patients, the enrollment is stopped.
- If DLT occurs in ≥ 2/3 or ≥ 2/6 patients, the sponsor will discuss with the investigator to decide whether or not to continue already ongoing treatment in subjects currently in the study. As necessary, the sponsor will seek opinion of the Data and Safety Monitoring Board.
- If the sponsor judges that more than 3 patients are required for assessment of the pharmacokinetics or safety, additional patients may be enrolled up to a total of 6, as necessary based on discussion with a coordinating investigator etc.

10.6 Concomitant Medications and Therapies

For the period from the start of study treatment to final evaluation in the follow-up observation

period, details of any concomitant medications (i.e., name of drug, route of administration, therapy dates, reason for use) and concomitant therapies (i.e., name of therapy, therapy dates, reason for use) will be recorded in the eCRF. For the following drugs, however, no recording in the eCRF is required (unless they caused adverse events).

- Drugs used for examinations (e.g., contrast agents, premedication, post-examination medication)
- Local anaesthesia (e.g., for tooth extraction)
- Preparations used for dilution (e.g., physiological saline)
- Fluid preparations used for other purposes than treating adverse events (e.g., heparin lock to prevent blood coagulation)

10.6.1 Prohibited Concomitant Medications and Prohibited Concomitant Therapies

From the date of enrollment until the date of last dosing, the following treatments will be prohibited.

1) Anticancer chemotherapy (other than Pem and CDDP as the components of protocol treatment), radiotherapy, hormonal therapy, immunotherapy, thermotherapy, surgical therapy, or other therapies for cancer
2) Other investigational drugs, post-marketing clinical study drugs, or drugs unapproved in Japan
3) Therapies with immunosuppressive effects (e.g., systemic steroids), with the exception of the following:
   - Intermittent use for antiemesis
   - Use at a less-than-immunosuppressive dose for malaise or appetite loss
   - Prophylactic use after onset of rash
4) Until the end of the DLT evaluation period in Phase 1 part, prophylactic use of granulocyte colony stimulating factor (G-CSF) products

10.6.2 Restricted Concomitant Medications

Drugs listed in “1)” to “3)” below should be in principle avoided from the date of initial dosing of BBI608 until the date of last dosing of BBI608, unless clinically required in the opinion of the investigator or subinvestigator. Drugs listed in “4)” below should be avoided from 2 or 5 days before Pem administration until 2 days after Pem administration. The investigator or subinvestigator will also instruct subjects to avoid consumption of products containing the following that could affect the metabolism of BBI608 by inhibiting or inducing CYP1A2: tobacco, herbs (e.g., St. John’s wort, Ginkgo), caffeine-rich beverages and food, burnt meat, Brussels sprouts.

1) Substrates of CYP1A2, 2D6, 2C19, 3A4, or 2C9, including but not limited to the following:
   - Non-steroidal anti-inflammatory drugs: ibuprofen, diclofenac, celecoxib, etc.
   - Proton-pump inhibitors: lansoprazole, omeprazole, etc.
   - Oral hypoglycemic agents: sulfonylureas, etc.
   - β-blockers: propranolol, metoprolol, etc.
   - Calcium antagonists: amlodipine, diltiazem, nifedipine, verapamil, felodipine, nisoldipine, etc.
   - Antidepressants: paroxetine, imipramine, amitriptyline, duloxetine, etc.
   - Antiepileptics: phenytoin, etc.
   - Antipsychotics: haloperidol, risperidone, quetiapine, perphenazine, pimozide, etc.
   - Antibiotics: clarithromycin, erythromycin, etc.
   - HMG CoA reductase inhibitors: atorvastatin, simvastatin, etc.
   - Anesthetics: fentanyl etc.
   - Anti-HIV drugs: saquinavir, indinavir, ritonavir, darunavir, etc.
   - Steroids: hydrocortisone, estradiol, budesonide, fluticasone, etc.
   - Antiemetics and antidiarrheals: aprepitant, etc.
2) CYP1A2 inhibitors, including but not limited to the following:
   Ciprofloxacin and other fluoroquinolone antimicrobials, fluvoxamine, verapamil, amiodarone, mexiletine, interferon, methoxsalen, ticlopidine, progestogen and estrogen drugs (oral contraceptives), acyclovir, allopurinol, cimetidine, disulfiram, famotidine, norfloxacin, propafenone, propranolol, terbinafine, etc.
3) CYP1A2 inducers, including but not limited to the following
   Montelukast, phenytoin, omeprazole, phenobarbital, etc.
4) Non-steroidal anti-inflammatory drugs (NSAIDs)
   In patients with mild to moderate renal impairment (defined as creatinine clearance 45–89 mL/min), NSAIDs with short half-life should be avoided for 5 days from 2 days before Pem administration until 2 days after Pem administration.
   In all subjects irrespective of renal impairment, NSAIDs with long half-life should be avoided for 8 days from 5 days before Pem administration until 2 days after Pem administration.
   - NSAIDs with short half-life include, but not limited to, ibuprofen and aspirin.
   - NSAIDs with long half-life include, but not limited to, nabumetone, naproxen, and piroxicam.

10.6.3 Permitted Concomitant Medications

Drugs and therapies not listed in Section 10.6.1 (page 52) or Section 10.6.2 (page 52) are permitted for concomitant use.

<Examples of permitted concomitant drugs and therapies>

- Symptomatic therapy and supportive therapy to relieve a symptom of the primary disease
- Treatment of a concurrent disease
- Treatment of an adverse event
- Premedication before administration of Pem and CDDP to reduce occurrence of serious adverse drug reactions
- G-CSF to treat neutropenia (in patients with febrile neutropenia or grade 4 neutropenia, or in patients with grade 3 neutropenia who had febrile neutropenia or grade 4 neutropenia in the previous cycle)

10.7 Restrictions

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

10.8 Contraception Requirements

Female subjects of childbearing potential and male subjects with female partners must avoid pregnancy by sexual abstinence or use of appropriate contraception from the time of consent until 30 days after the last dose of the study drug. Appropriate contraceptive measures available in Japan include condoms, oral contraceptive pills, pessaries, intrauterine devices and systems, vasectomy, and tubal ligation.

10.9 Treatment Assignment and Blinding

No randomization will occur in this open-label study. Both Phase 1 and Phase 2 parts will use the same starting doses.

11. STUDY ASSESSMENTS

The flowchart of study procedures in individual subjects in Phase 1 and Phase 2 parts is shown in Figure 2 (page 33) and Figure 4 (page 35), respectively. The schedule of investigations, observations and examinations in Phase 1 and Phase 2 parts is shown in Table 2 (page 10) and Table 5 (page 16), respectively. Investigations, observations and examinations and assessments will be performed at the scheduled time points, which are based on Day 1 of treatment in the subject as defined below.

In Cycle 1, Day 1 will be the first day of BBI608 administration. In Cycle 2 and later cycles, Day 1 will be the day of administration of Pem and CDDP (or the day of administration of Pem after discontinuation of CDDP in NSCLC patients in Phase 1 part).

Obtained clinical findings and results of observations and examinations and assessments will be recorded in source documents. For the items specified below, the dates of measurements and results after baseline examination will be recorded in the eCRF.

11.1 Demographic and Baseline Characteristics

Before the start of study treatment, the following data will be collected and recorded in the eCRF.

11.1.1 Phase 1 Part

1) Demographic data
   - Sex, date of birth, race, ethnicity
   - Height, body weight
2) Disease data
   - ECOG PS
   - Clinical Stage (Stage I, II, IIIA, IIIB, IV)
   - Diagnosis (MPM, NSCLC)
   - Histological type

     MPM: Epithelioid, sarcomatoid, biphasic, other (specify)

     NSCLC: Adenocarcinoma, squamous cell carcinoma, large cell carcinoma, other (specify)
   - Sites of metastases
   - Concurrent disease, symptoms associated with the primary disease
   - Date of diagnosis of the primary disease
3) Other
   - Subject Identification Code, Subject Number

For female subjects, the investigator or subinvestigator should confirm the status of menopause[Note)] and pregnancy before enrollment. Women before menopause will undergo pregnancy testing (urine) within 3 days before the start of study treatment.

Note) Menopause is defined as no occurrence of menstruation for 12 months or more without any medical reason (e.g., chemical menopause).

11.1.2 Phase 2 Part

1) Demographic data
   - Sex, date of birth, race, ethnicity
   - Height, body weight
2) Disease data

- ECOG PS
- Clinical stage (Stage I, II, IIIA, IIIB, IV)
- Histological type (epithelioid, sarcomatoid, biphasic, other [specify])
- Sites of metastases
- Concurrent diseases, symptoms associated with the primary disease
- Date of diagnosis of the primary disease

3) Other
- Subject Identification Code , Subject Number

For female subjects, the investigator or subinvestigator should confirm the status of menopause[Note)] and pregnancy before enrollment. Women before menopause will undergo pregnancy testing (urine) within 3 days before the start of study treatment.

Note) Menopause is defined as no occurrence of menstruation for 12 months or more without any medical reason (e.g., chemical menopause).

11.2 Efficacy Assessments

11.2.1 Tumor Response

11.2.1.1 Imaging Data Items

For imaging, the investigator or subinvestigator will collect the following data and record them in the eCRF. If tumor enlargement is clinically suspected, radiological examination such as CT or MRI should be performed for confirmation.

- Presence or absence of target lesions, organs of all selected target lesions, specific sites of lesions, size of lesions, imaging modality (CT, MRI, other), date of imaging
- Presence or absence of non-target lesions, organs of all non-target lesions, imaging modality (CT, MRI, other), date of imaging
- Presence or absence of new lesions, organ
- Assessment of overall response, date of imaging used for the assessment
- Best overall response

11.2.1.2 Imaging Assessments

11.2.1.2.1 Tumor Lesion Measurements

Imaging (CT, MRI or other) of tumor lesions will be obtained before the first dose of BBI608 (within 14 days before enrollment), every 6 weeks (±1 week) from the first dose of BBI608 (Day 1 of Cycle 1) until Week 30, and every 9 weeks (±1 week) from Week 31 on. The schedule of imaging is based only on Day 1 of Cycle 1, irrespective of Day 1 of Cycle 2 or any later cycle. The imaging modality used at baseline should be used throughout the study. For CT, the slice thickness must be ≤ 5 mm. Tumor measurements and evaluations will be performed according to the RECIST

1.1 for NSCLC or other carcinomas than MPM, and mRECIST for MPM.

11.2.1.2.2 Tumor Response and Overall Response

The study site and the imaging assessment committee (only the study site in Phase 1 part) will evaluate the tumor response and overall response based on imaging. In Phase 2 part, the results by the imaging assessment committee will be used as the results of final imaging assessment.

(1) RECIST1.1

The RECIST 1.1 will be used for the evaluation of tumor response and overall response in patients with NSCLC, and also the evaluation of any non-pleural lesions in patients with MPM. Baseline imaging will be obtained before the first dose of BBI608 (within 14 days before enrollment).

1) Selection and evaluation of target lesions
   For target lesions, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified. Target lesions should be selected on the basis of their size at baseline, and lend themselves to reproducible repeated measurements.
2) Evaluation of non-target lesions
   All other lesions than those selected as target lesions are non-target lesions, whether or not measurable.
3) Determination and recording of response
   For each imaging, the results of evaluation of target lesions (CR, PR, SD, PD, NE), evaluation of non-target lesions (CR, Non-CR/Non-PD, PD, NE), presence or absence of new lesions (if yes, specific site of the lesion), and overall response are recorded along with the date of imaging in the eCRF. At final assessment, best overall response (CR, PR, SD, PD, NE) will also be recorded in the eCRF. For a subject with no measurable lesions at baseline and with an overall response of "Non-CR/Non-PD," the overall response should be converted to "SD" in the assessment of best overall response. For determination of SD in terms of best overall response, the subject must fulfil the criteria for SD at least once based on Week 6 imaging or later imaging.

(2) mRECIST for MPM

The mRECIST will be used for the evaluation of tumor response and overall response in patients with MPM.[24] Baseline imaging will be obtained before the first dose of BBI608 (within 14 days before enrollment).

1) Selection and evaluation of target lesions

For target lesions, all lesions up to a maximum of 10 lesions total representative of all involved organs should be identified. Target lesions should be selected on the basis of their size, and lend themselves to reproducible repeated measurements. Of these, up to 6 lesions will be selected based on baseline evaluation as far as possible. For pleura lesions, the cross-sectional longest tumor thickness perpendicular to the chest wall or mediastinum will be measured.

2) Evaluation of non-target lesions

   All other lesions than those selected as target lesions are non-target lesions, whether or not measurable.

3) Determination and recording of response

   For each imaging, the results of evaluation of target lesions (CR, PR, SD, PD, NE), evaluation of non-target lesions (CR, Non-CR/Non-PD, PD, NE), presence or absence of new lesions (if yes, specific site of the lesion), and overall response are recorded along with the date of examination in the eCRF. At final assessment, best overall response (CR, PR, SD, PD, NE) will also be recorded in the eCRF. For a subject with no measurable lesions at baseline and with an overall response of "Non-CR/Non-PD," the overall response should be converted to "SD" in the assessment of best overall response. For determination of SD in terms of best overall response, the subject must fulfil the criteria for SD at least once based on Week 6 imaging or later imaging.

11.2.1.2.3 Submission of Imaging Data

Only in Phase 2 part, the investigator or subinvestigator will submit a copy of the imaging data used for evaluations in Section 11.2.1.2 (page 56). The study site shall put masking on information which may identify subjects, such as allocating subject ID codes, when providing the copies of imaging data.

11.2.1.2.4 Imaging Assessment Committee

In Phase 2 part, the imaging assessment committee will evaluate the tumor response and overall response in accordance with separately prepared written procedures, on the basis of the submitted imaging data.

11.2.2 Patient Outcome

Patient outcome (alive, dead, unknown), cause of death if dead (progression of the primary disease, other) and date of death, date of confirmation of patient outcome, any subsequent treatment and its details (chemotherapy [drug names], surgical therapy, radiotherapy, other) and therapy start date and end date will be investigated until 6 months and 1 year after last subject's treatment start date, and recorded in the eCRF. However, the patient outcome investigation may be continued beyond 1

year if judged necessary by the sponsor.

11.2.3 Respiratory Function Tests

VC, FVC, FEV1, and dates of testing

11.3 Safety Assessments

11.3.1 Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (e.g., "Has there been any change in your health status since your last visit?") (See Section 12, page 62).

Adverse events and serious adverse events will be monitored throughout the study at all visits (including telephone interviews).

11.3.2 DLT (Phase 1 Part)

DLT will be assessed as described in Section 10.5 (page 50).

11.3.3 Clinical Laboratory Tests

Clinical laboratory tests listed below will be performed in this study. Blood and urine specimens for laboratory tests will be collected and the dates will be recorded. All laboratory tests will be performed locally by the laboratory of the study site. For specific procedures for laboratory tests and sampling and shipping, written instructions by the laboratory of the study site should be observed.

- Hematology: white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Biochemistry: total protein, albumin, total bilirubin, AST, ALT, ALP, LDH, BUN, creatinine, Na, K, Cl, Ca, Mg
- Urinalysis (qualitative): glucose, protein, occult blood

11.3.4 Vital Signs and Body Weight

Blood pressure, pulse rate, body temperature (axillary), and body weight will be recorded with the dates of measurements.

11.3.5 Chest X-ray

X-ray results (assessment[Note)] and abnormal findings if any) will be recorded with the dates of X-rays.

Note) Assessment: Normal, Abnormal (not clinically significant), Abnormal (clinically significant)

11.3.6 12-lead ECG

ECG results (assessment[Note)] and abnormal findings if any) will be recorded with the dates of ECG.

Note) Assessment: Normal, Abnormal (not clinically significant), Abnormal (clinically significant)

11.3.7 ECOG PS

The ECOG PS score will be recorded.

11.4 Pharmacokinetic Assessments (Phase 1 Part)

11.4.1 Plasma Drug Concentrations

1) Analytes
   - Plasma BBI608 concentration
   - Plasma Pem concentration
   - Plasma CDDP concentration
2) Time points of the measurement of plasma BBI608 concentration
   - Days 1 and 2 of Cycle 1 (8 time points)

     Before the morning dose of BBI608, and at 2, 4, 6, 8, 10, 12, and 24 hours (i.e., pre-morning dose on Day 2)
   - Day 3 of Cycle 1 (3 time points)

     Before the morning dose of BBI608, immediately before Pem administration, before the evening dose of BBI608
   - Days 23 and 24 of Cycle 1 (8 time points)

     Before the morning dose of BBI608, and at 2, 4, 6, 8, 10, and 12 (i.e., pre-BBI608 evening dose), and 24 (pre-BBI608 morning dose on Day 24) hours
3) Time points of the measurement of plasma Pem concentration
   - Day 3 of Cycle 1 (3 time points)

     Immediately before Pem administration, immediately after Pem administration, before the evening dose of BBI608 on Day 3
4) Time points of the measurement of plasma CDDP concentration
   - Days 3 and 4 of Cycle 1 (3 time points)

     Immediately before or immediately after Pem administration or immediately before CDDP administration, immediately after CDDP administration, and before the morning dose of BBI608 on Day 4
5) Blood sampling volume and method

   A total of 75 mL of blood will be collected from each subject (using an anticoagulant EDTA-2K). Specifically, plasma BBI608 concentration measurements will require 3 mL

each of blood at 19 time points. Plasma Pem concentration measurements will require 3 mL each of blood at 3 time points. Plasma CDDP concentration measurements will require 3 mL each of blood at 3 time points.

6) Blood specimen processing

The collected blood specimens will be processed according to the written procedures prepared separately.

7) Documentation of blood sampling, meals, BBI608/Pem/CDDP administration, and anti-nephrotoxic fluid infusion, and results of drug concentration measurements

The investigator or subinvestigator will record the following information in the eCRF according to Table 4 (page 14).

- Date and time of blood sampling
- Date and time of meals
- Date and time of BBI608 administration, number of capsules taken
- Date and the start time and end time of each dosing of Pem and CDDP
- Date and the start time and end time of each fluid infusion for Pem/CDDP nephrotoxicity prophylaxis

The laboratory responsible for pharmacokinetic measurements will retrieve the specimens for drug concentration measurements, measure the plasma drug concentrations, and prepare the measurement result reports.

11.4.2 Exploratory Analysis of Metabolites in Plasma

When necessary, the sponsor may analyze metabolites in plasma in an exploratory manner using residual specimens. If any exploratory plasma metabolite analysis is performed, the results will not be contained in the clinical study report but a separate report will be prepared.

11.5 Biomarkers

1) Target patient population

Patients with a histological diagnosis of MPM (in Phase 2 part only)

2) Biomarkers to be measured

- β-catenin
- Phospho-STAT3 (p-STAT3)
- Merlin

3) Methods of specimen collection and measurements

From the available tumor tissue collected for the diagnostic purpose, 6 or more histology slides will be prepared and sent to the sponsor. The retrieval and staining of tumor tissue specimens will be performed according to the written procedures prepared separately by the

laboratory responsible for biomarker measurements.

4) Timing and method of specimen submission

   The samples and copies of pathology reports will be sent to the sponsor on or after the date of enrollment of the patient as appropriate, after patient-identifiable information is removed and replaced by the Subject Identification Code etc. at the study site.

5) De-identification of patients

   A unique Subject Identification Code will be assigned to each subject at the study site, which meets the standards for secure privacy protection in this clinical study. No further de-identification measures are taken.

6) Histopathological assessment

   A pathological assessment committee will be formed to perform the histopathological assessment. The histopathological assessment will be performed in accordance with separately prepared written procedures.

7) Reporting of the histopathological assessment results

   The sponsor will notify the investigator or subinvestigator of the histopathological assessment results by the pathological assessment committee.

8) Documentation in the eCRF

   The investigator or subinvestigator will record the date of tumor tissue collection in the eCRF.

9) Specimen disposal

   The sponsor will be responsible for destroying the submitted de-identified histology slides within 10 years after the end of this clinical study, while the slides remaining de-identified. For subjects who have withdrawn their consent to slide provision, the slides will be immediately destroyed.

12. SAFETY REPORTING

12.1 Definitions

12.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a study subject administered an investigational drug and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of an investigational drug, whether or not considered related to the investigational drug. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

In this study, adverse events refer to those occurring between initial dosing of the investigational drug and final evaluation in the follow-up observation period, as well as other unfavorable events

during the study period (e.g., events outside the treatment period [during the follow-up observation period etc.], events related to a study procedure or assessment).

Lack of efficacy may be an expected potential outcome and should not be reported as an adverse event unless the event is unusual in some way. Worsening of the primary disease or a metastasis of the primary disease should not be reported as an adverse event.

The investigator or subinvestigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event, and not the individual signs/symptoms.

12.1.2 Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening (i.e., a patient is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term “serious” is used for events that pose a threat to a subject’s life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure that was scheduled before the informed consent to this study because of a pre-existing condition since before participation in the study, the hospitalization is considered a therapeutic intervention and not the result of a serious adverse event. However, if the pre-existing condition worsens during the study, it should be reported as an adverse event (or serious adverse event if the condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. This definition does not include an event that

had it occurred in a more severe form might have caused death.

12.1.3 Adverse Drug Reactions

Adverse drug reactions are defined as adverse events assessed to be related to the investigational drug.

12.2 Abnormal Findings

Clinically significant abnormal findings (e.g., results of laboratory tests, ECG, chest X-ray and physical examination) will also be recorded as adverse events.

When a clear diagnosis is available that explains the findings, the diagnosis will be recorded as the adverse event, and not the abnormal findings (e.g., viral hepatitis will be recorded as the adverse event, not transaminase elevation). If a definite diagnosis is not available, then record the sign (e.g., clinically significant transaminase elevation) or symptom (e.g., abdominal pain).

The investigator or subinvestigator will review laboratory test results, and determine the clinical significance of all out-of-range values. Clinical laboratory tests with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the investigator or subinvestigator. Laboratory reports will be signed (or sealed) and dated on all pages by the investigator or subinvestigator.

The investigator or subinvestigator will review ECG results obtained at the study site, and determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the investigator or subinvestigator. ECG tracings will be signed (or sealed) and dated on all pages by the investigator or subinvestigator.

12.3 Collection and Recording of Adverse Events

All adverse events must be collected and recorded in the subject's study records/source documents, in accordance with the normal clinical practice of the investigator or subinvestigator, and those occurring between initial dosing of the investigational drug and final evaluation in the follow-up observation period recorded in the eCRF.

Each adverse event is to be recorded in the eCRF with the following information: event term (using the terminology of the CTCAE v4.0-JCOG), duration, severity, seriousness, action taken with the investigational drug/Pem/CDDP, event outcome, and causal relationship to the study treatment, as well as DLT (in Phase 1 part only). Definitions are provided below for severity, action taken with the investigational drug/Pem/CDDP, event outcome, and causal relationship to the study treatment,

as well as DLT evaluation.

Severity of an adverse event:

The severity will be graded according to the CTCAE v4.0-JCOG, and the highest grade during the course of the event will be recorded. Events not listed in the CTCAE v4.0-JCOG will be classified as "- Other (Specify)" at the bottom of the relevant category and graded.

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[Note 1)].

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[Note2)].

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Note 1) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Note 2) Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Action taken with the investigational drug due to the adverse event:

- Drug Interrupted: BBI608 stopped temporarily.
- Dose Reduced: BBI608 dose reduced.
- Drug Withdrawn: BBI608 stopped permanently.
- Dose Not Changed
- Not Applicable

Action taken with Pem due to the adverse event:

- Drug Interrupted: Pem stopped temporarily.
- Dose Reduced: Pem dose reduced.
- Drug Withdrawn: Pem stopped permanently.
- Dose Not Changed
- Not Applicable

Action taken with CDDP due to the adverse event:

- Drug Interrupted: CDDP stopped temporarily.
- Dose Reduced: CDDP dose reduced.
- Drug Withdrawn: CDDP stopped permanently.
- Dose Not Changed
- Not Applicable

Outcome of the adverse event:

- Recovered/Resolved
- Recovering/Resolving
- Not Recovered/Not Resolved
- Recovered/Resolved with Sequelae
- Fatal
- Unknown

Causal relationship of the adverse event to the study treatment:

- Not related
  - Not related: The event occurred with improbable temporal relationship and is plausibly related to other drugs or underlying disease.
  - Unlikely: The event occurred within a reasonable time frame after administration/discontinuation of the study drug, but there is a likely association of an intercurrent/underlying medical condition or other drugs.
- Related
  - Possible: The event occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - Probable: The event occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - Definite: The event occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

DLT evaluation:

- DLT
- Non-DLT [For events assessed as “non-DLT” although it is applicable to the “Definition of DLT” [Section 10.5.1, P.50], the basis for the assessment should also be recorded in the eCRF.]

If an adverse event has occurred, the investigator or subinvestigator will conduct follow-up tests and investigations in principle until the event resolves. If the investigator or subinvestigator judges that no further follow-up tests or investigations are allowed or required for certain plausible reasons, for example when the event is likely attributable to the subject's primary or concurrent disease or the subsequent treatment, the follow-up tests and investigations may be terminated after the protocol-defined final evaluation in the follow-up observation period.

The responsible medical monitor is the initial contact person for protocol-related questions or discussion of adverse events. The contact information for the responsible medical monitor as well as other emergency contact information is provided in Table 1 (page 3) of this protocol.

12.4 Immediately Reportable Events

The following medical events must be immediately reported to the sponsor:

- Serious adverse events
- Pregnancy

Emergency contact information can be found in Table 1 (page 3).

12.4.1 Serious Adverse Events

If the investigator or subinvestigator becomes aware of a serious adverse event that occurs in a study subject between initial dosing of the investigational drug and final evaluation in the follow-up observation period, this must be reported immediately to the sponsor. Serious adverse events occurring between initial dosing of the investigational drug and final evaluation in the follow-up observation period must be recorded in the eCRF, and the data recorded should match that on the serious adverse event report form.

Following the end of subject participation in the study, the investigator will spontaneously report serious adverse events to the sponsor if assessed to be related (i.e., definitely, probably, or possibly related) to the investigational drug.

Serious adverse events will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

When the investigator or subinvestigator becomes aware of a serious adverse event, the investigator or subinvestigator will immediately (roughly within 24 hours of becoming aware of the event) notify it to the sponsor directly orally or by telephone, fax or other means. The investigator will then, roughly within 3 days, complete and submit the serious adverse event report form to the

sponsor. As necessary, the sponsor provides the investigators with the blank serious adverse event report form used to report serious adverse events. The report form should include the following information:

- The subject's previous history of any adverse drug reactions, significant personal or familial diathesis, history of the present illness and treatment course, details of the adverse event including the circumstances of onset, specific symptoms, treatment, and course.
- For fatal cases, the date of death, cause of death, relationship between the death and the adverse event, and autopsy findings (if available)

The investigator will also immediately submit a written report on the serious adverse event to the head of the medical institution. In the report, the serious adverse event must be specified whether unexpected (i.e., not listed in the current Investigator's Brochure, or the nature, severity, specificity, or outcome is not consistent with the term or description used in the current Investigator's Brochure) or expected. The investigator will provide additional information regarding the reported serious adverse events, upon request of the sponsor, the head of the medical institution or the Institutional Review Board. Any update to the adverse event term or seriousness must be reported to the sponsor.

In accordance with applicable regulations, the sponsor will notify all study sites and investigators of adverse events determined to require expedited reporting to the regulatory authorities.

12.4.2 Pregnancy

If the investigator or subinvestigator becomes aware of pregnancy of a subject (or female partner of a male subject) between initial dosing of the investigational drug and final evaluation in the follow-up observation period, this must be reported promptly to the sponsor.

If a subject becomes pregnant (or is suspected to be pregnant) during the course of the study, the investigator or subinvestigator will instruct the subject to immediately discontinue taking the study drug. Further, the subject (or female partner of male subject) will be instructed to return promptly after the first notification of pregnancy to the study site and undergo a pregnancy test for confirmation of pregnancy. If positive, the subject will no longer receive any additional study medication. All pregnancies will be followed by the sponsor until resolution (i.e., termination [voluntary or spontaneous] or birth) with written consent to pregnancy evaluation and follow-up.

When the investigator or subinvestigator becomes aware of pregnancy, the investigator or subinvestigator will promptly notify it to the sponsor directly orally or by telephone, fax or other means, and then complete and submit the pregnancy report form to the sponsor. The sponsor

provides the investigators with the blank pregnancy report form in advance.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other adverse events were detected.

12.5 Data and Safety Monitoring Board

The Data and Safety Monitoring Board will review safety data according to the written procedures prepared separately.

13. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

13.1 Criteria for Study Drug Discontinuation

Administration of the study drug must be discontinued for any of the following reasons:

- Subject's request to withdraw the consent to the study
- Pregnancy
- Noncompliance with study treatment
  a) When the percentage of BBI608-treated days has become or is anticipated to become < 50% (during the first 23 days and then during every 21 days)
  b) When, on Day 3 of Cycle 1, the subject does not meet the criteria for starting administration of Pem and CDDP, and therefore cannot be started on Pem or CDDP.

If a subject requests to withdraw from the study, the investigator or subinvestigator will ask the patient's willingness about continued participation in the patient outcome investigation, and document the result in the medical record etc.

The date of discontinuation (or decision of discontinuation) and reason for discontinuation will be recorded in the eCRF.

Administration of the study drug may be discontinued for any of the following reasons. If, in the opinion of the investigator or subinvestigator, the subject may no longer safely participate due to a change in medical status, administration of the study drug must be discontinued.

- Adverse events
- Worsening of the primary disease
- Lost to follow-up
- Protocol deviation
- Other

13.2 Criteria for Subject Withdrawal from Patient Outcome Investigation

Subjects may be withdrawn from patient outcome investigation for any of the following reasons:

- Lost to follow-up
- Subject's request to withdraw the consent to patient outcome investigation
- Other

If a subject requests to withdraw from patient outcome investigation, at any time in the study period, the investigator or subinvestigator must discontinue patient outcome investigation on the subject.

13.3 Clinical Assessments After Protocol Treatment Discontinuation

For all treated subjects prematurely discontinuing protocol treatment, regardless of the reason for discontinuation, every effort should be made to perform tests at discontinuation shown in Table 2 (page 10) or Table 5 (page 16). If protocol treatment is discontinued because of other reason than imaging-documented worsening, imaging and respiratory function tests will be continued according to Table 3 (P.13) even after discontinuation of protocol treatment until worsening is judged by an imaging test. If subsequent treatment is started before the judgment of worsening by an imaging test, imaging and respiratory function tests will be performed before subsequent treatment as far as possible, and no further imaging and respiratory function tests is required after initiation of subsequent treatment.

For subjects discontinuing study visits, the investigator or subinvestigator will make every effort to determine the reason for discontinuing study visits and the clinical course after the last visit (including any onset of adverse events).

For subjects with confirmed willingness about continued participation in the patient outcome investigation, even after discontinuation of protocol treatment at the subject's request, patient outcome investigation will be performed according to Table 2 (page 10) or Table 5 (page 16).

14. STUDY TERMINATION

The sponsor reserves the right to discontinue the study at certain study sites for safety or administrative reasons at any time (e.g., serious or continued violation of or deviation from the Ministerial Ordinance on GCP or relevant regulatory notifications, this protocol, or study contract that affected proper conduct of this study). The sponsor also may suspend or discontinue the study when any new finding regarding the quality, efficacy or safety of the investigational drug becomes available that could significantly affect continuation of the study. If the sponsor suspends or discontinue the study, the sponsor will notify it in writing to the head of the medical institution. The head of the medical institution will then notify it in writing to the investigators and the Institutional

Review Board.

If the investigator decides to suspend or discontinue the study at the study site, the investigator will promptly notify it along with the reasons in writing to the head of the medical institution. The head of the medical institution will then notify it in writing to the Institutional Review Board and the sponsor.

If the study is terminated and/or the study site is closed for whatever reason, all study medications pertaining to the study must be returned to the sponsor. The investigator should promptly notify the subjects about study termination, and provide the subjects with appropriate treatment and take other necessary actions.

15. STATISTICS

Detailed methods of statistical analyses are specified in the statistical analysis plan. The sponsor will finalize the statistical analysis plan before the study database lock. The sponsor will also determine the specific handling of data, such as inclusion/exclusion for analysis sets, before the data lock.

15.1 Sample Size Determination

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.

Rationale for sample size:

Phase 1 part: In line with the 3 + 3 design, the sample size is set at 3 with a maximum of 6 as the number required for determination of the safety of BBI608 combined with Pem plus CDDP.

Phase 2 part: The sample size is set at 20 as the number required and feasible to explore the efficacy of BBI608 combined with Pem plus CDDP in patients with MPM. A sample size of 20 will allow observation (detection) of at least one case of adverse events occurring at an incidence of 10% with a ≥ 80% power. With Pem plus CDDP combination therapy, the 6-month PFS rate can be approximately 30–35% based on a phase 1/2 study of Pem plus CDDP in MPM patients in Japan that reported a median PFS of 4.7 months[6]; thus, this study needs to yield a 6-month PFS rate of ≥ 30% to demonstrate noninferiority of the protocol treatment with add-on BBI608 for the target disease. Given that an overseas study of add-on bevacizumab to Pem plus CDDP reported a 6-month PFS rate of 56%[25], the 6-month PFS rate with

add-on BBI608 to Pem plus CDDP may be assumed to be 60%. If the efficacy is measured by the 6-month PFS rate, with a threshold value of 30% and an expected value of 60%, a sample size of 20 with a two-sided significance level of 10% will yield 87.2% power.

15.2 Analysis Populations

15.2.1 Safety Analysis Population

All subjects who received the investigational drug.

15.2.2 DLT Evaluation Population

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/(Protocol-specified dose* × 45)] × 100 (%)

  *Protocol-specified dose = 480 mg
- Subjects with onset of DLT during the DLT evaluation period

15.2.3 Pharmacokinetics Population

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

15.2.4 Efficacy Analysis Population (Modified Intention-to-Treat Population)

Subjects who received the investigational drug

15.3 Data Analysis

15.3.1 Subject Disposition

The following will be summarized for the entire study and separately for Phase 1 part and Phase 2 part: number of patients enrolled, number of subjects given no dose of the investigational drug, number of treated subjects, number of subjects completing the DLT evaluation period (Phase 1 part only), and number of subjects who discontinued study treatment.

15.3.2 Drug Exposure and Compliance

In the safety and efficacy analysis sets, and separately for Phase 1 part and Phase 2 part, summary statistics will be calculated for the duration of treatment with the investigational drug, total cumulative dose, and treatment compliance rate.

15.3.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not fulfill the inclusion criteria or met any of the exclusion criteria.
- Used any prohibited concomitant medications or therapies.

Individual IPDs will be presented in a data listing. The number and percentage of subjects with IPDs will be summarized by type of deviation.

15.3.4 Demographic and Other Baseline Characteristics

In each analysis set, and separately for Phase 1 part and Phase 2 part, summary statistics will be calculated for demographic and other baseline characteristics.

15.3.5 Efficacy Analysis

Efficacy will be analyzed using the efficacy analysis population (i.e., modified ITT population), separately for Phase 1 part and Phase 2 part (including patients with MPM in Phase 1 part).

PFS is defined as the time from BBI608 administration to documented PD (as assessed according to the mRECIST or RECIST 1.1) or death, whichever is earlier. For imaging in Phase 2 part, the result by the imaging assessment committee will be used. Subjects with neither PD nor death will be censored at their last evaluation for tumor response. Patients who have not received any imaging test after starting the investigational drug administration will be censored on the day of first dose of investigational drug administration except for cases of death before the planned initial imaging test (in case of death before the initial imaging test, death will be handled as 1 event). Patients who have started a new subsequent treatment (chemotherapy, radiotherapy, hormonal therapy, immunotherapy, thermotherapy, or surgical therapy) before exacerbation observed will be censored on the date of imaging test that has lastly recorded no exacerbation observed before starting the new subsequent treatment.

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.

15.3.5.1 Phase 1 Part Efficacy Analysis

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

The best overall response of CR, PR, SD, PD, or NE according to the RECIST 1.1 or mRECIST

will be summarized in frequency tables.

For PFS and OS, the Kaplan-Meier curves will be plotted. The median PFS and median OS will be calculated.

Summary statistics of measurement values and changes from baseline at each evaluation time point will be calculated for respiratory function tests (VC, FVC, FEV1).

15.3.5.2 Phase 2 Part Efficacy Analysis

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

15.3.5.2.1 Primary Endpoints

For PFS, the Kaplan-Meier curve will be plotted, and the median PFS will be calculated. In addition, the 6-month PFS rate will be calculated.

15.3.5.2.2 Secondary Endpoints

- For OS, the Kaplan-Meier curve will be plotted, and the median OS will be calculated.
- The best overall response of CR, PR, SD, PD, or NE according to the RECIST 1.1 or mRECIST will be summarized in frequency tables. In addition, the RR and DCR will be calculated.
- In terms of respiratory function tests (i.e., VC, FVC, and FEV1) at each time of evaluation, summary statistics will be calculated for observed values and change from baseline.

15.3.5.3 Adjustment for Multiplicity

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

15.3.5.4 Subgroup Analysis

For PFS, OS, tumor response, and respiratory function tests (VC, FVC, FEV1), subgroup analyses will be performed according to histological type of mesothelioma (epithelioid, sarcomatoid, biphasic) or number of treatment cycles.

15.3.6 Safety Analysis

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 and Phase 2 part.

The safety data from MPM patients in Phase 1 part will be included in the Phase 2 part safety

analysis.

15.3.6.1 Dose Limiting Toxicity (DLT)

Number of patients with onset of DLT and incidence during the DLT evaluation period will be calculated in the DLT evaluation population.

15.3.6.2 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT). Adverse drug reactions are defined as treatment-related adverse events, i.e., those assessed as "Definitely related," "Probably related," or "Possibly related" to the investigational drug.

The following adverse events will be summarized by SOC and PT for the safety analysis population:

- All adverse events (number of events, number of subjects, and incidence)
- Adverse events by grade
- Adverse events by causal relationship to the investigational drug (adverse events, adverse drug reactions)
- Adverse events by time to onset
- Adverse events by dose at the time of onset

The following conventions will be followed in summarizing adverse events:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- If a subject reports more than one adverse event within a preferred term and/or a body system, the adverse event with the highest known severity within each body system and within each preferred term will be included in the summaries by severity.

Listing of fatal adverse events, serious adverse events, and adverse events leading to treatment discontinuation will also be presented, as with the listing of all adverse events.

15.3.6.3 Clinical Laboratory Assessments

The measured values at each time of evaluation will be summarized using summary statistics.

15.3.6.4 ECG

The measured values at each time of evaluation will be summarized using summary statistics.

15.3.6.5 Vital Signs

The measured values at each time of evaluation will be summarized using summary statistics.

15.3.6.6 Subgroup Analyses

No subgroup analysis will be performed on safety.

15.3.7 Pharmacokinetic Analysis

For the pharmacokinetics population, listings of the plasma concentrations of BBI608, Pem and CDDP at each time point of blood sampling as well as BBI608 pharmacokinetic parameters will be presented. Also, for individual subjects, graphs plotting plasma drug concentration (on the vertical axis) versus time (on the horizontal axis) will be constructed.

15.3.8 Interim Analysis

No interim analysis is planned.

15.3.9 Handling of Data

Individual data will be handled as described below.

15.3.9.1 Data Excluded from Analysis

No particular restriction is set.

When certain data need to be excluded from an analysis, the sponsor will discuss at a Data Review Meeting (DRM) to decide the handling of the data.

15.3.9.2 Definition of Baseline

Baseline is defined as the tests results obtained between Day −7 and the start of BBI608 administration. If multiple measurements are available, the last or later measurement obtained during this period will serve as the baseline.

15.3.9.3 Handling of Missing Data

Missing data will not be imputed.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL, DATA COLLECTION, DATA MANAGEMENT, AND QUALITY ASSURANCE

16.1 Data Collection/Electronic Data Capture (EDC)

This study will use an Electronic Data Capture (EDC) system. For all subjects enrolled in this study, eCRF will be completed with the data up to patient outcome investigation.

For the following items, however, the data will be collected as part of study data, but not recorded in the eCRF:

- Biomarker results by the pathological assessment committee
- Imaging assessment results by the imaging assessment committee
- Plasma drug concentration measurements

The investigator or subinvestigator will complete the eCRF promptly. The investigator will review all eCRFs for individual subjects, and verify the entries in the eCRFs by electronically signing the eCRFs.

Clinical research coordinators may be involved in completing eCRFs, provided that the following conditions are met:

1) The clinical research coordinators only transcribe data from source documents.
2) The investigator has submitted a list of the names of clinical research coordinators and duty assignments to the head of the medical institution in advance, and obtained his/her approval.

The sponsor will obtain the original eCRFs electronically signed by the investigator, while the investigator will retain a copy of the eCRFs. For any inconsistencies between the eCRF and source documents, the investigator will prepare a record explaining the reasons and submit it to the sponsor, while retaining a copy of the record.

Any changes or corrections to the eCRF will be made according to the written instructions provided by the sponsor.

For the following data among other data in the eCRF, the eCRFs may be regarded as source documents:

1) Route of administration and reason for use of concomitant drugs, reason for use of concomitant therapies
2) Lesion findings: target lesions (organs, specific sites of lesions, size), non-target lesions (presence or absence, organs), new lesions (site), tumor response assessment
3) Adverse event severity and seriousness
4) Assessment of causal relationship between adverse events and the investigational drug

5) Adverse event outcome and date of outcome
6) DLT evaluation
7) 12-lead ECG normal/abnormal assessment (specific abnormal findings if any)
8) Chest X-ray normal/abnormal assessment (specific abnormal findings if any)
9) Reason for discontinuation of administration of the investigational drug
10) Best overall response of tumors

16.2 Study Monitoring

This study will be monitored from initiation to completion by the sponsor. Monitoring will include personal visits and telephone communication to assure that the study is conducted in compliance with the protocol, GCP Ordinance and relevant regulatory notifications. On-site reviews of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.3 Audits

This study is subject to audits by the sponsor's auditor at the sponsor or study sites as needed. If such an audit occurs, the investigator will agree to allow access to required subject records. This is dependent on the subject granting consent by signing the informed consent form, which will be explained to subjects. By signing this protocol, the investigator grants permission to personnel from the sponsor for on-site auditing (of study-related documents and procedures employed in eCRF generation).

16.4 Study Documentation

Study records are comprised of source documents, eCRF and all other administrative documents. Source document is defined as any handwritten, computer generated output, or electronically recorded data that contain medical information or test results that have been collected for or are in support of the protocol specifications.

16.5 Clinical Laboratory Certification and Normal Values

A site laboratory will be used for laboratory tests for this study. The study site will provide the sponsor with laboratory certification or its copy, and a dated list of current normal range values for the site laboratory.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1 Ethical Conduct of the Study and GCP Compliance

The investigator agrees that the study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, protocol, "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products,

Gene Therapy Products, and Cosmetics”,, GCP Ordinance and relevant regulatory notifications, and ICH guidelines. The investigator will conduct all aspects of the study in accordance with applicable local laws and regulations.

The investigator will assure proper implementation and conduct of the study, including study-related duties delegated to other appropriately qualified individuals. The investigator will assure that study staff cooperate with monitoring and audits. The investigator will sign (or seal with name) and return the “Investigator Approval” page to the sponsor.

17.2 Institutional Review Board

In accordance with GCP Ordinance and relevant regulatory notifications, the head of the medical institution will obtain documented approval for conducting the study from appropriate Institutional Review Board (IRB) prior to initiation of the study, and forward it to the sponsor. When necessary, an amendment or renewal of the IRB approval must be obtained and also forwarded to the sponsor. The IRB must supply the sponsor a list of the IRB members, and a statement to confirm that the IRB is organized and operates according to GCP Ordinance and relevant regulatory notifications.

A copy of written IRB approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to the sponsor prior to start of the study. The approval or favorable opinion letter must be signed by the IRB chairperson or designee, identify the IRB name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval was granted. The IRB will conduct a continued review of the clinical study at intervals not to exceed one year or when judged to be required by the head of the medical institution. The sponsor must be supplied with written documentation of continued review of the clinical study.

17.3 Informed Consent

The investigator will prepare the informed consent form and provide the form to sponsor for approval prior to submission to the IRB. The sponsor may provide a template informed consent form. The informed consent form must contain the elements required by GCP Ordinance and relevant regulatory notifications, and will be subject to sponsor approval as well as IRB approval.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study from the investigator or subinvestigator, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the investigator or subinvestigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be

asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB review, and Japanese/overseas regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study treatment, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment and patient outcome investigation. The investigator or subinvestigator will provide a copy of the signed informed consent form to each subject, and will record the date of the informed consent in the eCRF.

Signed and dated consent of the subject must be obtained by the investigator or subinvestigator prior to any procedure or test for the study (e.g., collection of blood or other specimens, lifestyle restrictions, physical examination). Only in Phase 1 part, if treatment is continued to Cycle ≥ 2 in the subject, signed and dated voluntary re-consent of the subject must be obtained by the investigator or subinvestigator between Day 17 of Cycle 1 and the start of Cycle 2 therapy.

If the prospective subject is receiving treatment from another physician, the investigator or subinvestigator will contact the other physician with agreement of the prospective subject to notify about his/her participation in the study.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, this must be notified to the subject and documented, and the informed consent form must be revised and submitted to the IRB for review and approval or favorable opinion. The revised informed consent form must be used to obtain re-consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4 Subject Privacy

The sponsor affirms the subjects' confidentiality. The subjects will be identified by unique codes; subjects' names will be masked prior to transmission to the sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate local laws and regulations.

Subjects' privacy will be protected also in any publication of study results.

17.5 Protocol Amendments and Emergency Deviations

For any revisions and/or amendments to this protocol, the investigator must obtain written approval from the sponsor and the IRB. The investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject. Emergency deviations or modifications may be initiated without sponsor or IRB approval, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be immediately reported to the sponsor and the head of the medical institution, as well as the IRB via the head of the medical institution. In such instances, the investigator will submit a report of the specific deviation or modification and the reasons, and if necessary a draft protocol amendment, as promptly as possible to the sponsor and the head of the medical institution, as well as the IRB via the head of the medical institution. In addition, the investigator will obtain written approval from the head of the medical institution and from the sponsor via the head of the medical institution.

The investigator or subinvestigator will record all deviations. For emergency deviations to avoid an immediate hazard to subjects or for other unavoidable medical reasons, the investigator will prepare the record explaining the reasons and immediately submit it to the head of the medical institution and sponsor, while retaining its copy.

The sponsor may amend the protocol as necessary. Amendments will be discussed with and agreed upon by the investigators, and approved by the IRB, with the exception of administrative changes for which the sponsor will make necessary amendments to the protocol.

17.6 Records Retention

The head of the medical institution and the founder of the IRB will retain all study-related documents that need to be retained at the site in accordance with GCP Ordinance and relevant regulatory notifications, for at least 15 years from time of participation in the study or until 1) or 2) below, whichever is longer.

1) Market approval for the investigational drug (If the clinical development is discontinued, 3 years after the date of receipt of the notice that the clinical development is discontinued.)
   The sponsor will notify the medical institutions and IRBs when the market approval is granted or the clinical development is discontinued.
2) Three years after discontinuation or completion of the study.

The head of the medical institution and the founder of the IRB should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without

written sponsor authorization. The sponsor will inform the medical institutions and IRBs when the destruction of documents is permitted.

17.7 Inspection of Records by Regulatory Agencies

In the event of an inspection by Japanese or overseas regulatory agencies, the head of the medical institution and investigator agree to allow representatives of the sponsor and regulatory authorities to have access to all study records, and cooperate in the inspection. The medical institution or investigator will promptly notify the sponsor of all requests to inspect the study by regulatory agencies and will promptly forward a copy of all such inspection reports.

17.8 Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the principle coordinating investigator or the investigator and the sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication.

17.9 Compensation

1) In the event of study-related injury to subjects, the sponsor will compensate for it according to the compensation system established by the sponsor, even if the sponsor is not liable for the injury, with the exception of “a)” to “d)” below:
   a) No compensation will be paid when the health injury was causally unrelated to the study.
   b) No compensation will be paid when the health injury was caused by an act for which the medical institution or a third party is liable.
   c) No compensation will be paid for lack of expected pharmacological or other benefits.
   d) No or reduced compensation may be paid when the health injury is caused by an intentional act or serious negligence of the subject.
2) The sponsor will take appropriate measures for possible compensation, such as buying an insurance policy.

17.10 Payment of Transportation Fees and Other Expenses Associated with Participation in the Study to Reduce Financial Burdens on Subjects

To reduce burdens entailed in study participation, subjects may be paid money to cover transportation fees and other expenses in accordance with the rules of the medical institution.

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19. APPENDIX

APPENDIX I. Study Contacts

- Study Administrative Organization (List of Study Sites and Investigators) (in separate issues)
- Study Administrative Organization (Other) (Attachment)